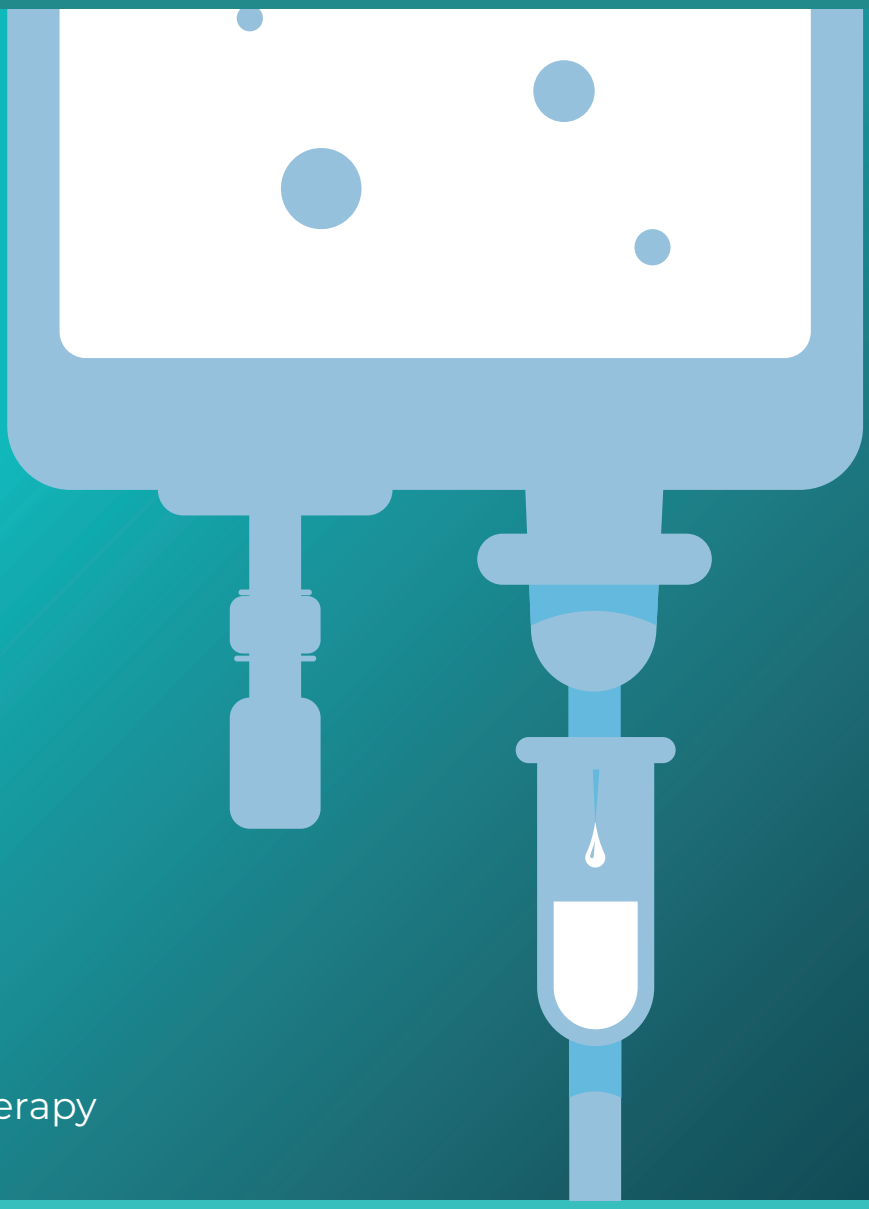
BJAN
bjan-sba.org

Vol. 72, N. 6 | Nov-Dec 2022 | ISSN 0104-0014

ELSEVIER

Brazilian Journal of ANESTHESIOLOGY

Revista Brasileira de Anestesiologia



Fluid therapy

BJAN

Brazilian Journal of Anesthesiology | Vol. 72 N. 6 | November/December 2022

SciELO

SBA Sociedade Brasileira de Anestesiologia

PROVIVE 1%

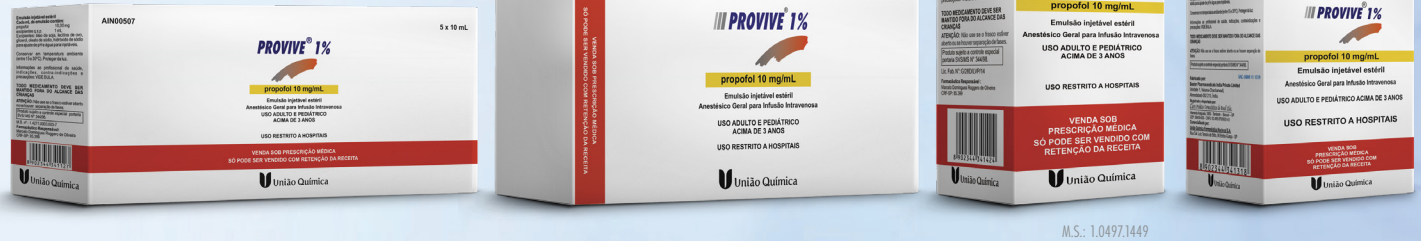
propofol

10 mg/mL

Short-acting sedation with **rapid and safe patient recovery**

Broad range of packaging content sizes

Appropriate for every kind of procedure



M.S.: 1.0497.1449

Packaging content sizes appropriate for all anesthesia steps, from ***induction*** *to* ***maintenance***

For ***further information***, scan the ***QR Code***.

SAC **0800 011 15 59**
A dose certa da INFORMAÇÃO

União Química farmacêutica nacional S/A
Hospitalar

Reference: 1. Drug package insert.

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

The Brazilian Journal of Anesthesiology (BJAN) is the official journal of Sociedade Brasileira de Anestesiologia (SBA). The BJAN only accepts original articles for publication that can be submitted in English or Portuguese, and are published in English. Before submitting a manuscript, authors must read carefully the Instructions to Authors. It can be found at: <https://bjan-sba.org/instructions>. Manuscripts must be submitted electronically via the Journal's online submission system <http://www.editorialmanager.com/bjan>.

The BJAN publishes original work in all areas of anesthesia, surgical critical care, perioperative medicine and pain medicine, including basic, translational and clinical research, as well as education and technological innovation. In addition, the Journal publishes review articles, relevant case reports, pictorial essays or contextualized images, special articles, correspondence, and letters to the editor. Special articles such as guidelines and historical manuscripts are published upon invitation only, and authors should seek subject approval by the Editorial Office before submission.

The BJAN accepts only original articles that are not under consideration by any other journal and that have not been published before, except as academic theses or abstracts presented at conferences or meetings. A cloud-based intuitive platform is used to compare submitted manuscripts to previous publications, and submissions must not contain any instances of plagiarism. Authors must obtain and send the Editorial Office all required permissions for any overlapping material and properly identify them in the manuscript to avoid plagiarism.

All articles submitted for publication are assessed by two or more members of the Editorial Board or external peer reviewers, assigned at the discretion of the Editor-in-chief or the Associate Editors. Published articles are a property of the Brazilian Society of Anesthesiologists (SBA), and their total ou partial reproduction can be made with previous authorization. The BJAN assumes no responsibility for the opinions expressed in the signed works.

Edited by | Editada por
Sociedade Brasileira de Anestesiologia (SBA)
Rua Prof. Alfredo Gomes, 36, Rio de Janeiro/RJ, Brazil - CEP 22251-080
Telefone: +55 21 3528-1050
E-mail: contato@sbahq.org
www.sbahq.org

Published by | Publicada por
Elsevier Editora Ltda.
Telefone RJ: +55 21 3970-9300
Telefone SP: +55 11 5105-8555
www.elsevier.com
ISSN: 0104-0014

Bryony®

sugamadex
sódico 100 mg/mL

Launch

Best option for
NMB reversal[1-3]

*Neuromuscular blocker

It provides **benefits**[1] for the patients during cirurgical procedures.

Rapid and safe reversal in **less than 3 minutes**[1,3]

M.S - 1.0497.1478

Dosage form:[1]

Solution for Injection 100 mg/mL; Packaging of 10 vials ampoules 2mL (sugammadex 200 mg); Adult and pediatric use >2 years of age; Intravenous use.

BRYONY (sugammadex sodium) **INDICATIONS:** It is indicated to provide the reversal of rocuronium- or vecuronium-induced neuromuscular blockade in patients aged more than 2 years. **CONTRAINDICATIONS:** This drug is contraindicated for use by patients with hypersensitivity to the active component or to any of the excipients of the product formula. **WARNINGS AND PRECAUTIONS:** Ventilatory support for patients is mandatory until proper spontaneous breathing is restored following neuromuscular blockade reversal. There was no clinically relevant effect of sugammadex alone or in combination with anticoagulants on the incidence of peri- or post-surgical bleeding complications. As the risk of bleeding has not been systematically studied, coagulation parameters should be carefully monitored according to routine clinical practice in patients with known coagulopathies and patients under anticoagulants. The use less than than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and and therefore, is not recommended. The use of sugammadex is not recommended in patients with severe renal impairment. When drugs that potentiate neuromuscular blockade are used postoperatively, attention should be given to the possibility of neuromuscular blockade recurrence. Due to the administration of sugammadex, certain drugs may become less effective because of the decrease in plasma concentrations. Due to administration of certain drugs after sugammadex, theoretically, rocuronium or vecuronium can be displaced from sugammadex. If neuromuscular blockade is reversed during anesthesia, additional doses of anesthetic and/or opioids should be administered as clinically indicated. Relevant bradycardia has been observed within minutes of sugammadex administration for neuromuscular blockade reversal. Sugammadex should not be used to reverse blockade induced by non-steroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinoline compounds and should not be used to reverse neuromuscular blockade induced by steroidal neuromuscular blocking agents other than rocuronium or vecuronium. This drug should not be used by pregnant women without medical or dental surgeon advice. Sugammadex can be used in lactating women, however, caution is recommended. BRYONY has no known effects on the ability to drive and use machines. **DRUG INTERACTIONS:** - Toremifene: some displacement of vecuronium or rocuronium from the sugammadex complex may occur. - Intravenous administration of fusidic acid: the use of fusidic acid in the preoperative stage may cause some delay in the recovery of the T4/T1 ratio of 0.9. - Hormonal contraceptives: administration of sugammadex in a bolus dose is considered equivalent to a daily missed dose of steroidal oral contraceptives. - Non-oral hormonal contraceptives: the patient must use an additional non-hormonal contraceptive method during the following 7 days. **DOSAGE AND HOW TO USE:** Sugammadex should only be administered by or under the supervision of an anesthesiologist. The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed. The same doses used in young adults are recommended for elderly patients. At a dosage of 100 mg/mL it can be diluted to 10 mg/mL to increase dose accuracy in the pediatric population. **ADVERSE REACTIONS:** resistance to the endotracheal tube, coughing, mild resistance, awakening during surgery, coughing during anesthetic procedure or surgery, or short breathing, movement of a limb or body or coughing during anesthetic procedure or surgery, grimaces, or endotracheal tube suction, cough, tachycardia, bradycardia, movement and increased heart rate, neuromuscular blockade recurrence, drug hypersensitivity reactions (anaphylaxis and anaphylactic shock), pulmonary complications, and bronchospasm. The safety profile of sugammadex (up to 4 mg/kg) is similar to the safety profile seen in adults. Caution: this product is a drug that has a new therapeutic indication in the country and, although research has indicated acceptable efficacy and safety, even if correctly indicated and used, unpredictable or unknown adverse events may occur. If so, please report adverse events. **SOLD UNDER MEDICAL PRESCRIPTION.** MS Registry 1.0497.1478

CONTRAINDICATIONS: This drug is contraindicated for use by patients with hypersensitivity to the active component or to any of the excipients of the product formula. **DRUG INTERACTIONS:** Hormonal contraceptives: administration of a sugammadex bolus dose is considered equivalent to a missed daily dose of steroidal oral contraceptives.

References: 1. Package Insert of Product Bryony® (sugammadex sodium). **2.** Herring WJ et al. Sugammadex efficacy for reversal of rocuronium- and vecuronium-induced neuromuscular blockade: A pooled analysis of 26 studies. J Clin Anesth. 2017;41:84-91. **3.** Hristovska AM et al. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2018;73(5):631-641.

If symptoms persist a doctor should be consulted

União Química conecta
www.uniaoquimicaconecta.com.br

Please access the complete package insert through **QR Code**:

SAC **0800 011 15 59**
The right amount of **INFORMATION**

União Química farmacêutica nacional S/A
Hospitalar

Please access our **União Química Conecta** portal and check out updated and exclusive content on the hospital environment.

 JULHO 2022.

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

ISSN 0104-0014 • Volume 72 • Number 6 • November/December, 2022

The Brazilian Journal of Anesthesiology is indexed by **Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)** since 1989, **Excerpta Médica Database (EMBASE)** since 1994, **Scientific Electronic Library Online (SciELO - Brasil)** since 2002, **MEDLINE** since 2008, **Scopus since** 2010 and **Web of Science (SCIE - Science Citation Index Expanded)** since 2011.

Editorials

683 **Perioperative fluid therapy: more questions than definitive answers**
Lais Helena Navarro e Lima, Fábio de Vasconcelos Papa, Célio Gomes de Amorim, Gabriel Magalhães Nunes Guimarães, Rodrigo Leal Alves

685 **Registration of clinical trials in anesthesiology: promoting transparency in clinical research**
André P. Schmidt, Maria José C. Carmona

Original Investigations

688 **Intraoperative fluid balance and cardiac surgery-associated acute kidney injury: a multicenter prospective study**
Henrique Palomba, Ricardo E. Treml, Tulio Caldonazo, Henrique T. Katayama, Brenno C. Gomes, Luiz M.S. Malbouisson, João Manoel Silva Junior

695 **Fluid administration in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: neither too much nor too little**
Maria Elvira Castellanos Garijo, Ana Sepúlveda Blanco, José Tinoco Gonzalez, Alicia Merinero Casado, Juan Ignacio Medina de Moya, Gabriel Yanes Vidal, Ana Forastero Rodriguez, Cristobalina Ángeles Martín García, Francisco Cristobal Muñoz-Casares, Javier Padillo Ruiz

702 **Fluid preloading before beach chair positioning for arthroscopic shoulder procedures: a randomized controlled trial**
Huru Ceren Gokduman, Elif Aygun, Nur Canbolat, Mert Canbaz, Taner Abdullah, Ali Ersen, Mehmet I. Buget

711 **Effects of Plasma-Lyte® and 0.9% saline in renal function after deceased-donor kidney transplant: a randomized controlled trial**
Paulo do Nascimento Junior, Lucas Esteves Dohler, Cindy Midori Uchida Ogawa, Luís Gustavo Modelli de Andrade, Leandro Gobbo Braz, Norma Sueli Pinheiro Módolo

720 **Impact of colloids or crystalloids in renal function assessed by NGAL and KIM-1 after hysterectomy: randomized controlled trial**
Murillo G. Santos, João Paulo Jordão Pontes, Saulo Gonçalves Filho, Rodrigo M. Lima, Murilo M. Thom, Norma Sueli P. Módolo, Daniela Ponce, Lais Helena Navarro

729 **The clinical impact of the systolic volume variation guided intraoperative fluid administration regimen on surgical outcomes after pancreaticoduodenectomy: a retrospective cohort study**
Daniel Negrini, Jacqueline Graaf, Mayan Ihsan, Ana Gabriela Correia, Karine Freitas, Jorge Andre Bravo, Tatiana Linhares, Patrick Barone

736 **Is Mallampati classification a good screening test? A prospective cohort evaluating the predictive values of Mallampati test at different thresholds**
Clístenes C. de Carvalho, Danielle M. da Silva, Marina S. Leite, Flávia A. de Orange

742 **Evaluation of thyromental height as a predictor of difficult laryngoscopy and difficult intubation: a cross-sectional observational study**
Smita Prakash, Parul Mullick, Rajvir Singh

749 **Reinforcing the valuable role of gastric ultrasound for volume and content assessment: an observational study**
Elena Segura-Grau, Ana Segura-Grau, Ricardo Araújo, Guillermo Payeras, Jorge Cabral, Vera Afreixo

757 **Preoperative fasting for the infusion of "yerba mate": a randomized clinical trial with ultrasound evaluation of gastric contents**
Paola Alcarraz, Liliana Servente, Federico Kuster, Leticia Duarte, Mariela Garau, María Desirello, Lourdes Blanc, Nelson Bracesco, Anahi Perlas

762 **Impact of extending prevention of postoperative nausea and vomiting for cancer surgical patients in the PACU: a before and after retrospective study**
Cyrus Motamed, Grégoire Weil, Jean Louis Bourgain

768 **Changes in gap junction proteins Connexin30.2 and Connexin40 expression in the sinoatrial node of rats with dexmedetomidine-induced sinus bradycardia**
Yong-Qiang Yin, Yi Zhong, Yu Zhu, Lei Tian

774 **An alternative approach for blocking the superior trunk of the brachial plexus evaluated by a single arm clinical trial**
Thiago Nouer Frederico, Rioko Kimiko Sakata, Luiz Fernando dos Reis Falcão, Paulo Cesár Castello Branco de Sousa, Fernanda Melhmann, Cesar Augusto Simões, Leonardo Henrique Cunha Ferraro

Systematic Review

780 **Prone ventilation in intubated COVID-19 patients: a systematic review and meta-analysis**
Ee Xin Chua, Zhen Zhe Wong, Mohd Shahnaz Hasan, Rafidah Atan, Nor'azim Mohd Yunos, Hing Wa Yip, Wan Yi Teoh, Mohd Afiq Syahmi Ramli, Ka Ting Ng

Narrative Review

790 **Multidisciplinary management of idiopathic intracranial hypertension in pregnancy: case series and narrative review**
Sara Alves, Natacha Sousa, Luísa Cardoso, Joana Alves

795 **Clinical use of tranexamic acid: evidences and controversies**
Maria J. Colomina, Laura Contreras, Patricia Guilabert, Maylin Koo, Esther Méndez, Antoni Sabate

Case Reports

813 **Approach and anesthetic management for kidney transplantation in a patient with bilateral lung transplantation: case report**
Sofia da Silva Ramos, Ana Isabel Leite, Ana Eufrásio, Isabel Rute Vilhena, Raquel Inácio

816 **Anesthesia strategy for factor X deficiency coagulopathy: case report**
Carla Isabel Ferreira, Fábio Costa, Ana Rita Arantes, Graça Horta, Elsa Soares, Filipa Félix

819 **Immunoadsorption therapy for a meningococcemia patient with myocarditis, adrenal hemorrhage, and purpura fulminans: a case report**
Nihal Akcay, Hasan Serdar Kihtir, Guner Ozcelik, Ulkem Kocoglu Barlas, Mey Talip Petmezci, Esra Sevketoglu

823 **Perioperative administration of recombinant activated factor VII in a Glanzmann□s thrombasthenia patient with platelet refractoriness: case report**
Flora Margarida Barra Bisinotto, Laura Bisinotto Martins, Giovanini Pires de Camargos, Marcelo de Paula Bianco

826 **Neuraxial block anesthetic technique in a patient with SCN8A encephalopathy: case report**
Eric Guimarães Machado, Isis da Rocha Costa Billé, Mariana Moraes Pereira das Neves Araújo, José Francisco Nunes Pereira das Neves, Gilson Lorena Maués, Marco Felipe Bouzada Marcos, Fernando de Paiva Araújo

Short Communication

829 **Non-reactive mydriasis after rocuronium infusion in patients with COVID-19: a case series**
Flávia Assis Fernandes, João Paulo Jordão Pontes, Celso Eduardo Rezende Borges, Erika Lopes Honorato, Sanzio Dupim Soares, Norma Sueli Pinheiro Módolo, Laís Helena Navarro e Lima

Clinical Images

832 **Improving the success rate of intravenous cannulation**
Anthony M.H. Ho, Gregory Klar, Glenio Bitencourt Mizubuti

834 **Anatomy variation of brachial plexus trunks during supraclavicular nerve block: clinical image**
Vendhan Ramanujam, Patrick Van Kirk

Letters to the Editor

836 **Does adding lateral femoral cutaneous nerve block improves the analgesia of pericapsular nerve group block in the fractured hip surgeries?**
Ashok Jadon, Surabhi Srivastawa, Apoorva Bakshi, Rajendra K. Sahoo, Bhupendra K. Singh, Neelam Sinha

839 **Immersive virtual reality on a pregnant patient during an elective orthopedic surgery**
Ramon Magalhães Mendonça Vilela, Enrique Goytizolo, Florentino Fernandes Mendes

841 **Comparison of incidence of emergence delirium in pediatric patients with three different techniques of general anesthesia using sevoflurane and propofol: a randomized controlled trial**
Deepak Modi, Shilpa Goyal, Nikhil Kothari, Ankur Sharma, Rakesh Kumar, Swati Chhabra Akhil Goel, and Pradeep Bhatia

843 **Letter to the Editor commenting on "Efficacy of serratus anterior plane block versus thoracic paravertebral block for postoperative analgesia after breast cancer surgery: a randomized trial"**
Matteo Zappaterra, Alessio Cittadini Andrea Sica, Domenico Pietro Santonastaso, Vanni Agnoletti

845 **Risk factors for prolonged ventilation in patients undergoing endovascular treatment of unruptured intracranial aneurysm: a retrospective cohort study**
Alessandro De Cassai, Federico Geraldini, Giacomo Cester, Sabrina Calandra, Massimiliano Caravello, Francesco Causin, Marina Munari

Brazilian Journal of Anesthesiology 2022;72(6): 683—684

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Perioperative fluid therapy: more questions than definitive answers

"Everything in excess is opposed to nature" — Hippocrates.

Fluid administration is a powerful instrument for anesthesiologists and intensivists to treat disturbances in total body water compartments, hemodynamic changes related to vascular smooth muscle tone, and disorders of cardiovascular function, all commonly encountered in critical care and perioperative settings. However, very few subjects are as controversial as fluid management in perioperative medicine literature. Accordingly, there is a wide variability of practice, both between individuals and institutions, and even within individuals and institutions, which means that the same practitioner can significantly vary in his/hers fluid strategy during different cases in the same settings.[1] While fluids can be a crucial tool for anesthesiologists to prevent or treat hemodynamic instability due to acute hypovolemia or changes in the loading conditions, inadequate fluid administration might also be harmful, leading to edema and impairment of the microcirculation oxygenation. As a consequence, considering numerous disrupted cellular transduction mechanisms related to surgical trauma and underlying diseases, it is unsurprising that perioperative morbidity is linked to the quantity of intravenous fluid administered during this period, whether in insufficient amounts or, more commonly, in excess. Both situations are potentially harmful and may be associated with poorer postoperative outcomes.[2] Moreover, adding one more layer of complexity to the topic, another question needs to be addressed: how much is too little or too much fluid?[3]

This issue of the *Brazilian Journal of Anesthesiology* highlights several controversial topics related to perioperative fluid therapy, including the volume of fluids infused during the perioperative period and its effects on postoperative outcomes. In a prospective, multicenter, observational cohort study that was set at two high-complexity teaching hospitals in Brazil, Palomba et al evaluated the relationship between restrictive versus liberal intraoperative fluid regimes with the incidence of cardiac-surgery-associated acute kidney injury (CSA-AKI) in patients that underwent on-pump coronary artery bypass grafting (CABG). Furthermore, their study also addressed the influence of intraoperative strategies on in-hospital mortality, cardiovascular complications, and length of stay in the ICU and hospital.[4] Although the authors found no significant association between CSA-AKI and intraoperative fluid delivery, their results suggested a higher relative risk of in-hospital mortality and cardiovascular complications among patients under a liberal fluid regime compared with those in the restrictive matched group. These results may offer a window for future observations, seeking to analyze what kind of additional mechanisms related to the myocardial cell and overall cardiac function can represent the "point of no return" in terms of degeneration.

The ideal perioperative fluid therapy strategy has been debated for decades due to its crucial role in the oxygen supply and demand balance, fluid and electrolyte homeostasis, and adequacy of tissue perfusion.[5] However, the most effective perioperative fluid management is still unclear. Paracelsus (1493—1541), a Swiss physician, alchemist, and lay theologist from the German Renaissance, mentioned that "Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy". Data from studies in patients undergoing non-major cardiac surgery comply with the Paracelsus philosophy, suggesting that the regime of intraoperative fluid therapy — i.e., liberal and restrictive strategies — affects patient outcomes.[2] In 2018, a paper published in the *New England Journal* evidenced poorer postoperative outcomes (a higher rate of AKI) in non-cardiac surgical patients treated with a restrictive fluid strategy and shook the scientific community.[6] Later, a systematic review with meta-analysis that excluded cardiac surgical patients from their data analysis confirmed those results, showing lower overall renal major events when liberal fluid therapy was compared to the restrictive approach.[2] Interestingly, the trial by Myles et al[5] enrolled more patients than 17 RCTs combined in the previous 15 years. For this reason, the weight of this trial significantly

https://doi.org/10.1016/j.bjane.2022.09.001

impacted the results of Messina et al's systematic review on postoperative major renal events.[2]

The literature analysis in this field is rather complex due to the number of variables potentially affecting the outcomes, which includes the overall complexity and the intrinsic risks of each specific type of surgery. The definition of liberal and restrictive strategies concerning perioperative fluid management is inconsistent among published papers on this matter, with different interpretations on how to define it and overlapping cut-off points referring to the volume of fluids given per day.[2] Although many comparative studies on the use of fluids in non-cardiac surgery have been published, there is a significant knowledge gap in the cardiac surgery setting. The great differences in the pathophysiology of patients' diseases and the higher burden of comorbidities in cardiac patients hinder a straightforward translation of existing knowledge from one field to another.

Systemic microcirculatory dysfunction is the primary pathophysiologic phenomenon of cardiac surgery, particularly with on-pump CABG, in the operating room and during the immediate postoperative phase. This may be caused by several common features of cardiac surgery such as cardiopulmonary bypass, inflammatory response, hypothermia, anemia, ischemia and reperfusion injury, and coagulation disturbances.[7] Specifically, cardiopulmonary bypass inflammatory response plays a vital role in the pathophysiology of hemodynamic alteration after cardiac surgery because it derives, among others, from the endothelial shear stress, which leads to a disruption in the endothelial membrane physiology including the glycocalyx surface, an intrinsic mechanism of the resultant Frank-Starling's flow forces. Not surprisingly, postoperative major adverse events frequently occur in this scenario, particularly considering the increasing number of older and clinically complex patients presenting for cardiac surgical care.[8]

Several clinical factors should be carefully judged and weighted to plan fluid administration in cardiac surgical patients. The patient's overall cardiac function and hemodynamic status should be considered to define the need for cardiovascular support, including fluid therapy, vasoactive drugs, and inotropes. Nonetheless, deciding when and how much fluid to infuse during surgery is notoriously tricky. For better guidance, many current protocols in perioperative fluid therapy are based on fluid responsiveness. Although fluid responsiveness may also apply to cardiac surgery patients, one must realize that, due to the swift changes in the patient's hemodynamic status, using this concept is not always feasible. Moreover, the fluid challenge technique tests the cardiovascular system function, allowing clinicians to assess whether a patient will benefit from additional fluid administration to increase stroke volume. Fluid therapy should be considered after a positive response to a fluid challenge. Nonetheless, fluids should not always be given when hemodynamic assessment suggests potential fluid responsiveness. An overzealous fluid optimization may not ultimately be beneficial, and a positive fluid balance has been repeatedly associated with worse outcomes in different settings.[9]

Currently, it is impossible to recommend the best evidence-based strategy for fluid therapy in cardiac surgery since existing trials are small, discordant, and inconclusive. For this reason, the contribution of Palomba et al's paper[4] is relevant, opportune, and valuable to cast some evidence on this controversial field.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Braz J Anesthesiol. 2015;114:767–76.
2. Messina A, Robba C, Calabrò L, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on randomized-controlled trials in major abdominal elective surgery. Crit Care. 2021;25:205.
3. Miller TE, Myles PS. Perioperative Fluid therapy for major surgery. Anesthesiology. 2019;130:825–32.
4. Palomba H, Treml RE, Caldonazo T, et al. Intraoperative fluid balance and cardiac surgery-associated acute kidney injury – a multicenter prospective study. Braz J Anesthesiol. 2022;72:688–94.
5. Navarro LHC, Bloomstone JA, Auler Jr. OC, Cannesson M, Della Rocca G, Gan TJ, et al. Perioperative fluid therapy: a statement from the international Fluid Optimization Group. Perioperative Med. 2015;4:3.
6. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378:2263–74.
7. Kara A, Akin S, Ince C. The response of the microcirculation to cardiac surgery. Curr Opin Anaesthesiol. 2016;29:85–93.
8. Bignami E, Guarnieri M, Gemma M. Fluid management in cardiac surgery patients: pitfalls, challenges and solutions. Minerva Anestesiol. 2017;83:638–51.
9. Brotfain E, Koyfman L, Toledano R, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. Am J Emerg Med. 2016;34:2122–6.

Lais Helena Navarro e Lima [a,b,*], Fábio de Vasconcelos Papa [c,d], Célio Gomes de Amorim [e], Gabriel Magalhães Nunes Guimarães [f,g], Rodrigo Leal Alves [b,h,i]

[a] *University of Manitoba, Department of Anesthesiology, Pain and Perioperative Medicine, Manitoba, Canada*

[b] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Programa de Pós-Graduação em Anestesiologia, Botucatu, SP, Brazil*

[c] *St. Michael's Hospital, Department of Anesthesia, Toronto, Canada*

[d] *University of Toronto, Department of Anesthesiology & Pain Medicine, Toronto, Canada*

[e] *Universidade Federal de Uberlândia, Uberlândia, MG, Brazil*

[f] *Universidade de Brasília, Brasília, DF, Brazil*

[g] *Hospital Sirio Libanès Brasília, Brasília, DF, Brazil*

[h] *Hospital São Rafael, Salvador, BA, Brazil*

[i] *Universidade Federal da Bahia, Salvador, BA, Brazil*

[*] Corresponding author.
E-mail: laishnlima@gmail.com (L.H. Navarro e Lima).

Brazilian Journal of Anesthesiology 2022;72(6): 685—687

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Registration of clinical trials in anesthesiology: promoting transparency in clinical research

According to the World Health Organization (WHO), the registration of all interventional trials is a scientific, ethical, and moral responsibility. The WHO has published a minimum dataset recommendation, which has been adopted by many registers and used as criteria for complete registration by many scientific journals.[1] For the purpose of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.[1] When a trial is accepted onto the database, it receives a registration number, which can be quoted on subsequent publications.

Clinical research produces information that is critical to our understanding of any medical intervention. Researchers, universities, governments, and pharmaceutical companies conduct clinical studies to evaluate if a promising medical procedure or medication can lead to a safe and effective treatment for patients. Therefore, quality of medical care is strongly influenced by evidence-based medicine and shared decision making, both of which are based on information originating from clinical studies.

Researchers usually start with experimental testing and preclinical studies that provide basic answers about the potential mechanisms of an intervention. Then, studies involving human subjects provide a clearer picture of how the medication, device, or procedure will work. In fact, clinical trials are considered the central means by which preventive, diagnostic, and therapeutic strategies are evaluated in medicine.[2] Notably, if clinical trials are conducted covertly, or if their results are not properly shared, publication bias may be generated, and scientific evidence and medical practice is strongly compromised, negatively affecting patient care.[3] Hence, clinical trial transparency is pivotal to achieve an optimal evidence-based medical care and this is not different for clinical studies involving interventions in anesthesiology.

There are essentially three steps toward achieving "clinical trial transparency" in anesthesiology: prospective registration of clinical trials, adequate reporting of results, and sharing analyzable data.[4] Registration involves entering details of a clinical trial's design on a public database and should be performed before starting the study. The registration must include the detailed study protocol and statistical analysis plan, with research objectives, design and endpoints clearly specified.[4]

Importantly, there are several reasons why trials should be registered. Trial registration helps to alleviate publication bias, since strong evidence of selective reporting exists.[5] If all studies are registered before starting recruiting patients, nonpublication is visible and can be followed afterwards by other researchers. Furthermore, trial registration provides a record of the trial's outcomes as stated in the protocol *a priori*, avoiding changing endpoints or introducing new ones, with this flawed strategy largely depending on exploratory analysis of the final results. Trial registration may also improve collaboration among researchers by allowing researchers to be aware of ongoing trials. In this context, it may help researchers to identify where research is really warranted. Lastly, trial registration informs the public about current research and may allow potential participants to be aware of recruiting trials for which they might be eligible.[3]

Although there is plenty of benefits for a clinical trial registration in terms of accuracy, compliance, and transparency, previous evidence has indicated an alarming proportion of published clinical studies in the anesthesia literature still inadequately registered despite long-standing international guidelines recommending it.[6-8] For instance, Jones et al[6] have demonstrated that anesthesiology clinical trials display low rates of adequate registration and high rates of discrepancies between outcomes registered and the outcomes actually reported following the publication. In 2015, the most common reason for inadequate registration was registering the study after the first patient enrollment, and shockingly 42% and 90% of the trials had respectively at least one primary outcome and one secondary outcome discrepancy.[6] Of note, De Oliveira et al have found similar

https://doi.org/10.1016/j.bjane.2022.09.002

results indicating a high rate of major discrepancies between the published results and the original registered protocols, even in high-impact anesthesiology journals.[9]

More recently, Chong et al[10] performed an interesting study addressing discrepancies between trial protocols and subsequent publications by reviewing all studies submitted as abstracts to the American Society of Anesthesiologists annual meetings between 2010 and 2016. Authors have shown that the proportion of randomized controlled trials being prospectively registered in anesthesia remains low, as only 21% of 1070 clinical trials were registered before patient enrollment. Consequently, discrepancies between registry entries and corresponding journal publications have also been common.[10]

Most importantly, there is growing evidence that prospective registration of clinical trials reduce bias in clinical research. For instance, Lindsley et al[11] examined the association between clinical trial registration and risk of bias in clinical trials included in systematic reviews. As a secondary objective, authors evaluated the risk of bias among trials registered prospectively and retrospectively. The analysis focused on clinical trials published as of 2005 and included in a sample of 100 Cochrane systematic reviews published from 2014 to 2019. Of 1177 clinical trials identified, the authors showed that only 31% had been registered, and 36.7% of which were registered prospectively. Interestingly, this study has also demonstrated that clinical trial registration was associated with low risk of bias in five out of six domains, including a lower risk of selection bias due to inadequate allocation concealment, performance bias, and detection bias compared with retrospective clinical trial registration.[11]

Publication bias can affect many levels of evidence in clinical studies. For example, within systematic reviews they may result in incorrect interpretation of the data leading to inappropriate clinical decisions. In order to reduce the risk of bias, searching clinical trial registries for unpublished data is a relevant strategy. Unfortunately, so far, the majority of systematic reviews in anesthesiology did not include data from clinical trial registries.[12,13] In fact, the registration of all types of medical research is considered by many as good practice. Therefore, the registration of clinical research could be largely extended to other study designs, including observational studies and systematic reviews, as prevention or at least control for selective publication. Currently, many registers accept the registration of any design of trial, although the fields are generally based on prospective and interventional trial designs. Systematic reviews, similar to clinical trials, also may not be published if they reach unfavorable conclusions, and their registration in a specialized platform (International Prospective Register of Systematic Reviews — PROSPERO) is strongly recommended.

Since 2019, the *Brazilian Journal of Anesthesiology* (BJAN) requires the registration of any clinical trial in a valid and official registry platform according to the International Clinical Trials Registry Platform (ICTRP). There are several clinical trials registries endorsed by the ICTRP, the largest being ClinicalTrials.gov (https://clinicaltrials.gov/), run by the National Library of Medicine, and the EU clinical trials registry in Europe (EU-CTR — https://www.clinicaltrialsregister.eu/). However, some other national entities are considered primary registries for the WHO, as they meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity, and administration. Examples of primary registries include: Brazilian Registry of Clinical Trials (ReBEC), Australian New Zealand Clinical Trial Registry (ANZCTR), Chinese Clinical Trial Registry (ChiCTR), Clinical Trial Registry — India (CTRI), Japan Registry of Clinical Trials (jRCT), German Clinical Trials Register (DRKS), among others. In the BJAN, Brazilian researchers are advised to register their studies at the ReBEC, a Brazilian publicly-owned entity currently managed by the government, the Oswaldo Cruz Foundation, and non-profit organizations. All details of the studies reported in the ReBEC are publicly available. These characteristics for a registry platform are relevant, since it is fundamental that all registries are free to the public and open to all, should be non-profit organizations, and have mechanisms that ensure data are valid.

In summary, prospective clinical trial registration seems to be mandatory in order to achieve more clinical research transparency. However, a substantial proportion of trials across many disciplines are still published without such registration, which unfortunately is a fact for anesthesiology as well. This leads to reporting bias and doubts about trial efficacy and its integrity. Editors, reviewers, and publishers must also take some responsibility and move forward by increasing their efforts to demand prospective trial registration, a strategy that should be implemented in all anesthesia journals, including the BJAN. The international recommendations for prospective trial registration must be universally incorporated into the anesthesiology research in order to minimize misconduct and ensure clinical research integrity and accuracy.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. International Clinical Trials Registry Platform (ICTRP). International Standards for Clinical Trial Registries (version 3.0) https://www.who.int/publications/i/item/international-standards-for-clinical-trial-registers [Accessed 18 September 2022].
2. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307:1838—47.
3. Pansieri C, Pandolfini C, Bonati M. The evolution in registration of clinical trials: a chronicle of the historical calls and current initiatives promoting transparency. Eur J Clin Pharmacol. 2015;71:1159—64.
4. Wager E, Elia N. Why should clinical trials be registered? Eur J Anaesthesiol. 2014;31:397—400.
5. Cook C, Jull G, Moore A. Registration of clinical trials for publication. Man Ther. 2014;19:279—80.
6. Jones PM, Chow JTY, Arango MF, et al. Comparison of registered and reported outcomes in randomized clinical trials published in anesthesiology journals. Anesth Analg. 2017;125:1292—300.
7. El-Boghdadly K, Wiles MD, Atton S, Bailey CR. Adherence to guidance on registration of randomised controlled trials published in Anaesthesia. Anaesthesia. 2018;73:556—63.

8. Østervig RM, Sonne A, Rasmussen LS. Registration of randomized clinical trials—a challenge. Acta Anaesthesiol Scand. 2015;59:986—9.
9. De Oliveira Jr GS, Jung MJ, McCarthy RJ. Discrepancies between randomized controlled trial registry entries and content of corresponding manuscripts reported in anesthesiology journals. Anesth Analg. 2015;121:1030—3.
10. Chong SW, Imberger G, Karahalios A, et al. Trial registration of abstracts from the American Society of Anesthesiologists Meetings 2010-2016: A review of prospective trial registration and selective outcome reporting. PLoS One. 2022;17:e0270841.
11. Lindsley K, Fusco N, Li T, Scholten R, Hooft L. Clinical trial registration was associated with lower risk of bias compared with non-registered trials among trials included in systematic reviews. J Clin Epidemiol. 2022;145:164—73.
12. Umberham BA, Detweiler BN, Sims MT, Vassar M. Clinical trial registry use in anaesthesiology systematic reviews: A cross-sectional study of systematic reviews published in anaesthesiology journals and the Cochrane Library. Eur J Anaesthesiol. 2017;34:797—807.
13. Barbosa FT, Lira AB, Oliveira Neto OB, et al. Tutorial for performing systematic review and meta-analysis with interventional anesthesia studies. Braz J Anesthesiol. 2019;69:299—306.

André P. Schmidt [a,b,c,d,e,f,*], Maria José C. Carmona [f]

[a] *Hospital de Clínicas de Porto Alegre (HCPA), Serviço de Anestesia e Medicina Perioperatória, Porto Alegre, RS, Brazil*

[b] *Universidade Federal do Rio Grande do Sul (UFRGS), Instituto de Ciências Básicas da Saúde (ICBS), Departamento de Bioquímica, Porto Alegre, RS, Brazil*

[c] *Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Santa Casa de Porto Alegre, Serviço de Anestesia, Porto Alegre, RS, Brazil*

[d] *Hospital Nossa Senhora da Conceição, Serviço de Anestesia, Porto Alegre, RS, Brazil*

[e] *Universidade Federal do Rio Grande do Sul (UFRGS), Faculdade de Medicina, Programa de Pós-graduação em Ciências Pneumológicas, Porto Alegre, RS, Brazil*

[f] *Universidade de São Paulo (USP), Faculdade de Medicina (FM), Programa de Pós-Graduação em Anestesiologia, Ciências Cirúrgicas e Medicina Perioperatória, São Paulo, SP, Brazil*

[*] Corresponding author.
E-mail: aschmidt@ufrgs.br (A.P. Schmidt).

Brazilian Journal of Anesthesiology 2022;72(6): 688—694

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Intraoperative fluid balance and cardiac surgery-associated acute kidney injury: a multicenter prospective study

Henrique Palomba [a], Ricardo E. Treml [b], Tulio Caldonazo [c], Henrique T. Katayama [d], Brenno C. Gomes [e], Luiz M.S. Malbouisson [d], João Manoel Silva Junior [d,*]

[a] *Hospital Alemão Oswaldo Cruz, Departamento de Medicina Intensiva, São Paulo, SP, Brazil*
[b] *Friedrich-Schiller-University, Department of Anaesthesiology and Intensive Care Medicine, Jena, Germany*
[c] *Friedrich-Schiller-University, Department of Cardiothoracic Surgery, Jena, Germany*
[d] *Universidade de São Paulo, Departamento de Anestesiologia, São Paulo, SP, Brazil*
[e] *Universidade Federal do Paraná, Departamento de Medicina Integrada, Setor de Ciências da Saúde, Curitiba, PR, Brazil*

Received 18 February 2022; accepted 24 July 2022
Available online 30 July 2022

KEYWORDS
Acute kidney injury;
Coronary artery bypass;
Cardiac surgery;
Fluid therapy;
Cardiovascular disease;
Cardiopulmonary bypass

Abstract
Background: Recent data suggest the regime of fluid therapy intraoperatively in patients undergoing major surgeries may interfere in patient outcomes. The development of postoperative Acute Kidney Injury (AKI) has been associated with both Restrictive Fluid Balance (RFB) and Liberal Fluid Balance (LFB) during non-cardiac surgery. In patients undergoing cardiac surgery, this influence remains unclear. The study objective was to evaluate the relationship between intraoperative RFB vs. LFB and the incidence of Cardiac-Surgery-Associated AKI (CSA-AKI) and major postoperative outcomes in patients undergoing on-pump Coronary Artery Bypass Grafting (CABG).
Methods: This prospective, multicenter, observational cohort study was set at two high-complexity university hospitals in Brazil. Adult patients who required postoperative intensive care after undergoing elective on-pump CABG were allocated to two groups according to their intraoperative fluid strategy (RFB or LFB) with no intervention.
Results: The primary endpoint was CSA-AKI. The secondary outcomes were in-hospital mortality, cardiovascular complications, ICU Length of Stay (ICU-LOS), and Hospital LOS (H-LOS). After propensity score matching, 180 patients remained in each group. There was no difference in risk of CSA-AKI between the two groups (RR = 1.15; 95% CI, 0.85-1.56,

Institutional Review Board: Ethics Committee of the Universidade de São Paulo. Approval Protocol. USP – CAAE 55828016.1.2007.0068.

* Corresponding author.
E-mail: joao.s@usp.br (J.M. Silva Junior).

https://doi.org/10.1016/j.bjane.2022.07.006

p = 0.36). The in-hospital mortality, H-LOS and cardiovascular complications were higher in the LFB group. ICU-LOS was not significantly different between the two groups. ROCcurve analysis determined a fluid balance above 2500 mL to accurately predict in-hospital mortality.

Conclusion: Patients undergoing on-pump CABG with LFB when compared with patients with RFB present similar CSA-AKI rates and ICU-LOS, but higher in-hospital mortality, cardiovascular complications, and H-LOS.

Introduction

The hemodynamic status of surgical patients, in particular the intravascular volume, plays a central role in the perioperative period and has a direct influence on their outcome. Additionaly, inadequate organ perfusion can have profound implications at the molecular level leading to organ dysfunction.[1,2] Patients undergoing cardiac surgery are at higher risk of greater intravascular volume changes during surgery and after admission to the Intensive Care Unit (ICU).[3] Different aspects inherent to the operation may influence the amount of fluid required perioperatively, however the most crucial period to the risk of developing impaired organ function is the intraoperative phase.[4] The cornerstone of fluid therapy is to maintain intraoperative adequate tissue perfusion, as malperfusion may progress to organ ischemia and consequently organ dysfunction with further acute and long-term clinical consequences.[4,5]

A relatively common complication is the development of renal dysfunction after cardiovascular procedures, especially those requiring cardiopulmonary bypass (on-pump procedures).[6] Postoperatively, the development of Cardiac-Surgery-Associated Acute Kidney Injury (CSA-AKI) has been associated with increased hospital length of stay and increased incidence of nosocomial infections and mortality.[7,8] The pathophysiological mechanism behind CSA-AKI presents a multifactorial nature and it is not yet fully understood.[6]

Recent data from studies in patients undergoing major abdominal surgery suggests that the regime of intraoperative fluid therapy – i.e., liberal and restrictive strategies – may affect patient outcomes.[9,10] For instance, the RELIEF trial[11] found a higher rate of Acute Kidney Injury (AKI) in patients treated with a restrictive fluid strategy, however more liberal fluid resuscitation has also been described as a risk factor in further studies.[12]

In this context, the benefit or harm of either strategy in patients undergoing cardiac surgery is discussed controversially.[13] This study aims to evaluate the relationship between both intraoperative fluid regimes and the incidence of CSA-AKI in patients undergoing on-pump Coronary Artery Bypass Grafting (CABG). Furthermore, this study addresses the influence of both intraoperative strategies on in-hospital mortality, cardiovascular complications, Length of Stay in the ICU (ICU-LOS), and length of stay in Hospital (H-LOS).

Methods

Study design

This prospective, multicenter, observational cohort study was conducted in two university hospitals from February to December 2017, in São Paulo, Brazil. This study was performed in accordance with the principles of the Declaration of Helsinki and the STROBE guidelines for reporting observational studies.[14] Ethical approval was obtained from the Ethics Committee of the University of São Paulo (USP – CAAE 55828016.1.2007.0068). All enrolled participants or their legal representatives provided written informed consent. Patient clinical, laboratory and outcome data were acquired prospectively. Enrolled patients were followed up to 48 hours after the surgical procedure to assess the primary outcome. Further, all patients were followed up during their hospital stay to assess secondary outcomes. Blood samples were collected and immediately processed in the respective institutes for clinical chemistry and laboratory diagnostics from each university hospital.

Study population, inclusion and exclusion criteria

Patients who received an indication for on-pump CABG were screened for inclusion in this cohort. Moreover, the Parsonnet score was determined preoperatively to assess the risk stratification of the collective.[15] Inclusion criteria were patients with age ≥18 undergoing on-pump CABG surgery. Exclusion criteria were severe chronic kidney diseases according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines defined as abnormalities of kidney structure or function, present > 3 months with a category of Glomerular Filtration Ratio (GFR) ≤ 59 mL.min^{-1}/1.73 m^2. Patients with NYHA class IV, ejection fraction on echocardiography less than 30%, intraoperative blood loss ≥ 750 mL corresponding to shock class II of the classification of hemorrhagic shock,[16] and pregnant or breastfeeding patients were also excluded from the study.

Definition of fluid balance

Lacking a clear definition,[4] based on the results of our previous studies evaluating fluid balance intraoperatively in patients undergoing noncardiac surgery, patients in this study who received ≤ 2000 mL fluids were defined as Restrictive Fluid Balance (RFB) and those who received > 2000 mL were defined as Liberal Fluid Balance (LFB).[17] For the fluid balance calculation, we considered all types of fluids

administered intraoperatively such as crystalloid solutions, colloids, priming, cardioplegic solutions and Transfusions (Red Blood cells [allogenic and autologous]; Platelets and Coagulator factors). Patients who had intraoperative blood loss of more than 750 mL, classified as grade II hemorrhagic shock, were excluded from the study (see exclusion criteria above). The influence of a specific type and duration of the fluid therapy were not assessed.

Study outcomes

The primary outcome was the development of CSA-AKI within 2 postoperative days. AKI was defined according to the KDIGO-guidelines as stage 1: increase in serum creatinine $\geq$ 0.3 mg.dL^{-1} ($\geq$ 26.5 μmoL.L^{-1}) within 48 hours or increase in serum creatinine to $\geq$ 1.5—1.9 $\times$ baseline or urinary output $<$ 0.5 mL.kg^{-1}.h^{-1} in 6—12 hours.[18] The secondary outcomes were in-hospital mortality, composite cardiovascular complications (postoperative low cardiac output syndrome: decreased Cardiac index [Cardiac index lower than 2.0 L.min^{-1}.m^{-2}] need of inotropic agent infusion and the use of intra-aortic balloon pump and new onset of Arrhythmias [Atrial fibrillation, Ventricular tachyarrhythmias, bradyarrhythmias]), ICU-LOS, and H-LOS.

Intraoperative fluid management

Intraoperatively, we categorized fluid management according to the American Society of Anesthesiologists (ASA)[4] and Enhanced Recovery After Surgery (ERAS)[19] guidelines in maintenance and therapy. The maintenance fluid serves to cover insensible loss and urine output with a baseline crystalloid infusion rate 1 to 1.5 mL.kg^{-1}.h^{-1}. Fluid therapy was performed by an independent anesthesiologist during the surgery regarding invasive, noninvasive hemodynamic parameters, and laboratorial parameters such as lactate and central venous oxygen saturation to assess the requirement of fluid resuscitation. The volume of fluid therapy needed was documented and the amount of fluid needed for maintenance was considered in the calculation of the fluid balance. The insensible loss of fluid was not calculated.

Statistical analyses

The categorical data in this study are shown as frequencies and percentages. Continuous variables are displayed as means and Standard Deviations (SDs) for normally distributed variables or, otherwise, as medians and Interquartile Ranges (IQRs). The choice of the statistical method used in assessing each variable was based on their distribution pattern. The categorical variables were analyzed by the chi-square test and the continuous variables by means of the Student's *t*-test. Continuous variables with irregular distribution were analyzed by the Mann-Whitney test. Values of $p <$ 0.05 were considered significant. The Statistical Package for Social Sciences (IBM Company, version 20.0) was used for statistical analysis.

Based on literature data[20] which indicates that 30% of patients undergoing cardiac surgery with cardiopulmonary bypass develop CSA-AKI, and considering a null hypothesis of 80% for CSA-AKI, with type I error of 0.05 and type II error of 0.2 (1-power), at least 124 patients would be necessary to perform the study.

In an attempt to minimize the bias due to confounding variables of this study and mimic randomization, we used a propensity score matching.[21] First, a logistic regression model was created using the group variable as the dependent variable. Age, sex, body mass index (BMI), Parsonnet score, time of surgery, previous myocardial infarction and baseline creatinine were entered as predictors, and the width of the matching tolerance caliper was set at 0.01 of the logit. Then, a match for each group patient was selected based on the closest logit. This model was constructed based on a sample of patients matched by propensity score 1:1 without replacement or repetition. The matching procedure was performed before the analysis of the study outcomes.

A Chi-Square analysis was conducted comparing the treatment groups for the primary and secondary outcomes, and the corresponding Relative Risk (RR) and 95% Confidence Interval (95% CI) calculated. Finally, the analysis of sensitivity and specificity considered the value of fluid balance with best accuracy to predict hospital mortality, and the value was chosen by Youden's index (sensitivity + specificity-1) and disposed as a ROC curve.

Results

Figure 1 shows the study flowchart. Initially, 669 patients who underwent CABG were selected from a group of 1143 patients who underwent cardiac surgery. According to the aforementioned exclusion criteria, 83 patients had to be excluded from the cohort. Then, 586 patients were enrolled and divided into two groups: RFB and LFB. A propensity score matching was performed based on demographic and clinical characteristics, finally presenting two groups of 180 patients.

Patient demographics

Table 1 shows the perioperative demographic and clinical data of the patient population separated by original cohort and matched cohort. Patients of the RFB group included more males and Caucasians, had significantly lower prior cardiac surgery, higher prior myocardial infarction, lower baseline glycemia levels, and slightly lower creatinine levels. There were no differences regarding age, BMI, Parsonnet score, hypertension, chronic heart failure, cardiopulmonary bypass time, and left ventricular ejection fraction. After propensity score matching, all the baseline characteristics regarding demographic data, comorbidities, Parsonnet score, frequency of prior cardiac surgery, cardiopulmonary bypass time, clinical and laboratory data showed no significant differences between the groups.

Primary and secondary outcomes

Table 2 summarizes the key outcomes. No significant difference was found between the two groups regarding the creatine values 48 hours postoperatively (Fig. 2). There was neither a significant difference in the incidence nor in the relative risk (RR = 1.15; 95% CI 0.85—1.56, p = 0.36) of CSA-AKI between the two groups (Fig. 3).

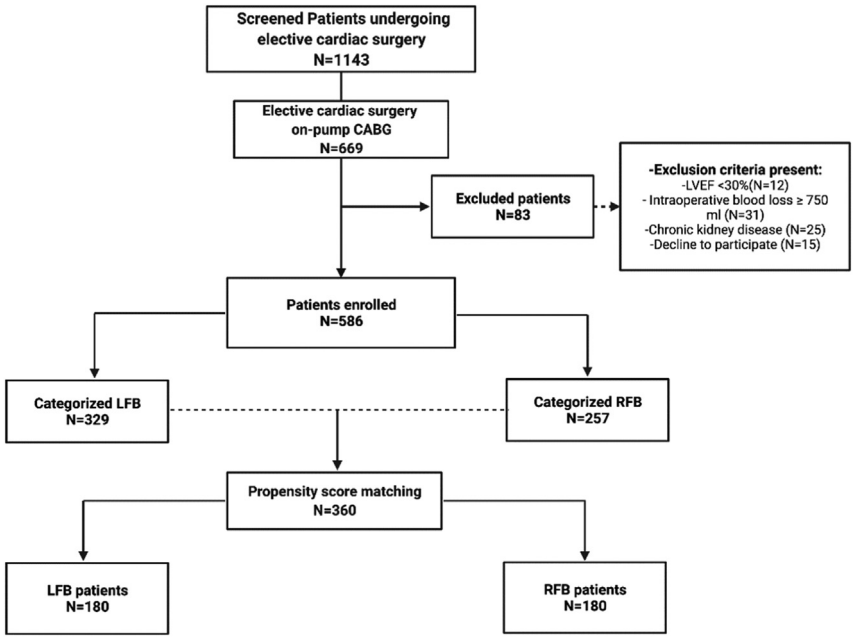


Figure 1 Study flow diagram. Patients involved in the study and the respective groups analyzed. CABG, Coronary Artery Bypass Grafting; LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

The in-hospital mortality was higher in the LFB group in the matched cohort (RR = 2.6, 95% CI 1.10−6.0, p = 0.02). The composite cardiovascular complications were higher in the LFB group in the original and in the matched cohort (RR = 1.52, 95% CI 1.19−1.94, p = 0.0006).

ICU-LOS was not significantly different between the two groups (RFB vs. LFB, 3 ± 0.75 vs. 2 ± 0.75, p = 0.29). Finally, H-LOS was higher in the LFB group in the matched population (RFB vs. LFB, 15 ± 3.7 vs. 22 ± 4.4, p = 0.01).

Table 1 Demographic, clinical and laboratorial data before and after propensity score matching.

	Original Cohort			Matched Cohort		
	RFB (n = 257)	LFB (n = 329)	*p*-value	RFB (n = 180)	LFB (n = 180)	*p*-value
Male, n (%)	154 (59.9%)	230 (69.9%)	0.01	117 (65.0%)	115 (63.9%)	0.83
Age (y), mean ± SD	62.6 ± 10.8	63.4 ± 10.7	0.35	63.1 ± 11.1	63.3 ± 1.0	0.89
BMI (kg.cm^{-2}), mean ± SD	27.8 ± 5.2	27.3 ± 4.4	0.19	27.4 ± 5.4	27.9 ± 4.9	0.27
Race			0.0001			0.16
Caucasian, n (%)	184 (71.8%)	292 (88.8)		143 (79.4%)	153 (85%)	
Black, n (%)	73 (28.4%)	37 (11.3%)		27 (15.0%)	37 (20.5%)	
Parsonnet score	13.6±8.0	14.0±6.1	0.72	14.1±2.0	14.0±2.1	0.99
Comorbidities						
Previous cardiac surgery, n (%)	7 (2.7%)	25 (7.6%)	0.01	7 (3.9%)	10 (5.6%)	0.45
Hypertension, n (%)	112 (76.2%)	88 (71.6%)	0.40	64 (76.2%)	65 (77.4%)	0.85
Prior myocardial infarction, n (%)	105 (40.9%)	58 (17.6%)	0.001	49 (26.7%)	48 (26.7%)	0.90
Chronic heart failure, n (%)	24 (9.3%)	31 (9.4%)	0.97	20 (11.1%)	11 (6.1%)	0.14
Intraoperative fluid balance mL, median (IQR)	497 (-440−1700)	3700 (3150 −4500)	0.001	900 (-157.5 −1700)	3740 (3105-4700)	0.001
Cardiopulmonary bypass time (min), median (IQR)	85 (65.0−110)	85 (53.5−115)	0.58	90 (69.2−109.8)	88 (69.7−115)	0.59
Preoperative tests						
Left ventricular ejection fraction						
> 50%	175 (68.1%)	230 (69.9%)	0.64	121 (67.2%)	136 (75.6%)	0.08
< 50%	82 (31.9%)	99 (30.1%)		59 (32.8%)	44 (24.4%)	0.76
Glycemia (mg.dL^{-1}), mean ± SD	131.8 ± 79.1	146.1 ± 94.6	0.05	133.9 ± 83.4	129.7 ± 0.63	0.17
Baseline creatinine (mg.dL^{-1})	1.05 ± 0.5	1.16 ± 0.4	0.002	1.06 ± 0.5	1.16 ± 0.4	0.3

RFB, Restrictive Fluid Balance; LFB, Liberal Fluid Balance; BMI, Body Mass Index; IQR, Interquartile Range; SD, Standard Deviation.
The categorical variables were analyzed by Chi-Square test and the continuous variables by mean with the Student's t-test. Continuous variables with irregular distribution were analyzed by the Mann-Whitney test (< 0.05 marked in bold).

Table 2 Outcomes summary.

	Original Cohort			Matched Cohort			
	RFB (n = 257)	LFB (n = 329)	*p*-value	RFB (n = 180)	LFB (n = 180)	RR (95% CI)	*p*-value
CSA-AKI (%)	209 (37.9%)	207 (35%)	0,32	61 (33. 9%)	53 (29.4%)	1.15 (0.85–1.56)	0.36[a]
Creatinine (mg.dL^{-1}) median (IQR)[c]	1 (0.9–2.2)	1.3 (0.8–2.1)	0.56	1.3 (1.2–2.4)	1.4 (1.3–2.7)		0.24[b]
Urinary output (mL) median (IQR)[d]				650 (30–2765)	1337.5 (1000–2235)		**0.001**[b]
In-hospital mortality	53 (9.0%)	66 (12%)	0.10	7 (3.9%)	18 (10.0%)	2.6 (1.10–6.0)	**0.02**[a]
Cardiovascular complications, n (%)	190 (34.4%)	270 (45.7%)	< 0.001	63 (35.0%)	96 (53.3%)	1.52 (1.19–1.94)	**0.0006**[a]
ICU-LOS (d), median (IQR)	2 (1–4)	2 (1–4)	0.59	3 (1–4)	2 (1–4)	–	0.29[b]
H-LOS (d), median (IQR)	17 (11–26)	16 (9–25)	0.30	15 (9–23.75)	22 (13–30.75)	–	**0.01**[b]

RFB, Restrictive Fluid Balance; LFB, Liberal Fluid Balance; RR, Relative Risk, 95% CI, Confidence Interval 95%; CSA-AKI, Cardiac Surgery-Associated Acute Kidney Injury; ICU-LOS, Intensive Care Unit Length of Stay; d, days, H-LOS, Hospital Length of Stay; IQR, Interquartile Range.

[a] *p*-values of Chi-Square.

[b] *p*-values of Mann-Whitney-*U* test (< 0.05 marked in bold).

[c] serum creatinine ≥ 0.3mg.dL^{-1} (≥ 26.5 μmoL.L^{-1}) within 48 hours or increase in serum creatinine to ≥ 1.5–1.9 × baseline.

[d] Urinary output in 12 hours.

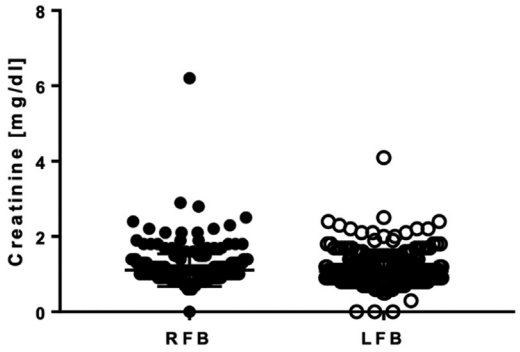


Figure 2 Creatinine values 48 hours postoperatively. Distribution of creatinine values (mg.dL^{-1}) among the evaluated groups. LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

Figure 4 correlates the fluid balance volume in milliliters with the main outcomes. Patients who received volumes greater than 2500 mL had higher rates of intra-aortic balloon pump use, composite cardiovascular complications, and in-hospital mortality. Figure 5 shows a ROC Curve which correlates sensitivity and specificity, and provides a cut-off value

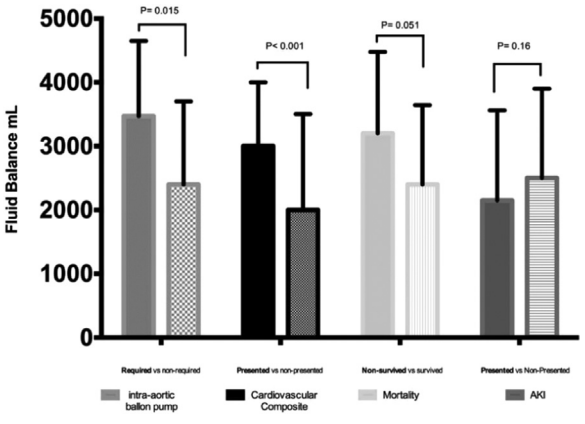


Figure 4 Intraoperative fluid balance and major postoperative outcomes. Bar graph showing the mean value and standard deviation of intraoperative fluid balance according to different outcomes. AKI, Acute Kidney Injury.

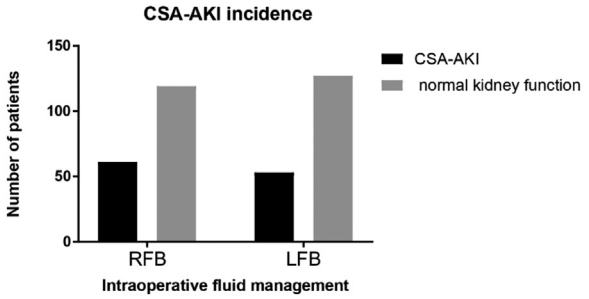


Figure 3 Primary outcome: incidence of cardiac surgery-associated acute kidney injury. Bar graph demonstrating the incidence of acute kidney injury during the study follow-up. CSA-AKI, Cardiac Surgery-Associated Acute Kidney Injury; LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

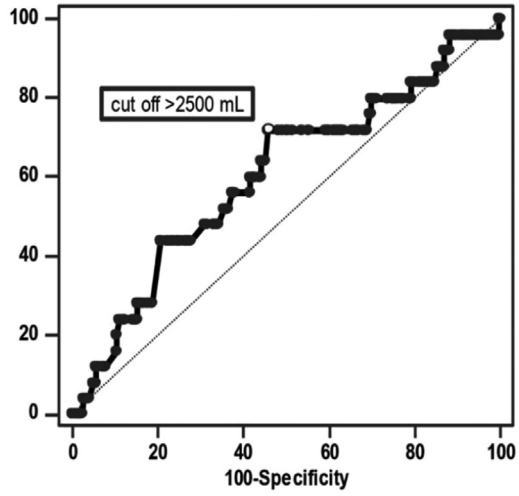


Figure 5 ROC Curve according to intraoperative fluid balance and in-hospital mortality. ROC curve correlating intraoperative fluid balance values with specificity and sensitivity for the endpoint in-hospital mortality. The area under the ROC was 0.62 (0.55 to 0.66), and the optimal fluid balance value found to discriminate hospital mortality was 2500 mL (sensitivity of 72% and specificity of 55%).

of 2500 mL with the best accuracy to predict in-hospital mortality. The area under the ROC was 0.62 (0.55 to 0.66) with sensitivity of 72% and specificity of 55%.

Discussion

In view of our primary outcome, our prospective longitudinal, multicenter cohort study found no significant difference in the incidence of CSA-AKI among patients receiving either liberal or restrictive intraoperative fluid balance after on-pump CABG. Therefore, we found no significant difference regarding relative risk of CSA-AKI under different regimes. Nevertheless, we found a higher relative risk towards in-hospital mortality and cardiovascular complications among patients under liberal fluid balance in comparison with those in the restrictive matched group.

In accordance with previous described epidemiologic data of CSA-AKI,[20] with some incidences being reported in a range of 10% to 30%, our cohort shared similar findings among both studied collectives. In our matched cohort, we found an incidence of 33.9% and 29.4% in patients receiving restrictive and liberal strategies, respectively. The risk association between the development of acute kidney injury after cardiac procedures and some related pathophysiologic mechanisms have been extensively studied.[22] Different demographic, clinical and laboratory variables are proposed as risk factors or predictive factors for the occurrence of postoperative CSA-AKI, but the role of the influence of intraoperative fluid balance remains unclear and not yet studied in patients undergoing cardiac surgery.[22,23]

Interestingly, we found no risk difference concerning the development of postoperative CSA-AKI after on-pump CABG in the 2-day follow-up. Possibly, these findings may suggest that, in the studied cohort, both intravascular fluid shortage and overload intraoperatively could contribute to the impairment of the renal function. Not only intraoperative hypotension during cardiopulmonary bypass is associated with increased incidence of AKI after CABG due to hypoperfusion, but also fluid overload has been described as risk factor for the development of CSA-AKI as a result of endothelial and glycocalyx injury.[24-26] Our findings may indicate that in moderate and high-risk patients undergoing on-pump CABG, both extremes of fluid balance may contribute to the development of CSA-AKI.

The current data regarding which intraoperative strategy is associated with clinical benefit are scarce and difficult to compare as a consequence of a variety of definitions regarding restrictive and liberal strategies as well different study applied methodologies in patients undergoing cardiac surgery.[4,9] A prospective observational study with 1280 enrolled patients undergoing on-pump CABG showed that intraoperative highly positive fluid balance (a total fluid balance of > 500 mL at the end of surgery) is associated with adverse outcomes such as increased length of stay.[27] Furthermore, another randomized study with 192 patients submitted to elective on-pump cardiac surgery receiving either restrictive or liberal intraoperative fluid administrations had observed that restrictive balance intraoperatively with autologous transfusion reduces the intraoperative allogenic red blood cell transfusions without an increase of postoperative requirement of transfusion.[28] The majority of the current studies observed the influence of postoperative fluid balance on cardiac-surgical patients with most evidence showing a negative influence of fluid overload on patient outcome,[25] and an increased incidence of AKI[29] and mortality.[30]

Our study showed findings similar to those described in the literature regarding the influence of fluid balance, especially fluid overload, on patient morbidity and mortality.[25] In our collective, a cut-off of 2500 mL intraoperative fluid was a predictor for in-hospital mortality. Fluid overload is associated with tissue edema, distortion of tissue architecture, capillary, and blood flow obstruction resulting in poor diffusion of oxygen and metabolites, contributing to the development and progression of organ dysfunction.[31]

Myocardial edema may worsen ventricular function, resulting in the deterioration of oxygen supply, pulse conduction, and cardiac contraction leading to cardiovascular dysfunction.[32] Excessive intraoperative volume can also lead to increased demand for cardiac function, displacing the heart's Starling curve and culminating in increased cardiac morbidity. Indeed, in the current study, we observed not just a significant incidence of cardiovascular complications in the group receiving the LFB, but also an increased relative risk of cardiovascular complications, H-LOS, and in-hospital mortality.

There are only few multicenter studies that prospectively observed and compared the influence of intraoperative fluid regimes in a large cohort of patients undergoing cardiac surgery, especially in patients receiving on-pump CABG on the incidence of CSA-AKI, therefore our study offers valuable results to the scientific community. Moreover, a propensity score was used to match and attempts to limit bias due to confounding variables in this observational study. Nevertheless, this study has some limitations. First, the quantification and evaluation of fluid balance performed postoperatively (based on the postoperative timepoints from the KDIGO criteria) without prior randomization and differentiation in two studied groups. Second, the influence of the type of fluid used on CSA-AKI was not addressed and an absence of a goal-directed therapy protocol for intraoperative fluid resuscitation as well as monitoring of intraoperative hemodynamic parameters could limit the interpretation of our results. Finally, the degree of atherosclerotic plaques in the aorta, aortic cross clamping time, the duration of the surgical procedure, and the postoperative fluid management were also not specifically assessed.

Conclusions

Patients undergoing on-pump coronary artery bypass grafting with liberal fluid balance when compared with patients with restrictive fluid balance present similar acute kidney injury rates and length of stay in ICU, but higher in-hospital mortality, cardiovascular complications, and length of stay in hospital. Additionally, in our cohort the cut-off value of 2500 mL showed the best accuracy to predict in-hospital mortality.

Funding

This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) Clinician Scientist Program OrganAge funding number 413668513 and by the Interdisciplinary Center of Clinical Research of the Medical Faculty Jena.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors thank all patients and healthcare personnel involved in the study. Ricardo Esper Treml and Túlio Caldonazo are supported by the Clinical Scientist Program of the Jena University Hospital.

References

1. Gumbert SD, Kork F, Jackson ML, et al. Perioperative Acute Kidney Injury. Anesthesiology. 2020;132:180—204.
2. Futier E, Lefrant J-Y, Guinot P-G, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. JAMA. 2017;318:1346—57.
3. Nelson M, Green J, Spiess B, et al. Measurement of blood loss in cardiac surgery: still too much. Ann Thorac Surg. 2018;105:1176—81.
4. Miller TE, Myles PS. Perioperative fluid therapy for major surgery. Anesthesiology. 2019;130:825—32.
5. Corredor C, Thomson R, Al-Subaie N. Long-Term Consequences of acute kidney injury after cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2016;30:69—75.
6. Kumar AB, Suneja M, Riou B. Cardiopulmonary bypass—associated acute kidney injury. Anesthesiology. 2011;114:964—70.
7. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med. 1998;104:343—8.
8. Thakar CV, Yared JP, Worley S, Cotman K, Paganini EP. Renal dysfunction and serious infections after open-heart surgery. Kidney Int. 2003;64:239—46.
9. Messina A, Robba C, Calabrò L, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on randomised-controlled trials in major abdominal elective surgery. Crit Care. 2021;25:205.
10. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010;69:488—98.
11. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. New Engl J Med. 2018;378:2263—74.
12. Patil VP, Salunke BG. Fluid overload and acute kidney injury. Indian J Crit Care Med. 2020;24(Suppl 3):S94—S7.
13. Osawa EA, Rhodes A, Landoni G, et al. Effect of perioperative goal-directed hemodynamic resuscitation therapy on outcomes following cardiac surgery: a randomized clinical trial and systematic review. Crit Care Med. 2016;44:724—33.
14. Cuschieri S. The STROBE guidelines. Saudi J Anaesth. 2019;13(1):S31—S4.
15. Berman M, Stamler A, Sahar G, et al. Validation of the 2000 Bernstein-Parsonnet score versus the EuroSCORE as a prognostic tool in cardiac surgery. Ann Thorac Surg. 2006;81:537—40.
16. Cannon JW. Hemorrhagic Shock. New Engl J Med. 2018;378:370—9.
17. Silva Jr JM, de Oliveira AM, Nogueira FA, et al. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. Crit Care. 2013;17:R288.
18. Kidney Disease KDIGO. Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of acute kidney disease. Kidney Int. 2012;2:1—141.
19. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Can J Anaesth. 2015;62:158—68.
20. Vives M, Hernandez A, Parramon F, et al. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis. 2019;12:153—66.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399—424.
22. Ortega-Loubon C, Fernández-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E. Cardiac surgery-associated acute kidney injury. Ann Card Anaesth. 2016;19:687—98.
23. Protsyk V, Rasmussen BS, Guarracino F, Erb J, Turton E, Ender J. Fluid Management in cardiac surgery: results of a survey in european cardiac anesthesia departments. J Cardiothorac Vasc Anesth. 2017;31:1624—9.
24. Rettig TCD, Peelen LM, Geuzebroek GSC, et al. Impact of intraoperative hypotension during cardiopulmonary bypass on acute kidney injury after coronary artery bypass grafting. J Cardioth Vasc Anesth. 2017;31:522—8.
25. Koc V, Delmas Benito L, de With E, Boerma EC. The effect of fluid overload on attributable morbidity after cardiac surgery: a retrospective study. Crit Care Res Pract. 2020;2020:4836862.
26. Inkinen N, Pettilä V, Lakkisto P, et al. Association of endothelial and glycocalyx injury biomarkers with fluid administration, development of acute kidney injury, and 90-day mortality: data from the FINNAKI observational study. Annals Intensive Care. 2019;9:103.
27. Toraman F, Evrenkaya S, Yuce M, et al. Highly positive intraoperative fluid balance during cardiac surgery is associated with adverse outcome. Perfusion. 2004;19:85—91.
28. Vretzakis G, Kleitsaki A, Stamoulis K, et al. Intra-operative intravenous fluid restriction reduces perioperative red blood cell transfusion in elective cardiac surgery, especially in transfusion-prone patients: a prospective, randomized controlled trial. J Cardioth Surg. 2010;5:7.
29. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. Pediatr Crit Care Med. 2014;15:131—8.
30. Stein A, de Souza LV, Belettini CR, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. Crit Care. 2012;16:R99.
31. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010;6:107—15.
32. Johnston WE. PRO: Fluid restriction in cardiac patients for non-cardiac surgery is beneficial. Anesth Analg. 2006;102:340—3.

Brazilian Journal of Anesthesiology 2022;72(6):695–701

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Fluid administration in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: neither too much nor too little

Maria Elvira Castellanos Garijo [a,*], Ana Sepúlveda Blanco [a], José Tinoco Gonzalez [b], Alicia Merinero Casado [a], Juan Ignacio Medina de Moya [a], Gabriel Yanes Vidal [a], Ana Forastero Rodriguez [a], Cristobalina Ángeles Martín García [b], Francisco Cristobal Muñoz-Casares [b], Javier Padillo Ruiz [b]

[a] *Virgen del Rocío Hospital, Department of Anesthesiology, Seville, Spain*
[b] *Virgen del Rocío Hospital, Department of Surgery, Seville, Spain*

Received 29 September 2020; accepted 19 July 2021
Available online 8 August 2021

KEYWORDS
Cytoreductive surgery;
Hyperthermic intraperitoneal chemotherapy;
Intraoperative Fluid Therapy;
Oncotic Pressure;
Major postoperative complications

Abstract

Introduction: Intraoperative fluid therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy plays an important role in postoperative morbidity. Studies have found an association between overload fluid therapy and increased postoperative complications, advising restrictive intraoperative fluid therapy. Our objective in this study was to compare the morbidity associated with restrictive versus non-restrictive intraoperative fluid therapy.

Methods: Retrospective analysis of a database collected prospectively in the Anesthesiology Service of Virgen del Rocío Hospital, from December 2016 to April 2019. One hundred and six patients who underwent complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were divided into two cohorts according to Fluid Therapy received 1. Restrictive ≤ 9 mL.kg^{-1}.h^{-1} (34 patients), 2. Non-restrictive ≥ 9 mL.kg^{-1}.h^{-1} (72 patients). Percentage of major complications (Clavien-Dindo grade III–IV) and length hospital stay were the main outcomes variables.

Results: Of the 106 enrolled patients, 68.9% were women; 46.2% had ovarian cancer, 35.84% colorectal cancer, and 7.5% peritoneal cancer. The average fluid administration rate was 11 ± 3.58 mL.kg^{-1}.h^{-1}. The restrictive group suffered a significantly higher percentage of Clavien-Dindo grade III–IV complications (35.29%) compared with the non-restrictive group (15.27%) ($p = 0.02$). The relative risk associated with restrictive therapy was 1.968 (95% confidence interval: 1.158–3.346). We also found a significant difference for hospital length of stay, 20.91 days in the restrictive group vs 16.19 days in the non-restrictive group ($p = 0.038$).

* Corresponding author.
E-mail: elvira.castellanos.sspa@juntadeandalucia.es (M.E. Castellanos Garijo).

https://doi.org/10.1016/j.bjane.2021.07.018

Conclusions: Intraoperative fluid therapy restriction below 9 mL.kg^{-1}.h^{-1} in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy was associated with a higher percentage of major postoperative complications.

Introduction

Although its etiology is heterogeneous, peritoneal cytoreductive surgery (CRS) is considered as a pathological entity with characteristics and peculiarities common to all of them. This procedure is characterized by long periods of extreme surface exposure, which results in a significant loss of fluids and proteins, decreases intravascular volume, and is followed by perfusion with intraperitoneal chemotherapy (HIPEC) at 42 °C. The associated morbidity ranges from 35% to 50%.[1–3]

Intraoperative replacement of the lost volume seems a fundamental point in the management of these patients to ensure an intravascular volume that allows adequate tissue perfusion[1–5]; however, avoiding intraoperative fluid overload is important to avoid the increased morbidity confirmed in multiple studies.[6–10]

It is indisputable that this surgery requires advanced hemodynamic monitoring that guarantees adequate cardiac output and splanchnic perfusion.[3–5] Recently, goal-directed therapy has been advised, and the use of stroke volume variation (SVV) to guide fluid therapy has become widespread.[12–15]

However, although these hemodynamic parameters are the best indices to predict a patient's cardiac index response to fluid administration, these parameters have limitations and should not be confused with a patient's actual intravascular volume or preload. In addition, recent work questions the accuracy of SVV as a predictor of volume response during major abdominal surgery,[15] and other authors have questioned the suitability of ''preload dependence'' because of its consequences in the microcirculation.[16]

Our aim in this study was to compare the morbidity associated with restrictive versus non-restrictive intraoperative fluid therapy in patients undergoing CRS and HIPEC.

Methods

This was a two-cohort observational study performed in the Anesthesiology Service of the Virgen del Rocío University Hospital between December 2016 and April 2019. The study was approved by the center's ethics committee (Portal de Etica de la Investigación Biomédica de Andalucía, protocol number 1472-N-19; approval date 23 October 2019).

Adult patients diagnosed with primary or secondary peritoneal carcinomatosis who underwent scheduled CRS and HIPEC were included in this study. Patients in whom complete reduction of the tumor mass was not possible, patients younger than 18 years of age, procedures in which the duration of surgery and the fluid therapy administered were not reliably recorded, and severely clinically deteriorated patients admitted for surgery were excluded (Fig. 1).

We used paclitaxel for ovarian and peritoneal tumors, and mitomycin C for colorectal cancer, appendiceal tumors, and peritoneal pseudomyxoma using an open abdominal coliseum technique.

We collected patients' data for age, comorbidities, American Society of Anesthesiologists (ASA) physical status, peritoneal cancer index, tumor type, intervention time (hours), number of anastomoses, amount and type of fluid therapy (total volume and weight-adjusted volume in mL.kg^{-1}.h^{-1}), blood products, pre- and postoperative blood protein levels, length of stay in the intensive care unit, and length of hospital stay.

As variable outcomes, we recorded the major complications (grade III–IV) according to the Clavien-Dindo classification,[17] and length of hospital stay.

Clavien-Dindo is a classification of surgical complications in 5 degrees:

- Grade I: Any deviation from the normal postoperative.
- Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications (blood transfusions).
- Grade III: Requiring surgical, endoscopic, or radiological intervention.
- Grade IV: Life-threatening complication requiring critical care management.
- Grade V: Death of a patient.

In all patients, we performed combined anesthesia using a thoracic epidural and general anesthesia. We monitored patients' cardiac index using the FloTrac or VolumeView EV1000 (Edwards Lifesciences; Irvine, CA) systems. As maintenance fluid therapy, we used a balanced crystalloid (Plasma-Lyte®; Baxter Healthcare, Toongabbie, NSW, Australia) and as a colloid, we use hydroxyethyl-starch solutions, under the restrictions applied by European Medicines Agency, and 20% albumin.

We extubated 75.5% of the patients in the operating room and the remainder within a few hours, without difficulty. Only one patient required mechanical ventilation, for 48 hours, and 38.7% of patients required norepinephrine during the first hours postoperatively. The average stay in the intensive care unit was 2 days.

In the first 16 patients patients monitored with EV1000 (Edwards Lifesciences; Irvine, CA), we performed a total of 47 Transpulmonary Thermodilutions, and despite an average fluid administration of 11.5 mL.kg^{-1}.h^{-1} [9.5–13.76] during surgery, the patients presented at the end of the surgery, a lower Global End-Diastolic Volume Index (GEDI) than the initial, 531 [460–603] versus 562 [495–624] mL.m^{-2} (nor-

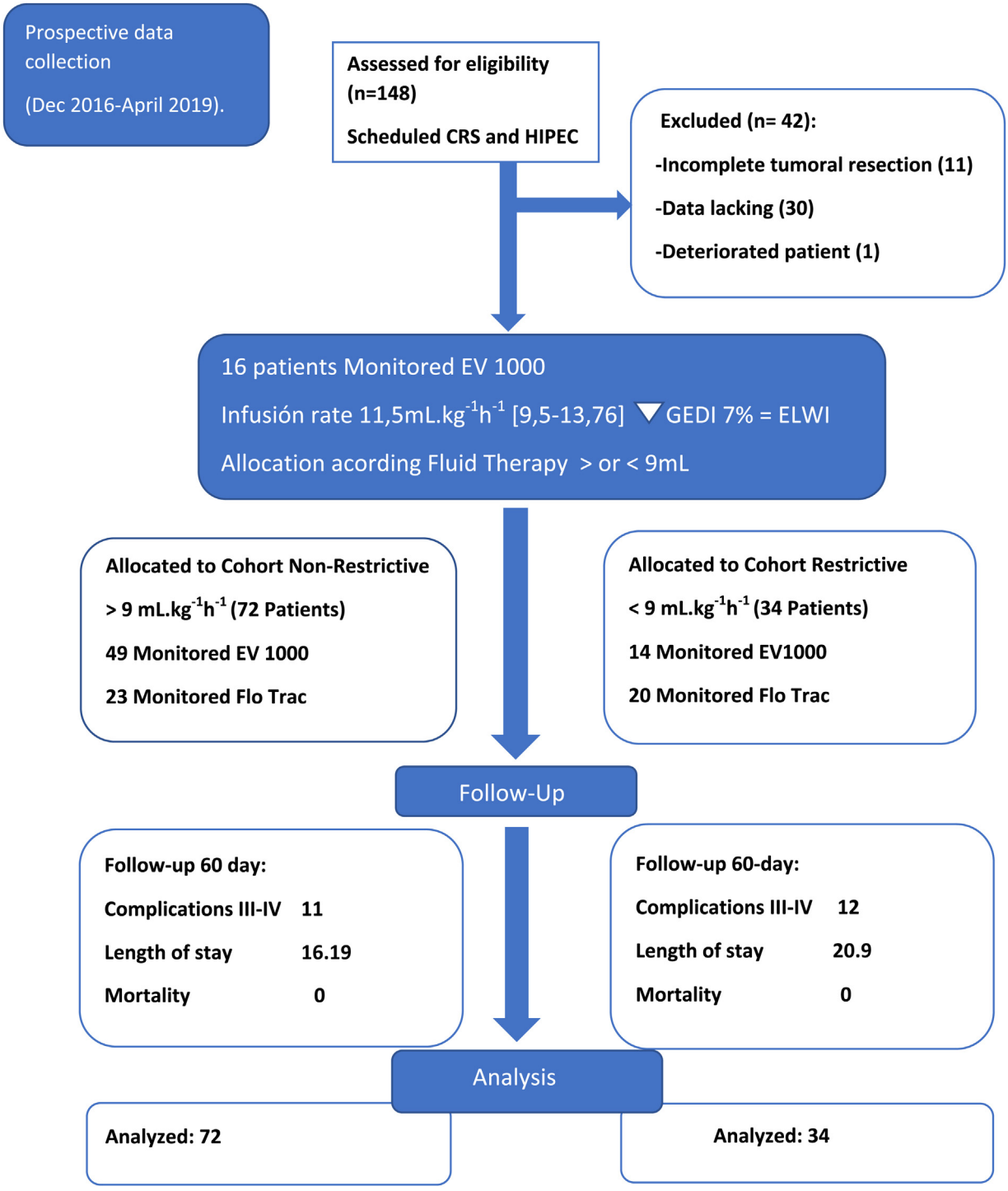


Figure 1 STROBE Flow Diagram.

mal value between 680–800 mL.m^{-2}). Using the indexed Extravascular Pulmonary Water (ELWI), we evaluated the passage of this fluid into the interstitial space and the possible repercussions of our fluid therapy on lung function, the mean of which remained unchanged at 8 mL·kg^{-1}. Therefore, we can conclude that therapy below 9 mL.kg^{-1}.h^{-1} is restrictive in most cases.

Regardless of the monitoring and endpoints used, we divided patients into two cohorts according to the fluid therapy: restrictive fluid therapy of < 9 mL.kg^{-1}.h^{-1} or non-restrictive fluid therapy of > 9 mL.kg^{-1}.h^{-1}.

Statistical analysis

Qualitative variables were expressed with absolute and relative frequencies. Quantitative variables were expressed with mean and standard deviation, and with median and

Table 1 Patients' characteristics.

	Non-restrictive therapy (n = 72)		Restrictive therapy (n = 34)	
	Percentage %	Count	Percentage %	Count
Sex				
Female	77.8%	56	50%	17
Male	22.2%	16	50%	17
ASA				
I	5.6%	4	8.8%	3
II	70.8%	51	52.9%	18
III	23.6%	17	38.2%	13
Diabetes Mellitus	13.9%	10	14.7%	5
Arterial hypertension	30.5%	22	23.52%	8
COPD	5.5%	4	2.9%	1
Primary tumor				
Ovary	52.7%	38	32.3%	11
Colorectal	29.2%	21	50%	17
Peritoneal	6.9%	5	8.8%	3
Pseudomyxoma	4.2%	3	5.9%	2
Appendix	4.2%	3	2.9%	1
	Mean	SD	Mean	SD
Age	57.06	10.65	57.24	11.43
Weight	64.04	11.08	77	14.05
BMI	23.11	6.32	27.23	4.04
PCI	23.22	8.17	17.25	10.08

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PCI, peritoneal cancer index.
Qualitative variables were expressed with absolute and relative frequencies Quantitative variables are expressed as Mean and SD (Standard Deviation).

interquartile range, if the distribution was not normal. The χ^2 test was used for qualitative variables, or Fisher's exact test, if necessary, and we used Student's *t*-test or analysis of variance for quantitative variables.

Differences between the groups were statistically significant at $p < 0.05$ or if the 95% confidence interval of the odds ratio excluded a value of 1. The data were processed and analyzed using the SPSS v 24.0 (IBM Corp., Armonk, NY) statistical package.

Results

We enrolled 106 patients undergoing cytoreductive surgery and HIPEC; 46.22% were diagnosed with ovarian cancer, 35.84% with colorectal cancer, 7.5% with peritoneal cancer, 4.7% with peritoneal pseudomyxoma, 3.77% with appendicular cancer, and 1.97% with other cancers. The general characteristics of our patients are shown in Table 1.

The average fluid administration rate, or the mean rate of intraoperative fluid therapy administered was 11 $\pm$ 3.58 $mL.kg^{-1}.h^{-1}$ When we analyzed data for all patients, we found marked variability in data for patients with weights at extreme values; patients weighing < 50 kg (n = 4) received a mean of 16.24 $\pm$ 1.7 $mL.kg^{-1}.h^{-1}$, while patients weighing > 85 kg (n = 12) received a mean of 8.4 $\pm$ 2.44 $mL.kg^{-1}.h^{-1}$, suggesting that anesthesiologists were not always aware that excess or insufficient fluid volumes were being administered.

Table 2 Characteristics of the patients in each group.

Parameters	Non-restrictive therapy (n = 72)	Restrictive therapy (n = 34)	*p*-value
ASA	2.18	2.29	0.325
Age	57.06	57.24	0.937
Anastomoses	0.82	0.79	0.871
PCI	23.22	17.2	0.006
Surgery hours	10.19	9.76	0.216
Packed red blood cells	0.43	0.18	0.101
Basal protein	7.26	8.96	0.208
Final protein	4.39	4.85	0.002
Relation albumin/Crystalloid (g/L)	5.62	4.10	0.22
Length of stay (days)	16.19	20.91	0.038

ASA, American Society of Anesthesiologists; PCI, peritoneal cancer index.
All data are expressed as mean.

In contrast, the fluid volume distribution in patients with average weight was more random. The body mass index of our patients was in the normal range, and similar in both groups.

The means in each group were similar for ASA physical status, age, number of anastomoses, and duration of the intervention. We found a significant difference only regard-

Table 3 Intraoperative fluid therapy.

Fluid therapy	Average total n = 106	Restrictive n = 34	Non-restrictive n = 72
mL.kg^{-1}. h^{-1} Total	11 ± 3.5	7.13 ± 1.4	12.82 ± 2.7
mL.kg^{-1}.h^{-1} Crystalloids	10.46 ± 3.4	6.68 ± 1.3	12.24 ± 2.6
Colloids mL.kg^{-1}.h^{-1}	0.54 ± 0.6	0.44 ± 0.6	0.59 ± 0.5
HES 6% mL.kg^{-1}.h^{-1}	0.22 ± 0.6	0.22 ± 0.6	0.24 ± 0.5
HES 6% mL	158.82 ± 360	183.8 ± 344	145.83 ± 369
Albumin g	43.68 ± 42.3	28 ± 31.0	50 ± 45.2
Relation g Alb/L Crist.	5.15 ± 5.2	4.10 ± 5.5	5.62 ± 5
Packed red blood cells	0.35 ± 0.74	0.18 ± 0.57	0.43 ± 0.80
Basal hemoglobin	12.31 ± 1.62	12.35 ± 1.35	12.30 ± 1.75
Final hemoglobin	11.05 ± 1.86	11.56 ± 2.08	10.82 ± 1.72
Basal creatinine	0.74 ± 0.20	0.77 ± 0.17	0.72 ± 0.21
Final creatinine	0.71 ± 0.21	0.75 ± 0.19	0.70 ± 0.22

HES, hetastarch.
All data are expressed as mean (standard deviation).

Table 4 Clavien-Dindo complications.

Clavien-Dindo complications	Restrictive (n = 34)	Non-restrictive (n = 72)	p-value
Grade I–II. Minor complications (%)	**(9/34) 26.5**	**(18/72) 25**	**p = 0.10**
-Postoperative ileus	2	3	
-Urinary infection	1	2	
-Transfusion red blood cells	1	8	
-Pleural effusion	0	1	
-AKI (Acute Kidney Injury)	5	4	p = 0.11
Grado III–IV. Major complications (%)	**(12/34) 35.3**	**(11/72) 15.3**	**p = 0.02**
Complication III	**6**	**7**	
-3a. Intraabdominal abcess (percutaneous drainage)	3	4	
-3b. Reoperation under general anaesthesia	3	3	
Complication IV (Re-admission ICU)	**6**	**4**	
-Pulmonary oedema	0	1	
-Septic shock	2	1	
-Anastomotic leakage	4	2	
Length of stay:			
-Mean	20.91	16.19	p = 0.038
-Median	18 [11.5–24.5]	13.5 [11–18.75]	p = 0.058
60-day mortality	0	0	

ICU, intensive care unit.
Complications count and proportion. Length of stay expressed as day.

ing the higher rate of peritoneal cancer in the group that received non-restrictive fluid therapy, and for postoperative blood protein levels, which were higher in the restrictive therapy group, as shown in Table 2.

Patients who received restrictive fluid therapy at a mean rate of 7.13 ± 1.43 mL.kg^{-1}.h^{-1} suffered a higher percentage (12 of 34 patients in restrictive group; 35.29%) of Clavien-Dindo grade III and IV complications compared with the non-restrictive therapy group, who received fluids at a mean rate of 12.45 ± 2.66 mL.kg^{-1}.h^{-1}, with a percentage of serious complications of 15.27% (11/72 patients) (Chi-square; p = 0.02). There were no mortalities at 60 days.

Table 3 shows the amount of crystalloid, colloid, and albumin that patients received. Although the median hospital length of stay in the 106 patients was 14.4 days (IQR, 11–21), we also found a longer length of stay for the patients receiving restrictive therapy, with an average of 20.91 days compared with 16.19 days in the non-restrictive therapy group (p = 0.02).

The different postoperative complications and the length of stay are shown in Table 4. The risk estimate for restrictive therapy was 1.968 (95% confidence interval: 1.158–3.346).

Discussion

Cytoreductive surgery and HIPEC involve much higher fluid losses compared with other abdominal surgeries because of the extensive resection surface and the prolonged duration (mean: 8–10 h).[3,6,18] It is of great importance to individualize the cut-off point regarding restricted or non-restrictive

therapy in this type of procedure, and to set an intraoperative fluid perfusion rate adjusted to the patient's weight and procedure duration to avoid unintended overload or deficit volumes associated with the most extreme weight values.

As a solution, goal-guided therapy has been recommended, which maintains a restrictive basal rate and guides the added bolus-shaped fluid therapy in response to increased SVV or pulse pressure variation (PPV).[11–15]

However, dynamic parameters, as the name suggests, change frequently during the different phases of surgery, and increasing a patient's cardiac index depends on preload as well as contractility, heart rate, and systemic vascular resistance. This is consistent with findings in the OPTIMISE trial[15] in which the precision of the predictive powers of SVV and PPV was insufficient to recommend their perioperative use in major abdominal surgery.

Furthermore, HIPEC involves a high intra-abdominal pressure of up 10–14 mmHg,[18,19] which also affects the predictive power of SVV and PPV. Díaz et al.,[20] in a study performed in pigs, described the loss of correlation between the increase in SVV and PPV and the response of the cardiac index to a fluid bolus after inducing intra-abdominal hypertension.

Moreover, a recent publication questioned the suitability of ''preload dependence'' because of the damage to the microvascular perfusion that this procedure produces.[16] This fact has been proven in sublingual circulation, which was highly correlated with gut and renal microcirculation in several studies.[21–23] These factors could explain our finding that a significant increase in major complications occurred in patients who received restrictive therapy, and a literature review revealed similar results.

Holte et al.,[6] conducted a randomized controlled double-blind trial comparing restrictive and liberal perioperative fluid therapy in 32 patients undergoing colonic surgery. Although the study was designed to detect changes in Pulmonary function, also found an increase in total complications in the restrictive therapy group vs the liberal therapy group: 18 vs. 1, respectively ($p < 0.01$). Six of 16 patients in the restrictive group (37.5%) suffered Clavien-Dindo grade III–IV complications compared with only one patient (6.25%) in the liberal fluid therapy group. The study also showed a significantly longer length of stay in the restrictive fluid therapy group vs the liberal fluid therapy group of 4 vs. 2.5 days, respectively ($p = 0.03$).

CRS is associated with an enormous loss of proteins and albumin,[3] which cause a fall in oncotic pressure and an increase in capillary permeability that we must try to mitigate. Some randomized clinical trials demonstrated a benefit with goal-guided therapy and showed a greater benefit with colloids compared with crystalloids,[12] but without confirming whether the benefit was secondary to significant restriction or a greater proportion of colloids to preserve osmotic pressure intraoperatively with marked protein loss.

It is difficult to reach consensus on the volume of fluid replacement if we use completely different solutions,[24] with different proportions of colloids/crystalloids or grams of albumin/L of crystalloid. Unlike previous studies, in our work, the proportion of colloids and albumin was similar in both groups.

Regarding crystalloids, in our study, we used a buffered crystalloid such as Plasma-Lyte®, which maintains a better acid–base balance during surgery compared with 0.9% saline. A 0,9% saline causes more metabolic disorders such as saline overload and hyperchloremic acidosis[25] and must be avoided as an intraoperative fluid.[26] Furthermore, hyperchloremia was associated with increased morbidity, kidney dysfunction, and mortality in different studies.[27,28]

Finally, unlike other surgeries, once the resection is complete, patients undergoing HIPEC receive intraperitoneal chemotherapy such as with mitomycin or paclitaxel. These agents are associated with cytotoxicity and nephrotoxicity,[29] which can occur at much higher rates in hypovolemic patients. Furthermore, patients who develop acute kidney injury with cytoreductive surgery and HIPEC have higher rates of major morbidity and longer lengths of stay.[30]

The main limitations in our study are its retrospective design and that all interventions were performed by the same surgical team who performed very careful and prolonged resections with high fluid losses but with little blood loss. Although the involvement of a single team increased the internal validity of our study, our results may not extrapolate to all centers.

Conclusions

Our results showed that volume restriction is not a solution and could increase morbidity. Future randomized studies comparing goal-directed fluid therapy with moderate fixed fluid administration will be required. But, the trial will only be valid if adequate cardiac output is controlled and guaranteed in both groups, and a similar colloid/crystalloid ratio is used.

Conflicts of interests

The authors declare no conflicts of interest.

Acknowledgements

We thank Jane Charbonneau, DVM, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

1. Gusani NJ, Cho SW, Colovos C, et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol. 2008;15:754–63.
2. Baratti D, Kusamura S, Laterza B, et al. Early and long-term postoperative management following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Gastrointest Oncol. 2010;2:36–43.
3. Raspé C, Flöther L, Schneider R, et al. Best practice for perioperative management of patients with cytoreductive surgery and HIPEC. Eur J Surg Oncol. 2017;43:1013–27.
4. Malfroy S, Wallet F, Maucort-Boulch D, et al. Complications after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis: Risk factors for ICU admission and morbidity prognostic score. Surg Oncol. 2016;25:6–15.
5. Esquivel J, Angulo F, Bland RK, et al. Hemodynamic and Cardiac Function Parameters During Heated Intraoperative Intraperi-

toneal Chemotherapy Using the Open ''Coliseum Technique''. Ann Surg Oncol. 2000;7:296–300.
6. Holte K, Foss NB, Andersen JL, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized double-blind study. Br J Anaesth. 2007;99:500–8.
7. Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. Anesth Analg. 2005;101:601–5.
8. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Danish Study Groupon Perioperative Fluid Therapy. Effects of intravenous fluid restriction non postoperative complications: comparison of two Perioperative fluid regimens: a randomized assessor-blinded multicentertrial. Ann Surg. 2003;238:641–8.
9. Nisanevich V, Felsenstein I, Almogy G, et al. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology. 2005;103:25–32.
10. Eng OS, Dumitra S, O'Leary M, et al. Association of Fluid Administration With Morbidity in Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy. JAMA Surg. 2017;152:1156–60.
11. Giglio MT, Marucci M, Testini M, et al. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth. 2009;103:637–46.
12. Colantonio L, Claroni C, Fabrizi L, et al. A randomized trial of goal directed vs. standard fluid therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. J Gastrointest Surg. 2015;19:722–9.
13. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002;97:820–6.
14. Brienza N, Giglio MT, Marucci M, et al. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med. 2009;7:2079–90.
15. MacDonald N, Ahmad T, Mohr O, et al. Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: an observational substudy of the OPTIMISE trial. Br J Anaesthesia. 2015;114:598–604.
16. Bouattour K, Teboul JL, Varin L, et al. Preload Dependence Is Associated with Reduced Sublingual Microcirculation during Major Abdominal Surgery. Anesthesiology. 2019;130:541–9.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
18. Raue W, Tsilimparis N, Bloch A, et al. Volume Therapy and Cardiocircular Function during Hyperthermic Intraperitoneal Chemotherapy. Eur Surg Res. 2009;43:365–72.
19. Schluermann CN, Hoeppner J, Benk C, et al. Intra-abdominal pressure, Cardiac Index and vascular resistance during hyperthermic intraperitoneal chemotherapy: a prospective observational study. Minerva Anestesiol. 2016;82:160–9.
20. Díaz F, Erranz B, Donoso A, et al. Influence of tidal volume on pulse pressure variation and stroke volume variation during experimental intra-abdominal hypertension. BMC Anesthesiol. 2015;15:127.
21. Verdant CL, De Backer D, Bruhn A, et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med. 2009;37:2875–81.
22. Jacquet-Lagrèze M, Allaouchiche B, Restagno D, et al. Gut and sublingual microvascular effect of esmolol during septic shock in a porcine model. Crit Care. 2015;19:241.
23. de Bruin AF, Kornmann VN, van der Sloot K, et al. Sidestream dark field imaging of the serosal microcirculation during gastrointestinal surgery. Colorectal Dis. 2016;18:103–10.
24. Ripollés J, Espinosa Á, Casans R, et al. Colloids versus crystalloids in objective-guided fluid therapy, systematic review and meta-analysis. Too early or too late to draw conclusions. Braz J Anesthesiol. 2015;65:281–91.
25. Berend K, de Vries AP, Gans RO. Physiological Approach to Assessment of Acid–Base Disturbances. N Engl J Med. 2014;371:14334–45.
26. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients. GIFTASUP. Powell-Tuck J, Gosling P, Lobo DN, et al. (Updated March 2011).
27. McCluskey SA, Karkouti K, Wijeysundera D, et al. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013;117:412–21.
28. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255:821–9.
29. Kusamura D, Baratti R, Younan B, et al. Impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on systemic toxicity. Ann Surg Oncol. 2007;14:2550–8.
30. Naffouje SA, Tulla KA, Chorley R, et al. Acute kidney injury increases the rate of major morbidities in cytoreductive surgery and HIPEC. Ann Med Surg. 2018;35:163–8.

Brazilian Journal of Anesthesiology 2022;72(6):702–710

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Fluid preloading before beach chair positioning for arthroscopic shoulder procedures: a randomized controlled trial

Huru Ceren Gokduman [a], **Elif Aygun** [a], **Nur Canbolat** [a,*], **Mert Canbaz** [a], **Taner Abdullah** [a], **Ali Ersen** [b], **Mehmet I. Buget** [a]

[a] *Istanbul University, Istanbul Faculty of Medicine, Anesthesiology, Istanbul, Turkey*
[b] *Istanbul University, Istanbul Faculty of Medicine, Traumatology and Orthopedics, Istanbul, Turkey*

Received 15 April 2021; accepted 28 August 2021
Available online 23 September 2021

KEYWORDS
Arthroscopic shoulder surgery;
Beach chair position;
Hemodynamic stability;
Postoperative nausea and vomiting;
Preloading

Abstract
Background and objectives: The Beach Chair Position (BCP) has many advantages such as less neurovascular injury and better intra-articular visualization, but it has also negative consequences, including hemodynamic instability. Although maintaining normal Mean Arterial Pressure (MAP) is important, fluid management is also a crucial concept for hemodynamic stability. The main objective of this study is whether preloading before positioning would be effective for less hemodynamic instability.
Methods: This randomized, controlled study was conducted in a single center in the Istanbul University, Istanbul Faculty of Medicine. Forty-nine patients undergoing elective arthroscopic surgery in the BCP were recruited. In the study group, crystalloid fluid at 10 mL.kg^{-1} of ideal body weight was administered intravenously 30 min before the BCP for preloading. The primary outcome measures were differences of hemodynamic variables as MAP, Stroke Volume (SV), Heart Rate (HR), and Cardiac Output (CO). The secondary outcome measures were Postoperative Nausea and Vomiting (PONV) rates in postoperative first day, surgical satisfaction scale, total ephedrine dose used during surgery, and total amount of fluid.
Results: The MAP, CO, and SV measurements of the study group were higher than those of the control group in the 5th minute after the BCP (respectively, $p = 0.001$, $p = 0.016$, $p = 0.01$). The total amount of crystalloid and surgical satisfaction scales were higher in the study group (respectively, $p = 0.016$, $p = 0.001$). Total amount of colloid and ephedrine dose used in the intraoperative period, and PONV rates were lower in the study group ($p = 0.003$, $p = 0.018$, $p = 0.019$, respectively).
Conclusion: Consequently, preloading can be favorable approach to preserve hemodynamic stability.

* Corresponding author.
E-mail: drnurekiz@gmail.com (N. Canbolat).

https://doi.org/10.1016/j.bjane.2021.08.007

Introduction

The Beach Chair Position (BCP) is the preferred patient position for arthroscopic shoulder procedures because it offers several advantages over the lateral decubitus position, including a lower risk of brachial plexus and vascular injury and better intra-articular visualization.[1,2] However, Mean Arterial Pressure (MAP), Stroke Volume (SV), and Cardiac Output (CO) decrease and total peripheral resistance increases in BCP.[3] For these reasons, maintaining cerebral perfusion and oxygenation, especially in patients taking antihypertensive medications, such as Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB), is challenging for physicians.[4] Salazar et al. reported cerebral desaturation in 18% of patients during shoulder surgery in the BCP.[5]

Perioperative fluid management is an important concept for preserving adequate tissue oxygenation and maintaining CO. While hypovolemia can reduce the oxygen delivery to the tissues and cause secondary organ diseases, hypervolemia can induce interstitial edema and the disruption of alveolar gas exchange through glycocalyx damage.[6–8] The aim of intraoperative fluid therapy is to maintain the patient in a normovolemic state by administering targeted fluid therapy and to prevent the harmful effects of hypovolemia and hypervolemia.[9] When patients are positioned in the BCP under anesthesia, significant hemodynamic changes, such as decreases in MAP, SV, and CO, may develop. Therefore, anesthesia management during surgery is performed with the patient in this position with the goal of ensuring the continuity of tissue perfusion and oxygenation.

The primary hypothesis of this study was that preloading before positioning the patient would be effective in minimizing hemodynamic changes, the need for vasopressors and aggressive intravenous fluid therapy, and the occurrence of hypertension-hypotension episodes secondary to vasoactive drugs; therefore, we aimed to examine whether there would be a significant difference in CO reduction as a result of the BCP in patients undergoing shoulder surgery. We speculated that since more stable hemodynamics would be achieved, there would be a decrease in the total ephedrine requirement and the amount of bleeding and an increase in surgical satisfaction due to the improvement in arthroscopic image quality resulting in shorter surgery and anesthesia durations, thereby leading to a decreased incidence of postoperative complications. Although there have been studies regarding of hemodynamic variables and monitorization techniques in the BCP, our study is one of the few studies investigating the effect of preloading before positioning.

Methods

Ethics

This prospective, randomized, controlled study was approved by the Clinical Studies Ethical Committee of the Istanbul Faculty of Medicine, Istanbul University (2018/166711, Chairperson Prof. A.Y. Uresın) on 25 May 2018, and was registered in a database with ClinicalTrials.gov (NCT04671537, https://clinicaltrials.gov/ct2/show/NCT04671537).

Study

The study was conducted between June 2018 and June 2019 at the Orthopaedics Clinic of the Istanbul Faculty of Medicine. Written informed consent was obtained from each of the participants after providing them with an explanation regarding the anesthesia procedure and publication of the present study. The inclusion criteria were patients aged from 18 to 65 years, with an American Society of Anesthesiologists (ASA) physical status I–II, who were scheduled to undergo elective arthroscopic shoulder surgery in the BCP, and who consented to the study protocol. The following exclusion criteria were used: patients with preoperative arrhythmia, significant heart failure, valvular heart disease or pre-existing cerebrovascular disease, and those using ACEI or ARB as antihypertensive medication.

Randomization was performed using a computer software. The study participants were allocated into two groups: Group C (control group) and Group P (study group). In the patients in Group P, after anesthesia induction and radial artery cannulation, crystalloid fluid was administered intravenously at 10 mL.kg^{-1} of the ideal body weight 30 minutes before positioning them in the BCP. After anesthesia induction and radial artery cannulation, we did not administer any interventions in Group C. In both groups, the patients were raised to a 70° upright position with the head secured in a neutral position using a beach chair. A pressure transducer was placed at the level of the external auditory canal in the BCP. Hemodynamic variables (MAP, Heart Rate [HR], Systolic Arterial Pressure [SAP], Diastolic Arterial Pressure [DAP], CO, and SV) were recorded after positioning the patient in the BCP, followed by at specific time intervals (5th, 10th, 30th, 60th min). We set the threshold Stroke Volume Variation (SVV) limit to 13% in order to administer goal-directed fluid therapy. In cases where SVV rised above 13, a mini fluid challenge was done by giving 250 cc crystalloid firstly, and if no response was obtained, bolus dose ephedrine was used to support CO. In cases where SVV was normal and CO was low, ephedrine bolus treatment was used to support contractility instead of fluid therapy. Hypotension was defined as a 15% decrease in MAP, which was initially treated with 5 mL.kg^{-1} colloid fluid replacement and subsequently with a bolus of ephedrine (5 mg). Patients who needed an infusion of vasoactive drugs were excluded from the study. Further, Postoperative Nausea and Vomiting (PONV) incidences, surgical satisfaction scale scores (0–10, being 0, lowest score; 10, highest score), total amounts of crystalloid and colloid fluids, ephedrine usage, and the durations of anesthesia and surgery were recorded as secondary outcomes. After standard monitoring, the first hemodynamic variables (SAP, DAP, and HR) were recorded. The operations were performed by the same surgeon, and the surgical team was blind to the type of intervention and treatment groups.

Anesthesia and patient monitoring

Probes/monitors for routine noninvasive monitoring were attached, including those for Noninvasive Blood Pressure

(NIBP), HR, pulse oximetry (SpO_2), Electrocardiography (ECG), and temperature (°C) monitoring. Anesthesia was induced using midazolam (2 mg), fentanyl (1 mcg.kg^{-1}), propofol (2–2.5 mg.kg^{-1}), and rocuronium (0.6 mg.kg^{-1}). The trachea was intubated, and anesthesia was maintained with sevoflurane (1–2%, 1 Minimum Alveolar Concentration (MAC)), remifentanil (0.25–0.5 mcg.kg^{-1}.min^{-1}) infusion, and oxygen/nitrous oxide (40%/60%) through the duration of procedure. The patient's lungs were ventilated with a tidal volume of 6–8 mL.kg^{-1} of the ideal body weight and Positive End-Expiratory Pressure (PEEP) of 5 cm H_2O, and the respiratory rates were adjusted to maintain an end-tidal CO_2 pressure of 35–40 mmHg. Subsequently, a radial artery cannula was inserted and connected to a FloTrac/Vigileo system (software version 3.02, Edwards Lifesciences, CA, USA) to measure CO, SV, and SVV.

Statistical analysis

All statistical analyses were performed using the Number Cruncher Statistical System (NCSS, 2007; Kaysville, Utah, USA). All demographic data, such as age, sex, body mass index (BMI), and ASA physical status, were analyzed using descriptive statistical methods (mean, standard deviation, frequency, median, minimum, and maximum). Data distribution was evaluated using the Kolmogorov-Smirnov test, Shapiro-Wilk test, and graphical evaluations. If the data were not normally distributed, non-parametric tests were performed. Comparisons between groups were performed using Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-parametric data. Fischer's exact test was used for all the categorical data. Post-hoc analyses with the Bonferroni correction were performed for multiple comparisons when repeatedly measured variables exhibited significant differences between the groups. A *p*-value < 0.05 was considered statistically significant.

A sample size of 44 patients achieved a power of 80%, which allowed for the detection of a 20% SV difference through a two-sided *t*-test at a significance level of 0.05, with possible dropouts, by using the Power Analysis Program (G-Power, P.S. version 3.1.2) according to study published in literature.[10]

Results

A total of 62 patients who were scheduled for elective arthroscopic shoulder surgery in the BCP were assessed for eligibility. Eleven patients were excluded from the study: 4 refused to participate in the study, and 7 did not meet the inclusion criteria. One of the 51 patients was excluded from the study because this patient was shifted to open surgery during the intraoperative period, and one of them was excluded because a noradrenaline infusion was required due to deep hypotension after anesthesia induction. Forty-nine patients allotted to two groups, 23 (46.9%) patients in Group C and 26 (53.1%) in Group P, completed the study and were included in the final analysis (Fig. 1).

There were no statistically significant differences in the mean age, sex distribution, BMI measurements, and ASA physical status of the patients between the groups ($p > 0.05$) (Table 1).

The crystalloid amounts administered to the patients ranged from 800 to 3500, with an average of 1967.35 ± 573.87; the administered colloid amounts varied between 0 and 500, with an average of 111.22 ± 204.96. A statistically significant difference was found between the crystalloid and colloid amounts administered to the patients between the groups. The crystalloid amounts administered in the study group were higher than those in the control group ($p = 0.016$; $p < 0.05$); by contrast, the colloid amounts administered in the study group were lower than those in the control group ($p = 0.003$; $p < 0.05$). A statistically significant difference was found between the ephedrine ratios in the patients between the groups ($p = 0.018$; $p < 0.05$); the ephedrine ratios in the study group patients were lower than those in the control group patients. A statistically significant difference was found in the PONV ratios in the patients between the groups ($p = 0.019$; $p < 0.05$); the PONV ratios in the study group were lower than those in the control group. A statistically significant difference was found in the surgical satisfaction levels between the groups ($p = 0.001$; $p < 0.05$), and the satisfaction levels in the study group were higher than those in the control group. There was no statistically significant difference in the operation duration in the patients between the groups ($p = 0.001$; $p > 0.05$) (Table 2).

There was no statistically significant difference in the MAP measurements in the supine position between the groups ($p > 0.05$). A statistically significant difference was found in the 0, 5, and 10-min MAP measurements in the BCP between the groups ($p = 0.035$; $p < 0.05$, $p = 0.001$; $p < 0.05$, $p = 0.027$; $p < 0.05$, respectively). The MAP measurements in the study group were higher than those in the control group. There was no statistically significant difference in the HR measurements in the supine position between the groups ($p > 0.05$) (Table 3).

There was no statistically significant difference in the CO measurements in the supine position between the groups ($p > 0.05$). A statistically significant difference was found in the 5, 10, and 30-min CO measurements in the BCP between the groups ($p = 0.016$; $p < 0.05$, $p = 0.009$; $p < 0.05$, $p = 0.018$; $p < 0.05$, respectively). The CO measurements in the study group were higher than those in the control group. There was no statistically significant difference in the SV measurements in the supine position between the groups ($p > 0.05$). The 0 and 60-min SV measurements in the BCP were not statistically significantly different between the groups ($p > 0.05$). A statistically significant difference was found in the 5 and 30-min SV measurements in the BCP between the groups ($p = 0.010$; $p < 0.05$, $p = 0.022$; $p < 0.05$, respectively). The SV measurements in the study group were higher than those in the control group (Table 4).

Discussion

The BCP facilitates better access to the surgical area and reduces the amount of bleeding during arthroscopic shoulder surgery compared to the lateral position; however, it has negative consequences such as venous blood pooling in the lower extremities, relative hypovolemia, and reduction of MAP, SV, and CO.[11] Therefore, the challenge associated with anesthesia management in patients in the BCP is the

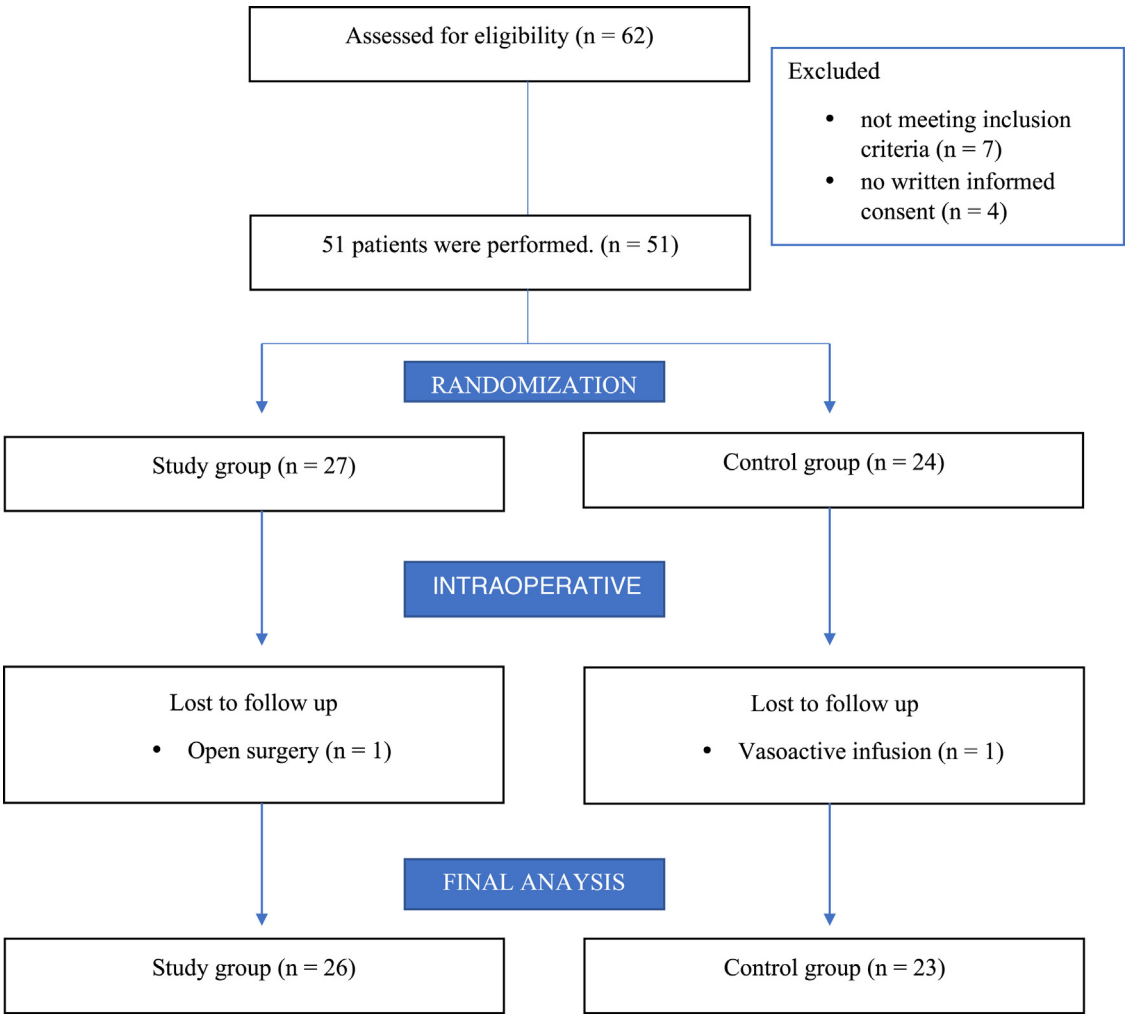


Figure 1 CONSORT flow.

maintenance of tissue perfusion and oxygenation.[12] For these reasons, fluid management is very important during the preoperative period in patients undergoing arthroscopic shoulder surgery in the BCP.

The BCP activates the sympathetic nervous system and baroreceptor reflexes, but the sympathetic response may weaken during anesthesia, leading to a greater reduction in MAP. It has been reported that epinephrine, norepinephrine, and cortisol levels secreted in response to surgical stimuli are lower in cases in which anesthesia is maintained with a propofol and remifentanil infusion than in those in which anesthesia is maintained with sevoflurane.[13] Hypotension (MAP < 50 mmHg) was more commonly observed in 55% of patients who received surgery under anesthesia with a propofol and remifentanil infusion in the BCP.[14] Therefore, anesthesia was maintained using sevoflurane during this study. Antihypertensive drugs, especially ACEIs and ARBs, can contribute to intraoperative hypotension, especially after general anesthesia induction.[15,16] Therefore, patients who were known to use ACEIs and ARBs for preventing deep hypotension were excluded from the study.

Triplet et al. stated that NIBP measurement is not reliable in the BCP, especially when used to predict cerebral perfusion pressure.[17] In their study, Papadonikolakis et al. emphasized that blood pressure can be inaccurately measured up to 50 mmHg depending on the location of the blood pressure cuff.[2] For this reason, the perspective that patients should be monitored more closely in terms of hemodynamics has become widespread over time. However, even if MAP is measured using technically accurate methods, it is recommended for the detection of acute intravascular fluid deficiencies that dynamic preload parameters, such as SVV, CO, cardiac index, SV, and Stroke Volume Index (SVI), be measured.[18,19] It is well known that blood flow depends on MAP and Systemic Vascular Resistance (SVR). The correction of low intraoperative MAP values with vasoconstrictor drugs alone does not guarantee good organ perfusion.[20,21] Buhre et al. showed a 14% volume transition from the intrathoracic area to the extra thoracic area after patients were positioned in the BCP.[22] It was reported that the preservation of normovolemia may be more beneficial than using vasoconstriction to increase MAP alone in order to preserve cerebral perfusion; therefore, increasing intravascular volume in a way that prevents rapid and relative hypovolemia would be effective in protecting patients from possible hypoperfusion.[23] The available information is consistent

Table 1 Patient characteristics.

	Control group (n = 23) n (%)	Study group (n = 26) n (%)	*p*
Age (years)			
Min–Max (Median)	20–77 (53)	24–86 (52)	0.209[a]
Mean ± SD	55.26 ± 14.89	49.92 ± 14.40	
< 45	4 (17.4)	9 (34.6)	
45–59	10 (43.5)	9 (34.6)	
≥ 60	9 (39.1)	8 (30.8)	
Gender			
Female	12 (52.2)	10 (38.5)	0.336[b]
Male	11 (47.8)	16 (61.5)	
BMI ($kg.m^{-2}$)			
Min–Max (Median)	18.5–42.2 (28.4)	18.8–43 (26.4)	0.335[a]
Mean ± SD	29.02 ± 6.41	27.42 ± 5.08	
Normal	6 (26.1)	9 (34.6)	
Overweight	8 (34.8)	12 (46.2)	
Obesity	9 (39.1)	5 (19.2)	
ASA			
I	5 (21.7)	6 (23.1)	0.911[b]
II	18 (78.3)	20 (76.9)	

BMI, Body Mass Index; ASA, American Society of Anaesthesiologists.
[a] Student's *t*-test.
[b] Pearson Chi Square Test.

Table 2 Patients' descriptive statistics.

	Control group (n = 23) n (%)	Study group (n = 26) n (%)	*p*
Crystalloid (mL)			
Min–Max (Median)	800–2600 (1900)	1200–3500 (2000)	0.016[a,d]
Mean ± SD	1760.87 ± 539.14	2150.00 ± 550.09	
Colloid (mL)			
Min–Max (Median)	0–500 (0)	0–500 (0)	0.003[b,e]
Mean ± SD	210.87 ± 246.78	23.08 ± 99.23	
Ephedrine			
No	18 (78.3)	26 (100)	0.018[c,d]
Yes	5 (21.7)	0 (0)	
PONV			
No	16 (69.6)	25 (96.2)	0.019[c,d]
Yes	7 (30.4)	1 (3.8)	
Surgical satisfaction			
Min–Max (Median)	3–10 (8)	7–10 (10)	0.001[c,e]
Mean ± SD	7.74 ± 1.68	9.31 ± 0.93	
Operation duration (min)			
Min–Max (Median)	65–290 (120)	55–210 (92.5)	0.127[c]
Mean ± SD	131.09 ± 61.46	105.77 ± 40.61	

PONV, Postoperative Nausea and Vomiting.
[a] Student's *t*-test.
[b] Mann Whitney U Test.
[c] Fisher's Exact Test.
[d] $p < 0.05$.
[e] $p < 0.01$.

with the SV decreases noted in the results of this study. In the BCP, statistically significant differences were found among the 5, 10, and 30-min SV measurements between the study and control groups ($p < 0.05$), and the SV values were higher in the study group. In our study, although the amount of administered crystalloid was higher in the study group, the need for colloid was found to be lower ($p < 0.05$). Based on this data, it can be concluded that the requirement for

Table 3 Comparison of MAP and HR values.

	MAP values			HR values		
	Control group (n = 23)	Study group (n = 26)	*p*	Control group (n = 23)	Study group (n = 26)	*p*
Supine position						
Min/Max (Median)	66/120 (80)	63/113 (76)	0.497[a]	50/104 (77)	53/103 (81.5)	0.667[a]
Mean ± SD	83.48 ± 14.93	80.54 ± 15.07		75.04 ± 12.84	76.69 ± 13.69	
BCP 0th min						
Min/Max (Median)	50/93 (69)	60/95 (79.5)	0.035[a,e]	48/97 (69)	50/98 (72)	0.186[a]
Mean ± SD	71.22 ± 11.94	77.92 ± 9.72		67.43 ± 11.81	72.15 ± 12.68	
BCP 5th min						
Min/Max (Median)	47/83 (65)	57/94 (75.5)	0.001[a,f]	44/95 (60)	45/95 (66.5)	0.308[a]
Mean ± SD	63.04 ± 10.38	74.81 ± 8.76		62.83 ± 13.08	66.54 ± 12.16	
BCP 10th min						
Min/Max (Median)	55/84 (71)	57/97 (75)	0.027[a],[e]	45/82 (58)	48/79 (60)	0.493[a]
Mean ± SD	71.00 ± 7.87	76.69 ± 9.38		59.96 ± 9.81	61.88 ± 9.68	
BCP 30th min						
Min/Max (Median)	56/89 (76)	52/101 (74)	[a]0.343	50/77 (57)	45/76 (65)	0.194[a]
Mean ± SD	73.52 ± 8.84	76.19 ± 10.47		59.17 ± 7.96	62.58 ± 10.09	
BCP 60th min						
Min/Max (Median)	51/86 (76)	58/99 (71.5)	0.557[a]	50/90 (57)	49/82 (59.5)	0.131[a]
Mean ± SD	73.35 ± 8.46	71.88 ± 8.78		58.65 ± 9.03	62.96 ± 10.58	
p[c]	0.001[f]	0.024[e]		0.002[f]	0.001[f]	
Supine – BCP 0th min						
Min/Max (Median)	-45/10 (-9)	-42/21 (-1)	0.020[b,e]	-29/19 (-9)	-38/20 (-3.5)	0.346[b]
Mean ± SD	-12.26 ± 15.32	-2.62 ± 15.92		-7.61 ± 11.48	-4.54 ± 13.44	
p[d]	0.013[e]	1.000		0.065	1.000	
Supine – BCP 5th min						
Min/Max (Median)	-52/2 (-22)	-35/16 (-2)	0.002[b,f]	-27/15 (-13)	-41/18 (-10.5)	0.428[b]
Mean ± SD	-20.43 ± 15.17	-5.73 ± 14.78		-12.22 ± 10.75	-10.15 ± 13.31	
p[d]	0.001[f]	0.887		0.001[f]	0.010[e]	
Supine – BCP 10th min						
Min/Max (Median)	-48/14 (-10)	-44/22 (-0.5)	0.054[b]	-40/9 (-14)	-37/6 (-12)	0.865[b]
Mean ± SD	-12.48 ± 16.62	-3.85 ± 17.53		-15.09 ± 13.62	-14.81 ± 13.12	
p[d]	0.024[e]	1.000		0.001[f]	0.001[f]	
Supine – BCP 30th min						
Min/Max (Median)	-45/16 (-6)	-44/25 (-6.5)	0.293[b]	-48/12 (-18)	-42/6 (-11.5)	0.595[b]
Mean ± SD	-9.96 ± 17.32	-4.35 ± 16.89		-15.87 ± 14.98	-14.12 ± 12.71	
p[d]	0.173	1.000		0.001[f]	0.001[f]	
Supine – BCP 60th min						
Min/Max (Median)	-50/11 (-7)	-46/23 (-4.5)	0.849[b]	-43/27 (-20)	-40/16 (-12)	0.336[b]
Mean ± SD	-10.13 ± 16.45	-8.65 ± 16.85		-16.39 ± 15.56	-13.73 ± 14.11	
p[d]	0.110	0.222		0.001[f]	0.001[f]	

MAP, Mean Arterial Pressssure; R, Heart Rate; CP, Beach Chair Position.
[a] Student *t* Test.
[b] Mann Whitney U Test.
[c] Repeated Measures Test.
[d] Bonferroni Test.
[e] $p < 0.05$.
[f] $p < 0.01$.

the use of colloid solution as a hypotension recovery maneuver decreases because of the smaller decrease in MAP, CO, and SV when pre-position fluid loading is performed.

Jeong et al. found a serious decrease of up to 60 ± 18 mmHg in MAP 5-minutes after patient positioning despite the administration of standard intravenous fluid treatment and ephedrine.[14] In this study, the lowest MAP of 47 mmHg was recorded during the 5-min measurements after positioning the patients in the BCP in the control group, and it was found that the MAP decrease was smaller in the study group ($p < 0.05$) at the 0th, 5th, and 10th min after positioning.

The number of studies focused on investigating the effects of intraoperative fluid management on postoperative outcomes is increasing day by day. A general decrease in PONV as a result of preloading intravenous solutions has

Table 4 Comparison of CO and SV values.

	CO values			SV values		
	Control group (n = 23)	Study group (n = 26)	*p*	Control group (n = 23)	Study group (n = 26)	*p*
Supine position						
Min/Max (Median)	3.4/10.4 (4.2)	2.7/8.1 (4.1)	0.385[a]	38/96 (62)	33/112 (64)	0.972[a]
Mean ± SD	5.14 ± 1.79	4.72 ± 1.59		65.26 ± 15.66	65.08 ± 19.76	
BCP 0th min						
Min/Max (Median)	2.3/6.9 (3.9)	3/7.6 (4.5)	0.109[a]	32/99 (58)	31/113 (69.5)	0.126[a]
Mean ± SD	4.17 ± 1.19	4.77 ± 1.36		61.61 ± 17.31	69.58 ± 18.34	
BCP 5th min						
Min/Max (Median)	1.6/7.4 (3.9)	2.8/7.6 (4.4)	0.016[a,e]	27/103 (60)	40/122 (72.5)	0.010[a,e]
Mean ± SD	3.73 ± 1.34	4.70 ± 1.36		59.74 ± 17.82	73.46 ± 17.86	
BCP 10th min						
Min/Max (Median)	2.2/5.2 (3.8)	2.7/7.1 (4.5)	0.009[a,f]	43/94 (63)	46/116 (77.5)	0.022[a,e]
Mean ± SD	3.78 ± 0.74	4.52 ± 1.15		63.39 ± 12.61	73.88 ± 17.59	
BCP 30th min						
Min/Max (Median)	1.9/5.2 (4)	2.3/6.7 (4.4)	0.018[a,e]	34/91 (64)	44/104 (79.5)	0.036[a,e]
Mean ± SD	3.83 ± 0.71	4.47 ± 1.05		65.96 ± 15.08	75.77 ± 16.56	
BCP 60th min						
Min/Max (Median)	3.2/5.2 (4.3)	2.4/7 (4.2)	0.083[a]	45/91 (74)	27/126 (81)	0.176[a]
Mean ± SD	4.20 ± 0.50	4.70 ± 1.30		71.52 ± 12.96	78.58 ± 21.40	
[c]*p*	0.001[f]	0.462		0.001[f]	0.001[f]	
Supine – BCP 0th min						
Min/Max (Median)	-3.5/0.2 (-0.8)	-1.2/1.6 (0)	0.001[b,f]	-23/23 (-4)	-15/23 (1.5)	0.001[b,f]
Mean ± SD	-0.97 ± 0.89	0.06 ± 0.70		-3.65 ± 10.93	4.50 ± 9.41	
[d]*p*	0.001[f]	1.000		1.000	0.333	
Supine – BCP 5th min						
Min/Max (Median)	-3.9/0.5 (-1.1)	-1/1.7 (0)	0.001[b,f]	-35/28 (-6)	-10/29 (9.5)	0.001[b,f]
Mean ± SD	-1.41 ± 1.11	-0.02 ± 0.72		-5.52 ± 14.45	8.38 ± 11.14	
[d]*p*	0.001[f]	1.000		1.000	0.01[e]	
Supine – BCP 10th min						
Min/Max (Median)	-6.7/1.3 (-0.7)	-3.5/2 (-0.1)	0.014[b,e]	-27/16 (-4)	-20/40 (10.5)	0.031[b,e]
Mean ± SD	-1.36 ± 1.83	-0.20 ± 1.05		-1.87 ± 13.42	8.81 ± 15.08	
[d]*p*	0.026[e]	1.000		1.000	0.095	
Supine – BCP 30th min						
Min/Max (Median)	-7.5/0.5 (-0.5)	-3.8/1.8 (-0.1)	0.029[b,e]	-33/24 (-1)	-25/44 (12)	0.042[b,e]
Mean ± SD	-1.30 ± 1.87	-0.24 ± 1.18		0.70 ± 15.53	10.69 ± 15.61	
[d]*p*	0.044[e]	1.000		1.000	0.027[e]	
Supine – BCP 60th min						
Min/Max (Median)	-5.2/0.6 (-0.3)	-4/3 (0)	0.048[b,e]	-26/33 (6)	-32/47 (12)	0.133[c]
Mean ± SD	-0.93 ± 1.48	-0.02 ± 1.18		6.26 ± 15.63	13.50 ± 20.55	
[d]*p*	0.092	1.000		1.000	0.039[e]	

CO, Cardiac Output; SV, Stroke Volume; BCP, Beach Chair Position.
[a] Student *t* Test.
[b] Mann Whitney *U* Test.
[c] Repeated Measures Test.
[d] Bonferroni Test.
[e] $p < 0.05$.
[f] $p < 0.01$.

been reported by Holte et al. in laparoscopic cholecystectomies and by Magner et al. in gynecological laparoscopic surgeries.[24,25] Ghafourifard et al. demonstrated a lower incidence of PONV in both their study groups that were formed for comparing the effects of administering a preoperative intravenous bolus of 7 mL.kg^{-1} 3% modified gelatin (Haemaccel) and 7 mL.kg^{-1} Ringer's lactate solution, respectively.[26] Similar to the findings in the literature, in our study, PONV was observed less frequently in the study group in which fluid replacement was performed during the preoperative period compared to in the control group, and this difference was statistically significant ($p < 0.05$).

In our study, larger amounts of colloid and ephedrine were administered in the control group, and hypertension-hypotension episodes were more common in this patient group. Arthroscopic image quality is adversely affected by

such fluctuations in blood pressure. Therefore, surgical satisfaction was higher in the study group. Although there was a statistically significant difference between the amount of crystalloids used for the patients in the study group and the control group, there was no clinically significant difference. In our opinion, the most important reason for this is the amount of crystalloids used to compensate the clinical situation as a result of SVV elevations and hypotension attacks in the control group.

This study has some limitations. The data and results presented are entirely dependent on the numerical values of the hemodynamic parameters. Tests to evaluate organ functions in order to control the continuity of tissue perfusion were not performed in our patients (preoperative and postoperative creatinine values, preoperative and postoperative cognitive function tests, etc.). Bispectral Index (BIS) monitoring ensures that the patients' anesthesia depths are standardized and that hemodynamic data are not affected by reasons such as superficial anesthesia; however, this parameter was not monitored in this study. Although the lack of BIS monitoring is one of the important limitations of our study, standardization of the anesthetic depth of the patients included in the study was achieved with the end-tidal inhaler anesthetic agent concentration and the same dose of remifentanil infusion. The fact that cerebral Near Infrared Spectrometry (NIRS) monitoring was not used in our study is also our limitation. The use of monitoring methods such as BIS and NIRS and the examination of microhemodynamic variables should be evaluated in future studies.

Conclusion

In conclusion, in this study, the outcomes between patients undergoing arthroscopic shoulder surgery in the BCP who received fluid loading before beach chair positioning and those undergoing the same surgery who were switched to the BCP without fluid loading were compared. In patients undergoing shoulder surgery in the BCP, crystalloid fluid loading before positioning appears to be an effective alternative for protecting patients from hemodynamic instability. However, to confirm our results, this study needs to be repeated in larger patient groups, and further studies are required for investigating the type and efficacy of the fluid to be loaded.

Funding

This study was granted by our own institution Istanbul university scientific academic project department with code number TTU-2018-32155.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Larsen SL, Lyngeraa TS, Maschmann CP, Van Lieshout JJ, Pott FC. Cardiovascular consequence of reclining vs. sitting beach-chair body position for induction of anesthesia. Front Physiol. 2014;5:187.
2. Papadonikolakis A, Wiesler ER, Olympio MA, Poehling GG. Avoiding catastrophic complications of stroke and death related to shoulder surgery in the sitting position. Arthroscopy. 2008;24:481–2.
3. Haršanji Drenjančević I, Drenjančević D, Davidović-Cvetko E, Drenjančević I, Gulam D, Kvolik S. Does the anesthesia technique affect arterial pressure and regional cerebral oxygen saturation during shoulder arthroscopy in the beach chair position? Acta Clin Croat. 2018;57:473–9.
4. Trentman TL, Fassett SL, Thomas JK, Noble BN, Renfree KJ, Hattrup SJ. More hypotension in patients taking antihypertensives preoperatively during shoulder surgery in the beach chair position. Can J Anaesth. 2011;58:993–1000.
5. Salazar D, Sears BW, Aghdasi B, et al. Cerebral desaturation events during shoulder arthroscopy in the beach chair position: patient risk factors and neurocognitive effects. J Shoulder Elbow Surg. 2013;22:1228–35.
6. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg. 1995;130:423–9.
7. Cao RN, Tang L, Xia ZY, Xia R. Endothelial glycocalyx as a potential theriapeutic target in organ injuries. Chin Med J (Engl). 2019;132:963–75.
8. Chappell D, Bruegger D, Potzel J, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. Crit Care. 2014;18:538.
9. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth. 2012;108:384–94.
10. Jo YY, Jung WS, Kim HS, Chang YJ, Kwak HJ. Prediction of hypotension in the beach chair position during shoulder arthroscopy using pre-operative hemodynamic variables. J Clin Monit Comput. 2014;28:173–8.
11. Dalrymple DG, MacGowan SW, MacLeod GF. Cardiorespiratory effects of the sitting position in neurosurgery. Br J Anaesth. 1979;51:1079–82.
12. Laflam A, Joshi B, Brady K, et al. Shoulder surgery in the beach chair position is assocaited with diminished cerebral autoregulation but no difference in postoperative cognition or brain injury biomarker levels compared with supine positioning: the anesthesia patient safety foundation beach chair study. Anesth Analg. 2015;120:176–85.
13. Martynyuk AE, Ju LS, Morey TE, Zhang JQ. Neuroendocrine, epigenetic, and intergenerational effects of general anesthetics. World J Psychiatry. 2020;10:81–94.
14. Jeong H, Lee SH, Jang EA, Chung SS, Lee J, Yoo KY. Haemodynamics and cerebral oxygenation during arthroscopic shoulder surgery in beach chair position under general anaesthesia. Acta Anaesthesiol Scand. 2012;56:872–9.
15. Salim F, Khan F, Nasir M, Ali R, Iqbal A, Raza A. Frequency of intraoperative hypotension after the induction of anesthesia in hypertensive patients with preoperative angiotensin-converting enzyme inhibitors. Cureus. 2020;41:1–9.
16. Hollmann C, Fernandes NL, Biccard BM. A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before noncardiac surgery. Anesth Analg. 2018;127:678–87.
17. Triplet JJ, Lonetta CM, Everding NG, Moor MA, Levy JC. Association between temporal mean arterial pressure and brachial noninvasive blood pressure during shoulder surgery in the beach chair position during general anesthesia. J Shoulder Elb Surg. 2015;24:127–32.
18. Lee SH, Chun YM, Oh YJ, et al. Prediction of fluid responsiveness in the beach chair position using dynamic preload indices. J Clin Monitoring Computing. 2016;30:995–1002.

19. Marx G, Schindler AW, Mosch C, et al. Intravascular volume therapy in adults: Guidelines from the Association of the Scientific Medical Societies in Germany. Eur J Anaesthesiol. 2016;33:488–521.
20. Hamzaoui O, Scheeren TWL, Teboul JL. Norepinephrine in septic shock: when and how much? Curr Opin Crit Care. 2017;23:342–7.
21. Mercier FJ. Reply from the authors: 6% Hydroxyethyl starch (130/0.4) vs Ringer's lactate preloading before spinal anaesthesia for Caesarean delivery. Br J Anaesth. 2015;115:328–9.
22. Buhre W, Weyland A, Buhre K, et al. Effects of the sitting position on the distribution of blood volume in patients undergoing neurosurgical procedures. Br J Anaesth. 2000;84:354–7.
23. Frey K, Rehm M, Chappell D, et al. Preemptive volume therapy to prevent hemodynamic changes caused by the beach chair position: hydroxyethyl starch 130/0.4 versus Ringer's acetate-a controlled randomized trial. J Shoulder Elbow Surg. 2018;27:2129–38.
24. Holte K, Klarskov B, Christensen DS, et al. Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: A randomized, double-blind study. Ann Surg. 2004;240:892–9.
25. Magner JJ, McCaul C, Carton E, Gardiner J, Buggy D. Effect of intraoperative intravenous crystalloid infusion on postoperative nausea and vomiting after gynaecological laparoscopy: comparison of 30 and 10 mL.kg^{-1}. Br J Anaesth. 2004;93:381–5.
26. Ghafourifard M, Zirak M, Broojerdi MH, Bayendor A, Moradi A. The effect of ringer versus haemaccel preload on incidence of postoperative nausea and vomiting. J Caring Sci. 2015;4:105–13.

Brazilian Journal of Anesthesiology 2022;72(6):711–719

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Effects of Plasma-Lyte® and 0.9% saline in renal function after deceased-donor kidney transplant: a randomized controlled trial

Paulo do Nascimento Junior [a,*], Lucas Esteves Dohler [a], Cindy Midori Uchida Ogawa [a], Luís Gustavo Modelli de Andrade [b], Leandro Gobbo Braz [a], Norma Sueli Pinheiro Módolo [a]

[a] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Especialidades Cirúrgicas e Anestesiologia, Botucatu, SP, Brazil*
[b] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Hospital das Clínicas, Programa de Transplante Renal, Botucatu, SP, Brazil*

Received 24 March 2021; accepted 28 August 2021
Available online 23 September 2021

KEYWORDS
Anesthesia;
Crystalloid solutions;
Delayed graft function;
Kidney transplantation;
Electrolytes;
Acid-base equilibrium

Abstract
Background: The influence of different crystalloid solutions infused during deceased-donor kidney transplant on the incidence of delayed graft function remains unclear. We investigated the influence of Plasma-Lyte® vs. 0.9% saline on the incidence of delayed graft function in deceased-donor kidney transplant recipients.
Methods: We conducted a single-blind randomized controlled trial of 104 patients aged 18 to 65 years who underwent deceased-donor kidney transplant under general anesthesia. Patients were randomly assigned to receive either Plasma-Lyte® (n = 52) or 0.9% saline (n = 52), at the same infusion volume, for intraoperative fluid replacement. The primary outcome was the occurrence of delayed graft function. Secondary outcomes included metabolic and electrolytic changes at the end of surgery.
Results: Two patients in the Plasma-Lyte® group and one in the 0.9% saline group died postoperatively and were not included for analysis. The incidence of delayed graft function in Plasma-Lyte® and 0.9% saline groups were 60.0% (95% Confidence Interval [95% CI 46.2–72.4]) and 74.5% (95% CI 61.1–84.4), respectively (p = 0.140). Mean (standard deviation) values of immediate postoperative pH and serum chloride levels in Plasma-Lyte® and 0.9% saline groups were 7.306 (0.071) and 7.273 (0.061) (p = 0.013), and 99.6 (4.2) mEq.L^{-1} and 103.3 (5.6) mEq.L^{-1}, respectively (p < 0.001). All other postoperative metabolic and electrolyte variables were not statistically different at the immediate postoperative period (p > 0.05).

* Corresponding author.
E-mail: paulo.nascimento-junior@unesp.br (P. do Nascimento Junior).

https://doi.org/10.1016/j.bjane.2021.08.015

Conclusion: In deceased-donor kidney transplant recipients, the incidence of delayed graft function is not influenced by Plasma-Lyte® or 0.9% saline used for intraoperative fluid replacement.

Introduction

Kidney transplant provides an important treatment option for patients with end-stage renal disease, with an increase in 5-year survival compared to those who remain on dialysis.[1,2] In addition, transplant recipients have an important improvement in quality of life in terms of physical, psychosocial, and overall well-being perceptions.[3]

In the United States, in 2018, approximately 60% of patients waiting for an organ transplant were in the kidney waiting list, and most of the performed transplants were from deceased donors.[4] In Brazil, kidney transplant was the most common solid organ transplant performed in 2019 and approximately 80% of these organs were from deceased donors.[5]

Deceased-donor kidney transplant is still associated with some challenges in postoperative management, especially the occurrence of delayed graft function. This is a form of acute kidney injury that occurs immediately after the transplant, affecting up to 80% of deceased-donor graft recipients.[6–8] Morbidity and mortality increase with this condition, which alone represents a risk factor for acute rejection and long-term graft survival.[9]

Intraoperative fluid replacement has important hemodynamic implications and impact on postoperative morbidity. In kidney transplant, fluid replacement solutions must be used with caution, avoiding fluid overload and providing good renal perfusion and good kidney function to allow early diuresis, which is an important prognostic factor associated with early and 1-year graft function.[10,11] Isotonic saline solutions can cause hyperchloremic acidosis accompanied by hyperkalemia if compared to the same volume of lactated Ringer's solution.[12] Plasma-Lyte® is a crystalloid solution similar to plasma in electrolyte concentration, osmolarity, and pH. This solution has been shown to better maintain the acid-base balance in major abdominal surgery and even in kidney transplant.[13,14]

Current knowledge of the results of the use of different fluid replacement solutions in kidney transplant is limited to metabolic and acid-base changes. Few studies have evaluated the impact of using different crystalloid solutions on post-transplant complications, and none have evaluated their impact on the incidence of delayed graft function and its duration.

This study aimed to compare the influence of two crystalloid solutions used for intraoperative fluid replacement, Plasma-Lyte® vs. 0.9% saline, on the incidence of delayed graft function in deceased-donor kidney transplant recipients. We also evaluated the influence of these solutions on immediate postoperative acid-base and electrolyte balance.

Methods

Participants and eligibility criteria

After approval by the Research Ethics Committee of our institution, we conducted a single-blind, randomized, controlled trial of adult patients undergoing deceased-donor kidney transplant. The trial was designed and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement and is registered at the Brazilian Clinical Trials Registry platform (ReBEC, number RBR-9t7r5p, https://ensaiosclinicos.gov.br/rg/RBR-9t7r5p). We prospectively included patients in the study from July 2017 to July 2019.

Eligible participants were all patients aged 18 to 65 years, of both sexes, with American Society of Anesthesiologists (ASA) physical status III and IV, and on regular hemodialysis for treating end-stage renal disease. Patients with hemoglobin < 8 $g.dL^{-1}$ at the time of admission for transplant were excluded. During preanesthetic evaluation, patients were informed of the study purpose and procedures, and those interested in participating provided written informed consent for enrollment in the study.

Interventions

In the operating room, patients were monitored with a cardioscope, pulse oximeter, automated noninvasive blood pressure monitor, and capnograph with a gas analyzer after tracheal intubation. A peripheral venous line was obtained with a 16G or 18G catheter. After the induction of anesthesia and after the performance of the Allen's test, invasive blood pressure was monitored with the insertion of a 20G catheter in one of the radial arteries. The use of a central intravenous line was obtained according to clinical judgment of the anesthesiologists.

Patients in both groups underwent balanced general inhalational anesthesia. Induction of anesthesia was standardized for all patients, who received midazolam (3 to 5 mg, intravenously [IV]), fentanyl (5 $\mu g.kg^{-1}$ IV), etomidate (0.3 $mg.kg^{-1}$ IV), and cisatracurium (0.15 $mg.kg^{-1}$IV). Anesthesia was maintained with remifentanil (0.1 to 0.3 $\mu g.kg^{-1}.min^{-1}$ IV) and isoflurane at an alveolar concentration of 1.2 to 1.6%, fresh gas flow of 1.6 $L.min^{-1}$, and fraction of inspired oxygen of 40%. Additional doses of cisatracurium were administered according to clinical judgment. Ventilation was controlled with a tidal volume of 8 $mL.kg^{-1}$, calculated according to ideal body weight, with the respiratory rate necessary to maintain the fraction of expired carbon dioxide between 30 and 40 mmHg.

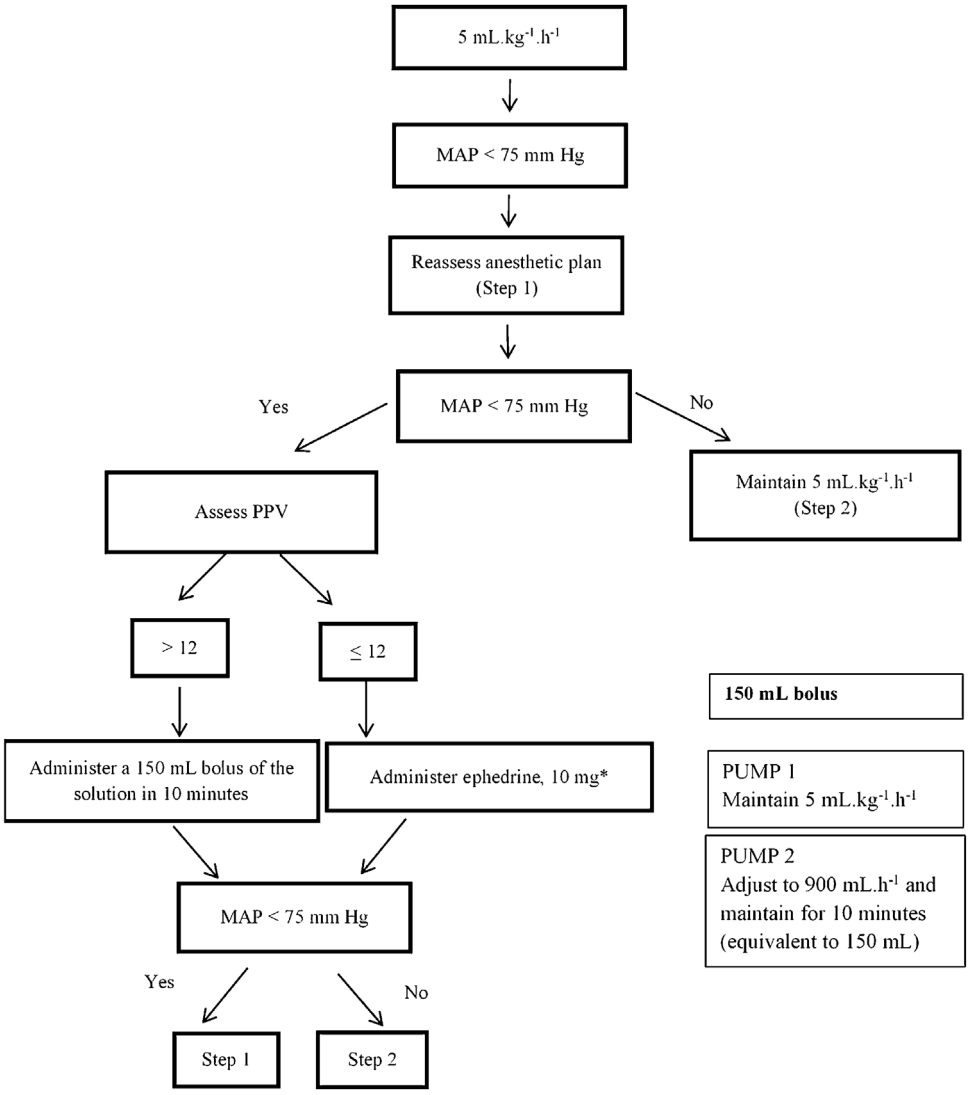


Figure 1 Flow diagram for controlling the administration of crystalloids according to invasive Mean Arterial Pressure (MAP) and Pulse Pressure Variation (PPV). Administer 5 mL.kg^{-1}.h^{-1} of the drawn solution. *If the patient is permanently with MAP < 75 mmHg (after 5 boluses of 150 mL and/or 50 mg of ephedrine), initiate norepinephrine and do not administer additional boluses (unless indicated by the analysis of other clinical criteria: heart rate; peripheral perfusion; mucous membranes; central venous pressure, if any).

In the operating room, the solution to be administered was randomly drawn for each patient using previously sealed opaque envelopes containing the name of the crystalloid to be used. The anesthesiologist was not blinded to the solution to be used. The volume of crystalloid infused in each patient was 5 mL.kg^{-1}.h^{-1}, and the necessary adjustments were guided by mean arterial pressure and pulse pressure variation, according to the protocol established for this study (Fig. 1). Thus, the patients differed only in the type of crystalloid solution, either Plasma-Lyte® (n = 52) (balanced crystalloid solution containing 140 mEq.L^{-1} sodium, 5 mEq.L^{-1} potassium, 3 mEq.L^{-1} magnesium, 98 mEq.L^{-1} chloride, 27 mEq.L^{-1} acetate, and 23 mEq.L^{-1} gluconate; osmolarity = 294 mOsmol.L^{-1} and pH = 7.4) or 0.9% saline (n = 52) (crystalloid solution with 154 mEq.L^{-1} sodium and 154 mEq.L^{-1} chloride; osmolarity = 308 mOsmol.L^{-1} and pH∼5.5). The use of packed red blood cells was indicated when the hemoglobin concentration was below 8 mg.dL^{-1} during surgery or according to clinical judgment. The use of other blood components as well as the correction of low serum calcium values were done at the discretion of the anesthesiologist.

All patients received 40 mg of intravenous furosemide and 0.5 g.kg^{-1} of 20% mannitol solution 5 to 10 minutes before completion of the arterial anastomosis. Immunosuppression followed the institution's protocol.

For postoperative analgesia, patients received tramadol (100 mg IV), metamizole (2 g IV) and morphine (0.05 mg.kg^{-1} IV) as a rescue treatment. The prophylaxis for postoperative nausea and vomiting was provided with ondansetron (8 mg IV) and metoclopramide (10 mg IV) administered at the end of the surgical procedure. We did not plan to reverse neuromuscular block, but it could be done according to clinical judgment. With return of adequate ventilatory function

and after awakening, patients were extubated and taken to the postanesthesia care unit, where they stayed for at least 90 minutes. Patients were discharged to the ward after achieving a score of 9 or 10 on the Aldrete-Kroulik scale.

After surgery, patients with diuresis received 0.45% saline in a volume corresponding to 80% of the volume of diuresis observed in the preceding hour. This fluid replacement strategy was applied every hour for 12 hours following transplant. Patients who remained without diuresis received no parenteral solution. Twelve hours after transplant, all patients were started on a light diet as tolerated.

Outcomes

The primary outcome was the occurrence of delayed graft function, defined as the need for postoperative dialysis within 7 days of transplant, assessed in a dichotomous manner (i.e., yes/no). Secondary outcomes included the duration of delayed graft function (in days, assessed as the time elapsed from transplant to the last postoperative dialysis session before hospital discharge), the number of dialysis sessions after transplant, and acid-base and electrolyte changes determined by the solutions at the end of the surgical procedure (immediate postoperative period). To this end, arterial and venous blood samples were collected 1 hour before surgery (preoperative period) and at the end of the surgical procedure. Blood pH, sodium bicarbonate, and excess base values were considered in this analysis. We also analyzed sodium, potassium, chloride, and calcium levels.

Evaluators blinded to group allocation assessed all the outcomes. The variables used to control sample homogeneity were the time of the last dialysis session performed before transplant, operative time, graft cold ischemia time, and venous and arterial anastomosis time.

Statistical analysis

To detect a reduction of 50% in the incidence of delayed graft function with the use of Plasma-Lyte® compared with 0.9% saline, considering that 60% of deceased-donor kidney transplant recipients develop this condition, with a power of 80% and significance level of 5%, a sample size of at least 49 patients per group was necessary to test the hypothesis. Thus, the total number of patients was divided into two groups with a 1:1 allocation ratio by electronic randomization using 13 blocks of eight patients, with an equal distribution of groups in each block (52 patients per group). The allocation sequence was concealed by placing the results in opaque and sealed envelopes that were opened only in the operating room. The envelopes were sequentially numbered from 1 to 104, and the study followed the numerical order of the envelopes.

Qualitative variables were compared by the Chi-Square test for proportions. The Shapiro-Wilk test was assessed for normality. Quantitative variables were compared by independent or paired Student's *t*-test, as appropriated. Non-normally distributed values were compared by Mann-Whitney test for independent variables. A p-value < 0.05 was considered statistically significant (GraphPad Prism 7.0, San Diego, CA, USA).

Results

Of all 104 randomized patients, three patients (two in the Plasma-Lyte® group and one in the 0.9% saline group) died of surgical complications in the immediate postoperative period and were not included in the statistical analysis. In both groups, some blood analyses were not done due to clotted or inappropriate blood samples. Patient recruitment and the randomization flow diagram are summarized in Figure 2.

The groups did not differ in demographic characteristics (Table 1) or intraoperative variables (Table 2).

There was no statistically significant difference in the incidence of delayed graft function between the two groups. The number of postoperative dialysis sessions up to patient discharge was not different between groups, neither was the number of elapsed days until the last postoperative dialysis session, before hospital discharge (Table 3). The immediate postoperative pH values were significantly different between groups, with higher values in the Plasma-Lyte® group. The analysis of serum chloride levels showed a statistically significant difference in both, preoperative and immediate postoperative values between groups. Although not statistically significant, as compared to their own preoperative values, postoperative serum chloride levels were reduced in the Plasma-Lyte® group, while they increased in the 0.9% saline group. No other significant differences were seen in immediate postoperative electrolytes or acid-base balance between groups (Table 4).

Discussion

Changes in the acid-base and electrolyte balance are frequently observed during the perioperative period, regardless of the type of surgery. Multiple factors can affect fluid homeostasis and renal function, including preoperative fasting time, insensible losses, underlying disease, surgical site, the magnitude of the surgical procedure, and intravenous fluid type and volume.[15] Administration of intravenous solutions is one of the factors that can be controlled by the anesthesiologist, particularly the use of crystalloid solutions.

The use of solutions with supraphysiological concentrations of chloride, such as 0.9% saline, increases the filtered load of sodium chloride, which leads to an increased detection of chloride in the dense macula at the end of the nephron. This situation is followed by the release of signaling substances (such as adenosine) by the macula densa. These mediators increase the tone of the afferent arteriole (vasoconstriction) and, consequently, decrease the glomerular blood flow and glomerular filtration rate. The importance of this pathophysiological mechanism was discussed in a review conducted by Mårtensson and Bellomo.[16] In this review, some studies comparing chloride-rich solutions with restrictive chloride administration showed a decrease in acute kidney injury incidence when less chloride was administered. These studies involved patients in intensive care unit or undergoing major surgery, and for this reason, a direct comparison with our results cannot be done. Similarly, to our results, a systematic review of randomized controlled trials examining the effect of lower-chloride solutions versus normal saline on delayed graft function, hyperkalemia, and

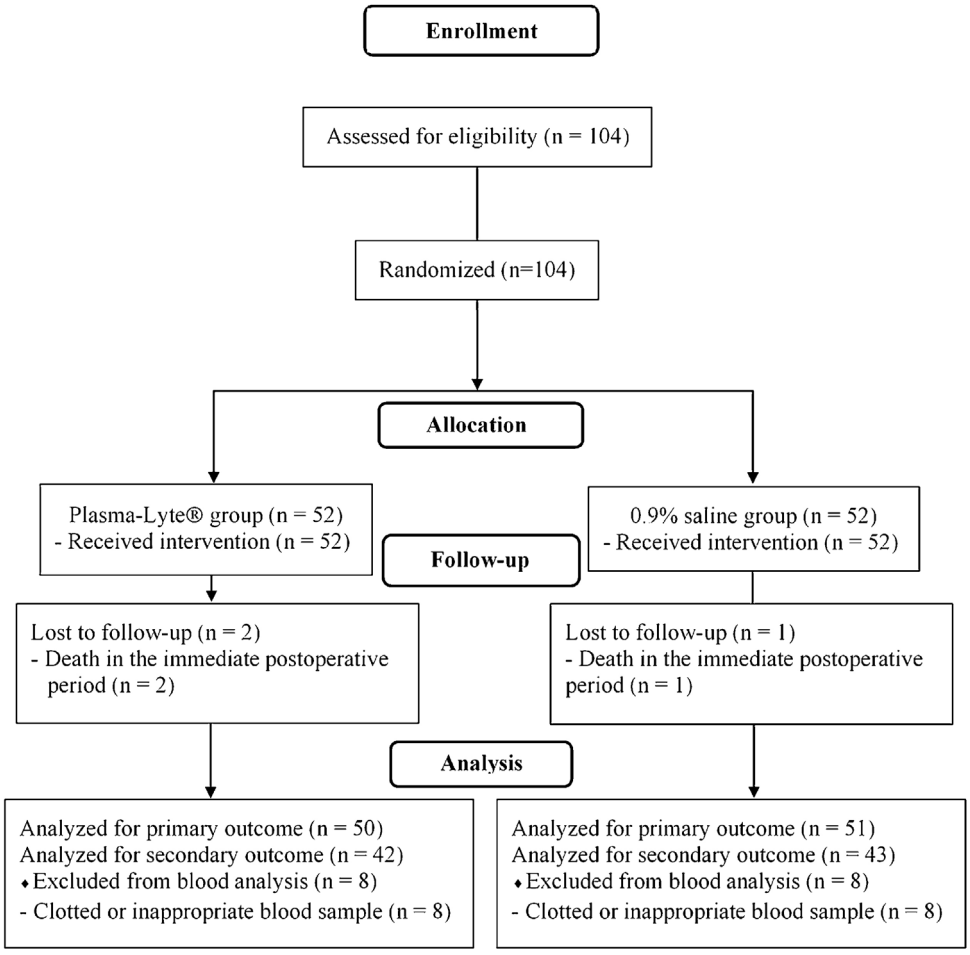


Figure 2 CONSORT flow diagram.

Table 1 Patients' characteristics.

Characteristic	Plasma-Lyte® group (n = 50)	0.9% saline group (n = 51)	*p*-value
Sex (female)	20 (40.0)	19 (37.3)	0.839
Age (years)	45.9 (10.7)	47.2 (10.5)	0.533
Height (cm)	167.6 (8.0)	167.1 (8.8)	0.799
Dry weight (kg)	71.0 (12.8)	74.6 (13.5)	0.171
Current weight (kg)	71.5 (13.0)	75.9 (13.7)	0.108
Graft cold ischemia time (h)	23 (4)	23 (7)	0.826
Time since last dialysis (h)	15 (4–48)	13 (2–32)	0.634
Main associated clinical conditions			
Hypertension	40 (80.0)	40 (78.4)	1.000
Diabetes mellitus	13 (26.0)	11 (21.6)	0.645
Smoker	5 (10.0)	12 (23.5)	0.109

Values are presented as absolute number (percentage), mean (Standard Deviation [SD]), or median (1^{st}–3^{rd} quartiles).

acid-base status in kidney transplant recipients showed no difference on the incidence of delayed graft function.[17] Nonetheless, this systematic review included three small studies not designed to evaluate delayed graft function and also performing living-donor transplantation. Overall, the incidence of delayed graft function reported in this systematic review was very low, usually that seen with living-donor kidney transplants. So far, no randomized prospective studies have yet been designed to analyze the incidence of delayed graft function comparing solutions with different chloride concentrations.

The fact that the administration of solutions with a higher chloride concentration in the perioperative period leads to worsening renal function in the postoperative period of major surgery has been a matter of debate. The results have been conflicting even in patients at higher risk for postopera-

Table 2 Intraoperative variables.

Variable	Plasma-Lyte® group (n = 50)	0.9% saline group (n = 51)	*p*-value
Operative time (min)	212 (39)	208 (42)	0.578
Anesthesia time (min)	282 (55)	269 (41)	0.167
Venous anastomosis time (min)	26 (11)	26 (10)	0.953
Arterial anastomosis time (min)	25 (9)	26 (11)	0.664
Total volume of crystalloid administered intraoperatively (mL)	1.628 (595)	1.627 (532)	0.996
Administration of packed red blood cells (n)	2 (4.0)	1 (1.9)	0.617
Use of vasopressors (n)	33 (66.0)	36 (70.6)	0.672
Correction of calcium (n)	6 (12.0)	10 (19.6)	0.414

Values are presented as absolute number (percentage) or mean (SD). n, number of patients.

Table 3 Perioperative variables.

Variable	Plasma-Lyte® group (n = 50)	0.9% saline group (n = 51)	*p*-value
Delayed graft function (n)	30 (60.0 [46.2–72.4])	38 (74.5 [61.1–84.4])	0.140
Weight gain on postoperative day 1 (kg)	1.6 (1.9)	2.2 (2.3)	0.136
First dialysis session after surgery (days)[a]	3 (2–4)	2 (2–3)	0.292
Postoperative dialysis (n)[a]	3 (2–4)	3 (2–4)	0.719
Last postoperative dialysis session before hospital discharge (d)[a]	6 (5–11)	7 (5–11)	0.433
Length of hospital stay (days)	13 (9–17)	17 (11–21)	0.061

Values are presented as number (percentage [95% Confidence Interval]), mean (SD), or median (1^{st}–3^{rd}quartiles). n, number of patients; d, days after surgery.
[a] Refer to 30 and 38 patients with delayed graft function in the Plasma-Lyte® and 0.9% saline groups, respectively.

tive renal dysfunction.[18] However, in experimental models, the use of high volumes of solutions with a high chloride concentration was unable to show worsening of hemodynamics and renal function compared to balanced solutions with a lower chloride concentration.[19,20]

The use of balanced solutions with a pH equal or close to 7.0 has been associated with fewer changes in ions and acid-base balance, especially in kidney transplant.[21,22] In our study, higher postoperative pH values and lower serum chloride values were observed for the Plasma-Lyte® group. The difference in the serum chloride values between the groups was already noted in the preoperative analysis. Nonetheless, it was enhanced in the immediate postoperative period as there was a decrease in the serum chloride values in the Plasma-Lyte® group and an increase in its values in the 0.9% saline group. These interpretations have to be done considering the losses in blood sample tests and a smaller number of subjects analyzed than those for the primary outcome. We considered these changes to be mild, as no immediate clinical intervention was judged necessary to correct them.

The present trial showed a mean reduction of approximately 15% in the incidence of delayed graft function in deceased-donor kidney transplant recipients who received Plasma-Lyte® as fluid replacement therapy compared with those who received 0.9% saline. Even considering this difference, this outcome did not have statistical significance and, for this reason, the Plasma-Lyte® solution cannot be considered superior to the 0.9% saline solution on the reduction of the incidence of delayed graft function.

We also showed a mean reduction of approximately 24% in length of hospital stay but this difference was not statistically significant, either. Length of hospital stay is associated with increased susceptibility to surgical site infections and consequently increased patient mortality and morbidity,[23,24] which is particularly concerning in patients receiving immunosuppressive therapy, such as kidney transplant recipients. Nonetheless, similarly to the findings for delayed graft function, according to the statistical analysis, the Plasma-Lyte® solution does not reduce the length of hospital stay when compared to the 0.9% saline solution.

Administering intravenous fluids to patients undergoing kidney transplant is a complex process that goes beyond the crystalloid type and infusion regimen. We based our fluid infusion on hemodynamic goals, but there is not a consensus on this issue. Goal-directed fluid therapy has shown a reduction in postoperative complications, length of hospital stays, mortality, and hospital costs in high-risk surgical patients.[25] Even though the infusion of crystalloids guided by central venous pressure resulted in better short-term renal function in kidney transplants from living donors,[26] recent studies have provided more questions than answers.[27]

The comparative analysis of electrolyte and acid-base changes between the Plasma-Lyte® and 0.9% saline groups showed that our regimen of crystalloid infusion, as a goal-directed therapy, ended up in a total amount of fluid infused unable to promote major changes in the acid-base and electrolyte balance. The occurrence of minimal changes, according to the range of variation, especially in serum chloride and pH values, may justify, at least in part, the absence of statistical differences in the primary outcome.

Table 4 Variables related to intraoperative acid-base and electrolyte balance.

Variable	Plasma-Lyte® group (n = 42)	0.9% saline group (n = 43)	Between-group difference	*p*-value
pH				
Preoperative	7.363 (0.070)	7.340 (0.070)	0.023 (-0.005 to 0.051)	0.109
Postoperative	7.306 (0.071)	7.273 (0.061)	0.033 (0.007 to 0.059)	0.013
Intragroup variation	0.057 (0.029 to 0.085)	0.067 (0.042 to 0.093)		0.339
p-value	< 0.001	< 0.001		
Base excess ($mEq.L^{-1}$)				
Preoperative	-1.9 (4.4)	-3.3 (4.1)	1.4 (-0.28 to 3.08)	0.117
Postoperative	-4.6 (4.3)	-6.0 (4.5)	1.4 (-0.34 to 3.14)	0.115
Intragroup variation	2.7 (0.94 to 4.37)	2.7 (1.03 to 4.41)		0.642
p-value	0.002	0.002		
Sodium bicarbonate ($mEq.L^{-1}$)				
Preoperative	22.9 (3.5)	21.3 (4.1)	1.6 (0.09 to 3.11)	0.039
Postoperative	20.7 (3.3)	19.6 (3.0)	1.1 (-0.15 to 2.35)	0.087
Intragroup variation	2.2 (0.86 to 3.58)	1.7 (0.28 to 3.10)		0.439
p-value	0.001	0.018		
Sodium ($mEq.L^{-1}$)				
Preoperative	138.7 (4.0)	140.9 (4.0)	-2.2 (-3.78 to -0.62)	0.008
Postoperative	134.8 (3.6)	135.7 (4.6)	-0.9 (-2.53 to 0.73)	0.275
Intragroup variation	3.93 (2.39 to 5.46)	5.13 (3.41 to 6.86)		0.067
p-value	< 0.001	< 0.001		
Potassium ($mEq.L^{-1}$)				
Preoperative	4.9 (0.8)	5.0 (0.8)	-0.1 (-0.42 to 0.22)	0.598
Postoperative	5.1 (0.9)	5.1 (0.8)	0 (-0.34 to 0.34)	0.934
Intragroup variation	-0.18 (-0.52 to 0.16)	-0.11 (-0.42 to 0.20)		0.811
p-value	0.299	0.494		
Chloride ($mEq.L^{-1}$)				
Preoperative	100.8 (4.1)	102.9 (5.5)	-2.1 (-4.02 to -0.18)	0.033
Postoperative	99.6 (4.2)	103.3 (5.6)	-3.7 (-5.66 to -1.74)	< 0.001
Intragroup variation	1.2 (-0.50 to 2.91)	-0.4 (-2.65 to 1.87)		0.084
p-value	0.164	0.733		
Calcium ($mg.dL^{-1}$)				
Preoperative	9.5 (1.2)	9.5 (1.6)	0 (-0.56 to 0.56)	0.996
Postoperative	8.2 (1.6)	8.0 (2.2)	0.2 (-0.56 to 0.96)	0.644
Intragroup variation	1.2 (0.65 to 1.82)	1.4 (0.66 to 2.17)		0.618
p-value	< 0.001	< 0.001		

Values are presented as mean (SD) or number (95% Confidence Interval). Intragroup variation is preoperative minus postoperative values, and between group difference is Plasma-Lyte® group minus 0.9% saline group.

The extent of ischemia-reperfusion injury causing delayed graft function is a multifactorial process in which the contribution of the individual components has not been fully elucidated because many factors are interrelated. Cold ischemia time (time interval between organ cold storage and warming by restoration of blood flow) is considered one of the most important factors contributing to the occurrence of delayed graft function after kidney transplant. Prospective complement-dependent cytotoxicity crossmatching accounts for most of the time consumed.[28] In our study, the long cold ischemia time seen in both groups may have contributed to the high incidence of delayed graft function. Delayed graft function remains a cause of great concern due to its implications for the patient and the health care system. Given the wide variety of agents involved, Irish et al.[29] developed a model to predict the risk of delayed graft function using donor and recipient data at the time of transplant. They found that the main risk factors are cold ischemia time, donor serum creatinine, recipient body mass index, deceased donor, and donor age greater than 16 years.

The type of intravenous fluid used intraoperatively adds a new element to be investigated in the list of causes of delayed kidney graft function. With the same purpose of our study, i.e., elucidating whether a simple measure such as changing the fluid to be used during a renal transplant could influence the incidence of delayed graft function, Collins et al.,[30] in a multi-center ongoing trial, are comparing a balanced low-chloride fluid (Plasma-Lyte®) with the traditional 0.9% saline in deceased-donor kidney transplant. Their trial will allow to overcome some limitations of the present study, such as the limited sample size and the fact that it was conducted in a single center and allow the generalization of the results to the population of patients undergoing kidney transplant. Other limitation of our study, involving our secondary outcomes, was the inability to analyze some blood samples due to clotting or insufficient blood.

Conclusions

In deceased-donor kidney transplant recipients, the incidence of delayed graft function is not influenced by the solution used for intraoperative fluid replacement, Plasma-Lyte® or 0.9% saline. A small reduction in immediate postoperative serum chloride values together with higher pH values are also observed in patients receiving Plasma-Lyte®.

Funding

The study was approved by the Research Ethics Committee of Botucatu School of Medicine, Universidade Estadual Paulista, Brazil (UNESP, protocol number 1.874.338 and *Plataforma Brasil* CAAE number 62033816.0.0000.5411).

The trial was designed and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement and is registered at the Brazilian Clinical Trials Registry platform (ReBEC, number RBR-9t7r5p, https://ensaiosclinicos.gov.br/rg/RBR-9t7r5p).

Authors contributions

Conception and design: PNJ, LED, LGMA, NSPM

Analysis and interpretation: PNJ, LGMA, LGB, NSPM

Data collection: PNJ, LED, CMUO

Writing the article: PNJ, LED

Critical revision of the article: PNJ, LED, CMUO, LGMA, LGB, NSPM

Final approval of the article: PNJ, LED, CMUO, LGMA, LGB, NSPM

Statistical analysis: PNJ

Overall responsibility: PNJ

Financing

PNJ had a research grant from the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq),#305109/2017-0.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol. 1998;9:2135–41.
2. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patient's vs cadaveric renal transplant recipients. JAMA. 1993;270:1339–43.
3. Dew MA, Switzer GE, Goycoolea JM, et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. Transplantation. 1997;64:1261–73.
4. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 Annual data report: kidney. Am J Transplant. 2020;20 suppl 1:20–130.
5. Organ Transplantation in Brazil (2012 - 2019). Associação Brasileira de Transplante de Órgãos (ABTO). Brazilian Transplantation Registry. XXV(4):1-26. https://site.abto.org.br/publicacao/rbt-ingles-2019/ [accessed 23 March 2021].
6. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet. 2004;364:1814–27.
7. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011;11:2279–96.
8. Nga HS, Andrade LGM, Contti MM, Valiatti MF, Silva MMD, Takase HM. Evaluation of the 1000 renal transplants carried out at the University Hospital of the Botucatu Medical School (HCFMB) - UNESP and their evolution over the years. J Bras Nefrol. 2018;40:162–9.
9. Gjertson DW. Impact of delayed graft function and acute rejection on graft survival. Transplant Proc. 2002;34:2432.
10. Hirata ES, Baghin MF, Pereira RI, Alves Filho G, Udelsmann A. Influence of the anesthetic technique on the hemodynamic changes in renal transplantation: a retrospective study. Rev Bras Anestesiol. 2009;59:166–76.
11. Lai Q, Pretagostini R, Poli L, et al. Early urine output predicts graft survival after kidney transplantation. Transplant Proc. 2010;42:1090–2.
12. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology. 1999;90:1265–70.
13. Hadimioglu N, Saadawy I, Saglam T, Ertug Z, Dinckan A. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg. 2008;107:264–9.
14. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255:821–9.
15. Weinberg L, Li M, Churilov L, et al. Associations of fluid amount, type, and balance and acute kidney injury in patients undergoing major surgery. Anaesth Intensive Care. 2018;46:79–87.
16. Mårtensson J, Bellomo R. Does fluid management affect the occurrence of acute kidney injury? Curr Opin Anaesthesiol. 2017;30:84–91.
17. Wan S, Matthew A, Roberts MA, Mount P. Normal saline versus lower-chloride solutions for kidney transplantation. Cochrane Database Syst Rev. 2016;9:CD010741.
18. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701–10.
19. Olivier PY, Beloncle F, Seegers V, et al. Assessment of renal hemodynamic toxicity of fluid challenge with 0.9% NaCl compared to balanced crystalloid (PlasmaLyte®) in a rat model with severe sepsis. Ann Intensive Care. 2017;7:66.
20. Wu CY, Chan KC, Cheng YJ, Yeh YC, Chien CT, Research NCoMM. Effects of different types of fluid resuscitation for hemorrhagic shock on splanchnic organ microcirculation and renal reactive oxygen species formation. Crit Care. 2015;19:434.
21. Potura E, Lindner G, Biesenbach P, et al. An acetate-buffered balanced crystalloid versus 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial. Anesth Analg. 2015;120:123–9.
22. Pfortmueller CA, Funk GC, Reiterer C, et al. Normal saline versus a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomised controlled study. Br J Anaesth. 2018;120:274–83.
23. Coskun D, Aytac J, Aydinli A, Bayer A. Mortality rate, length of stay and extra cost of sternal surgical site infections following coronary artery bypass grafting in a private medical centre in Turkey. J Hosp Infect. 2005;60:176–9.
24. Mujagic E, Marti WR, Coslovsky M, et al. Associations of hospital length of stay with surgical site infections. World J Surg. 2018;42:3888–96.

25. Gurgel ST, do Nascimento P. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg. 2011;112:1384–91.
26. Othman MM, Ismael AZ, Hammouda GE. The impact of timing of maximal crystalloid hydration on early graft function during kidney transplantation. Anesth Analg. 2010;110:1440–6.
27. Fernandes MHC, Schricker T, Magder S, Hatzakorzian R. Perioperative fluid management in kidney transplantation: a black box. Crit Care. 2018;22:14.
28. Lauronen J, Peräsaari JP, Saarinen T, Jaatinen T, Lempinen M, Helanterä I. Shorter cold ischemia time in deceased donor kidney transplantation reduces the incidence of delayed graft function especially among highly sensitized patients and kidneys from older donors. Transplant Proc. 2020;52:42–9.
29. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant. 2010;10:2279–86.
30. Collins MG, Fahim MA, Pascoe EM, et al. Study Protocol for Better Evidence for Selecting Transplant Fluids (BEST-Fluids): a pragmatic, registry-based, multi-center, double-blind, randomized controlled trial evaluating the effect of intravenous fluid therapy with Plasma-Lyte 148 versus 0.9% saline on delayed graft function in deceased donor kidney transplantation. Trials. 2020;21:428.

Brazilian Journal of Anesthesiology 2022;72(6): 720—728

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Impact of colloids or crystalloids in renal function assessed by NGAL and KIM-1 after hysterectomy: randomized controlled trial

Murillo G. Santos [a,*], **João Paulo Jordão Pontes** [a,b], **Saulo Gonçalves Filho** [a], **Rodrigo M. Lima** [a,c], **Murilo M. Thom** [d], **Norma Sueli P. Módolo** [d], **Daniela Ponce** [e], **Lais Helena Navarro** [c,d]

[a] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Botucatu, SP, Brazil*
[b] *Santa Genoveva Complexo Hospitalar, Uberlândia, MG, Brazil*
[c] *Queen's University, Department of Anesthesiology and Perioperative Medicine, Kingston, Canada*
[d] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Anestesiologia, Botucatu, SP, Brazil*
[e] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Clínica Médica, Botucatu, SP, Brazil*

Received 23 June 2021; accepted 30 October 2021
Available online 27 November 2021

KEYWORDS
Hydroxyethyl Starch Derivatives;
Hysterectomy;
Kidney function tests

Abstract

Background: Hydroxyethyl starches are colloids used in fluid therapy that may reduce volume infusion compared with crystalloids, but they can affect renal function in critical care patients. This study aims to assess renal effects of starches using renal biomarkers in the perioperative setting.

Methods: This prospective, controlled, randomized study compared Hydroxyethyl starch 6% (HES) with Ringer's lactate (RL) in hysterectomy. Each episode of mean arterial pressure (MAP) below 60 mmHg guided the fluid replacement protocol. The RL group received 300 mL bolus of RL solution while the HES group received 150 mL of HES solution. All patients received RL (2 mL. $kg^{-1}.h^{-1}$) intraoperatively to replace insensible losses. Blood and urine samples were collected at three time points (preoperatively, 24 hours, and 40 days postoperatively) to assess urinary NGAL and KIM-1, as primary outcome, and other markers of renal function.

Results: Seventy patients were randomized and 60 completed the study. The RL group received a higher crystalloid volume (1,277 ± 812.7 mL vs. 630.4 ± 310.2 mL; $p = 0.0002$) with a higher fluid balance (780 ± 720 mL vs. 430 ± 440 mL; $p = 0.03$) and fluid overload (11.7% ± 10.4% vs. 7.0% ± 6.3%; $p = 0.04$) compared to the HES group. NGAL and KIM-1 did not differ between groups at each time point, however both biomarkers increased 24 hours postoperatively and returned to preoperative levels after 40 days in both groups.

* Corresponding author.
E-mail: murillogsantos@gmail.com (M.G. Santos).

https://doi.org/10.1016/j.bjane.2021.10.009

Conclusion: HES did not increase renal biomarkers following open hysterectomy compared to RL. Moreover, HES provided better hemodynamic parameters using less volume, and reduced postoperative fluid balance and fluid overload.

Introduction

Intraoperative fluid replacement is controversial in the literature, and it is related to the clinical outcomes of patients undergoing surgical procedures.[1,2] On one hand, restrictive fluid therapy can lead to hypovolemia, tissue hypoxia, and acute kidney injury (AKI); while a liberal regimen can lead to tissue edema impairing pulmonary, cardiac, and gastrointestinal function.[3—5] Goal-directed fluid therapy (GDT) seems to be better than previous fixed fluid regimens, and has shown reduction in complications related to hypervolemia, such as gastrointestinal dysfunction and infections, and also related to perioperative hypovolemia, such as AKI.[3—7]

Besides fluid regimen, the type of fluid is also challenging.[5] Crystalloids, such as Ringer's lactate (RL), are standard solutions for fluid replacement, but when in excess, can damage the vascular endothelium, and result in interstitial edema due to its 20% limited capacity of intravascular expansion.[4,5,7,8] Colloids are considered intravascular plasma expanders remaining longer in the intravascular compartment, and Hydroxyethyl starch 6% (HES) solution is a type of colloid with intermediate molecular weight used in major surgeries, and that may reduce hypervolemia related to crystalloids.[4—6,8] Although more efficient as a plasma expander, the safety of using HES in the surgical context has been questioned due to concerns on kidney damage.[6,7]

Perioperative acute kidney injury is related to inadequate fluid replacement and increases morbidity and mortality of surgical patients.[2,8—10] Thus, early diagnosis and immediate treatment are essential.[9,10] Normally, plasma creatinine and urine output are used to diagnose AKI according KDIGO guidelines,[10] although the first may take 48 hours to rise, and the latter can be affected by endocrine-metabolic response to surgery[10] The advent of new renal biomarkers, such as NGAL (neutrophil gelatinase-associated lipocalin), and KIM-1 (kidney injury molecule-1), has enabled early diagnosis of kidney injury.[10—12] NGAL is absent in the urine and plasma of healthy individuals and is expressed as early as 2 hours after renal ischemia.[10] KIM-1 is a membrane glycoprotein that is upregulated after an ischemic or nephrotoxic injury and increases after 6 hours in urine.[10]

The aim of this study was to assess kidney effects of either HES or RL solutions used for volume resuscitation, using GDT, in patients without previous renal dysfunction undergoing elective open hysterectomy. The study hypothesis was that these solutions differ in terms of kidney damage assessed by urinary NGAL, and other traditional and novel markers of renal function.

Methods

This randomized, prospective, controlled, double-blind clinical study was conducted at the Hospital das Clínicas da Faculdade de Medicina de Botucatu — UNESP and approved by the Research Ethics Committee (registry number: 1246806) of the same institution. The study was registered in the Brazilian Clinical Trials Registry (REBEC): RBR-7J75Q5, and described in accordance with the Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) statement.

All participants provided informed consent and were considered eligible if they met the following criteria: physical status I and II of the American Society of Anesthesiologists (ASA), ages between 18 and 65 years, and scheduled to undergo elective open abdominal hysterectomy under general anesthesia. We did not include patients who declined to participate in the study, those with any previous kidney dysfunction (glomerular filtration rate < 60 mL.min^{-1}.1.73m^{-2} according to the CKD-EPI formula, or urinary protein/creatinine ratio > 0.3),[13] uncontrolled hypertension (SBP > 180 mmHg or DBP > 120 mmHg), uncontrolled diabetes mellitus (fasting blood glucose > 200 mg.dL^{-1}), chronic use of non-steroidal anti-inflammatory drugs or diuretics, preoperative anemia (Hb < 7 g.dL^{-1}), or obesity II (BMI > 35 kg.m^{-2}). Exclusion criteria were: patients with severe intraoperative bleeding in the operating room or in the first 24 hours after the surgical procedure, requiring blood transfusion; perioperative diuretic use; and patients who did not return 40 days after the surgery for medical consultation.

Patients were randomized into two groups (HES group and RL group) according to the fluid replacement protocol with codes generated by computer software (random.org) and allocated at a proportion of 1:1. The protocols were stored in opaque envelopes that were only opened by the medical team immediately prior to anesthesia administration. The patients and the physician responsible for the evaluation of laboratory test results and possible complications presented by the study patients, were blinded to patient grouping.

Patients were monitored via continuous 5-lead cardioscopy, pulse oximetry, capnography with a gas analyzer, non-invasive blood pressure (NIBP), neuromuscular blockade monitor (TOF-Watch® SX, Organon, Swords Co., Dublin, Ireland), and urinary output (UO) by a bladder indwelling catheter. Induction of general anesthesia used propofol 2 mg.kg^{-1}, sufentanil 0.5—0.7 μg.kg^{-1}, and rocuronium 0.6 mg.kg^{-1}. After tracheal intubation, anesthesia was maintained with isoflurane 1—1.5% combined with continuous infusion of remifentanil (0.1—0.3 μg.kg^{-1}.min^{-1}).

Additionally, all patients received intravenous 5 mg of methadone and 8 mg of dexamethasone after induction of anesthesia, and 2 g of dipyrone, 100 mg of tramadol and 8 mg of ondansetron at the end of surgery. Neuromuscular blockade was reversed using neostigmine and atropine, guided according to neuromuscular blockade depth. Possible pain in the postanesthesia care unit (PACU) was treated with intravenous morphine as rescue medication, with a dose

titrated according to the verbal Numeric Rating Scale (NRS), and pain scores ranged from 0 to 10.

Both groups received 300 mL of RL during the induction of anesthesia and a standard baseline RL infusion of 2 mL. $kg^{-1}.h^{-1}$ through a continuous infusion pump (Samtronic® ST550 T2, São Paulo/SP, Brazil) in order to maintain mean arterial pressure (MAP) between 60—80 mmHg and replace insensible losses and diuresis. For every episode of MAP < 60 mmHg, volume expansion was performed according to the patient group: 150 mL of Hydroxyethyl starch 6% (Voluven®, Fresenius Kabi, Bad Homburg, Germany) in the HES group, or 300 mL of Ringer's lactate solution in the RL group, both infused over 5 minutes and repeated one time if necessary. If the MAP < 60 mmHg after two solution boluses in each group, ephedrine 5 mg was administered to restore MAP > 60 mmHg. The fluid protocol above mentioned is outlined in Figure 1. The same protocol was also used during the stay in the PACU. For the HES group, dose of HES was limited to 20 $mL.kg^{-1}$ intraoperatively and in PACU (below that stipulated as safe: up to 50 $mL.kg^{-1}.day^{-1}$),[14] when the solution for resuscitation was switched to RL.

Hemodynamic data were recorded electronically throughout surgery and at the PACU each five and fifteen minutes, respectively, and stored for later analysis. The absolute number of episodes of hypotension, as determined through mean arterial pressure (MAP < 60 mmHg) and systolic blood pressure (SBP < 90 mmHg), was recorded. We also analyzed vital signs at 0, 30, 60, 90, and 120 minutes during surgery, and upon awakening. Time-point 0 corresponded to general anesthesia induction and the "upon awakening" time corresponded to the moment when the orotracheal tube was removed.

Intraoperative bleeding was estimated by the difference in the weight of the surgical pads used during surgery (the dry weight of each small pad was 10 g and of each large pad 20 g). Blood loss was also assessed by the blood volume present in the surgical aspirator prior to peritoneal irrigation at the end of surgery. Total blood loss was recorded in milliliters.

Urine output was calculated by the relationship between the total urine volume preoperative weight from each patient and period during intraoperatively, and PACU. The perioperative fluid balance was calculated by the difference

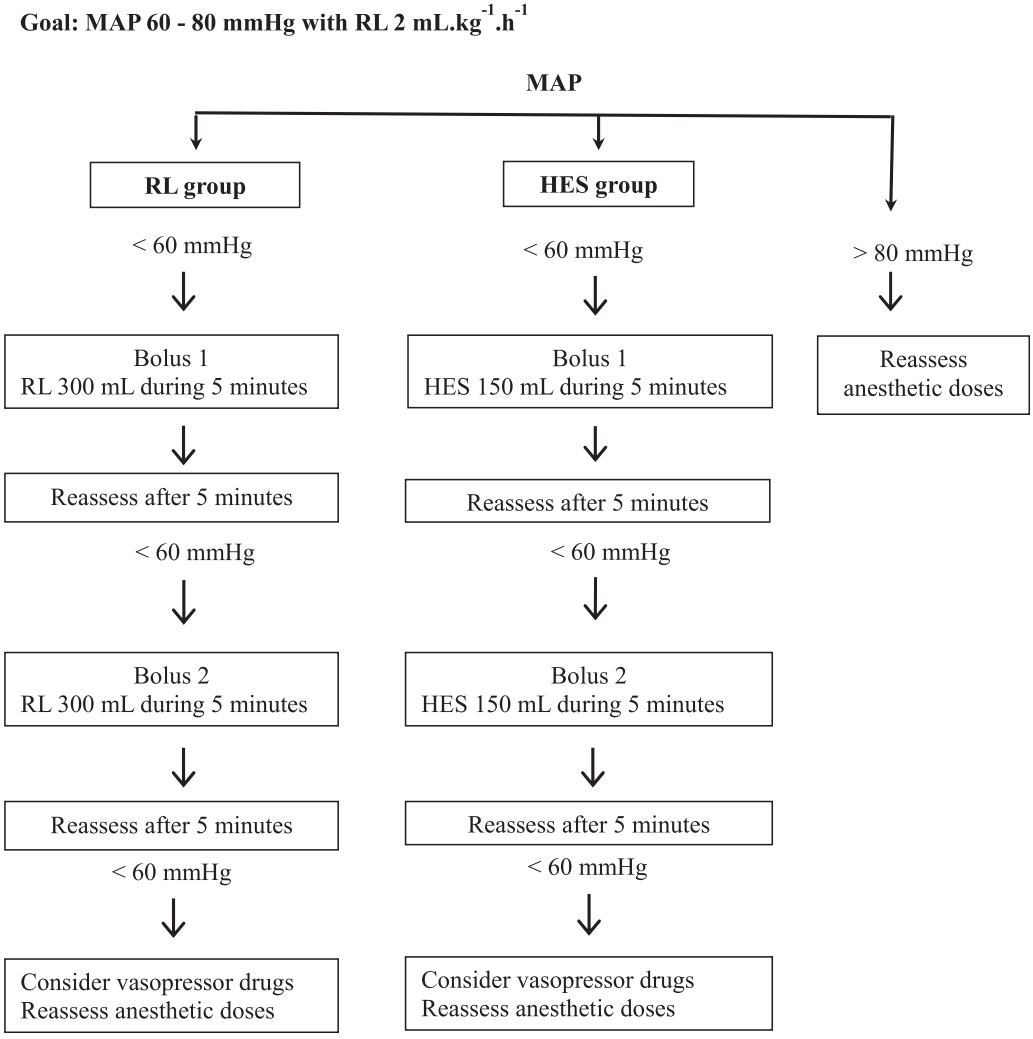


Figure 1 Algorithm for fluid replacement protocol. HES, Hydroxyethyl starch 6%; MAP, mean arterial pressure; RL, Ringer's lactate. Goal: MAP 60 - 80 mmHg with RL 2 $mL.kg^{-1}.h^{-1}$

between the volume of solution infused and the volume of losses (bleeding and diuresis). Fluid overload was calculated as the ratio between fluid balance and the preoperative weight of each patient multiplied by 100, considering volume overload when greater than 10%.[15]

Blood samples (4 mL) were collected for hemoglobin (Hb), hematocrit (Ht), plasma creatinine (CrP), and plasma urea (Ur) analyses in the preoperative and 24 hours after surgery. Urine samples (2 mL) were also collected for urinary creatinine (CrU), proteinuria, NGAL and KIM-1 analyses. Measurements of biomarkers NGAL and KIM-1 were performed for a single time-point at a specific laboratory of the Experimental Research Unit — UNESP Botucatu by a trained professional who did not have any contact with the patients or study protocols. The measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits from Elabscience (Wuhan, Hubei, China) according to the manufacturer's instructions. Forty days after surgery, only urine samples were collected to compare to previous samples. The measurements of CrU and proteinuria were used to calculate the urine protein/creatinine (P/CrU) ratio, which relates the loss of protein in urine in an isolated sample (equivalent to 24-hour proteinuria), to a normal range between 0.03—0.3.[16] Thus, values above 0.3 indicate renal injury.

As primary outcome, we used the comparison between groups in urinary NGAL. As secondary outcomes, in order to also assess perioperative renal function, we collected other urinary biochemical data (urinary KIM-1 and P/CrU), serum biochemical data (CrP and Ur), and urine output changes. Other secondary outcomes assessed were: fluid balance, fluid overload, intraoperative hemodynamic data, total surgical bleeding, postoperative Hb and Ht, volumes of administered fluids, and vasopressor requirement. Other perioperative data collected included: age; BMI; ASA physical status; estimated preoperative renal function[13]; duration of surgery; length of PACU stay; pain scores according to NRS; total morphine consumption at PACU; possible immediate complications (cardiac ischemia, arrhythmias, pulmonary edema, pneumonia, respiratory failure, sepsis, AKI, early reoperation and death); and late postoperative complications within 40 days (wound infection, wound dehiscence, reoperation and death).

For a significance level of 5% and test power of 90%, a total of 22 patients per group would be necessary to detect a 100 $ng.mL^{-1}$ difference in urinary NGAL levels, with a standard deviation of 100 $ng.mL^{-1}$, according to previous investigations.[17,18] We estimated that at least 66 patients should be enrolled in the study due to the possibility of losing 50% of the sample in a 40-day follow-up, as we have already observed in our institution.

The Shapiro-Wilk test was used to determine normality of data. Continuous variables with normal distribution were expressed as mean ± SD and tested with the Student's *t*-test with equal or different variances. Continuous variables with asymmetrical distribution comparisons were made by fitting a gamma distribution model. Categorical variables were expressed as absolute counts (%) and analyzed using Pearson's Chi-square test.

In order to compare variables of the tests at three time points, a repeated measurement design was used to evaluate group *versus* time interaction. In the case of data with symmetrical distribution, repeated measurement ANOVA followed by Tukey's multiple comparison test were used. If the data had an asymmetric distribution, a gamma distribution was fitted, followed by the Wald test for multiple comparisons. All analyses were performed considering a significance level of 5% or the corresponding p-value, and using SAS® 9.4 for Windows.

Results

Figure 2 illustrates details of the study. Patients were recruited between November 1, 2015, and March 28, 2018. Seventy patients were randomized, and 60 patients completed the study. The demographic characteristics of patients and intraoperative data are shown in Table 1. Except for total volume of crystalloid administered, which was lower in the HES group, the other variables did not differ between groups.

Regarding hemodynamic parameters, participants in the HES group showed higher systolic blood pressure at 30 minutes and MAP at 30 and 60 minutes after induction of anesthesia compared to the RL group. Mean heart rate values did not differ between groups at the time points studied, as shown in Figure 3. Vasopressor requirement was similar between groups, ranging from 5 to 30 mg in both groups (Table 1).

During PACU assessment, the volume of crystalloid, fluid balance and fluid overload were significantly higher in the RL group than in the HES group, as shown on Table 2. There were no differences in urine output, length of stay, pain scores, and morphine consumption between groups.

All patients were discharged 48 hours after surgery, and immediate complications were not observed. Although not significant, within 40 days after the procedure, late complications were more common in the RL group compared to the HES group (13.3% vs. 3.3%; $p = 0.16$). There was surgical wound infection in 2 patients in the RL group, and in 1 patient in the HES group, and suture dehiscence requiring reoperation in 2 patients in the RL group.

Preoperative serum laboratory analysis did not differ between the groups. In both groups, urea values in the postoperative period increased when compared to the preoperative period, whereas plasma creatinine levels decreased comparing these time points. Evaluating NGAL and KIM-1 mean values, comparing both groups within each time point, no significant differences were found between the groups; however, the mean of these biomarkers increased in both groups 24 hours after surgery, followed by a return to preoperative levels 40 days after surgery. The urine protein/creatinine ratio increased in the RL group and decreased in the HES groups at different time points within each group. When comparing the groups within each time point, there was a statistically significant difference between groups in the preoperative period and 40 days after surgery. These results are shown in Table 3.

Discussion

The main finding of the present study is that HES when compared to Ringer's lactate did not cause renal impairment,

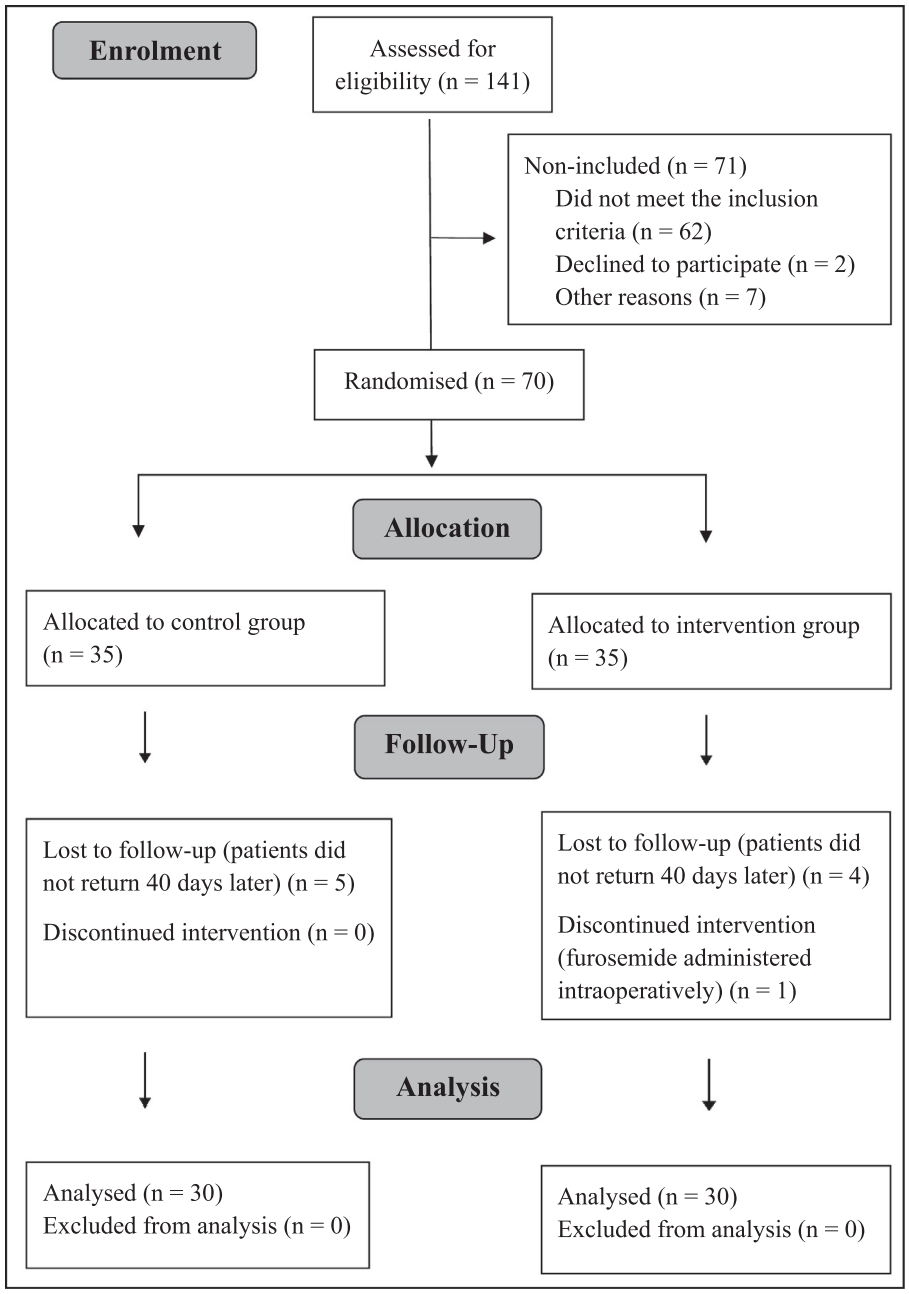


Figure 2 CONSORT flow diagram. n, number of patients.

reflected by urinary NGAL elevation, when using goal-directed fluid therapy in patients with normal renal function undergoing open abdominal hysterectomy under general anesthesia. In addition, other markers of renal function such as plasma creatinine, urinary output, urea, and KIM-1 were similar between groups. This finding is in accordance with previous investigations in which RL was compared to HES in orthopedic and urological surgery, and did not show any differences in postoperative urinary NGAL between groups.[17–20]

In both groups, urinary NGAL and KIM-1 measurements increased postoperatively compared to baseline values, but not plasma creatinine. The same finding was observed by Kancir et al regarding urinary NGAL, and the explanations for this phenomenon probably are surgical and hemodynamic stress leading to transient worsening in renal function. This corroborates the usefulness of these biomarkers on early diagnosis and intervention in AKI compared to traditional plasma creatinine levels.[10,12] Moreover, this was the first trial to include urinary KIM-1 measurements alongside NGAL to detect absence of early kidney damage with intraoperative HES administration.

We also assessed late renal function after 40 days as secondary outcome using P/Cr ratio and, like late urinary NGAL and KIM-1 measurements, there was no difference between groups, showing that patients who received HES intraoperatively did not have their renal function affected in the long term. This result is in line with Feldheiser et al, who showed that even after HES doses of 50 mL.kg^{-1} in patients undergoing cytoreductive cancer surgery, there was no difference in

Table 1 Characteristics of the patients and intraoperative data of the studied groups (mean ± standard deviation).

Variables	RL (n = 30)	HES (n = 30)	*p*-value
Age (years)	43.7 ± 5.4	46 ± 5.5	0.11
Weight (kg)	75.0 ± 11.8	72.6 ± 12.3	0.43
ASA physical status (n)			0.41
1	12 (40%)	9 (30%)	
2	18 (60%)	21 (70%)	
Height (cm)	160.2 ± 6.2	160.5 ± 6.1	0.85
BMI ($kg.cm^{-2}$)	29.2 ± 3.8	28.2 ± 4.7	0.38
GFR ($mL.min^{-1}/1.73m^2$)	103 ± 11.9	104.8 ± 11.9	0.56
RL volume (mL)	1277.4 ± 812.7	630.4 ± 310.2	0.0002
HES volume (mL)	-	439.6 ± 243	-
Bleeding (mL)	495.5 ± 338.2	439.8 ± 286.9	0.49
SBP < 90 mmHg	8.3 ± 8.5	7.87 ± 6.2	0.55
MAP < 60 mmHg	3.87 ± 4.9	3.5 ± 4.1	0.46
Vasopressor requirement (n)	8 (27%)	8 (27%)	1.0
Surgical time (min)	150 ± 40.6	149.67 ± 41.6	0.97

Student's t-test, $p < 0.05$, 95% CI.
n, number of patients; BMI, body mass index; GFR, glomerular filtration rate estimated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; HES, hydroxyethyl starch 6% group; MAP, mean arterial pressure; SBP, systolic blood pressure; RL, Ringer's lactate group.

NGAL, creatinine and urine output after 3 months compared to balanced crystalloids.[21] Using standard renal function tests, Joosten et al also showed that even after 12 months, HES did not cause renal dysfunction compared to crystalloids in abdominal surgery.[22] Interestingly, when compared to baseline values, late P/Cr ratio was increased in the RL group, but not in the HES group. The higher volume of solution administered in the RL group might be the reason for this, since the relationship between hypervolemia and glomerular damage, expressed by proteinuria, has been discussed.[23] However, we do underline that our study was not powered to detect differences in late outcomes.

In critically ill patients under intensive care, Hydroxyethyl starches were more likely to cause AKI compared to crystalloids for fluid resuscitation.[24,25] However, it is well known that intravascular fluid dynamics and behavior depend on the integrity of endothelial glycocalyx that make up the barrier between intravascular and interstice.[4] In the studies in intensive care units,[24,25] most of the patients evaluated were in sepsis and this severe clinical condition is naturally related to glycocalyx damage and increased capillary permeability.[4] In these patients, intravascular fluids shift rapidly to the interstice and tissue edema ensues, which can be worse with osmotically active solutions such as starches.[4] Conversely, in elective surgical patients, otherwise healthy, endothelial glycocalyx is intact and, in accordance with other studies, HES can be used for fluid resuscitation without increasing morbidity and mortality.[17—20,26—28]

As expected by the design of the study's protocol, the RL group received higher volumes of fluids, once every episode of hypotension was treated with twice the volume of crystalloids compared to colloids. This became necessary because of the dynamics of crystalloids staying shorter time and in lower volumes in the intravascular compartment compared to colloids.[4] Thus, using the same volume of both solutions could have delayed hypotension treatment in the RL group. However, even receiving less volume, the HES group had the same incidence of hypotension episodes and showed a better hemodynamic profile, expressed by higher MAPs at almost every moment assessed after anesthetic induction. This is in accordance with Joosten et al, who showed that a HES group had better volume expansion reflected by higher hemodynamic variables using less volume of fluid.[28] Kancir et al confirmed this greater intravascular expansion effect of HES measuring vasoactive plasmatic hormones such as renin, angiotensin II and aldosterone, which were lower compared to crystalloids in the perioperative period.[18]

In order to achieve the hemodynamic goals of our study, the RL group had significantly greater perioperative fluid balance and fluid overload than the HES group. Although we used MAP < 60 mmHg as our target for fluid resuscitation, this excess of fluid was also observed in other studies using perioperative GDT with either stroke volume variation[19,28] or esophageal doppler[21] in the balanced crystalloid group compared to the HES group. Fluid overload during surgery decreases tissue oxygen tension, delays recovery of gastrointestinal function and is associated with postoperative complications.[28] It is well known that fluid overload > 10% is associated with increased adverse events in critical patients[15] and, in our study, the RL group overcame this limit, whereas the HES group did not.

Although the new HES solutions, such as Hydroxyethyl starch 6%, were designed to minimize adverse effects in coagulation,[7] they can still impair thrombin generation and platelet function[1,29] Kancir et al used up to 2,500 mL of HES for fluid resuscitation in prostatectomy and showed significant increased bleeding compared to the crystalloid group.[17] Rasmussen et al used up to 3,500 mL of HES and found both increase in blood loss and coagulation impairment on thromboelastography after cystectomy when compared to crystalloids.[29] Due to bleeding and coagulopathy concerns, recently, the European Medicines Agency (EMA) banned the use of HES in the European Union. Our study, however, did not find increased bleeding in the HES group, probably due to the lower mean HES volume used and the lower risk of blood loss associated with elective abdominal hysterectomy,

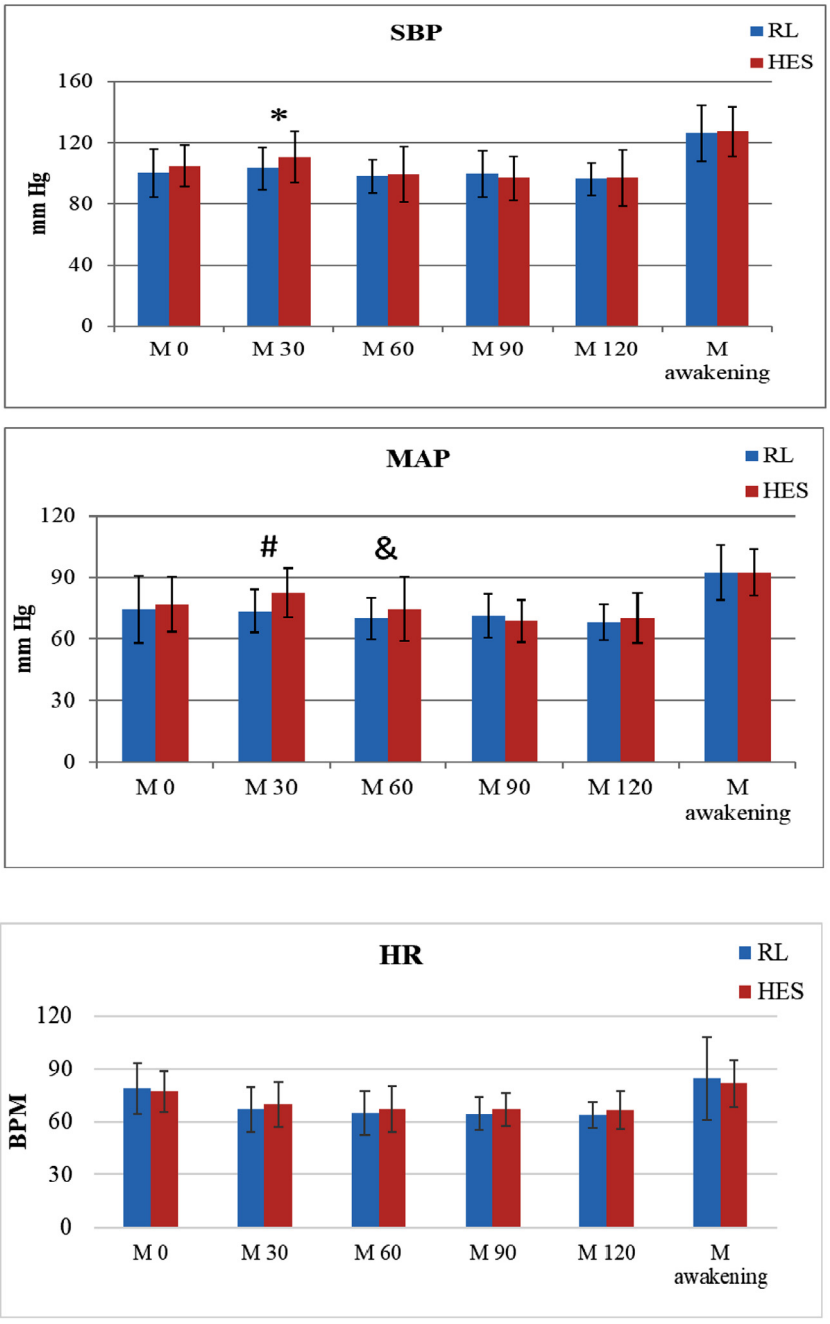


Figure 3 Behavior of hemodynamic parameters at the different moment studied. Student's t-test; * $p < 0.05$, 95% CI; # $p < 0.05$, 95% CI; & $p < 0.05$, 95% CI.
BPM, beats per minute; HES, Hydroxyethyl starch 6% group; HR, heart rate; M, moments studied after anesthetic induction, in minutes; MAP, mean arterial pressure; RL, Ringer's lactate group; SBP, systolic blood pressure.

when compared to those trials.[17,29] Other trials using up to 1,500 mL of HES intraoperatively, such as ours, also did not find increased bleeding using HES 6% showing that coagulation impairment is dose dependent.[18–20,28]

Our findings should be interpreted in the context of study limitations. Firstly, open hysterectomy is not frequently associated with postoperative AKI, and none of the patients had this complication postoperatively. Thus, a larger sample size would be necessary to detect any difference in such outcome between groups. Since our primary outcome was to detect differences in urine biomarkers of kidney damage due to type of fluid administered, we chose a procedure without great hemodynamic stress that would add minimal bias over kidney function. Secondly, following the fluid replacement protocol, we used different volumes of fluid between groups, and, therefore, the anesthesiology attending staff was not blinded to the intervention both in the operating room and in the PACU, what may be considered a performance bias. However, the researcher responsible for analyzing the results was blinded regarding the groups and the variables in the study. Thirdly, we used only MAP values in order to guide fluid administration in our GDT protocol,

Table 2 Variables evaluated in the post-anesthesia recovery period in the PACU (mean ± standard deviation).

Variables	RL	HES	*p*-value
Length of stay in the PACU (min)	101.7 ± 65.7	84.7 ± 41	0.23
RL volume (mL)	294.2 ± 176.7	214.6 ± 125.4	0.049
Pain (NRS)	5.03 ± 3.26	4.47 ± 4.06	0.55
Morphine dose (mg)	4.1 ± 4.2	3.9 ± 4.3	0.85
Fluid balance (mL)	780 ± 720	430 ± 440	0.03
Fluid overload (%)	11.7 ± 10.4	7.0 ± 6.3	0.04
Urine output ($mL.kg^{-1}.h^{-1}$)	1.05 ± 0.60	1.4 ± 0.97	0.09

Student's *t*-test, $p < 0.05$, 95% CI.
HES, hydroxyethyl starch 6% group; PACU, post-anesthesia care unit; RL, Ringer's lactate group; NRS, numeric rating scale.

Table 3 Mean of the laboratorial analysis between the groups and moments studied.

		Preoperative	Postoperative	40 days after surgery	
Variables	Groups	Mean ± SD	Mean ± SD	Mean ± SD	*p*-value
Hemoglobin ($g.dL^{-1}$)	RL	13.21 ± 2.1^{aA}	11.82 ± 2.0^{bA}	.	0.48
	HES	12.13 ± 1.9^{aA}	11.26 ± 1.9^{aA}	.	
Hematocrit (%)	RL	40.60 ± 5.6^{aA}	36.18 ± 5.5^{bA}	.	0.42
	HES	37.64 ± 5.1^{aA}	34.83 ± 5.7^{aA}	.	
Urea (mg)	RL	25.73 ± 7.3^{aA}	32.86 ± 10.1^{bA}	.	0.49
	HES	27.72 ± 6.8^{aA}	32.73 ± 8.8^{aA}	.	
Plasma Cr ($mg.dL^{-1}$)	RL	0.69 ± 0.1^{aA}	0.58 ± 0.1^{bA}	.	0.72
	HES	0.67 ± 0.1^{aA}	0.54 ± 0.1^{bA}	.	
Urine P/Cr	RL	0.07 ± 0.1^{aA}	0.21 ± 0.4^{bA}	0.36 ± 1.3^{bA}	0.04
	HES	0.15 ± 0.2^{aB}	0.12 ± 0.1^{aA}	0.10 ± 0.1^{aB}	
Urine NGAL ($ng.mL^{-1}$)	RL	55.27 ± 27.3^{aA}	73.85 ± 41.4^{bA}	42.08 ± 24.1^{cA}	0.64
	HES	51.13 ± 22.7^{aA}	75.74 ± 48.2^{bA}	38.10 ± 19.1^{cA}	
Urine KIM-1 ($ng.mL^{-1}$)	RL	0.09 ± 0.3^{aA}	0.26 ± 0.4^{aA}	0.03 ± 0.1^{aA}	0.12
	HES	0.17 ± 0.6^{aA}	0.46 ± 1.0^{aA}	0.15 ± 0.4^{aA}	

Mean values followed by the same lowercase letter (setting groups and testing moments) do not differ significantly at the 5% level.
Mean values followed by the same capital letter (setting moments and testing groups) do not differ significantly at the 5% level.
ANOVA repeated measures, $p < 0.05$, 95% CI.
ANOVA, analysis of variance; Cr, creatinine; HES, hydroxyethyl starch 6% group; P/Cr, protein creatinine ratio; RL, Ringer's lactate group.

and this choice could be criticized since dynamic parameters may predict fluid responsiveness more reliably. Finally, our study was not powered to examine the effects of intravenous solutions on hospital length of stay, bleeding events or postoperative complication rates, probably due to the reduced sample size, although adequate to analyze the main outcomes.

Conclusion

In conclusion, this study did not find a harmful effect of intraoperative infusion of HES on kidney function using renal biomarkers following open hysterectomy compared to Ringer's lactate solution. We also found that colloidal solutions can achieve better hemodynamic parameters using less volume and reduce postoperative fluid balance and fluid overload.

Funding

This study was financed by CAPES-DS (funding code 1764506) and FAPESP (funding code 16713-3/2015) and departmental sources.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank Maria Regina Moretto from the laboratory of the Experimental Research Unit of UNESP — Botucatu Campus/SP for measuring the NGAL and KIM-1 urinary biomarkers. We thank Professor José Eduardo Corrente for the statistical analysis and sample size calculation.

References

1. Boer C, Bossers SM, Koning NJ. Choice of fluid type: physiological concepts and perioperative indications. Br J Anaesth. 2018;120:384—96.
2. Plumb B, Brown J. Fluid therapy for anaesthetists and intensivists. Anaesth Intensive Care Med. 2015;16:439—42.
3. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low—moderate risk surgical patients: a multicentre

randomised controlled trial (FEDORA trial). Br J Anaesth. 2018;120:734–44.
4. Doherty M, Buggy DJ. Intraoperative fluids: how much is too much? Br J Anaesth. 2012;109:69–79.
5. Navarro LHC, Bloomstone JA, Auler JOC, et al. Perioperative fluid therapy: a statement from the international Fluid Optimization Group. Perioper Med. 2015;4:3.
6. Schol PBB, Terink IM, Lancé MD, et al. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. J Clin Anesth. 2016;35:26–39.
7. Strunden MS, Tank S, Kerner T. Perioperative fluid therapy: defining a clinical algorithm between insufficient and excessive. J Clin Anesth. 2016;35:384–91.
8. McCahon R, Hardman J. Pharmacology of plasma expanders. Anaesth Intensive Care Med. 2017;18:418–20.
9. Drury N, Lewington A. Prevention and management of acute kidney injury in the perioperative patient. Surgery. 2018;36:705–9.
10. Gumbert SD, Kork F, Jackson ML, et al. Perioperative acute kidney injury. Anesthesiology. 2020;132:180–204.
11. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol. 2017;31:331–44.
12. Vanmassenhove J, Vanholder R, Nagler E, et al. Urinary and serum biomarkers for the diagnosis of acute kidney injury: An in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254–73.
13. Michels WM, Grootendorst DC, Verduijn M, et al. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010;5:1003–9.
14. Lewis SR, Pritchard MW, Evans DJW, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8(8):CD000567.
15. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrology. 2016;17:1–9.
16. Lane C, Brown M, Dunsmuir W, Kelly J, Mangos G. Can spot urine protein/creatinine ratio replace 24 h urine protein in usual clinical nephrology? Nephrology. 2006;11:245–9.
17. Kancir ASP, Johansen JK, Ekeloef NP, et al. The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: a randomized controlled trial. Anesth Analg. 2015;120:608–18.
18. Kancir ASP, Pleckaitiene L, Hansen TB, et al. Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: a randomized controlled trial. Anesthesiology. 2014;121:948–58.
19. Tyagi A, Verma G, Luthra A, et al. Risk of early postoperative acute kidney injury with stroke volume variation-guided tetrastarch versus Ringer's lactate. Saudi J Anaesth. 2019;13:9–15.
20. Zhang Y, Yu Y, Jia J, et al. Administration of HES in elderly patients undergoing hip arthroplasty under spinal anesthesia is not associated with an increase in renal injury. BMC Anesthesiol. 2017;17:29.
21. Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth. 2013;110:231–40.
22. Joosten A, Delaporte A, Mortier J, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology. 2019;130:227–36.
23. Nishimoto M, Murashima M, Kokubu M, et al. Positive association between intra-operative fluid balance and post-operative acute kidney injury in non-cardiac surgery: the NARA-AKI cohort study. J Nephrol. 2020;33:561–8.
24. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
25. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34.
26. Kabon B, Sessler DI, Kurz A, et al. Effect of intraoperative goal-directed balanced crystalloid versus colloid administration on major postoperative morbidity. Anesthesiology. 2019;130:728–44.
27. Joosten A, Delaporte A, Mortier J, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology. 2019;130:227–36.
28. Rasmussen KC, Johansson PI, Højskov M, et al. Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: results from a randomized controlled trial. Ann Surg. 2014;259:249–54.
29. Roberts I, Shakur H, Bellomo R, et al. Hydroxyethyl starch solutions and patient harm. Lancet. 2018;391:736.

Brazilian Journal of Anesthesiology 2022;72(6): 729—735

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

The clinical impact of the systolic volume variation guided intraoperative fluid administration regimen on surgical outcomes after pancreaticoduodenectomy: a retrospective cohort study

Daniel Negrini [a,b,*,1], **Jacqueline Graaf** [b], **Mayan Ihsan** [c], **Ana Gabriela Correia** [d], **Karine Freitas** [e], **Jorge Andre Bravo** [b,f], **Tatiana Linhares** [g], **Patrick Barone** [h,1]

[a] *Universidade Federal do Estado do Rio de Janeiro, Departamento de Anestesiologia, Rio de Janeiro, RJ, Brazil*
[b] *Faculdade de Medicina da Fundação Universitária Serra dos Órgãos, Teresopolis, RJ, Brazil*
[c] *Medical City Teaching Hospitals, Department of Anesthesiology, Iraq*
[d] *Universidade Estácio de Sá, Faculdade de Medicina, Rio de Janeiro, RJ, Brazil*
[e] *Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Rio de Janeiro, RJ, Brazil*
[f] *Instituto Nacional do Câncer, Departamento de Medicina Interna, Rio de Janeiro, RJ, Brazil*
[g] *Unimed Barra Hospital, Departamento de Medicina Interna, Rio de Janeiro, RJ, Brazil*
[h] *Universidade Federal do Rio Grande do Sul, Departamento de Anestesiologia,Porto Alegre, RS, Brazil*

Received 21 October 2021; accepted 21 June 2022
Available online 7 July 2022

KEYWORDS
Fluid therapy;
Patient outcome assessment;
Pancreatico-duodenectomy;
Stroke volume

Abstract

Background: Pancreaticoduodenectomy is associated with high morbidity. Many preoperative variables are risk factors for postoperative complications, but they are primarily non-modifiable. It is not clear whether an intraoperative goal-directed fluid regimen might be associated with fewer postoperative surgical complications compared to current conservative, non-goal-directed fluid practices. We hypothesize that the use of Systolic Volume Variation (SVV)-guided intraoperative fluid administration might be beneficial.

Methods: Data from 223 patients who underwent pancreaticoduodenectomy in our institution between 2015 and 2019 were reviewed. Patients were classified into two groups based on the use of intraoperative use of SVV to guide the administration of fluids. The decision to use SVV or not was made by the attending anesthesiologist. Subjects were classified into SVV-guided intraoperative fluid therapy (SVV group) and non-SVV-guided intraoperative fluid therapy (non-SVV group). Uni and multivariate regression analyses were conducted to determine if SVV-guided fluid therapy was significantly associated with a lower incidence of postoperative surgical complications, such as Postoperative Pancreatic Fistula (POPF), Delayed Gastric Emptying (DGE), among others, after adjusting for confounders.

* Corresponding author.
E-mail: dan_negrini2000@yahoo.com.br (D. Negrini).
[1] Authors contributed equally to this work.

https://doi.org/10.1016/j.bjane.2022.06.008

Results: Baseline, demographic, and intraoperative characteristics were similar between SVV and non-SVV groups. In the multivariate analysis, the use of SVV guidance was significantly associated with fewer postoperative surgical complications (OR = 0.48; 95% CI 0.25—0.91; $p = 0.025$), even after adjusting for significant covariates, such as perioperative use of epidural, pancreatic gland parenchyma texture, and diameter of the pancreatic duct.
Conclusions: VV-guided intraoperative fluid administration might be associated with fewer postoperative surgical complications after pancreaticoduodenectomy.

Introduction

Pancreaticoduodenectomy is associated with many postoperative morbid outcomes. The postoperative complication rate varies from 35% to 58%, and perioperative mortality is around 2—4% in reference centers.[1] Pancreaticoduodenectomy is, however, the standard of treatment for pancreatic and periampullary tumors.[2] Because of its high morbidity, a multidisciplinary approach is mandatory to achieve favorable outcomes.[3]

A regimen of liberal intraoperative fluid administration is known to be associated with higher rates of complications and unfavorable outcomes in colorectal surgery, such as anastomotic leak, since excessive fluid administration is associated with edema and tissue hypoxia.[4] On the other hand, hypovolemic states were reported to be associated with ischemia-related events, such as acute renal failure.[5] In the scenario of pancreatic surgery, it is not clear whether an intraoperative goal-directed fluid regimen is associated with fewer postoperative surgical complications. Results from previous studies are controversial and difficult to compare because the definition of what was considered as a more restrictive or liberal fluid regimen was neither objective, nor individualized.[2,6,7] Moreover, previous studies did not consider the effects of well-known surgical variables, such as pancreatic gland texture and duct size in their analysis.

In recent years, emerging evidence has shown that intraoperative fluid replacement should be guided by more objective measures of real-time perfusion and/or adequate volume status for each individual patient. Since then, the use of Systolic Volume Variation (SVV) has been increasingly implemented due to its simple use, accuracy, and minimal invasiveness.

Although SVV appears to accurately predict fluid responsiveness, its impact on surgical or clinical outcomes remains unclear.[8] The aim of this study is to compare the short-term postoperative outcomes, namely postoperative surgical complications, of patients who received an SVV- or non-SVV-guided fluid regimen intraoperatively to determine the clinical impact of intraoperative SVV guidance on postoperative pancreaticoduodenectomy outcomes.

Methods

This was a retrospective, observational cohort study of patients who underwent pancreaticoduodenectomy in our institution, from 2015 to 2019, using our prospectively managed database. This study was approved by our Ethical Committee (# 51194021.5.0000.5258) and adhered to the STROBE checklist for reporting of cohort studies.

The rationale for SVV predicting responsiveness to a volume challenge is based on changes in Systolic Volume (SV) or pulse pressure during alterations in cardiac preload provoked by positive-pressure mechanical ventilation.[9] Under positive pressure mechanical ventilation, specifically during inspiration, the intrapleural pressure rises and the venous pressure gradient is lowered. This causes a reduction in the patient's Right Ventricular (RV) preload. Additionally, the RV afterload is increased due to an increase in transpulmonary pressure. The result is a reduction in RV Stroke Volume (SV) leading to a reduced Left Ventricular (LV) filling volume.[10] LV output is ultimately reduced after 2—3 subsequent heartbeats, reaching its minimum during the expiratory phase. The amplitude of these changes is greater if the patient is in a low volume status, on the ascending part of Frank Starling's curve. Therefore, SVV can be used to see an arterial swing on an arterial trace suggesting that the patient is in a low volume status and would benefit from more fluids,[9] with the use of the Vigileo/Flo trac (Edwards Lifeciences®) monitor. Even though the algorithms and protocols for the use of SVV may vary depending on institution and clinician preference, most tend to be very similar. In our institution we use the one shown in Figure 1.[11]

The primary outcome measure was the occurrence of any postoperative surgical complication, according to the Clavien-Dindo classification.[12] We also collected perioperative data regarding the type of fluid regimen administered intraoperatively (SVV-guided or non-SVV-guided), and other factors we reasonably assumed could possibly impact the relationship between the regimen of intraoperative fluid administration and our outcomes of interest. These factors included the total amount of intraoperative fluids used, the type of fluid used (crystalloids only or both crystalloids and colloids), intraoperative use of vasopressors, and intraoperative use of epidural analgesia. Intraoperative data regarding the texture of the pancreatic gland parenchyma and pancreatic duct size, since the relationship between pancreatic gland texture/duct size and postoperative surgical complications has been well established, were also collected. Soft pancreatic texture and ductal size of ≤ 3 mm are associated with a higher risk of postoperative complications such as Postoperative Pancreatic Fistula (POPF). Soft pancreas and small ductal size are significantly relevant factors in the Fistula Risk Score (FRS), based on the 2005 and 2016 International Study Group of Pancreatic Fistula classification (ISGPFc).[13,14] Patients with serious cardiovascular or pulmonary diseases were excluded from the study. We also

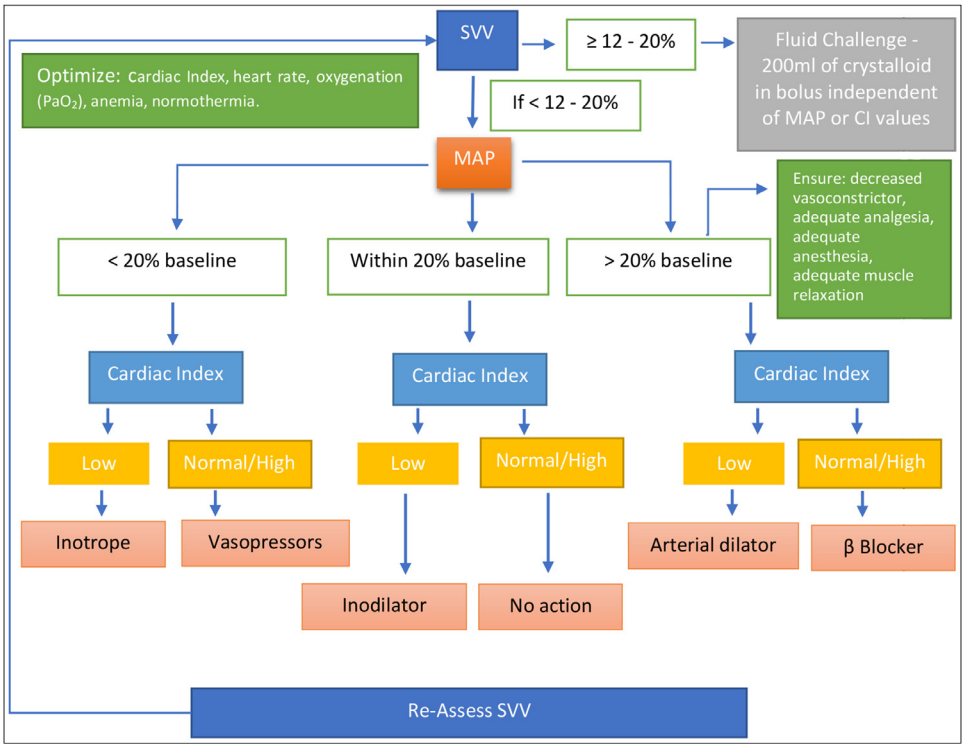


Figure 1 Our Institution's algorithm for intraoperative fluid management guided by SVV and CI using Vigileo/FloTrack (MAP, Mean Arterial Pressure; SVV, Stroke Volume Variation).

collected data regarding demographic characteristics and preoperative diagnosis (Tables 1 and 2).

Patients were first classified into SVV and non-SVV groups. The decision of using or not SVV was made by the attending anesthesiologist. In our institution, high complex surgeries such as pancreaticoduodenectomy have anesthesia care performed by a small number of clinicians, and the use of SVV implies adherence to the protocol described on Figure 1. The Vigileo/Flo trac (Edwards Lifeciences®) monitor was used on the SVV group. MAP and CI were used only when, based on the values of the SVV, we had no reason to believe that volume challenge wouldn't be beneficial for that specific patient. If so, we used MAP and CI to decide what was the most appropriate care for that patient (Vasopressors, Inodilators). In the non-SVV group, none of those variables were considered to guide intraoperative fluid management.

Table 1 Demografic, preoperative diagnosis and pancreas characteristics of SVV and non-SVV groups.

	SVV (n = 73)		No SVV (n = 150)		Total (n = 223)		*p*
	n or Mean	% or SD	n or Mean	% or SD	n	%	
Sex							
Female	33	45.21	69	46	102	45.74	0.911
Male	40	54.79	81	54	121	54.26	
Age	66.74	11.32	64.29	12.39			0.156
BMI	25.12	4.78	25.92	5.80			0.35
Pancreatic gland texture							
Hard	35	47.95	66	44	101	45.29	0.579
Soft	38	52.05	84	56	122	54.71	
Pancreatic Duct Size							
< 3 mm	12	16.44	21	14	33	14.8	0.357
3–6 mm	46	63.01	73	48.67	119	53.36	
> 6 mm	15	20.55	56	32.48	71	31.84	
Diagnosis							
Cancer (vs. Benign)	58	79.45	110.00	74.32	168.00	76.02	0.56
NET (vs. Benign)	5	5.48	15	9.46	20	8.14	
Beningn	11	15.07	24	16.22	35	15.84	

Table 2 Intra- and postoperative caracteristics of SVV and non-SVV groups.

	SVV (n = 73)		No SVV (n = 150)		Total (n = 223)		
	n or Mean	% or SD	n or Mean	% or SD	n	%	*p*
Any Surgical Complications							
Yes	43	57.35	104	72.99	147	67.8	**0.024**
No	34	42.65	42	27.01	76	32.2	
Major Surgical Complications (≥ Grade 3)							
Yes	42	57.53	82	54.67	124	55.61	0.686
No	31	42.47	68	45.33	99	44.39	
Type of Surgical Complication							
DGE	13		45		58		0.719
Fistula	11		28		39		
Other	19		31		50		
Amount of Fluids (mL.KgH)	8.49	2876	7.67	2695			**0.036**
Type of Surgical fluids							
Cristalloids	21.00	28.77	58.00	38.67	79.00	35.43	0.147
Both cristalloids and colloids	52.00	71.23	92.00	61.33	144.00	64.57	
Vasopressors used intraoperatively							
Yes	71.00	97.26	145.00	96.67	216.00	96.86	0.811
No	2.00	2.74	5.00	3.33	7.00	3.14	
Estimated Blood Loss (mL)	420.00	348.33	376.77	233.417			0.273
Perioperative use of epidural							
Yes	59.00	81.94	126.00	84.46	185.00	83.64	0.64
No	14.00	18.06	24.00	15.54	38.00	16.36	
Lengh of Hospital Stay (Days)	123.088	8.639	13.197	7.339			0.443
Lengh of CU Stay (Days)	1.68	2.033	1.445	18.709			0.397
Readmission to ICU in 90 days							
Yes	21.00	26.42	46	29.41	67	28.49	0.688
No	50.00	73.58	106	70.59	156	71.51	
Duration of Surgery (min)	400.70	63479	400.48	91.61			0.985

All the previously mentioned variables were compared between both groups. Following this, both uni and multivariate analyses were conducted to assess factors that were significantly associated with our outcome of interest. For continuous variables, we used unpaired two-sample *t*-test (two tailed) for group comparison. For categorical variables, we used the chi-square test. For the uni and multivariate analyses, we used logistic regression. For the multivariate analysis, we used forward selection of variables, starting with the one with the lowest *p*-value on univariate analysis, ending only with the variables with *p*-values less than 0.05 in the univariate analysis. We had previously estimated a sample size of 140 patients (70 patients in each group) to power the study to detect a difference in any grade postoperative surgical complications of at least 20% between groups (80% power), assuming a type I error (α) of 0.05, accounting for five predictors in a multiple regression model. We used the free online software G-Power® for sample size calculation. We ended up including 223 cases. All analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, Texas, USA).

Results

Baseline demographic and preoperative factors did not have statistical difference between the SVV and non-SVV groups (Table 1**)**. Intraoperative and postoperative factors also did not have statistical difference between groups, except for surgical complications (p = 0.024) and the total amount of fluids given (p = 0.036). Nearly half of the complications on the SVV group consisted of Delayed Gastric Emptying (DGE) and postoperative pancreatic fistula. In the non-SVV group, those two complications comprised nearly two thirds of the total complications. Other postoperative complications, such as bleeding, intra-abdominal collection, among others were individually in small numbers. Thus, we decided to group them as "others". Additionally, estimated blood loss and the use of blood products did not differ between groups (Table 2). The uni and multivariate analyses of factors potentially associated with the occurrence of any postoperative surgical complication are shown in Table 3. In the univariate analyses, the regimen of intraoperative fluid administration (SVV- or non-SVV-guided), perioperative use of epidural, pancreatic gland texture, and pancreatic duct diameter $\leq$ 3 mm were all associated with postoperative surgical complications. In the multivariate analyses, the use of SVV guidance was significantly associated with fewer postoperative surgical complications (OR = 0.48; 95% CI 0.25—0.91; p = 0.025), along with perioperative use of epidural (OR = 0.33; 95% CI 0.13—0.87; p = 0.025) and hard pancreas (OR = 0.45; 95% CI 0.22—0.89; p = 0.022). The total amount of intraoperative fluid administered was not a relevant factor associated with postoperative surgical complications in either analysis.

Table 3 Uni and multivariate analyses of clinical factors affecting surgical complications.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Male	0.84	0.46–1.51	0.568			
Age > 65	1.53	0.85–2.58	0.156			
BMI > 25	1.31	0.72–2.36	0.378			
Regimen of fluid administration was SVV-guided	0.50	0.27–0.92	**0.025**	0.48	0.25–0.91	**0.025**
Amount of fluids > 8 mL KgH	0.74	0.41–1.33	0.314			
Type of fluids (both cristaloids and colloids)	0.80	0.59–1.09	0.168			
Intraoperative use of vasopressors	3.26	3.26–20.01	0.201			
Estimated blood loss was > 400 mL	0.92	0.51–1.66	0.771			
Perioperative use of epidural	0.38	0.15–0.96	**0.042**	0.33	0.13–0.87	**0.025**
Soft pancreatic gland texture	2.29	1.26–4.17	**0.007**	2.22	1.12–4.40	**0.022**
Pancreatic Duct Size						
< 3 mm (vs. > 6 mm)	0.39	0.16–0.96	**0.041**	0.64	0.23–1.75	0.382
3–6 mm (vs. > 6 mm)	0.68	0.34–1.38	0.283	1.08	0.49–2.41	0.842
> 6 mm	1.00					
Diagnosis		–				
Cancer (vs. Benign)	0.94	0.41–2.12	0.873			
NET (vs. Benign)	1.14	0.29–4.52	0.856			
Benign	1.00					
Duration of sugery > 400 min	0.74	0.41–1.33	0.316			

Discussion

Recently, attention has been focused on intraoperative factors that might impact immediate and long-term postoperative surgical outcomes. The adoption of protocols like that of ERAS by many institutions around the world shows the extent of attention this topic has acquired in the past years.[15] The perioperative use of epidural anesthesia, vasopressor, blood products, total amount of fluid administered, type of fluid used, and, most importantly, the regimen of fluid administration (goal-directed or not), based on patient's real-time individualized needs are all controversial topics in modern intraoperative fluid management.

In our study, we failed to find any significant effects from the use of SVV in clinically relevant postoperative outcomes, such as length of hospital and ICU stay and readmission to the ICU (Table 3). Previous retrospective studies that compared restrictive intraoperative fluid approach and liberal intraoperative fluid approach in pancreaticoduodenectomy also failed to show any significant difference in short term surgical outcomes, such as length of hospital stay, or postoperative surgical complications, such as Postoperative Pancreatic Fistula (POPF), Delayed Gastric Empty (DGE), infections, or hemorrhage.[2,6,16,17] A systematic review of the literature with meta-analysis comparing a restrictive versus liberal intraoperative fluid approach (fixed total amount of fluid administered) found no difference between groups in terms of postoperative surgical complications.[18] The largest known clinical trial (n = 330) that compared different intraoperative fluid regimens and surgical outcomes after pancreaticoduodenectomy also found no difference in the incidence of postoperative surgical complications between patients given restrictive and liberal fluid administration.[19] Our group succeeded in showing a statistically significant difference between SVV and non-SVV groups regarding postoperative surgical complications.

Another group performed a clinical trial comparing the postoperative outcomes of SVV-guided approach and ERAS protocol-guided for intraoperative fluid administration. In this trial, the results for postoperative surgical complications and length of hospital stay favored the SVV group, in which patients received a lower mean total volume of fluid administered.[10] It is important to take note that the ERAS protocol is also supposed to perform intraoperative fluid administration in an individualized manner for every patient.[7] Differently from our study, this group was in fact comparing two different Goal Directed Fluid Therapy (GDFT) strategies.

Gottin et al performed a randomized clinical trial (n = 86), that compared postoperative surgical complications in the SVV-guided group, a restrictive fluid regimen group (< 4 $mL.Kg^{-1}.H^{-1}$), and a liberal fluid regimen group (> 12 $mL.Kg^{-1}.H^{-1}$). The results favored both the SVV and the restrictive fluid group.[20] It is important to take note that the total amount of fluids administered in both restrictive and liberal regimen groups in the same study seemed relatively excessive, based on our experience. However, those results coincide with ours.

None of the studies consider the role of other possible covariates in their analysis. Pancreaticoduodenectomy is associated with many postoperative complications, including POPF. Studies have described the texture of the pancreas as an independent predictive factor of the occurrence of POPF and other pancreatic surgery complications.[21] Soft-textured pancreases are associated with a higher incidence of POPF and pancreatic surgery complications[22] and are characterized by increased pancreatic fat and decreased pancreatic fibrosis.[23] Conversely, hard-textured pancreases due to fibrosis are associated with lower POPF formation, as these pancreases allow firmer holding of sutures and tend to have a smaller amount of pancreatic juice secretion. Usually, the assessment of pancreas texture is determined intraoperatively by surgeons although there are only a few

experimental approaches that are not yet fully implemented in clinical practice.[24]

To the best of our knowledge, Andrianello et al were the only authors so far to perform a study that considered the potential role of the pancreatic gland texture in the relationship between fluid regimen and postoperative outcomes. This prospective clinical trial of 350 patients who underwent major pancreatic surgeries compared the difference in POPF incidence between the groups that either received liberal fluid regimen or received fluids based on the ERAS protocol. The incidence of POPF was lower in the ERAS-guided group, suggesting that the use of a strategy for individualized intraoperative fluid administration might, indeed, reduce surgical complications. In the same study, they also stratified patients by the texture of pancreatic gland parenchyma (hard vs. soft). In patients whose pancreases were classified as "soft pancreases", the use of an ERAS-guided approach for intraoperative fluid therapy was associated with a higher incidence of POPF.[25] One could argue that "soft pancreas" itself is already a strong predictor for postoperative surgical complications, so the regimen of intraoperative fluid administration would not matter. Our data indeed show, in the univariate analysis, that "soft pancreas" is associated with more postoperative surgical complications. However, in the multiple logistic regression model, even adjusting for the covariate "soft pancreas", SVV was still associated with fewer postoperative surgical complications.

The literature has also shown that the use of perioperative epidural anesthesia might potentially impact short- and long-term surgical outcomes.[26] We considered that it was reasonable to evaluate whether perioperative use of epidural anesthesia was associated with postoperative surgical complications and could potentially affect the relationship between the regimen of intraoperative fluid administration and postoperative surgical complications. It is important to note that the perioperative use of epidural analgesia did not differ between SVV and non-SVV groups, with 81% of SVV subjects using epidural vs. 84% of non-SVV subjects (Table 2). This difference was considered statistically non-significant. In the univariate logistic regression analysis perioperative use of epidural was, in fact, associated with fewer postoperative surgical complications. For this reason, this important variable was added in a forward step model to the multiple logistic regression equation, and SVV was still associated with fewer postoperative surgical complications, independently of the effects of epidural. We believe that the potential role of perioperative use of epidural and its clinical implications in the context of high-risk pancreatic surgeries deserves more investigation in future studies.

The results of the current study are consistent with the hypothesis that administering intraoperative fluids using SVV guidance is associated with fewer postoperative surgical complications after pancreaticoduodenectomy. It is also interesting to note that the average total amount of fluids administered in the SVV group was significantly higher than that of the non-SVV group. Due to the need for multiple reassessments of intraoperative SVV mentioned in different guidelines, it is our assumption that a higher total volume of intraoperative fluid administration might be a reasonable finding. The literature regarding SVV shows inconsistent results regarding its relationship with the total intraoperative amount of fluids administered.[27]

However, in our study, the total amount of intraoperative fluids administered was not independently associated with postoperative surgical complications in the univariate analyses. This implies the possibility that the method of fluid management (goal-directed or not) is the variable significantly associated with postoperative surgical complications, rather than the total amount of fluid administered. Additionally, the type of fluids used, crystalloids or both crystalloids and colloids, was not associated with postoperative surgical complications.

The difficulty in establishing a causal relationship between the SVV-guided intraoperative fluid regimen and postoperative surgical complications is a potential limitation to our study. Since this is a retrospective study, causality between factors and the outcome of interest could not be defined. Additionally, adherence to protocols constitutes a problem in institutions around the world, and the fact that the clinician responsible for the anesthetic care could not adhere strictly to the protocol showed in Figure 1 should be considered another potential source of bias. Moreover, one could argue that the decision of using SVV, or any other monitor, to improve the quality of anesthetic care by the attending anesthesiologist would imply a different perception of the impact of a more accurate intraoperative anesthetic care in postoperative outcomes, and potentially lead to less postoperative complications. This should also be considered an additional potential source of bias. Even though we certainly must be extremely careful in any analysis and interpretation of the present findings, and the extent of how far we can extrapolate our conclusions based on the present study, our predictive factor was significantly associated with our measured outcome. Consequentially, based on the strength and significance of the evidence we found, future randomized clinical trials on this topic should be performed, especially taking into consideration the role of other potential covariates known to be associated with postoperative surgical complications after pancreaticoduodenectomy.

Based on the data from our institution, we conclude that the use of SVV-guided intraoperative fluid therapy might be associated with fewer minor postoperative surgical complications after pancreaticoduodenectomy, i.e., grade I and II, even after adjusting for factors known to be associated with postoperative surgical complications, such as pancreatic gland parenchyma texture, pancreatic duct size, and perioperative use of epidural anesthesia. Facing the yearly increase in the number of complex surgical procedures, anesthesiologists and surgeons need to be aware of the importance of intraoperative care and its significant relevance to surgical outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Pugalenthi A, Protic M, Gonen M, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Surg Oncol. 2016;113:188–93.

2. Kulemann B, Fritz M, Glatz T, et al. Complications after pancreaticoduodenectomy are associated with higher amounts of intra- and postoperative fluid therapy: a single center retrospective cohort study. Ann Med Surg (Lond). 2017;16:23—9.
3. Alemanno G, Bergamini C, Martellucci J, et al. Surgical outcome of pancreaticoduodenectomy: high volume center or multidisciplinary management? Minerva Chir. 2016;71:8—14.
4. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. Int J Surg. 2016;36(Pt A):183—200.
5. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378:2263—74.
6. Gill P, Chua TC, Huang Y, et al. Pancreatoduodenectomy and the risk of complications from perioperative fluid administration. ANZ J Surg. 2018;88:E318—E23.
7. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;55:91—115.
8. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37:2642—7.
9. Guerin L, Monnet X, Teboul JL. Monitoring volume and fluid responsiveness: from static to dynamic indicators. Best Pract Res Clin Anaesthesiol. 2013;27:177—85.
10. Willars C, Dada A, Hughes T, et al. Functional haemodynamic monitoring: the value of SVV as measured by the LiDCORapid™ in predicting fluid responsiveness in high risk vascular surgical patients. Int J Surg. 2012;10:148—52.
11. Weinberg L, Ianno D, Churilov L, et al. Restrictive intraoperative fluid optimisation algorithm improves outcomes in patients undergoing pancreaticoduodenectomy: A prospective multicentre randomized controlled trial. PLoS One. 2017;12. e0183313-e.
12. Téoule P, Bartel F, Birgin E, et al. The Clavien-Dindo classification in pancreatic surgery: a clinical and economic validation. J Invest Surg. 2019;32:314—20.
13. Pratt WB, Maithel SK, Vanounou T, et al. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg. 2007;245:443—51.
14. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161:584—91.
15. Kagedan DJ, Ahmed M, Devitt KS, et al. Enhanced recovery after pancreatic surgery: a systematic review of the evidence. HPB (Oxford). 2015;17:11—6.
16. Sandini M, Fernández-Del Castillo C, Ferrone CR, et al. Intraoperative fluid administration and surgical outcomes following pancreaticoduodenectomy: external validation at a tertiary referral center. World J Surg. 2019;43:929—36.
17. Melis M, Marcon F, Masi A, et al. Effect of intra-operative fluid volume on peri-operative outcomes after pancreaticoduodenectomy for pancreatic adenocarcinoma. J Surg Oncol. 2012;105:81—4.
18. Chen BP, Chen M, Bennett S, et al. Systematic review and meta-analysis of restrictive perioperative fluid management in pancreaticoduodenectomy. World J Surg. 2018;42:2938—50.
19. Grant F, Brennan MF, Allen PJ, et al. Prospective randomized controlled trial of liberal vs restricted perioperative fluid management in patients undergoing pancreatectomy. Annals Surg. 2016;264:591—8.
20. Gottin L, Martini A, Menestrina N, et al. Perioperative fluid administration in pancreatic surgery: a comparison of three regimens. J Gastrointest Surg. 2020;24:569—77.
21. Belyaev O, Munding J, Herzog T, et al. Histomorphological features of the pancreatic remnant as independent risk factors for postoperative pancreatic fistula: a matched-pairs analysis. Pancreatology. 2011;11:516—24.
22. Crippa S, Salvia R, Falconi M, et al. Anastomotic leakage in pancreatic surgery. HPB (Oxford). 2007;9:8—15.
23. Mathur A, Pitt HA, Marine M, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg. 2007;246:1058—64.
24. Marchegiani G, Ballarin R, Malleo G, et al. Quantitative assessment of pancreatic texture using a durometer: a new tool to predict the risk of developing a postoperative fistula. World J Surg. 2017;41:2876—83.
25. Andrianello S, Marchegiani G, Bannone E, et al. Clinical implications of intraoperative fluid therapy in pancreatic surgery. J Gastrointest Surg. 2018;22:2072—9.
26. Cummings III KC, Zimmerman NM, Maheshwari K, et al. Epidural compared with non-epidural analgesia and cardiopulmonary complications after colectomy: a retrospective cohort study of 20,880 patients using a national quality database. J Clin Anesth. 2018;47:12—8.
27. Joosten A, Hafiane R, Pustetto M, et al. Practical impact of a decision support for goal-directed fluid therapy on protocol adherence: a clinical implementation study in patients undergoing major abdominal surgery. J Clin Monit Comput. 2019;33:15—24.

Brazilian Journal of Anesthesiology 2022;72(6):736–741

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Is Mallampati classification a good screening test? A prospective cohort evaluating the predictive values of Mallampati test at different thresholds

Clístenes C. de Carvalho[a,b,*], **Danielle M. da Silva**[c], **Marina S. Leite**[c], **Flávia A. de Orange**[a,c]

[a] *Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil*
[b] *Universidade Federal de Campina Grande, Campina Grande, PB, Brazil*
[c] *Hospital das Clínicas de Pernambuco, Recife, PE, Brazil*

Received 23 March 2020; accepted 5 September 2021
Available online 12 October 2021

KEYWORDS
Airway management;
Laryngoscopy;
Intubation, intratracheal;
Sensitivity and specificity

Abstract
Background: There is currently some discussion over the actual usefulness of performing preoperative upper airway assessment to predict difficult airways. In this field, modified Mallampati test (MMT) is a widespread tool used for prediction of difficult airways showing only a feeble predictive performance as a diagnostic test. We therefore aimed at evaluating if MMT test would perform better when used as a screening test rather than diagnostic.
Methods: An accuracy prospective study was conducted with 570 patients undergoing general anesthesia for surgical procedures. We collected preoperatively data on sex, age, weight, height, body mass index (BMI), ASA physical status, and MMT. The main outcome was difficult laryngoscopy defined as Cormack and Lahane classes 3 or 4. Bivariate analyses were performed to build three different predictive models with their ROC curves.
Results: Difficult laryngoscopy was reported in 36 patients (6.32%). Sex, ASA physical status, and MMT were associated with difficult laryngoscopy, while body mass index (BMI) was not. The MMT cut-off with the highest odds ratio was the class II, which also presented significantly higher sensitivity (94.44%). The balanced accuracy was 67.11% (95% CI: 62.78–71.44%) for the cut-off of class II and 71.68% (95% CI: 63.83–79.54) for the class III.
Conclusion: MMT seems to be more clinically useful when the class II is employed as the threshold for possible difficult laryngoscopies. At this cut-off, MMT shows the considerable highest sensitivity plus the highest odds ratio, prioritizing thus the anticipation of difficult laryngoscopies.

* Corresponding author.
E-mail: clistenescristian@hotmail.com (C.C. de Carvalho).

https://doi.org/10.1016/j.bjane.2021.09.008

Introduction

Difficult airway management is one of the major causes of severe complications during general anesthesia.[1–5] It makes the accurate prediction of difficult airways a desired faculty amongst the anesthesiologists as they would have more time to define the best managing strategy for such airways, bringing then more safety to the patients.[6] Nevertheless, the ability to anticipate difficult airways remains fairly poor as no accurate predictor available so far presents great predictive performance.[5–11] It consequently leads some professionals to question the actual benefit of performing preoperative upper airway assessment.[8]

In 1985, Mallampati et al. presented for the first time a bedside test that would posteriorly become one of the most widely used tools for prediction of difficult airways – the Mallampati classification.[12] From that time to the present moment, several studies have been conducted to better evaluate the predictive performance of both Mallampati and modified Mallampati[13] (MMT) tests. Afterwards, an appraisal throughout these studies shows us a questionable predictive performance of the MMT and a disappointing ability of the test to segregate easy and difficult airways.[6,14]

On the other hand, it is well accepted that a screening test should focus its predictive performance in hitting those patients with the positive outcome. To achieve this target, a screening test is supposed to have a great sensitivity, even if at the expense of a compromised specificity. This way, focusing on MMT as a screening test and hence choosing a lower threshold with highest sensitivity might improve its predictive performance and patients' safety.[15]

Therefore, we conducted this study to evaluate if a threshold other than the conventional Mallampati class III might be more clinically useful by performing better as a screening test and focusing on hitting difficult laryngoscopies.

Methods

This prospective study was performed at the surgical theater of the Federal University of Pernambuco's Teaching Hospital between October 2015 and January 2020. The study started only after the Ethical Committee approval and patients were only included if they agreed to participate and signed the informed consent form or the informed assent form in the case of patients under 18 years of age.

We consecutively included patients expected to undergo surgical procedures under general anesthesia, aging above 15 years. We excluded patients submitted to awake laryngoscopy and patients not submitted to direct laryngoscopy with a Macintosh blade. The variables evaluated were age; sex; height; weight; body mass index (BMI); American Society of Anesthesiologists (ASA) physical status; MMT; and difficult laryngoscopy.

Laryngoscopy was described as difficult when the airway manager (experienced 1 to 32 years), using direct laryngoscopy, classified the patient as 3a or higher according to Cormack and Lehane's classification system modified by Cook.[16]

A preanesthesia evaluation was performed just before surgeries assessing the MMT, determined with patient seated, examiner's eyes at the level of patient's mouth, and patient with her/his mouth opened as widely as possible without phonation. The individual was then classified as Mallampati I, II, III, or IV.[13] Posteriorly, three different cut-offs were used to indicate possible difficult laryngoscopies: test 1 (I = easy; II, III, and IV = difficult); test 2 (I and II = easy; III and IV = difficult); and test 3 (I, II, and III = easy; IV = difficult). The preanesthetic evaluation was performed by DdaS and ML, who were not involved in induction of anesthesia or laryngoscopies.

Following the intravenous access and the routine monitoring (i.e., ECG, pulse oximetry, and noninvasive blood pressure), the patients were put in sniffing position and pre-oxygenated. General anesthesia was induced according to the clinical judgment of the attending anesthesiologist. After neuromuscular blockade, a manual facemask ventilation was performed for 3–5 minutes, and laryngoscopies and tracheal intubations were then carried using the appropriate Macintosh blade by one of the residents or attending anesthesiologists. No measure of the depth of neuromuscular blockade was performed. The degree of glottic visualization was then recorded from the best view achieved without external laryngeal manipulation according to the Cormack and Lehane classification system modified by Cook.[16]

Statistical analysis

The data analysis was performed using the R project software program.[17–21] First, a descriptive analysis was performed, with percentages and measures of central tendency and dispersion (means and standard deviation, SD) being calculated. For categorical variables, the chi-square and Fisher's exact tests were used. Student's t-test was used for quantitative variables, which presented normal distribution.

A logistic regression analysis was performed to build three different univariable prediction models based on different cut-offs (II, III, and IV) of the MMT and to build their ROC curves.

For the sample size estimation, we assumed MMT sensitivity to be 70% at the threshold of class III.[14] A target sensitivity of 90% was then assumed to improve test performance at a different threshold. A sample of 31 positive outcomes would be needed to catch the sensitivity of 90% for the MMT with the new threshold for a p-value of 0.048 and a power of 0.807.[21] Considering 20% of possible missing data, we aimed to get 37 difficult laryngoscopies. A total of 578 patients would be necessary considering 6.4% of frequency of difficult laryngoscopies.[22]

Results

From the initial 573 eligible patients, 570 were submitted to statistical analysis, with 3 being excluded because of missing data on Cormack and Lehane's classification (Fig. 1). Difficult laryngoscopy was presented by 36 patients (6.32%). Modified Mallampati classification was reported as follows: 214 with class I (37.54%), 191 with class II (33.51%), 113 with class III (19.82%), and 51 with class IV (8.95%). Table 1 summarizes the descriptive analysis of demographic data and ASA physical status.

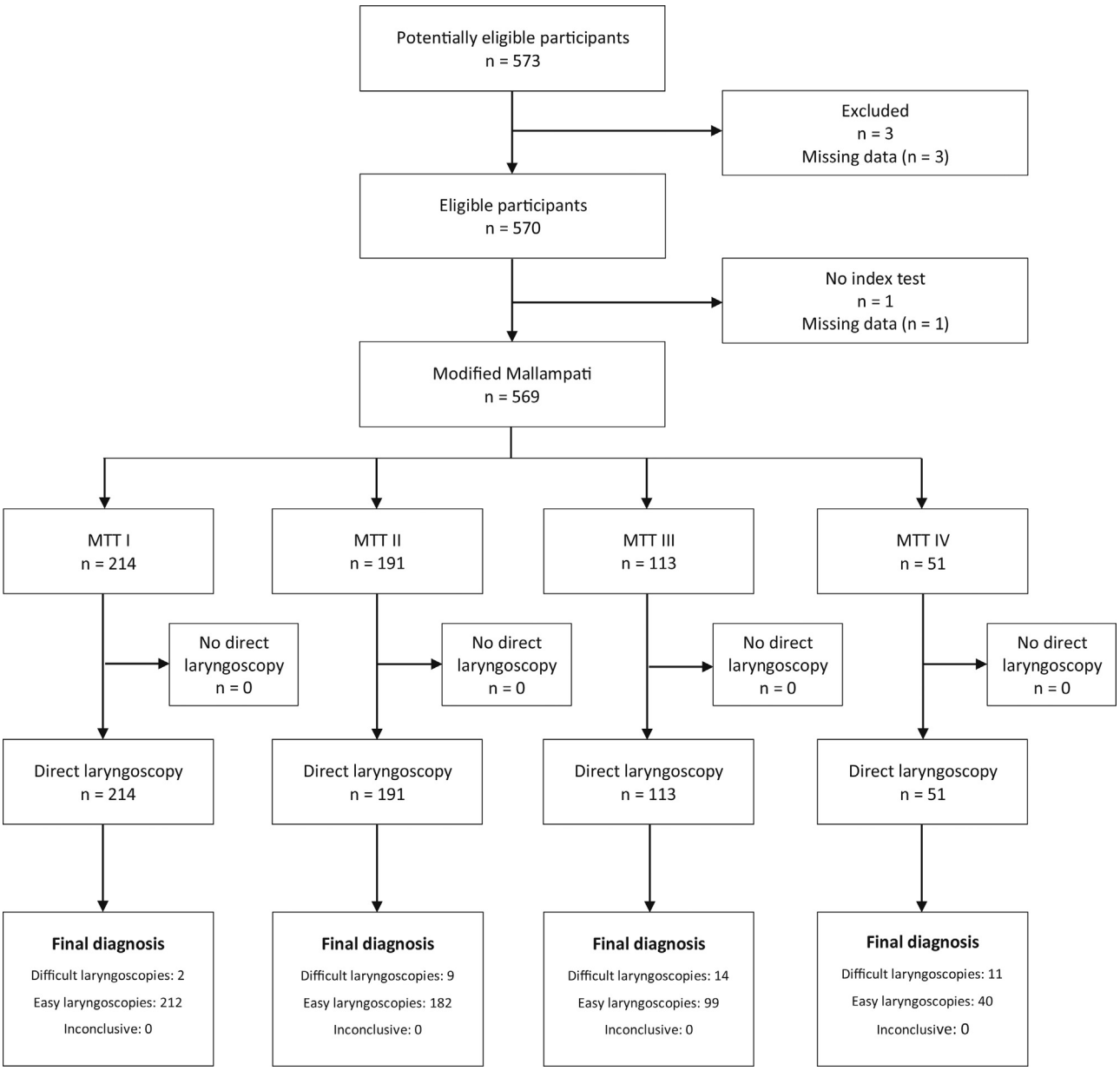


Figure 1 STARD flow chart.

Table 2 shows the analyses based on chi-square and Fisher's exact tests. These analyses found association between difficult laryngoscopy and sex, ASA physical status, and MMT. The male gender was indicative of greater odds of difficult laryngoscopy (OR: 3.119; 95% CI:1.476–6.866; $p = 0.001$). The cut-off for ASA physical status was chose based on Youden Index, being ASA $\geq$ 2 associated with difficult laryngoscopy (OR: 2.71; 95% CI:1.21–6.69; $p = 0.014$). For the MMT, using the class III as the cut-off point for difficult airways showed the highest balanced accuracy (71.68%; 95% CI: 63.83–79.54%). However, the class II was the cut-off point related to the highest increase in odds of facing a difficult laryngoscopy (OR: 11.2; 95% CI:2.82–97.23; $p = 0.000$) as well as to the highest sensitivity (94.44%).

The Student's *t*-test demonstrated difficult laryngoscopies to be associated with age ($p = 0.032$), weight ($p = 0.000$), and height ($p = 0.000$).

The statistical analysis made to evaluate the predictive values of MMT at different cut-off points is summarized in Table 3. Also, a ROC curve was constructed to compare the predictive performance of MMT at different cut-offs (Fig. 2).

Three predictive logistic regression models for difficult laryngoscopy were constructed including the statistically significant variables at the bivariate analyses (Table 4). Each model accounted for a different MMT threshold.

Discussion

The main result of the present study is the considerable highest sensitivity (94.44%) demonstrated by the test 1 as compared to the tests 2 (69.44%) and 3 (30.56%). Therefore, using Mallampati class II as the cut-off point for possible difficult laryngoscopies performs better as a screening test

Table 1 Demographic data and ASA physical status. Values are mean (SD) or n (%).

Characteristics	Total	Laryngoscopy:		*p-value*
	n = 570	easy and difficult n = 534	n = 36	
Age (years)	43.5 (17.4)	43.1 (17.2)	50 (18.2)	0.033
Height (cm)	161.2 (12.5)	160.7 (12.5)	168.6 (9.9)	0.000
Weight (kg)	70.9 (21.2)	70 (20.8)	84.1 (22.4)	0.001
BMI (kg. m^{-2})				
<30	437 (76.6)	413 (77.3)	24 (66.7)	0.206
≥30 (obese)	133 (23.4)	121 (22.7)	12 (33.3)	
Sex				
Female	354 (62.1)	341 (63.9)	13 (36.1)	0.001
Male	216 (37.9)	193 (36.1)	23 (63.9)	
ASA				
I	263 (46.1)	254 (47.6)	9 (25)	0.014
II	236 (41.4)	218 (40.8)	18 (50)	
III	69 (12.1)	60 (11.2)	9 (25)	
IV	2 (0.4)	2 (0.4)	–	

SD, standard deviation; ASA, physical status classification according to the American Society of Anesthesiologists system; BMI, body mass index; < Less; ≥ greater or equal.

Table 2 Distribution of the patients according to preoperative predictors in the bivariate analysis as a function of whether laryngoscopy was easy or difficult.

Variables		Laryngoscopy		Bivariate analysis	
		Easy N	Difficult N	Odds ratio Fisher (95%CI)	Chi-square *p*-value
Sex	Female	341	13	3.119 (1.476–6.866)	0.001
	Male	193	23		
Obesity	Non-obese	413	24	1.704 (0.753–3.668)	0.206
	Obese	121	12		
ASA	I	254	9	2.71 (1.21–6.69)	0.014
	≥ II	280	27		
Test 1 (Mallampati)	Easy (I)	212	2	11.20 (2.82–97.23)	0.000
	Difficult (II, III, IV)	321	34		
Test 2 (Mallampati)	Easy (I, II)	394	11	6.42 (2.95–14.85)	0.000
	Difficult (III, IV)	139	25		
Test 3 (Mallampati)	Easy (I, II, III)	493	25	5.40 (2.23–12.39)	0.000
	Difficult (IV)	40	11		

Tests 1, 2, and 3 are modified Mallampati tests as follows: test 1, easy (Mallampati I) or difficult (II, III, and IV); test 2, easy (I and II) or difficult (III and IV); test 3, easy (I, II, and III) or difficult (IV). Odds ratios are presented for bottom classes as related to top classes (e.g., male has 3.119 more chances of presenting difficult laryngoscopies as compared to female).

Table 3 Predictive values for three different approaches of modified Mallampati test to predict the occurrence of difficult laryngoscopy.

Model	Sens	PPV	Spec	NPV	Bal Acc (95% CI)	Acc (95% CI)
Test 1	94.44%	9.57%	39.77%	99.06%	67.11% (62.78–71.44%)	43.23% (39.12–47.42%)
Test 2	69.44%	15.24%	73.92%	97.28	71.68% (63.83–79.54)	73.64% (69.81–7722%)
Test 3	30.56%	21.57%	92.49%	95.17%	61.53% (53.81–69.24%)	88.58% (85.67–91.07%)

TP, true positive; TN, true negative; FP, false positive; FN, false negative; Sens, sensitivity; PPV, positive predictive value; Spec, specificity; NPV, negative predictive value; Bal Acc, balanced accuracy; Acc, overall accuracy; 95% CI, confident interval 95%; test 1: Mallampati II, III, and IV as difficult; test 2: Mallampati III and IV as difficult; test 3: Mallampati IV as difficult.

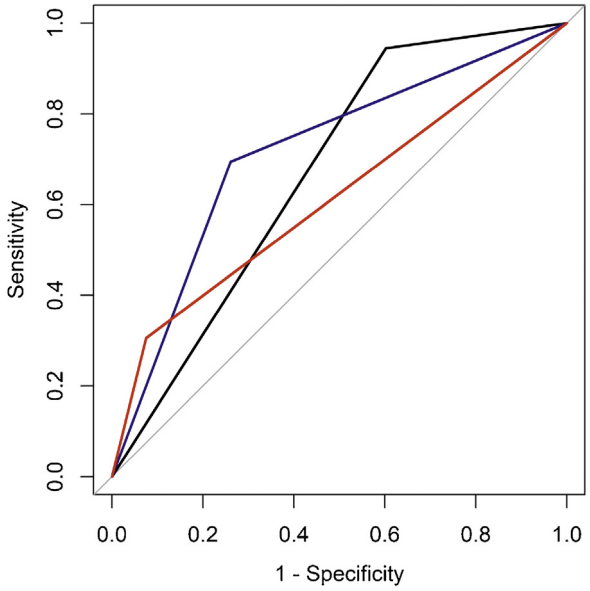


Figure 2 ROC curves for different approaches of modified Mallampati test. Black line: Mallampati II, III, and IV as difficult (AUC = 67.11%); blue line: Mallampati III and IV as difficult (AUC = 71.68%); red line: Mallampati IV as difficult (AUC = 61.53%).

than the other thresholds. Seemingly endorsing test 1 as the best screening test is its highest odds ratio (OR: 11.20) demonstrating the highest increase in chances of facing a difficult laryngoscopy when the test is indicative of doing so (test 2 OR: 6.42; test 3 OR: 5.40).

The MMT has been used in a bid to correctly segregate easy and difficult airways. As trying to do so, its performance has been demonstrating to be only of poor value.[6,10,14] A recent meta-analysis summarized the frequency of difficult laryngoscopies as 11% (95% CI: 6–19%). The same study reported MMT sensitivity as 53% (95% CI: 47–59%) and specificity as 80% (95% CI: 74–85%).[14] It makes around half of difficult laryngoscopies unanticipated and hence likely to be improperly approached. Besides, such sensitivity and specificity values lead to an overall accuracy of 77.3%. In turn, setting every patient as easy would present a considerable higher overall accuracy of 89% (100% [all patients]−11% [frequency of difficult laryngoscopies]). Additionally, these predictive values are linked to a balanced accuracy of 66.5%, also demonstrating a poor ability of the MMT to efficiently segregate easy and difficult laryngoscopies. In brief, as advocated by Yentis, to correctly classify the largest number of patients, assigning all patients as easy would do better than MMT, while the attempt to discriminate difficult laryngoscopies through the use of the conventional MMT still remains a practice of low sensitivity.[8]

On the other hand, it seems clear the focus of preoperative upper airway assessment should be on hitting the difficult airways. These are the patients who would suffer the worst damage if unanticipated. To achieve this target, a screening approach is more useful than an attempt to correctly classify the largest number of patients.[9,15,23] This way, highest sensitivity and odds ratio would fit better than highest overall and balanced accuracy. It might be the focus of the MMT and, accordingly, in the present study, the best screening performance for the Mallampati classification was achieved with the class II as the cut-off − test 1.

Additionally, the test 1 presented a balanced accuracy (Bal Acc = 67.11%; 95% CI: 62.78–71.44%) comparable to the best one, of the test 2 (Bal Acc = 71.68%; 95% CI: 63.83–79.54%). This is achieved by the compensation between the high sensitivity and low specificity of the test 1 and the high specificity and low sensitivity of the test 2. In other words, when changing the threshold from Mallampati class III to class II, the anesthesiologist apparently transfers comparable proportion of correct classification from easy laryngoscopies to difficult ones. It seems to make test 1 more clinically useful since the focus is supposed to be on difficult airways.

It's worth noticing that when taking the Mallampati classification for a screening approach by changing the threshold from class III to class II, the test is less likely to correctly hit a difficult laryngoscopy when predicting so. We should keep in mind that the purpose shifts as well − we are no longer interested in getting all predictions right. On top of this,

Table 4 Summary of the three multivariable models including Mallampati test at different thresholds for prediction of difficult laryngoscopies. Model I includes test I (ease: Mallampati I; difficulty: Mallampati II-IV). Model II includes test II (ease: Mallmpati I-II; difficulty: Mallampati III-IV). Model III includes test III (ease: Mallampati I-III; difficulty: Mallampati IV). Rows with p < 0.05 are highlighted.

Characteristic	Model I			Model II			Model III		
	OR	95% CI	$p>\|z\|$	OR	95% CI	$p>\|z\|$	OR	95% CI	$p>\|z\|$
(Intercept)	0.000	0.000–0.000	0.000	0.000	0.000–0.000	0.000	0.000	0.000–0.000	0.000
Sex (male)	1.024	0.378–2.776	0.963	1.176	0.431–3.209	0.752	1.278	0.472–3.459	0.629
Mallampati	10.065	2.33–43.420	0.002	5.026	2.363–10.688	0.000	4.141	1.773–9.670	0.001
Age	1.015	0.990–1.042	0.244	1.014	0.986–1.041	0.304	1.017	0.992–1.044	0.186
Weight	1.020	1.001–1.039	0.035	1.020	1.002–1.039	0.033	1.020	1.002–1.039	0.030
Height	1.063	1.009–1.119	0.021	1.056	1.002–1.114	0.042	1.053	1.001–1.108	0.047
ASA (≥ 2)	1.23	0.677–2.231	0.499	1.322	0.725–2.411	0.363	1.322	0.720–2.429	0.368

ASA, American Society of Anesthesiologists physical status; OR, odds ratio; 95% CI, 95% confidence interval.

it's worth highlighting that test accuracy is dependent on how frequent an outcome is and that the positive predictive value is specially impaired by the relatively low frequency of difficult laryngoscopies –, not bringing further concern to the screening performance of the test.

ASA physical status was also associated with difficult laryngoscopies in the bivariate analysis, showing an odds 2.7 times greater of facing difficult laryngoscopies when managing patients with ASA II or higher. It may reflect anatomic alterations caused by systemic diseases, although this association found should be interpreted with caution, also because it was lost in the multivariable analysis.

Some limitations must be taken into account. The relatively small number of difficult laryngoscopies impairs more conclusive results. The interobserver variability of the Mallampati classification as well as of the Cormack and Lehanes graduation system may have also skewed the conclusions. Additionally, the lack of a standard protocol of anesthetic induction and the lack of a neuromuscular-blockade-depth measurement may have interfered the degree of difficulty during the airway manipulations.

Conclusions

In conclusion, the results of the present study suggest the Mallampati class II as the more clinically useful threshold for airway prediction. At this cut-off, anesthesiologists would be able to anticipate further difficult laryngoscopies making airway manipulation a safest intervention. This way, we recommend airway managers to be more careful with their approaching strategy for airway manipulation from MMT class II.

Funding

Departmental funding only.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Cook TM, Woodall N, Harper J, et al. Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth. 2011;106:632–42.
2. Cook TM, Woodall N, Frerk C. Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. Br J Anaesth. 2011;106:617–31.
3. Tikka T, Hilmi OJ. Upper airway tract complications of endotracheal intubation. Br J Hosp Med. 2019;80:441–7.
4. Umobong EU, Mayo PH. Critical care airway management. Crit Care Clin. 2018;34:313–24.
5. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth. 2018;120:323–52.
6. Vannucci A, Cavallone LF. Bedside predictors of difficult intubation: a systematic review. Minerva Anestesiol. 2016;82:69–83.
7. Baker P. Assessment before airway management. Anesthesiol Clin. 2015;332:257–78.
8. Yentis SM. Predicting difficult intubation—worthwhile exercise or pointless ritual? Anaesthesia. 2002;572:105–9.
9. Pandit JJ, Heidegger T. Putting the ''point'' back into the ritual: a binary approach to difficult airway prediction. Anaesthesia. 2017;723:283–8.
10. Shiga T, Wajima Z, Inoue T, et al. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology. 2005;103:429–37.
11. Nørskov AK, Rosenstock CV, Wetterslev J, et al. Diagnostic accuracy of anaesthesiologists' prediction of difficult airway management in daily clinical practice: a cohort study of 188 064 patients registered in the Danish Anaesthesia Database. Anaesthesia. 2015;70:272–81.
12. Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation; a prospective study. Can Anaesth Soc J. 1985;32:429–34.
13. Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. Anaesthesia. 1987;42:487–90.
14. Roth D, Pace NL, Lee A, et al. Bedside tests for predicting difficult airways: an abridged Cochrane diagnostic test accuracy systematic review. Anaesthesia. 2019;74:915–28.
15. Teos WH, Kristensen MS. Prediction in airway management: what is worthwhile, what is a waste of time and what about the future? Br J Anaesth. 2016;117:1–3.
16. Cook TM. A new practical classification of laryngeal view. Anaesthesia. 2000;55:274–9.
17. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. Available at: https://www.R-project.org/. [Accessed 12 August 2019].
18. Kuhn M. caret: Classification and Regression Training. R package version 6.0-85; 2020. Available at: https://CRAN.R-project.org/package=caret. [Accessed 25 February 2020].
19. Sing T, Sander O, Beerenwinkel N, et al. ROCR: visualizing classifier performance in R. Bioinformatics. 2005;21:3940–1.
20. Lopez-Raton M, Rodriguez-Alvarez MX, Suarez CC, et al. Optimal cutpoints: an R package for selecting optimal cutpoints in diagnostic tests. J Stat Software. 2014;61:1–36.
21. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics. 2011;12:77.
22. Bujang MA, Adnan TH. Requirements for minimum sample size for sensitivity and specificity analysis. J Clin Diagn Res. 2016;10:YE01–6.
23. de Carvalho CC, da Silva DM, de Carvalho Junior AD, et al. Pre-operative voice evaluation as a hypothetical predictor of difficult laryngoscopy. Anaesthesia. 2019;74:1147–52.

Brazilian Journal of Anesthesiology 2022;72(6):742–748

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Evaluation of thyromental height as a predictor of difficult laryngoscopy and difficult intubation: a cross-sectional observational study

Smita Prakash [a], **Parul Mullick** [a,*], **Rajvir Singh** [b]

[a] *Vardhman Mahavir Medical College and Safdarjung Hospital, Department of Anaesthesia and Intensive Care, New Delhi, India*
[b] *Hamad General Hospital, Lead Clinical Research, Doha, Qatar*

Received 28 February 2020; accepted 2 July 2021
Available online 2 August 2021

KEYWORDS
Laryngoscopy;
Intubation, intratracheal;
Anthropometry

Abstract
Background and objectives: Several anthropometric measurements have been suggested to identify a potentially difficult airway. We studied thyromental height (TMH) as a predictor of difficult laryngoscopy and difficult intubation. We also compared TMH, ratio of height to thyromental distance (RHTMD), and thyromental distance (TMD) as predictors of difficult airway.
Methods: This cross-sectional observational study was conducted in 300 adult surgical patients requiring tracheal intubation. Preoperatively airway characteristics were assessed. Standard anesthesia was administered. Degree of difficulty with mask ventilation, laryngoscopic view, duration of laryngoscopy, and difficulty in tracheal intubation (intubation difficulty scale score) were noted. Multivariate logistics regression analysis was performed to identify independent predictors for difficult laryngoscopy.
Results: Laryngoscopy was difficult in 46 of 300 (15.3%) patients; all 46 patients had Cormack-Lehane grade 3 view. Duration of laryngoscopy was 27 ± 11 s in patients with difficult laryngoscopy and 12.7 ± 3.9 s in easy laryngoscopy; $p = 0.001$. Multivariate analysis identified that TMH, presence of short neck, and history of snoring were independently associated with difficult laryngoscopy. Incidence of difficult intubation was 17.0%. A shorter TMH was associated with higher IDS scores; $r = -0.16$, $p = 0.001$. TMH and duration of laryngoscopy were found to be negatively correlated; a shorter TMH was associated with a longer duration of laryngoscopy; $r = -0.13$, $p = 0.03$. The cut-off threshold value for TMH in our study is 4.4 cm with a sensitivity of 66% and a specificity of 54%.
Conclusion: Thyromental height predicts difficult laryngoscopy and difficult intubation.
TMD and RHTMD did not prove to be useful as predictors of difficult airway.

* Corresponding author.
E-mail: parash93@yahoo.com (P. Mullick).

https://doi.org/10.1016/j.bjane.2021.07.001

Introduction

Unexpected difficult laryngoscopy (DL) or intubation, or failed tracheal intubation is an important etiological factor in anesthesia-related morbidity and mortality.[1] Several anthropometric measurements have been proposed to identify potentially difficult airways for reducing the risk related to difficult airway. Thyromental distance (TMD), though widely used in the preoperative airway evaluation, has a debatable role, as the sensitivity and specificity of TMD as a predictor for difficult laryngoscopy is low.[1] TMD varies with patient size. The ratio of height to TMD (RHTMD) has been found to have a better predictive value for difficult laryngoscopy than TMD alone, as the TMD cut-off value is adjusted for patient size.[2]

Etezadi et al.[3] studied the thyromental height (TMH), the height between the anterior borders of the mentum and thyroid cartilage with the patient in supine position and mouth closed, as a predictor of difficult laryngoscopy. They found TMH to be a more accurate predictor of difficult laryngoscopy compared to TMD, Mallampati oropharyngeal class, and sternomental distance (SMD). The authors, however, did not evaluate TMH as a predictor of difficult intubation in their study. We planned to study TMH as a predictor of difficult laryngoscopy and difficult intubation and to compare TMH, RHTMD, and TMD as predictors of difficult laryngoscopy (primary aim) and difficult intubation (secondary aim) in adult patients undergoing surgery under general anesthesia. We hypothesized that thyromental height is a better predictor of difficult laryngoscopy compared with RHTMD and TMD. We also determined the optimum threshold value of TMH for difficult laryngoscopy.

Methods

After obtaining clearance from hospital ethics committee and written informed consent from all patients, this prospective cross-sectional observational study was conducted in 300 American Society of Anesthesiologists (ASA) physical status grade I or II adult patients, aged 18 years and above, who were scheduled to undergo elective surgery under general anesthesia requiring tracheal intubation between January 2017 till November 2018. Patients with obvious abnormality of the airway requiring awake tracheal intubation, neck swelling or contractures, unstable cervical spine, interincisor distance < 2.5 cm, obese, pregnant patients, and those at increased risk of aspiration were excluded from the study. The study was registered with Clinical Trials Registry India, Number CTRI/2016/09/007313 [Registered on 27/09/2016].

The following airway characteristics were assessed preoperatively by one investigator to reduce inter-observer variability: Modified Mallampati class (MMC)[4,5] of oropharyngeal view obtained with the patient sitting (tongue protruding, without phonation); Thyromental distance (TMD) obtained by measuring the straight distance from the thyroid notch to the inner mentum with the head in extension; Thyromental height, the vertical distance between the anterior borders of the mentum and the thyroid cartilage (on the thyroid notch between the two thyroid laminae), while the patient lies supine with the head in neutral position and the mouth closed was measured using a digital depth gauge (Yuri precision instruments digital depth gauge)[3]; Ratio of height to thyromental distance was calculated by dividing the patient's height (cm) by the thyromental distance (cm)[2]; Sternomental distance (SMD) obtained by measuring the straight distance from the sternal notch to the inner mentum with the head in extension; Inter-incisor distance (IID) with the mouth fully open (inter-gingival distance in edentulous patients); Range of head and neck movement < or > 80° as described by Wilson et al.[6]; Mandible protrusion limitation class A: the lower incisors can be brought in front of the upper incisors, class B: the lower incisors can be advanced only to the level of upper incisors, class C: cannot reach the level of the upper incisors; Upper lip bite test class 1: lower incisors can bite above the vermilion border of the upper lip, class 2: lower incisors can bite the vermilion border of the upper lip, and class 3: unable to bite the upper lip; Dentition: loose, missing, protruding upper incisors, or edentulous; Other features such as history of snoring, short muscular neck, beard, or cervical spondylosis were noted. The age, gender, height, weight of each patient was noted. Body mass index (BMI), $kg.m^{-2}$ was calculated.

All patients fasted overnight. Oral alprazolam 0.25 mg was given as premedication the night before and on the morning of surgery. In the operating room, standard monitoring was established (electrocardiogram, noninvasive blood pressure, pulse oximetry and capnography). Intravenous access was secured. The height of the operating table was adjusted such that the plane of the patient's face was at the level of xiphisternum of the anesthesiologist performing direct laryngoscopy and intubation. A difficult airway cart was kept at hand.

Standard anesthesia protocol was followed in each patient. Anesthesia was induced with fentanyl 2 $\mu g.kg^{-1}$ and propofol 2–2.5 $mg.kg^{-1}$ until loss of verbal contact. Vecuronium 0.1 $mg.kg^{-1}$ was administered to facilitate intubation. The lungs were ventilated with O_2, N_2O (50:50) and isoflurane 0.6% for a period of 3 minutes.

The ability to ventilate by mask was graded according to the classification by Han et al.[7] with grade 0: ventilation by mask not attempted; grade1: ventilated by mask; grade 2: ventilated by mask with oral airway or other adjuvant; grade 3: difficult mask ventilation (inadequate, unstable or requiring two practitioners); grade 4: unable to ventilate.

Direct laryngoscopy was performed using Macintosh size 3 blade with the patients' head in sniffing position by an anesthesiologist with at least five years' experience, who was unaware of the airway measurements. Laryngoscopic view was graded by Cormack-Lehane grading[8] without external laryngeal manipulation (ELM). Grade 1: complete visualization of the vocal cords; grade 2: visualization of the inferior portion of the glottis; grade 3: visualization of only the epiglottis; and grade 4: non-visualized epiglottis. No external laryngeal manipulation was done for grading the laryngoscopic view. Difficult laryngoscopy was defined by Cormack-Lehane grade 3 and 4. External laryngeal manipulation was permitted, if necessary, after evaluation of laryngoscopy grade to facilitate intubation. The Cormack-Lehane grade obtained following application of ELM was also noted.

Tracheal intubation was performed using cuffed tracheal tube size 7 and 8 in female and male patients, respec-

tively. Difficulty in intubation was assessed by the intubation difficulty scale (IDS) score.[9] The number of attempts and operators, alternate intubation techniques used, Cormack-Lehane grade, lifting force used, need for ELM, and vocal cord position were noted. Alternative intubation techniques used such as patient repositioning, change of blade or tracheal tube, use of stylet, laryngeal mask airway (LMA), intubating LMA, fiberoptic intubation, or intubation through LMA as described by Adnet et al.[9] were noted. The IDS score was calculated in each case. IDS score = 0 represents easy intubation, IDS score = 1–5 represents slight difficulty and IDS score > 5 represents moderate to major difficulty in intubation.[9]

Duration of laryngoscopy (defined as the time from the instant the laryngoscope blade touches the patient until tracheal intubation and removal of the laryngoscope blade from the mouth) was noted. Laryngoscopy was considered prolonged if its duration exceeded 15 seconds. The stance of the anesthesiologist performing laryngoscopy and intubation (upright or leaning backwards, bending at the knee, or stooping) was noted. The study period ended after successful tracheal intubation had been confirmed by assessment of chest movement, auscultation for bilateral air entry and capnography. Anesthesia was maintained with O_2, N_2O (40:60) and isoflurane with intermittent doses of vecuronium and narcotic as per requirement. At the end of surgery, residual neuromuscular block was antagonized with neostigmine (0.05 mg.kg^{-1}) and glycopyrrolate (10 μg.kg^{-1}). The trachea was extubated when the patient followed commands with adequate respiration and return of protective reflexes.

Statistical methods

The incidence of difficult laryngoscopy is reported in the range of 1.5% to 20%.[3] Assuming the incidence of difficult laryngoscopy to be 10% in the population with 95% confidence interval (95% C.I.) and 5% margin error, a sample size of 150 would be sufficient for the study. We selected 300 consecutive patients who were planned for elective surgery under general anesthesia requiring tracheal intubation between January 2017 to November 2018.

Descriptive statistics in the form of mean and standard deviation for interval/continuous variables and frequency, and percentage for categorical variables were performed. All continuous variables were found with normal distribution, that is, mean, median, and mode were approximately the same. Student t-tests were performed to see mean differences between easy versus difficult laryngoscopy for all interval variables and *p*-values were selected using Levene's test for equal variance. Chi-square tests were performed to see association between categorical variables and easy versus difficult laryngoscopy. Multivariate logistic regression with enter method was performed to see risk factors associated with difficult laryngoscopy using all important and significant variables at univariate analysis. Adjusted odds ratios and 95% CI with *p*-values were presented in the table. C-statistics and ROC with Youden index was calculated to see discriminating accuracy for the difficult laryngoscopy. *P*-value 0.05 (two tailed) was used for the statistically significant level. SPSS 22.0 statistical package was used for the analysis.

Table 1 Overall patient demographic data and airway characteristics.

Patient characteristics (n= 300)	Values
Age (year)	40.9 ± 14.8
Gender (M/F)	182/118
Weight (kg)	60.3 ± 12.3
Height (cm)	162.4 ± 9.6
Body mass index (kg/m^2)	22.9 ± 4.2
Inter-incisor distance (cm)	4.4 ± 0.5
Mallampati class 0/1/2/3/4 (sitting)	1/142/112/36/9
Mallampati class 0/1/2/3/4 (supine)	5/108/115/52/20
Thyromental height (cm)	4.8 ± 0.9
Thyromental distance (cm)	6.7 ± 1.0
RHTMD	24.9 ± 3.5
Sternomental distance (cm)	16.0 ± 2.0
Mandibular length (cm)	9.2 ± 0.7
Mandibular protrusion test Class 1/2/3	284/8 / 0
Upper lip bite test class 1/2/3	277 / 15 / 0
Range of neck movement <80°	3 (1)
Short muscular neck	24 (8)
Neck circumference (cm)	35.7 ± 4.0
Receding mandible	1 (0.3)
Cervical spondylosis	4 (1.3)
History of snoring	72 (24)

RHTMD, ratio of height to thyromental distance.
Values are mean ± SD, numbers, or numbers (per cent).

Results

There were 314 potentially eligible patients. Of these, 308 patients were examined for eligibility as six patients refused to participate in the study. Eight patients did not meet the inclusion criteria, hence the number of confirmed eligible patients was 300. All of them were included in the study, completed follow-up, and analysed.

Mask ventilation was grade 0, 1, 2, 3, and 4 in 0 (0%), 203 (67.7%), 43 (14.3%), 54 (18%), and 0 (0%) patients, respectively. Laryngoscopy was difficult in 46 of 300 (15.3%) patients; all 46 patients presented with Cormack-Lehane grade 3 and no patient had grade 4 view at laryngoscopy. Duration of laryngoscopy was 27 ± 11 (mean ± SD) seconds in patients with difficult laryngoscopy and 12.7 ± 3.9 seconds in easy laryngoscopy; $p = 0.001$. There was no failed intubation.

Overall patient demographic data and airway characteristics are presented in Table 1. The distribution of Cormack-Lehane grades, without and with external laryngeal manipulation, in patients with easy and difficult laryngoscopy are shown in Table 2. Incidence of difficult intubation was 17.0%. Moderate to major difficulty in tracheal intubation was evident in 40 of 46 (87%) patients in whom laryngoscopy was difficult, compared with 11 of 254 (4.3%) patients in whom laryngoscopy was easy (Table 3). Patients with difficult laryngoscopy had a significantly greater number of intubation attempts and number of operators, increased lifting force, need for external laryngeal manipulation, and increased use of alternative techniques; all $p = 0.001$ (Table 3). A statistically significant difference in patients with easy and difficult laryngoscopy was observed in the stance adopted by the anesthesiologists

Table 2 Distribution of Cormack-Lehane grades, without and with external laryngeal manipulation, in patients with easy and difficult laryngoscopy.

Cormack-Lehane grade	Laryngoscopy Easy (n = 254)	Laryngoscopy Difficult (n = 46)	*P*-value
Without external laryngeal manipulation			
1	172 (67.7)	0 (0)	0.000
2	82 (32.3)	0 (0)	
3	0 (0)	46 (100)	
4	0 (0)	0 (0)	
With external laryngeal manipulation (n = 101)			
1	33 (32.7)	0 (0)	0.001
2	67 (66.3)	0 (0)	
3	0 (0)	1 (0.01)	
4	0 (0)	0 (0)	

Values are numbers (per cent).

Table 3 Intubation difficulty scale (IDS) score and variables of IDS.

Variables	Laryngoscopy Easy (n = 254)	Laryngoscopy Difficult (n = 46)	*P*-value
IDS score	1.2 ± 2.0	8.9 ± 3.5	0.001
IDS break score			
0	156 (61.4)	0 (0)	0.001
1-5	87 (34.3)	6 (13)	
>5	11 (4.3)	40 (87)	
Variables of IDS			
Attempts >1	11 (4.3)	29 (63.0)	0.001
Operators >1	5 (2)	9 (19.6)	0.001
Cormack grade 3 and 4	0 (0)	46 (100)	-
Increased lifting force	24 (9.4)	41 (89.1)	0.001
ELM	55 (21.7)	46 (100)	0.001
Alternative techniques	15 (5.9)	32 (69.6)	0.001
Vocal cords adducted	0 (0)	0 (0)	-

ELM, External laryngeal manipulation.
Values are numbers (percent) or mean ± SD.

performing laryngoscopy and intubation; in patients with difficult laryngoscopy, the anesthesiologist leaned backwards, bent at the knee, or stooped to bring the face closer to the patient during laryngoscopy and intubation to obtain the best laryngeal view in 87% (40 of 46 patients) of cases compared with 11.4% (29 of 254 patients) in patients with easy laryngoscopy ($p = 0.001$).

Amongst the patient demographic variables, increasing age ($p = 0.002$) was associated with difficult laryngoscopy (Table 4). Univariate analysis demonstrated the following airway characteristics to be associated with difficult laryngoscopy: modified Mallampati class 3 and 4, TMH, TMD, RHTMD, SMD, IID, short neck, increased neck circumference, receding mandible, cervical spondylosis, and history of snoring (Table 5). Multivariate analysis identified TMH, short neck, and a history of snoring that were independently associated with difficult laryngoscopy (Table 6).

Area under the curve (AUC) of receiver operating characteristic (ROC) curve to predict difficult laryngoscopy from the multivariate regression model and that for TMH for predicting easy laryngoscopy are shown in Figs. 1 and 2, respectively. In our study, the cut-off threshold value for TMH is 4.4 cm with a sensitivity of 66%, specificity of 54% and AUC of ROC curve for TMH with 95% confidence interval (95% CI) is 0.63 (0.54–0.72). If the cut-off threshold value for TMH is taken as 5.0 cm, then the sensitivity decreased to 39%, specificity increased to 76%, AUC of ROC for TMH with 95% CI being the same; 0.63 (0.54 – 0.72). Youden index for RHTMD is 0.41 and the cutoff for prediction of difficult laryngoscopy is 26.7 with a sensitivity of 72% and specificity of 70%.

TMH influenced the duration of laryngoscopy and IDS score severity. Analysis of data showed that a shorter TMH is associated with a higher IDS score; r = -0.16, $p = 0.001$. TMH and duration of laryngoscopy were found to be negatively correlated; a shorter TMH was associated with a longer duration of laryngoscopy; r = -0.13, $p = 0.03$.

Discussion

We found an incidence of 15.3% and 17% for difficult laryngoscopy and difficult tracheal intubation (IDS score > 5), respectively. We identified three risk factors associated with

Table 4 Demographic data of patients with easy and difficult laryngoscopy.

Parameters	Laryngoscopy Easy (n = 254)	Laryngoscopy Difficult (n = 46)	*P*-value
Age (year)	39.8 ± 14.7	47.1 ± 14.4	0.002
Sex ratio (M/F)	153 /101	29/ 17	0.75
Weight (kg)	59.8 ± 12.2	63.2 ± 12.6	0.08
Height (cm)	162.3 ± 9.8	162.9 ± 8.2	0.70
Body mass index (kg/m^2)	22.7 ± 4.0	23.9 ± 4.8	0.07

Values are mean ± SD or numbers.

Table 5 Airway characteristics of patients with easy and difficult laryngoscopy.

Parameter	Laryngoscopy Easy (n = 254)	Laryngoscopy Difficult (n = 46)	*P*-value
Mallampati class sitting 0/1/2/3/4	1/132/95/23/3	0/10/17/13/6	0.001
Mallampatti class supine0/1/2/3/4	0/245/4/0/0	0/39/4/0/0	0.02
Thyromental height (cm)	4.9 ± 0.9	4.4 ± 0.9	0.005
Thyromental distance (cm)	6.8 ± 1.0	6.1 ± 0.9	0.001
RHTMD	24.4 ± 3.2	27.3 ± 3.8	0.001
Sternomental distance (cm)	16.2 ± 1.9	15.0 ± 2.3	0.002
Interincisor distance (cm)	4.5 ± 0.5	4.2 ± 0.7	0.03
Mandibular length (cm)	9.2 ± 0.7	9.2 ± 0.7	0.46
Neck movement < 80°	1 (0.4)	2 (4.3)	0.06
Neck circumference (cm)	35.5 ± 3.9	36.8 ± 4.3	0.04
Upper lip bite test class 1/2/3	239/10/0	38/5/0	0.05
Short neck	13 (5.1)	11 (23.9)	0.001
Beard	2 (0.8)	1 (2.2)	0.39
Facial malformation	0 (0)	1 (2.2)	0.15
Receding mandible	0 (0)	1 (2.2)	0.02
Cervical spondylosis	1(0.4)	3 (6.5)	0.01
History of snoring	46 (18.1)	26 (56.5)	0.001

RHTMD, ratio of height to thyromental distance.
Values are mean ± SD or numbers (per cent).

Table 6 Predictors of difficult laryngoscopy through multivariate logistic regression.

Variable	Adjusted OR	95% C.I.	*P*-value
Age	1.03	1.0 – 1.06	0.05
Gender Male	0.77	0.18 – 3.39	0.73
Body mass index	0.97	0.84 – 1.11	0.66
Thyromental height	0.53	0.31 – 0.89	0.02
TMD	1.36	0.24 – 7.67	0.73
RHTMD	1.35	0.91 – 2.0	0.14
SMD	1.06	0.75 – 1.50	0.74
Incisors	0.51	0.25 – 1.03	0.06
Neck Circumference	0.95	0.80 – 1.11	0.50
ULBT class 3	2.39	0.29 – 19.5	0.42
MPT class C	8.22	0.58 – 115.9	0.12
Cervical Spondylosis	1.01	0.86 – 166.0	0.10
Short Neck	6.90	1.63 -33.3	0.008
Snoring	3.78	1.50 -9.60	0.005
Constant	0.23	-	0.80

TMD, thyromental distance; RHTMD, ratio of height to thyromental distance; SMD, sternomental distance; ULBT, upper lip bite test; MPT, mandibular protrusion test.
Hosmer and Lemeshow test (chi-square 7.26, df = 8, $p = 0.58$) suggesting observed and expected proportions were same across all data in the model.

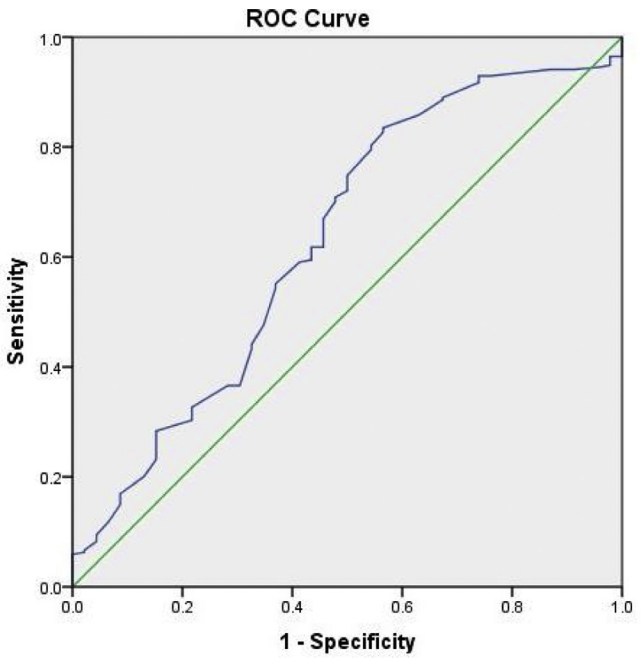


Figure 1 Receiver operating characteristic (ROC) curve to predict difficult laryngoscopy from the multivariate regression model. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve from the multivariate regression model to predict difficult laryngoscopy was 0.85; 95% confidence interval 0.79–0.92.

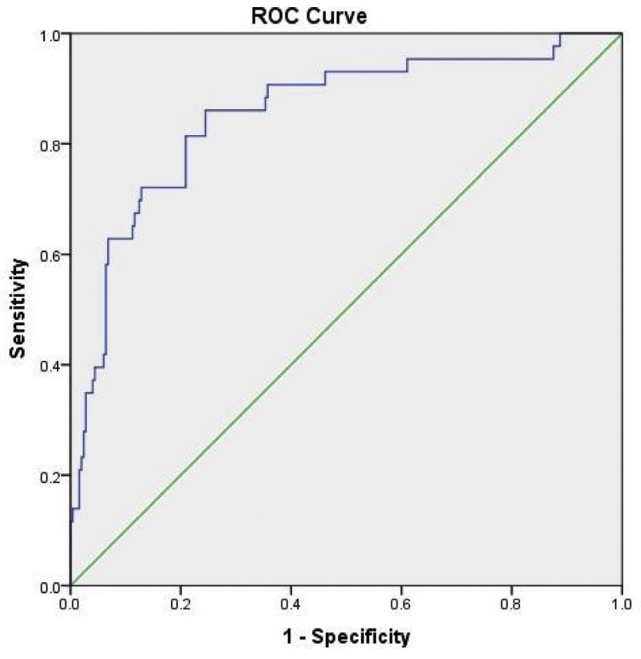


Figure 2 Receiver Operating Characteristic (ROC) curve for thyromental height to predict easy laryngoscopy. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve is 0.63 with 95% confidence interval 0.54–0.72.

difficult laryngoscopy: thyromental height, presence of a short neck, and history of snoring. TMH influenced the duration of laryngoscopy and IDS score severity. The cut-off threshold value for TMH in our study is 4.4 cm with a sensitivity of 66% and a specificity of 54%.

TMD is a frequently used airway assessment test. However, its role as a predictive test for identifying patients with a difficult airway is limited. The mean TMD in our study was 6.7 ± 1.0 cm. Other studies in the Indian population have reported mean TMD values as 7.48 cm, 9.03 cm, 5.95 cm, and 6.5 cm.[10–13] This wide difference in the reported TMD is possibly due to incorrect method of measurement of TMD. The TMD should be measured as a straight distance between the thyroid notch (not thyroid prominence) to the inner bony mentum (not outer aspect of mentum) as TMD is an indicator of ''mandibular space''. In our study, TMD was identified as one of the parameters associated with difficult laryngoscopy in univariate analysis, but not in multivariate analysis. A wide range of TMD cut-off values ranging from 5.5 to 7.0 cm have been used in the literature to predict difficult laryngoscopy.[2] A meta-analysis concluded that the diagnostic value of TMD was unsatisfactory due to a wide range in sensitivity, possibly due to different cut off points (4–7 cm).[14]

TMD is related to body size and proportion. Schmitt et al. introduced the RHTMD to allow for individual body proportions which are not taken into account in the use of TMD.[2] They reported that RHTMD had a better predictive value compared with TMD and suggested a cut-off value of ≥ 25 for this ratio to predict difficult laryngoscopy in Caucasians.[2] Cut-off values for RHTMD recommended for predicting difficult laryngoscopy are 25 in Caucasians,[2] 24 in Iranian patients[15] and 23.5 in Thai patients.[16] The cut-off value derived in the Indian population is 22.1 with a sensitivity of 81.3% and specificity of 84.9 %.[17] In the present study, although there was a statistically significant difference between patients with an easy laryngoscopy and those with difficult laryngoscopy in TMD (6.8 ± 1.0 cm versus 6.1 ± 0.9 cm, respectively) and RHTMD (24.4 ± 3.2 versus 27.3 ± 3.8, respectively), both failed to be of use in the prediction of difficult laryngoscopy and intubation in multivariate analysis.

The thyromental height could be a surrogate for the degree of mandibular protrusion, the submandibular space, and anterior position of the larynx.[3] TMH was proposed by Etezadi et al.[3] and found to be a more accurate predictor of difficult laryngoscopy than the modified Mallampati test, TMD and SMD. They found that the optimal sensitivity and specificity values for TMH ranged between 47.46 to 51.02 mm. They chose a cut-off value of 50 mm to facilitate clinical application. Using the 50-mm cut-off point for TMH, Selvi et al.[18] reported a high sensitivity (91.89%) and high NPV (98.63%) with low specificity (52.2%) and low PPV values (14.7%).

Rao et al.[14] reported that the ROC curve for TMH, modified Mallampati class and inter-incisor gap had AUC value > 0.7, with that of TMH being the highest (0.92). Another study in the Indian population found a sensitivity of 81.25% and specificity of 92.33%, using a TMH cut-off value of 52.17 mm.[19] Contrary to the above results, we could not verify the high efficiency of TMH as a predictive test. The cut-off value of TMH was 4.4 cm with a sensitivity of 66%,

specificity of 54% and AUC of ROC curve for TMH was 0.63. If the cut-off threshold value is increased to 5.0 cm, the sensitivity decreased to 39% and specificity increased to 76%. We found TMH, presence of a short neck and a history of snoring to be independently associated with difficult laryngoscopy.

Intubation Difficulty Scale (IDS) is one of the frequently used methods to determine difficult intubation in which a total score over 5 indicates a difficult intubation.[9] TMH influenced the duration of laryngoscopy and IDS score severity. We found that a shorter TMH was associated with longer duration of laryngoscopy and higher IDS scores. Our results are consistent with those of Palczynski et al.,[20] who reported that patients with difficult intubation had a significant lower thyromental height (46 mm vs. 54 mm) and a higher Cormack-Lehane class. An increase in TMH by 1 mm decreased the risk of difficult intubation by 7%.[20] A recent study reported that TMH was the best predictive test for difficult laryngoscopy compared with TMD, RHTMD and Mallampati test.[21] The TMH cut-off value for predicting difficult laryngoscopy was 5.1 cm.[21] Similarly, in our study, TMH was 4.9 ± 0.9 cm in patients with easy laryngoscopy (Cormack-Lehane grade 1 and 2) and was 4.4 ± 0.9 cm in those with difficult laryngoscopy (Cormack-Lehane grade 3 and 4).

TMH is a simple and easily applicable objective measure of difficult laryngoscopy and intubation. Unlike TMD and SMD, that need to be measured in head extension position, TMH is measured in the neutral head position. Therefore, TMH is independent of cervical spine mobility, dentition, and patient's cooperation.[14] A depth gauge is required for accurate measurement of TMH.

Our study has some limitations. We did not include pregnant and obese patients in our study. Hence, our results may not be applicable to this patient population and to those belonging to other racial/ethnic groups, for example, Caucasians.

Conclusion

Thyromental height is a simple bedside test to predict difficult laryngoscopy and difficult intubation. Thyromental height, presence of a short neck, and a history of snoring were independently associated with difficult laryngoscopy in adult patients. On multivariate analysis, thyromental distance and ratio of height to thyromental distance did not prove to be useful as predictors of difficult airway.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

No funding received. All the expenses were borne by Vardhman Mahavir Medical College and Safdarjung Hospital.

References

1. Patel B, Khandekar R, Diwan R, et al. Validation of modified Mallampati test with addition of thyromental distance and sternomental distance to predict difficult endotracheal intubation in adults. Indian J Anaesth. 2014;58:171–5.
2. Schmitt HJ, Kirmse M, Radespiel-Troger M. Ratio of patient's height to thyromental distance improves prediction of difficult laryngoscopy. Anaesth Intensive Care. 2002;30:763–5.
3. Etezadi F, Ahangari A, Shokri H, et al. Thyromental height: a new clinical test for prediction of difficult laryngoscopy. Anesth Analg. 2013;117:1347–51.
4. Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. Anaesthesia. 1987;42:487–90.
5. Ezri T, Cohen I, Geva D, et al. Pharyngoscopic views. Anesth Analg. 1998;87:748.
6. Wilson ME, Spiegelhalter D, Robertson JA, et al. Predicting difficult intubation. Br J Anaesth. 1988;61:211–6.
7. Han R, Tremper KK, Kheterpal S, et al. Grading scale for mask ventilation. Anesthesiology. 2004;101:267.
8. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39:1105–11.
9. Adnet F, Borron SW, Racine SX, et al. The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology. 1997;87:1290–7.
10. Krishna HM, Agarwal M, Dali JS, et al. Prediction of difficult laryngoscopy in Indian population: role of patient's height to thyromental distance. J Anaesth Clin Pharmacol. 2005;21:257–60.
11. Balakrishnan KP, Chockalingam PA. Ethnicity and upper airway measurements: a study in South Indian population. Indian J Anaesth. 2017;61:622–8.
12. Dhanger S, Gupta SL, Vinayagam S, et al. Diagnostic accuracy of bedside tests for predicting difficult intubation in Indian population: an observational study. Anesth Essays Res. 2016;10:54–8.
13. Prakash S, Kumar A, Bhandari S, et al. Difficult laryngoscopy and intubation in the Indian population: an assessment of anatomical and clinical risk factors. Indian J Anaesth. 2013;57:569–75.
14. Rao KV, Dhatchinamoorthi D, Nandhakumar A, et al. Validity of thyromental height test as a predictor of difficult laryngoscopy: a prospective evaluation comparing modified Mallampati score, interincisor gap, thyromental distance, neck circumference, and neck extension. Indian J Anaesth. 2018;62:603–8.
15. Farzi F, Mirmansouri A, Forghanparast K, et al. Difficult laryngoscopy; the predictive value of ratio of height to thyromental distance versus other common predictive tests of upper airway. Prof Med J. 2012;19:6.
16. Krobbuaban B, Diregpoke S, Kumkeaw S, et al. The predictive value of the height ratio and thyromental distance: four predictive tests for difficult laryngoscopy. Anesth Analg. 2005;101:1542–5.
17. Kaniyil S, Anandan K, Thomas S. Ratio of height to thyromental distance as a predictor of difficult laryngoscopy: a prospective observational study. J Anaesthesiol Clin Pharmacol. 2018;34:485–9.
18. Selvi O, Kahraman T, Senturk O, et al. Evaluation of the reliability of preoperative descriptive airway assessment tests in prediction of the Cormack-Lehane score: a prospective randomized clinical study. J Clin Anesth. 2017;36:21–6.
19. Jain N, Das S, Kanchi M. Thyromental height test for prediction of difficult laryngoscopy in patients undergoing coronary artery bypass graft surgical procedure. Ann Card Anaesth. 2017;20:207–11.
20. Palczynski P, Bialka S, Misiolek H, et al. Thyromental height test as a new method for prediction of difficult intubation with double lumen tube. PLoS One. 2018;13:e0201944.
21. Panjiar P, Kochhar A, Bhat KM, et al. Comparison of thyromental height test with ratio of height to thyromental distance, thyromental distance, and modified Mallampati test in predicting difficult laryngoscopy: a prospective study. J Anaesthesiol Clin Pharmacol. 2019;35:390–5.

Brazilian Journal of Anesthesiology 2022;72(6):749–756

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Reinforcing the valuable role of gastric ultrasound for volume and content assessment: an observational study

Elena Segura-Grau [a,*], **Ana Segura-Grau** [b], **Ricardo Araújo** [a], **Guillermo Payeras** [c], **Jorge Cabral** [d], **Vera Afreixo** [d]

[a] *Centro Hospitalar Tondela-Viseu, Viseu, Portugal*
[b] *San Francisco de Asís Hospital, Ultrasonography Unit, Ecographic Diagnostic Center, Madrid, Spain*
[c] *San Francisco de Asís Hospital, Madrid, Spain*
[d] *University of Aveiro, Mathematics Department, Aveiro, Portugal*

Received 13 April 2020; accepted 10 July 2021
Available online 26 July 2021

KEYWORDS
Gastric antrum;
Pulmonary aspiration;
Gastric ultrasound;
Point of care ultrasound;
Gastric volume

Abstract
Background: Pulmonary aspiration is one of the most important complications in anesthesiology. Assessment of gastric content by ultrasound is a good method to quantify gastric volume and to determine the risk of intraoperative pulmonary aspiration. The aim of this study is to determine the accuracy of the gastric ultrasonography in the qualitative analysis of gastric content, mainly in the analysis of small amounts of liquid content.
Methods: Gastric ultrasound was performed to 36 patients before upper gastrointestinal endoscopy (UGI), making two longitudinal scans at the epigastric level, one in supine position and the other in right lateral decubitus position, measuring two diameters and the area of the gastric antrum and assessing the content characteristics determining whether it was an empty stomach or contained fluid or solid content. Subsequently, the ultrasound findings were compared with UGI findings.
Results: Gastric areas were analyzed by the trace and the lengths of the craniocaudal and anteroposterior axes concluding that there are no significant differences between the two methods. No statistically significant difference was found between UGI and US assessment technics. No statistically significant difference was found between the estimated volume by UGI and US.

* Corresponding author.
E-mail: elenasegura12@hotmail.com (E. Segura-Grau).

https://doi.org/10.1016/j.bjane.2021.07.008

Conclusions: Though our study has some limitations, qualitative analysis of gastric content using ultrasound followed by endoscopy enabled the conclusion that there are no differences in the qualitative assessment regarding these two techniques, supporting the important role of point-of-care gastric ultrasound (POCGUS) in the assessment of pulmonary aspiration risk by the anesthesiologist in the perioperative period.

Introduction

Pulmonary aspiration, defined as the entry of liquid or solid content in the trachea and lungs,[1] is one of the most important complications in anesthesiology.[2] Several studies have shown that the evaluation of gastric content by ultrasound is a good method to qualitatively and quantitatively assess the gastric volume and thus determine the risk of perioperative pulmonary aspiration.[3–6] Occasionally, small volumes of clear fluid are identified in a gastric ultrasound, being difficult to discriminate if they are clinically irrelevant or there may be a risk of aspiration.[5]

The aims of this study, performed in patients undergoing upper gastrointestinal endoscopy (UGI), were as follows: (1) determine the accuracy of the gastric ultrasonography in the qualitative analysis of gastric content, mainly in the analysis of small amounts of liquid content; (2) to quantitatively determine gastric volume after a period of fasting.

Methods

After Institutional Research Ethics Board approval and informed consent, we conducted this observational prospective study, which took place between March and June 2019 at two different clinics. Two different raters, all with experience in gastric ultrasound, had variable proficiency level: first rater, a certified sonographer with more than 15-year clinical experience and second rater, a clinical anesthesiologist with more than 7 years in ultrasound clinical application.

A convenience sample of 40 patients was recruited. Inclusion criteria were scheduled for elective UGI with age greater than 18 years and American Society of Anesthesiologists (ASA) physical status I to III. Exclusion criteria were presence of preexisting abnormal anatomy of the upper gastrointestinal tract and pregnancy. Patients subjected to treatments with opioids, octreotides or tricyclics were also excluded from the study. All patients followed institutional guidelines for UGI. No medication that would alter gastric emptying was administered to the patient between the ultrasound examination and the endoscopies.

Ultrasound examination was performed with a low-frequency (2 to 6 MHz) curvilinear array transducer using a Samsung RS60 or Sonoscanner U-lite ultrasound machines. Patients were scanned in the supine position (SP) and subsequently in the right lateral decubitus position (RLDP). The transducer was placed in a sagittal plane in the epigastric region in order to see gastric antrum between the left lobe of the liver and the pancreas, at the level of the aorta. The cross-sectional area of the gastric antrum (CSA) was measured in both positions and was determined using two methods, the first one based on the two-diameter method formula (TDM), the craniocaudal (CC) and anteroposterior (AP) diameters as previously described[7] ($CSA = (AP \times CC \times \pi)/4$) and the second one using the free-tracing method (FTM) (Fig. 1).

Primarily, gastric content was qualitatively evaluated in both patient's position by the sonographer as: (1) empty if it appeared flat with anterior and posterior walls juxtaposed; (2) fluid content when a hypoechoic content was observed; or (3) solid content if lumen was distended with an internal ''frosted-glass appearance''.[8] Second, total gastric fluid volume was estimated using the models suggested by Perlas et al.[3,5] V1, V2 and V3.

$$V1 = 1199.99 + 483.09 \times \log(\text{supineCSA}) - 5.84 \times \text{age} - 9.94 \times \text{height}*$$

$$V2 = -372.54 + 282.49 \times \log(\text{right-latCSA}) - 1.68 \times \text{weight}*$$

$$V3 = 27.0 + 14.6 \times \text{right-latCSA} - 1.28 \times \text{age}*$$

* age in *years*, supine CSA and right-lat CSA in cm^2, height in *cm*, and weight in *kg*

V3 model is the most accepted in the literature. The ultrasound measures, obtained by TDM and FTM, were later compared to the volume measured in UGI.

Subsequently, UGI was performed by two gastroenterologists and evaluated the characteristics of the gastric content. It was determining if it was empty stomach or if it had liquid or solid content. The quantitative assessment of gastric volume was performed by measurement of the volume of gastric content in an aspiration container, approximated to nearest 10 mL. This volume was named Measured Volume (VolM).

Individual data was also recorded regarding age, sex, weight, causes of gastroparesis, time between ultrasound and UGI, fasting time of solids and liquids and test period (morning or afternoon).

Statistical analysis

A descriptive analysis of the data was performed using RStudio Version 1.2.5033 running R version 3.6.3. The statistical quantitative variables were summarized through the mean, standard deviation, interquartile range, minimum and maximum and the qualitative statistical variables through count

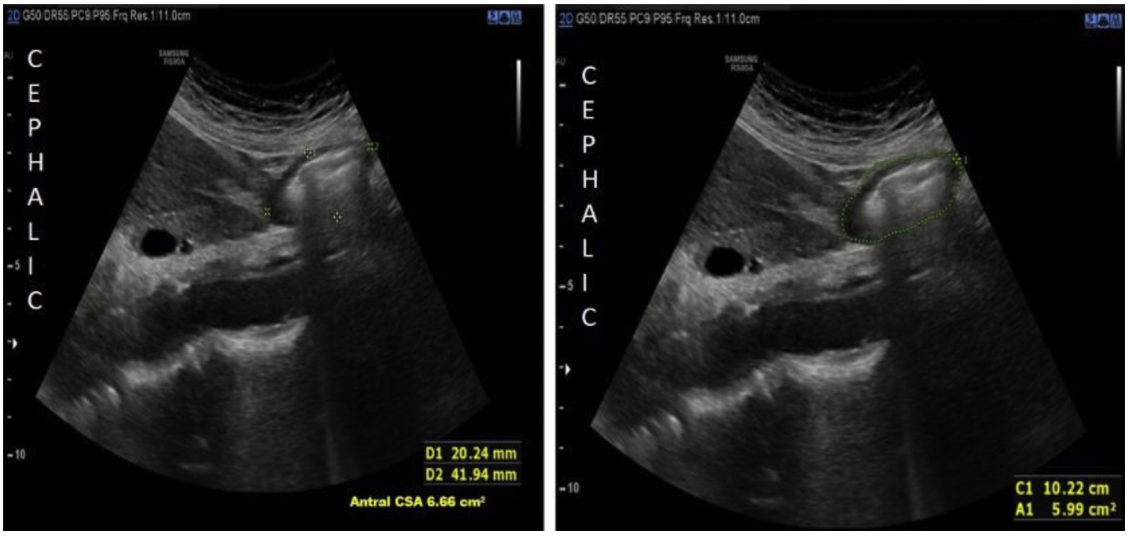


Figure 1 CSA (cross-section area) with TDM (two-diameter method formula) and FTM (free-tracing method) Method.

values. Shapiro-Wilk test was used to assess the normality of the variables. Statistically linear dependence between TDM and FTM measures, fluid fasting time and gastric volume measured, CSA and volumes, CSA and age, different volumes, was tested using Pearson's correlation tests and Spearman's correlation tests. *T*-tests for paired samples were used to compare the area determined by TDM and FTM in the two positions. A Bland-Altman analysis, along with McNemar tests and measures of accuracy, sensitivity, and specificity, was performed to analyze differences between two measurement technics. Quade test and Quade test with Benjamini and Hochberg correction for multiple comparisons of repeated measures were used when comparing volumes calculated by all three models based on areas obtained either by FTM or TDM and the Measured Volume. When applied, a significance level of 0.05 was considered.

Results

A total of 40 patients were included, providing 36 measurements of antral area. Antral CSA could not be measured in two patients due to obesity with Body Index Mass (BMI) over 40, due to the presence of a significant amount of gas in the stomach in one patient and due to error in the registration measures in one patient. Hence, sample was reduced to 36 patients with conditions for the application of V3 model (Fig. 2). Although this is the reference model used in most studies, we also considered two samples of 9 patients each to apply V1 and V2 models to estimate gastric volume.

Demographic variables are presented in Table 1. Not statistically significant difference between demographic variables were evidenced. Patient's fasting time of solids were > 10 hours and liquid fasting period > 4 hours. Not statistically significant difference between fasting time and test period was evidenced.

No significant difference between different sonographer's measures was found.

Information obtained through gastric ultrasound in relation to the antrum area included two diameters method and free-tracing method. Statistically linear dependence was found between TDM and FTM in supine position ($p < 0.0001$, r = 0.89) and in the right lateral decubitus position ($p < 0.0001$, r = 0.93). The *t*-tests for differences between the values of TDM and FTM in the two positions allow us not to reject the hypothesis that the differences are equal to zero ($p = 0.9143$ and $p = 0.1740$ respectively).

The difference of measurements in the SP was normally distributed ($p = 0.92$), homoscedastic ($p = 0.90$), with a mean (bias) of -0.015 (CI95% = [-0.288, 0.259]). The upper limit of agreement (LOA) was 1.570 (CI95% = [1.098, 2.042] and the lower LOA was -1.599 (CI95% = [-2.071, -1.127]). The difference of measurements in the RLDP was normally distributed ($p = 0.67$), homoscedastic ($p = 0.86$), with a bias of 0.259 (CI 95% = [-0.120, 0.637]). The upper limit of agreement (LOA) was 2.451 (CI95% = [1.798, 3.103] and the lower LOA was -1.933 (CI95% = [-2.586, -1.281]) (Fig. 3).

By endoscopy, no solid content was found with solid fasting period of 11.5 ± 1.68 hours and fluid fasting period of 8.17 ± 3.57 hours. No correlation was found between fluid fasting time and gastric volume measured ($p = 0.8213$, r = 0.04). The volume measured in the stomach of 18 individuals was approximately 0 mL. The average gastric antrum FTM area in right lateral decubitus position for these patients was $6.66 \pm 3.02\ cm^2$ with a minimum of $2\ cm^2$. The correlation between FTM area and age was not statistically significant ($p = 0.3251$, r = 0.25).

The qualitative assessment of gastric content through ultrasonography identified 22 individuals with no solid or liquid content and 14 individuals with fluid content.

Mean time between the ultrasound and subsequent endoscopic examination was 34.78 minutes.

The McNemar test shows no statistically significant differences between the classification of the presence of gastric content between the two assessment technics ($p = 0.2888$). The US technic, independently of the ultrasound device used showed, an accuracy of 0.78 (CI 95% = [0.61, 0.90]), a balanced error of 0.22, a sensitivity of 0.67 and a specificity of 0.89. When considering the 21 patients that used the Samsung RS60 we found an accuracy of 0.67 (CI 95% = [0.43,

Table 1 Summary of variables.

		Model V1			Model V2			Model V3		
Sex (female/male)		4/5			4/5			20/16		
US Empty Stomach (yes/no)		7/2			7/2			14/22		
UGI Empty Stomach (yes/no)		6/3			7/2			18/18		
Test period (morning/afternoon)		6/3						22/14		
		Mean ± SD	[Q1:Q3]	min;max	Mean ± SD	[Q1:Q3]	min;max	Mean ± SD	[Q1:Q3]	min;max
Age		43.78 ± 15.02	[32;57]	21;57	45.78 ± 12.97	[41;57]	21;59	59.44 ± 16.13	[50.75;69.25]	21;88
Weight		71.44 ± 13.31	[60;80]	56;94	69.78 ± 13.04	[60;72]	56;94	70.03 ± 11.32	[61.5;78.0]	53;98
Height		1.71 ± 0.15	[1.63;1.84]	1.52;1.90	1.69 ± 0.13	[1.63;1.8]	1.52;1.90	1.66 ± 0.11	[1.6;1.7]	1.47;1.90
BMI		24.22 ± 2.12	[22.40;25.77]	21.08;26.85	24.29 ± 2.06	[23.03;25.77]	21.08;26.85	25.40 ± 3.32	[22.99;26.82]	20.45;34.24
Time between US and UGI		36.33 ± 16.50	[30;47]	5;60	34.11 ± 17.27	[20;47]	5;60	34.78 ± 18.70	[20.0;45.5]	5;90
Fasting time for solids		12 ± 0	[12;12]	12;12	11.33 ± 2.00	[12;12]	6;12	11.50 ± 1.68	[12;12]	6;12
Fasting time for liquids		8 ± 4.03	[4;12]	3;12	8.22 ± 3.83	[5;12]	3;12	8.17 ± 3.57	[5;12]	2;12
Supine position	CSA	4.40 ± 1.03	[3.46;5.35]	3;5.6	4.22 ± 1.33	[3.28;5.35]	1.8;5.6	4.31 ± 1.58	[3.29;5.25]	1.4;8.6
	AP diameter	16.11 ± 4.17	[13;18]	10;22	15.78 ± 4.63	[13;18]	9;22	17.11 ± 5.85	[13;21]	7;35
	CC diameter	30.67 ± 4.56	[28;35]	24;37	32.11 ± 4.23	[29;35]	25;37	32.33 ± 5.86	[28;37]	22;43
Right-lateral position	CSA	8.38 ± 2.92	[6.1;8.8]	5.5;13.3	7.98 ± 3.16	[5.92;8.80]	4.76;13.30	6.66 ± 3.02	[4.59;8.50]	2.0;13.3
	AP diameter	24.33 ± 6.46	[19;28]	16;35	23.56 ± 6.65	[19;28]	16;35	21.86 ± 6.80	[18.5;26.0]	7;38
	CC diameter	43.78 ± 6.08	[41;48]	34;53	42.89 ± 5.44	[41;44]	34;53	39.53 ± 8.47	[33.75;45.25]	23;55

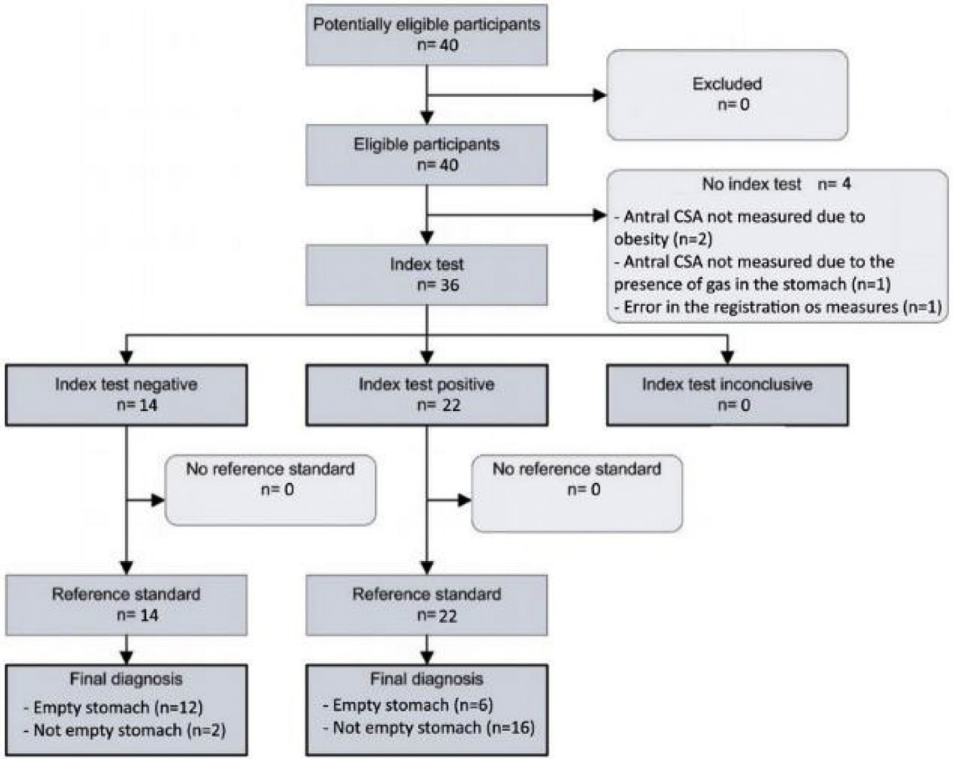


Figure 2 Standards for Reporting of Diagnostic Accuracy (STARD) flow chart of the 40 patients enrolled in the study. Index test – US, Reference test – UGI.

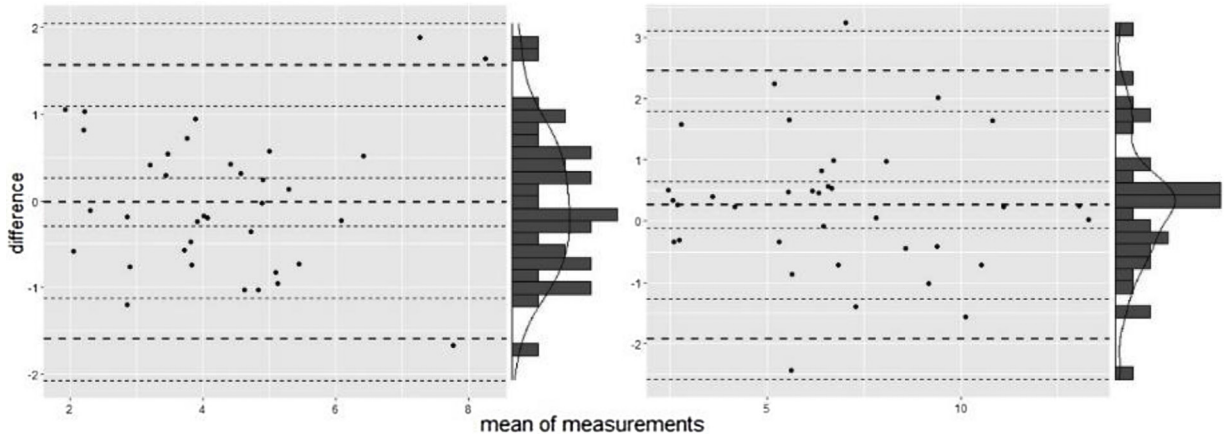


Figure 3 Bland-Altman (B-A) plot for the measurements of the antral CSA in the SP (left) and in the RLDP (right) by the two methods with the representation of the bias) and LOA, with thick dashed lines, and the 95% CI, with thin dashed lines. Histogram and density plot of the difference of the measurements on the right margin of the plot.

0.85]), a balanced error of 0.36, a sensitivity of 0.44, a specificity of 0.83 and a $p = 0.45$ in the McNemar's test. For the remaining 15 patients that used the Sonoscanner U-lite we found an accuracy of 0.93 (CI 95% = [0.68, 1]), a balanced error of 0.06, a sensitivity of 0.89, a specificity of 1 and a $p = 1$ in the McNemar's test.

No significant correlation was found between the CSA calculated by FTM and the Measured Volume (by UGI) nor between the estimated volume (V3) using the area obtained by FTM and the Measured Volume ($p = 0.2673$, r = -0.19 and $p = 0.9655$, r = -0.01 respectively). The difference of the volume V3 and the Measured Volume in the RLDP was normally distributed ($p = 0.07$), with a bias of 35.805 (CI 95%= [18.559, 53.050]). The upper limit of agreement (LOA) was 135.705 (CI 95% = [105.956, 165.453] and the lower LOA was -64.095 (CI 95% = [-93.844, -34.347]).

We found statistically significant positive correlations between: volume calculated based on areas obtained by FTM (VxT) and TDM (VxE) for all 3 models V1, V2 and V3; volume calculated based on areas obtained by FTM in models V2 and V3; volume calculated based on areas obtained by TDM in models V2 and V3; volume calculated based on areas

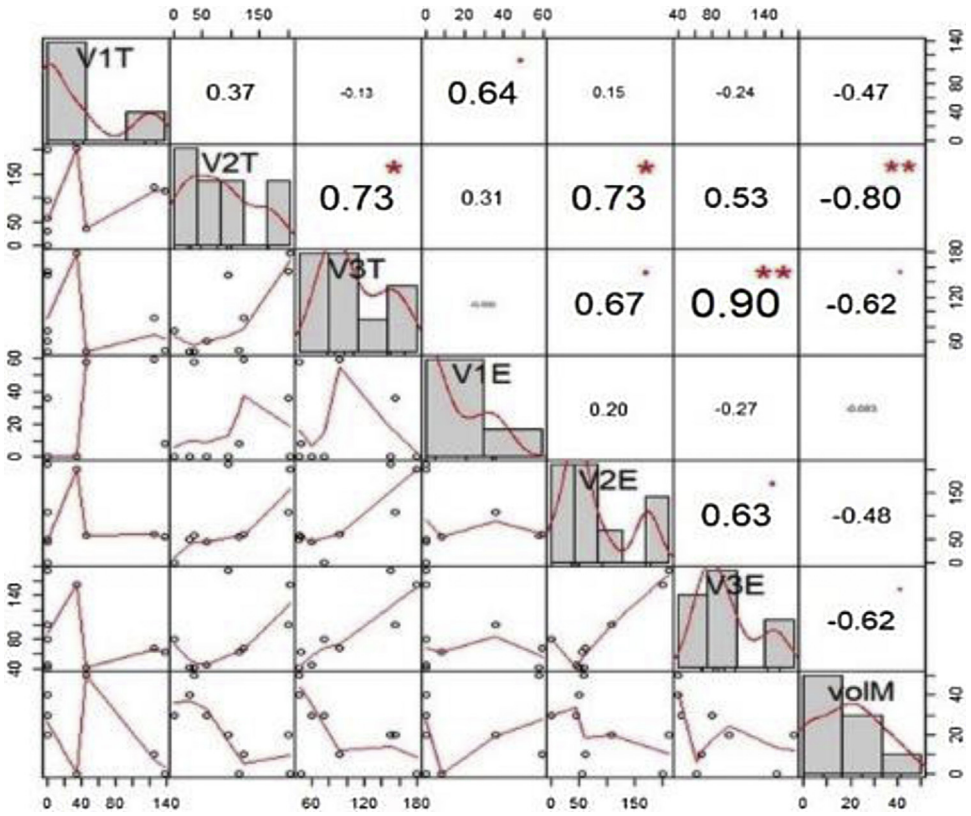


Figure 4 Correlogram. Volume's distribution (diagonal panel), Spearman's correlation coefficients and tests (upper panel; $*p < 0.05$, $**p < 0.01$) and pairwise scatterplot (lower panel). VxT, volume calculated based on areas obtained by FTM using model x, where x = 1,2,3; VxE, volume calculated based on areas obtained by TDM using model x; volM, volume measured.

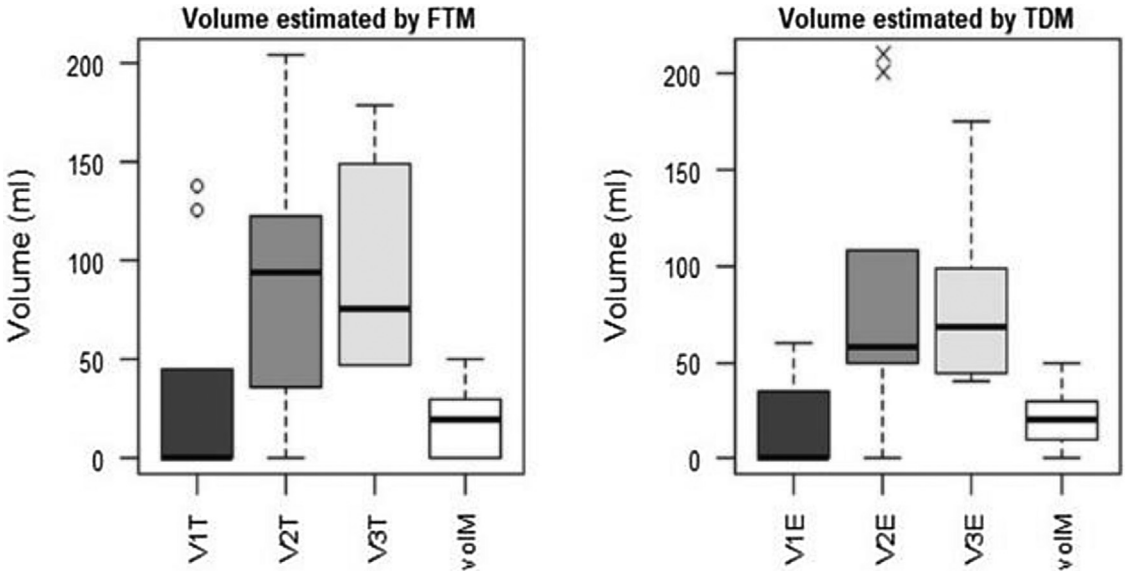


Figure 5 Volumes estimated by different models and differences between these volumes and the measured volume.

obtained by TDM in model V2 and volume calculated based on areas obtained by FTM in model V3.

Although all Spearman's correlation coefficients obtained between the Measured Volume and all the other volumes were negative, only the correlations between the Measured Volume and the volume calculated based on areas obtained by TDM in model V2, the volume calculated based on areas obtained by FTM in model V3 and the volume calculated based on areas obtained by TDM in model V3 were statistically significative (Fig. 4).

Quade's test returned $p = 0.0317$ when comparing volumes calculated based on areas obtained by FTM in all 3

models and the Measured Volume. The multiple comparison test showed statistically significant differences between the volume estimated by model V2 and the Measured Volume ($p = 0.0420$) and the volume estimated by model V3 and the Measured Volume ($p = 0.0420$). When comparing volumes calculated based on areas obtained by TDM and the Measured Volume we concluded that there are statistically significant differences between those volumes ($p = 0.0006$). The multiple comparison test showed statistically significant differences between the volume estimated by model V1 and model V2 ($p = 0.0041$), the volume estimated by model V1 and model V3 ($p = 0.0041$), the volume estimated by model V2 and the Measured Volume ($p = 0.0041$) and the volume estimated by model V3 and the Measured Volume ($p = 0.0047$). Finally, we cannot reject the hypothesis that volumes estimated by models V1 are equal to the measured volumes (Fig. 5).

Discussion

In this study performed on 36 patients undergoing elective gastric ultrasound evaluation before elective UGI, we assessed gastric contents and antrum area. The results verified that the totality of individuals had a gastric volume of less than 1.5 mL.kg^{-1}, which corresponds to a perioperative low risk aspiration according to Perlas et al.[9]

Furthermore, if considering the value of 0.8 mL.kg^{-1} suggested by Bouvet et al.[6] only 5.56% would have an intermediate risk. This could be because individuals underwent the necessary fasting period for emptying the stomach before UGI. Some studies argument an average time of 248 ± 39 min[7] and 276.4 ± 58.9 min[10] for emptying the stomach. However, even after an average time of 490.2 ± 214.2 min, liquid content of about 17 ± 21 mL was found in the stomach of 18 patients. However, this residual volume had no correlation with liquid fasting time contrary to the result of Sugita et al.[1] whilst confirming the result of Sadhvi et al.[11] This result can be due to the fact that the average fasting time in our study was much higher than the average fasting time considered necessary to clear the stomach.

The Bland-Altman analysis of the areas obtained by the FTM and TDM allowed us to conclude that the two methods are interchangeable, which corroborates the results obtained by Kruisselbrink et al.[12]

The V3 model proposed by Perlas et al.[5] to estimate gastric volume is the most widely used model both in the literature and in practice clinic. Nevertheless, we found no statistically significant correlation with the measured volume. Study limitations or the lack of sensibility of this model to estimate very low gastric volumes (< 80 mL) could provide explanation regarding this finding. However, these volumes represent low risk for perioperative aspiration and have minor clinical significance.

The analysis of the difference between volumes estimated by the 3 models revealed statistically significant differences between the estimated volume by V2 and V3 models and the Measured Volume. Perlas et al.[5] had previously described that the V2 model had a tendency to overestimate gastric volume. On the other hand, no statistically significant difference was found between the estimated volume by V1 model and the Measured Volume, suggesting that this model was better adjusted to our dataset.

The study has other limitations: it was performed with a reduce number of individuals $n_1 = 9$, $n2 = 9$ and even $n3 = 36$; the qualitative analysis of gastric content was not based on 3-point grading system;[5] individuals had high fasting period with small gastric volumes that were difficult to aspirate; no clinically relevant gastric volumes (> 1.5 mL.kg^{-1}) were found.

Summary

Regarding qualitative and quantitative evaluation of gastric content, we concluded that there is no difference between ultrasound and UGI assessments, even without finding differences in the evaluation of small amounts of liquid content.

There were no differences in the results obtained by the two sonographers with different degrees of experience, which allows us to conclude that gastric ultrasound in the perioperative period can be performed by anesthesiologist in order to evaluate full stomach risk.

Such conclusions support the use of point-of-care gastric ultrasound (POCGUS) in the evaluation of perioperative aspiration risk. Different clinical algorithms have been suggested by Van de Putte and Perlas A.[4] and Bouvet et al.[13] to accomplish this.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Nason KS. Acute Intraoperative Pulmonary Aspiration. Thorac Surg Clin. 2015;25:301–7.
2. Lienhart A, Auroy Y, Péquignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology. 2006;105:1087–97.
3. Perlas A, Chan VW, Lupu CM, et al. Ultrasound Assessment of Gastric Content and Volume. Anesthesiology. 2009;111:82–9.
4. Van de Putte P, Perlas A. Ultrasound assessment of gastric content and volume. Br J Anaesth. 2014;113:12–22.
5. Perlas A, Mitsakakis N, Liu L, et al. Validation of a mathematical model for ultrasound assessment of gastric volume by gastroscopic examination. Anesth Analg. 2013;116:357–63.
6. Bouvet L, Mazoit JX, Chassard D, et al. Clinical assessment of the ultrasonographic measurement of antral area for estimating preoperative gastric content and volume. Anesthesiology. 2011;114:1086–92.
7. Bolondi L, Bortolotti M, Santi V, et al. Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology. 1985;89:752–9.
8. Kaydu A, Gokcek E. Sonographic gastric content evaluation in patients undergoing cataract surgery. Niger J Clin Pract. 2019;22:1483–8.
9. Van de Putte P, Vernieuwe L, Jerjir A, et al. When fasted is not empty: a retrospective cohort study of gastric content in fasted surgical patients. Br J Anaesth. 2017;118:363–71.
10. Sugita M, Matsumoto M, Tsukano Y, et al. Gastric emptying time after breakfast in healthy adult volunteers using ultrasonography. J Anesth. 2019;33:697–700.

11. Sharma S, Deo SA, Raman P. Effectiveness of standard fasting guidelines as assessed by gastric ultrasound examination: A clinical audit. Indian J Anaesth. 2018;62:747–52.
12. Kruisselbrink R, Arzola C, Endersby R, et al. Intra- and Interrater Reliability of Ultrasound Assessment of Gastric Volume. Anesthesiology. 2014;121:46–51.
13. Bouvet L, Chassard D. Ultrasound assessment of gastric contents in emergency patients examined in the full supine position: an appropriate composite ultrasound grading scale can finally be proposed. J Clin Monit Comput. 2020;34:865–8.

Brazilian Journal of Anesthesiology 2022;**72(6):** 757—761

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Preoperative fasting for the infusion of "yerba mate": a randomized clinical trial with ultrasound evaluation of gastric contents

Paola Alcarraz [a,*], Liliana Servente [b], Federico Kuster [a], Leticia Duarte [a], Mariela Garau [c], María Desirello [b], Lourdes Blanc [d], Nelson Bracesco [d], Anahi Perlas [e]

[a] *Facultad de Medicina UDELAR, Hospital de Clínicas "Dr. Manuel Quintela", Departmento de Anestesiología, Montevideo, Uruguay*
[b] *Facultad de Medicina UDELAR, Hospital de Clínicas "Dr. Manuel Quintela", Departmento Clínico de Imagenología, Montevideo, Uruguay*
[c] *Facultad de Medicina UDELAR, Departmento de Métodos Cuantitativos, Montevideo, Uruguay*
[d] *Facultad de Medicina UDELAR, Laboratorio de Radiobiología Departmento Biofísica, Montevideo, Uruguay*
[e] *University Health Network and University of Toronto, Toronto Western Hospital, Department of Anesthesia, Toronto, Canada*

Received 19 February 2021; accepted 26 December 2021
Available online 1 February 2022

KEYWORDS
Gastric emptying;
Gastric contents;
Ultrasound measures;
Yerba mate;
Preoperative fasting

Abstract
Background: The traditional infusion of "yerba mate" is widely consumed in South America and exported to countries around the world. Although generally considered a "clear fluid", there is no data to date on the gastric emptying time of yerba mate and safe preoperative fasting intervals. The objective of this study was to evaluate the gastric emptying time of a standardized infusion of yerba mate using bedside ultrasound and compare it with the time confirm of hot and cold tea.
Methods: This was a prospective, randomized crossover experimental study. Thirty healthy volunteers were evaluated after 8 hours of fasting for both fluids and solids. Gastric antral area and gastric volume were evaluated at baseline and every 20 minutes after drinking 300 mL of randomly assigned infusion of "yerba mate", hot tea, or cold tea.
Results: The mean gastric emptying time was: 69.7 ± 22.1 min, 63.1 ± 14.5 min, and 64.3 ± 23.5 min for the mate, hot tea, and cold tea respectively. No significant differences were found in emptying time among the infusion groups (p-value = 0.043). When same time measures were compared, the only significant difference detected was between hot teas and mate infusion at 20 minutes (p-value = 0.012)
Conclusion: Yerba mate infusion has a similar gastric emptying time to that of tea. All subject's gastric volume returned to baseline values by 100 minutes. It is reasonable to recommend a similar fasting period of 2 hours for mate infusion prior to elective surgery.

* Corresponding author.
E-mail: palcarraz@gmail.com (P. Alcarraz).

https://doi.org/10.1016/j.bjane.2021.12.010

Introduction

Broncho-pulmonary aspiration of gastric contents may occur during general anesthesia in an unprotected airway given the abolition of protective airway reflexes. This is a rare but serious complication.[1]

To reduce this risk and enhance patient safety in the perioperative period, fasting guidelines have been used for a long time. However, a traditional period of total fasting for 8 hours may lead to metabolic and hydro-electrolytic alterations, patient discomfort, hunger, thirst, and irritability.[2] In recent years, more flexible guidelines for fasting have been developed by different scientific societies. These include fasting recommendations from the American Society of Anesthesiologists published in 2011[3] and updated in 2017[4] and those by the European Society of Anesthesiology published in 2011.[5] They recommend the intake of clear liquids until 2-hours before an elective procedure. An exemption to these guidelines is patients with pre-existing comorbidities or physiologic conditions that may prolong gastric emptying time such as pregnancy, obesity, diabetes, hiatal hernia and gastroesophageal reflux disease.

These guidelines do not include the infusion of yerba mate (Ilex Paraguariensis –IP) as a clear fluid, as this is not a popular drink in North America or Europe. The guidelines refer to water, black coffee (without added milk), tea, juice without pulp, and isotonic clear fluids, as they leave no residue, and quickly leave the stomach. Iso-osmolar or hypo-osmolar drinks (compared to plasma) are considered clear fluids for the purpose of preoperative fasting.[6]

Yerba mate infusions are consumed daily by millions of people in Brazil, Uruguay, Argentina, Chile, and Paraguay where they represent a deeply rooted social tradition. For example, it is estimated that 85% of Uruguayans consume yerba mate infusions on a regular basis at least once a week.[7] The consumption of mate is not only limited to this region; according to official data of the producing countries, yerba mate is exported to more than 50 countries in the five continents.

Research shows that yerba mate infusions have positive effects on human health, such as antioxidant activity, radioprotective effect, antihypercholesterolemic activity, inhibition of auto oxidation of LDL. Based on its high content of polyphenols, vitamins and minerals, yerba mate can be considered a medicinal plant.[8-14]

Up until recently, there were no tools available to evaluate gastric content in the immediate preoperative period. Gastric ultrasonography has become a clinically useful, non-invasive tool to accurately determine the volume of gastric content and evaluate gastric emptying, with important implications for assessing the risk of perioperative aspiration.[15]

The main objective of this study was to evaluate the gastric emptying time of a yerba mate infusion using bedside ultrasound and compare it with that of tea. We hypothesized that the gastric emptying time of a yerba mate infusion would be similar to that of tea. The secondary aim was to identify possible differences between the gastric evacuation of cold and hot drinks.

Methods

Study design

After approval by the Research Ethics Committee of the Hospital de Clínicas, Montevideo, Uruguay, and registration with the Ministry of Public Health (registry number 4477845), a prospective, randomized crossover experimental study was conducted. Written informed consent was obtained from all participants.

An exploratory study was carried out with a convenience sample size, where thirty healthy volunteers were evaluated on three different occasions, at least 24 hours apart, over a period of 2 months. The inclusion criteria were age over 18 years old, ASA (American Society of Anesthesiologists) physical status I or II. Exclusion criteria: co-morbidities or physiologic states that may alter gastric emptying (diabetes, obesity, gastroesophageal reflux disease and pregnancy).

For the evaluation of the gastric antral area and gastric volume, a previously described standardized scanning protocol and a validated volume model were used.[16-17] The gastric antrum was identified with the volunteer in the right lateral decubitus position, placing the curved low frequency transducer (2–4 MHz) in a sagittal plane over the epigastrium, identifying the antrum between the left lobe of the liver in the anterior part and the pancreas and aorta in the back. The area was measured from serosa to serosa and with the antrum at rest without peristaltic contractions. All examinations were performed with the same portable ultrasound equipment (General Electric Vivid II, GE Healthcare) and by the same imaging physician with 5 years of experience and blinded to the nature of the liquid ingested by each participant in turn, this was supervised directly by an imaging specialist with 20 years of experience in abdominal ultrasound.

The gastric antral area was measured using the free tracing technique as previously described.[18] Then the gastric content volume was determined by means of a mathematical model described and validated by Perlas et al.[17] (Fig. 1), using the following formula: Vol (mL) = 27.0+14.6 CSA (cm^2) – 1.28 Age (years). Gastric emptying time was defined as the time in minutes elapsed from taking the infusion until the antral area (and gastric volume) returned to fasting baseline values.

Each participant was assigned the infusion to ingest on each day of the study (yerba mate, hot tea or cold tea) in an order determined by a random number generator, in a 1:1:1 ratio.

With fasting of at least 8 hours for liquids and solids, the participants were given an ultrasound examination to measure the baseline antral area, and then the measurement was repeated after they ingested the 300 mL of the infusion

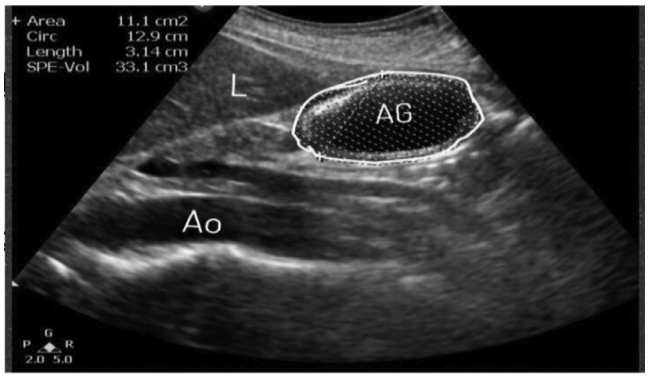


Figure 1 Abdominal ultrasound, longitudinal section in the epigastrium. Ao, Abdominal aorta; Dotted line, antral gastric area, presents anechoic (liquid) content.

assigned for that day, and every 20 minutes until the antral area was found to be equal to or smaller than the initial one. The sonographer did not know the nature of the swallowed fluid.

Preparation of infusions

The Yerba Mate infusion was prepared using 30 g of Ilex paraguariensis (Yerba Mate, Canarias SA, Pando, Uruguay) infused for 15 minutes in 700 mL of non-carbonated mineral water (Salus SA, Minas, Uruguay) at 90°C. It was then filtered and served in thermal glasses (300 mL) at 50°C.[19]

The tea Infusion was prepared using 2 g of *Camellia sinensis* (Té Negro, Canarias SA, Pando, Uruguay) infused in 300 mL of non-carbonated mineral water (Salus SA) at 90°C for 4 minutes, filtered and served in thermal cups (300 mL) at 50°C.

The cold tea infusion was prepared in the same manner and then allowed to cool down to room temperature. Osmolarity, pH, and Caffeine Concentration of the three infusions were analyzed with an OSMOMETRO-Advanced Instrument Model 3250 (Table 1).

Statistical analysis

One way analysis of variance (ANOVA) for repeated measures was performed. To verify that the conditions for this test were met, the normality of the independent variable was investigated with the Shapiro-Wilk test and the sphericity of the variances with the Greenhouse-Geisser epsilon. The *t*-test for paired means was used for post hoc comparisons when differences were detected among the infusion groups.

Table 1 Characteristics of infusion and water.

	pH	Kcal	Osmolarity $mmoL.Kg^{-1}$
Yerba Mate infusion	4.5–5	45	128
Black Tea infusion	6.5–7	< 0.5	10
Water used for the infusion	7	0	4

A p-value < 0.05 was considered significant. The statistical analysis was performed with the software STATA, version 15.1. (2017).

Results

A total of 30 volunteers were studied. Demographics are presented in Table 2. Each participant was evaluated once after drinking each infusion, except for two volunteers, who underwent two of the three measures. A total of 88 measurements were obtained, of which 29 corresponded to the mate group, 29 to hot tea and 30 to cold tea.

The gastric emptying time was similar in the three groups with mean and standard deviation of 69.7 ± 22.1 min, 63.1 ± 14.5 and 64.3 ± 23.5 for yerba mate, hot tea and cold tea respectively. No significant differences were detected (ANOVA for repeated measures, p-value = 0.41).

Figures 2 and 3 shows gastric volume as a function of time: at each time point the mean and its 95% Confidence Interval was represented for each infusion. Volumes were considered stable after returning to baseline.

Mean volumes at 0, 20, 40, 60, 80, and 100 minutes were compared using one way ANOVA for repeated measures. *P*-values are shown in Table 3. Differences were only significant at 20 minutes (p-value = 0.043), post hoc comparisons using t-test for paired observations showed that mean volume between hot tea and mate was significantly different (p-value = 0.012), while volume at 20 minutes had no significant differences between hot and cold tea (p-value = 0.325) nor between mate and cold tea (p-value = 0.158)

We found that gastric volume returned to baseline in 60% of cases by 40-minutes, 93% of cases by 60-minutes, and in 100% of cases by 100 minutes (Table 3).

Discussion

Our results suggest that the mean gastric emptying time for a yerba mate infusion is approximately 1 hour and is similar to that of hot or cold tea, and that all healthy subjects return to baseline gastric volume within 100 minutes of yerba mate ingestion. This suggests that a similar preoperative fasting time of 2 hours could be recommended for an infusion of yerba mate. The current flexible fasting guidelines of different societies recommend the intake of clear liquids up to 2 hours before an elective procedure.[3-5] The infusion of yerba mate is consumed in several countries of South America, and other countries of the world. Given the lack of data on the emptying time of yerba mate infusions to date, many anesthesiologists in South America request

Table 2 Demographic characteristics of the 30 volunteers.

	n = 30
Age (mean ± SD)	26.9 ± 4.2
Weight (mean ± SD)	67.7 ± 13.2
Height (mean ± SD)	168.8 ± 8.3
Sex (M/F)	12/18
ASA (I/II)	20/10

SD, Standard Deviation.

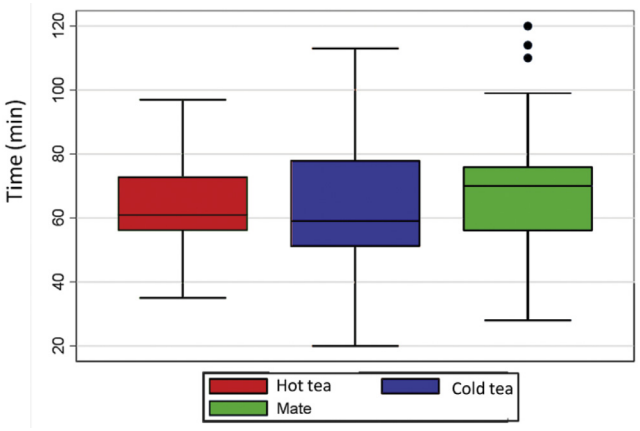


Figure 2 Gastric emptying time after ingestion of 300 mL of infusion in 30 volunteers.

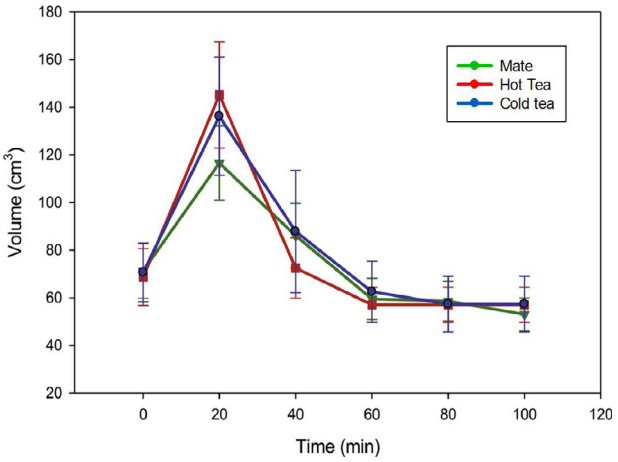


Figure 3 Gastric volume estimation as a function of time for 30 volunteers having 300 mL of mate, hot tea and cold tea. Measures obtained at time 0, 20, 40, 60, 80 and 100. Vertical lines show 95% Confidence Intervals for the means.

longer fasting time for yerba mate out of an abundance of caution. Our results suggest that this is overly conservative and that a fasting time of 2 hours is indeed safe for yerba mate infusions.

Vist and Maughan[6] demonstrated in 1995 that the two main determinants of gastric evacuation of liquids are osmolarity and carbohydrate content. More recently, Okabe et al.[20] studied the influence of fluid content for gastric emptying and concluded that the intake of a beverage whose content did not exceed 220 kcal and 500 mL (except beverages with high osmolarity, very high viscosity or both) was safe until 2 hours before an elective procedure. Our studied liquid was the infusion of yerba mate, a hypo-osmolar and hypocaloric drink, and would therefore be expected to behave like a clear liquid. This was confirmed by our results, thus suggesting that yerba mate infusion should be treated as other clear fluids in terms of pre-operative fasting.

Given that yerba mate infusions are usually ingested hot, we decided to compare the emptying time of hot and cold tea to establish if the temperature of the ingested fluid has any impact on gastric emptying rates. Our results showed that the temperature of the liquid ingested does not change the rate of gastric emptying, and it should not be considered a significant variable.

In 10% of all measurements obtained 20 minutes after ingestion, the gastric volume was lower than the ingested volume of 300 mL. Mendes et al.[21] similarly found that the gastric volume 10 minutes after ingesting 400 mL of coconut water was less than the volume ingested. These two observations suggest that gastric emptying of liquids starts very soon after, if not immediately after, ingestion. Unlike the study by Mendes, we made our measurements every 20 minutes after ingestion, rather than every 60 minutes, which allowed us to determine the emptying rate more accurately. We found that the gastric volume returned to baseline in 60% of cases by 40 minutes, 93% of cases by 60 minutes and in 100% of cases by 100 minutes.

Despite presenting with at least 8 hours of fasting, and not having co-morbidities that would alter gastric emptying, in 11 evaluations (12%), the baseline gastric content prior to intake of the infusion was greater than the one considered safe (> 1.5 $mL.kg^{-1}$). These findings are consistent with other studies that have previously described that even in healthy individuals, standard fasting periods may not be sufficient to guarantee an empty stomach in all patients.[22]

The crossover design of our study, where the same 30 volunteers underwent the 3 measurements of liquids studied, reduced the possibility of interindividual variations, assuring the homogeneity of the sample and its comparison among the 3 infusions. In turn, the measurement bias was reduced when all the ultrasound examinations were done by the same expert.

One of the limitations of our study was that the mate infusion was ingested by sipping from a mug. We did that to standardize the conditions of ingestion in all 3 groups. It is

Table 3 Estimated mean gastric volume 20, 40, 60, 80, and 100 minutes after drinking 300 mL of Mate, hot tea or cold tea in 30 volunteers.

Time (min)	Mean volume for MATE measures	Mean volume for HOT TEA measures	Mean volume for COLD TEA measures	ANOVA *p*-value
0	71.3	68.5	70.0	0.998
20	116.6	147.8	136.4	0.043[a]
40	86.1	72.7	87.2	0.432
60	59.5	57.7	62.8	0.660
80	58.6	57.7	57.7	0.978
100	53.0	57.7	57.7	0.533

customary however, to drink mate infusions from a straw. It is unknown if drinking from a straw would result in greater air ingestion that could impact emptying time. Secondly, our study was performed in relatively healthy volunteers without comorbidities that could affect gastric emptying time and who were not in a preoperative period, where stress and anxiety could also potentially affect gastric emptying.

Conclusion

We concluded that the infusion of yerba mate has a gastric emptying time that is similar to that of tea, thus it should be considered a clear liquid for the purpose of preoperative fasting. Its consumption within a period of up to 2-hours before an elective surgery, may be considered safe.

Conflicts of interest

The authors declare no conflicts of interest.

Aknowledgements

We thank Canarias SA for Providing the yerba and the tea.

We also thank Prof. Associate Professor. Dra Anna Barindelli for her help in studying the osmolarity of the yerba mate infusion.

References

1. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology. 2006;105: 1087—97.
2. Pimenta GP, de Aguilar-Nascimento JE. Prolonged preoperative fasting in elective surgical patients. Nutr Clin Pract. 2014;29: 22—8.
3. Apfelbaum JL, Caplan RA, Connis RT, et al. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. Anesthesiology. 2017;114:495—511.
4. Apfelbaum JL, Caplan RA, Connis RT, et al. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. Anesthesiology. 2017;126:376—93.
5. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Sreide E, in't Veld B. Perioperative fasting in adults and children. Eur J Anaesthesiol. 2011;28:556—69.
6. Vist GE, Maughan RJ. The effect of osmolality and carbohydrate content on the rate of gastric emptying of liquids in man. J Physiology. 1995;486:523—31.
7. Encuesta STEP, OPS 2007, Ministerio de Salud Pública, Uruguay: http://www.msp.gub.uy/sites/default/EncuestaFactores-Riesgo.pdf.
8. Bastos D, Fornari A, Queiroz Y, Torres E. Bioactive compounds content of chimarrão infusions related to the moisture of yerba mate (Ilex Paraguariensis) Leaves brazilian archives of biology and technology. 2006;49:399-404.
9. Filip R, Ferraro G, Bandoni A, et al. Chapter: 5 Mate (Ilex paraguariensis) Recent advances in phytochemistry. 2009,000-000 ISBN: 978-81-308-0309-8 Editor: Filippo Imperato.
10. Bracesco N, Sánchez AG, Contreras V, Menini T, Gugliucci A. Recent advances on Ilex paraguariensis research: minireview. J Ethnopharmacol. 2011;136:378—84.
11. Bracesco N, Dell M, Rocha A, et al. Ilex paraguariensis extracts prevent peroxide damage to biomolecules: a study on DNA double strand breaks in Saccharomyces cerevisiae and human low-density lipoprotein. J Altern Complemen Med. 2003;3:379—87.
12. Bracesco N, Sosa V, Blanc L, et al. Analysis of radioprotection and antimutagenic effects of Ilex paraguariensis infusion and its component rutin. Braz J Med Biol Res. 2018;51(9).
13. Falconi A, Gutierrez M, Benedetto L, Abin-Carriquiri J, Bracesco N, Torterolo P. Waking-promoting action of yerba mate (Ilex paraguariensis). Sleep Science. 2013;6:9—15.
14. Bracesco N. Ilex Paraguariensis as a Healthy food supplement for the future world. Biomed J Sci Tech Res. 2019;16(1).
15. Perlas A, Chan VW, Lupu CM, et al. Ultrasound assessment of gastric content and volume. Anesthesiology. 2009; 111:82—9.
16. Bolondi L, Bortolotti M, Santi V, et al. Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology. 1985;89:752—9.
17. Perlas A, Mitsakakis N, Liu L, et al. Validation of a mathematical model for ultrasound assessment of gastric volume by gastroscopic examination. Anesth Analg. 2013;116:357—63.
18. Kruisselbrink R1, Arzola C, Endersby R, et al. Intra- and inter-rater reliability of ultrasound assessment of gastric volume. Anesthesiology. 2014;121:46—51.
19. Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of drinking coffee, mate, and very hot beverages. International Agency for Research on Cancer Monograph Working Group. Lancet Oncology. 2016;17:877—8.
20. Okabe T, Terashima H, Sakamoto A. Determinants of liquid gastric emptying: comparisons between milk and isocalorically adjusted clear fluids. Br J Anaesth. 2015;114:77—82.
21. Mendes B, Claudino C, de Brito W, et al. Ultrasound dynamics of gastric content volumes after the ingestion of coconut water or a meat sandwich. A randomized controlled crossover study in healthy volunteers. Rev Bras Anestesiol. 2018;68:584—90.
22. Van de Putte P, Perlas A. Evaluación ecográfica del contenido y volumen gástrico. H. J Anaesth. 2014;113:12—22.

Brazilian Journal of Anesthesiology 2022;72(6):762–767

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Impact of extending prevention of postoperative nausea and vomiting for cancer surgical patients in the PACU: a before and after retrospective study

Cyrus Motamed *, Grégoire Weil, Jean Louis Bourgain

Gustave Roussy Institute, Department of Anesthesia, Villejuif, France

Received 24 February 2020; accepted 11 June 2021
Available online 30 June 2021

KEYWORDS
Postoperative nausea and vomiting

Abstract
Backgrounds: Procedures for Postoperative Nausea and Vomiting (PONV) prevention are mostly based on identification of the risk factors before administering antiemetic drugs. The purpose of this study was to evaluate the impact of the extended use of antiemetic on the PONV in the Postanesthetic Care Unit (PACU).
Methods: Two separate 4-year periods (2007–2010, P1, and (2015–2018, P2) were evaluated. During P1, the protocol consisted of dexamethasone and droperidol for patients with a locally adapted high PONV score, followed by ondansetron for rescue in the PACU. For Period 2, dexamethasone (8 mg) and ondansetron (4 mg) were administered in patients under general or regional anesthesia, or sedation longer than 30 minutes, while droperidol (1.25 mg) in rescue was injected in cases of PONV in the PACU. An Anesthesia Information Management System was used to evaluate the intensity score of PONV (1 to 5), putative compliance, sedation, and perioperative opioid consumption upon arrival in the PACU.
Results: A total of 27,602 patients were assessed in P1 and 36,100 in P2. The administration of dexamethasone and ondansetron increased several fold ($p < 0.0001$). The high PONV scores were more improved in P2 than in P1, with scores (3+4+5) for P1 vs. P2, $p < 0.0001$. Overall, 99.7% of the patients in P2 were asymptomatic at discharge. Morphine consumption decreased from 6.9±1.5 mg in P1 to 3.5 ± 1.5 mg in P2 ($p < 0.0001$).
Discussion: The extension of pharmacological prevention of PONV was associated with a decrease in the intensity of severe PONV. However, uncertainty regarding confounding factors should not be ignored.
IRB: nº 92012/33465

* Corresponding author.
E-mail: cyrus.MOTAMED@gustaveroussy.fr (C. Motamed).

https://doi.org/10.1016/j.bjane.2021.06.007

Introduction

Postoperative Nausea and Vomiting (PONV) is one of the oldest and most frequently cited complications of surgical anesthesia. This complication continues to occur despite risk-adapted local or general protocols and multiple new medications developed for its treatment.[1–5] An extensive body of research and publications exists on this topic, but the prevention of PONV remains a substantial matter of debate. We consider treatment of PONV to be a very essential part of our quality assurance program[6]; therefore, we continuously monitor it through our Anesthesia Information Management System (AIMS) and adjust our protocols to improve its outcome and incidence.[6]

A previous retrospective single center database analysis conducted as part of our quality assurance program assessed the incidence and trend of intensity of PONV in our PACU over a 5-year period.[7] However, to improve outcomes, we changed our local protocol (2013) by shifting from a previous risk-tailored preventive prophylaxis (dexamethasone droperidol, ondansetron) to a generally simpler and broader prophylaxis to further reduce the incidence of PONV. In addition, in response to new general guidelines for the prevention of PONV[8] we replaced intraoperative droperidol i ntravenous (IV) with ondansetron IV and used droperidol IV for rescue injection in the PACU.[8–11]

We hypothesized that a better outcome would be achieved with the new protocol; therefore, we reevaluated outcomes by an AIMS interrogation. Our primary objective was to reassess the intensity score of PONV from 2015–2018 (P2) and to compare it to the trend of our historical data from 2007 to 2010 (P1), when PONV had been assessed based on a local riskadapted PONV score protocol and had consisted of the same doses of dexamethasone, followed by intraoperative droperidol and then ondansetron in the PACU as a rescue.[7] Our secondary outcomes included the putative compliance, defined as the application of the algorithm by expecting a steep increase in anti-PONV medication, the number of antiemetic including rescue medications, and the declared specific or other possible related side effects.

Methods

This study was a retrospective database analysis. Our institutional review board authorized the publication of data extracted from our AIMS system. All patients gave their written consent for the care teams to use anonymized data from their medical records for investigation during the first medical consultation (Avis nº 92012/33465). The study was in compliance with the Declaration of Helsinki and general data protection regulations.

As part of our quality assurance program, all patients were assessed with several multiple mandatory endpoints, which were submitted by the anesthesia providers to the AIMS database using our anesthesia software (Centricity, GE, USA). These points included the intensity of the PONV score, as assessed by the nurse in charge in the PACU, with the following 5-grade scale (1 = no sign, 2 = minor nausea, 3 = mild nausea and vomiting, 4 = severe nausea and vomiting, 5 = incoercible vomiting). If the PONV intensity was above scale 1 upon arrival in the PACU, droperidol (1.25 mg) was given. Other mandatory manual entry endpoints included pain scores, sedation scores, analgesic requirements, and temperature upon arrival in the PACU.

Sedation scores were recorded on a scale of 0 to 4, being 0: not sedated, 1: lightly sedated, 2: mild sedation, 3: heavily sedated but awakable, 4: not awakable by physical stimulus.

The Centricity anesthesia databases (for P2) and Datex Ohmeda (for P1) servers were interrogated by a Sequential Query Language method (SQL) using Crystal reporting software V8 (USA) and Archive Browser®, respectively. The anesthesia database administrators (JLB-GW) underwent several cycles of formal training to master appropriate data extraction from the database.

Our cancer hospital performs major cervicofacial and general surgery, interventional radiology, brachytherapy, some pediatric surgery, and other diagnostic procedures. All anesthesia providers in our institution used the same classes of different anesthetic medications and identical monitoring for most procedures, although they have liberty to deviate from the established guidelines depending on the patient. Nevertheless, a continuous quality assurance program was ongoing in several areas during P1 through P2.

In this new locally approved protocol, the inclusion criteria were all patients who had undergone general anesthesia or conscious sedation with or without regional or anesthesia longer than 30 minutes, including day care surgery. Patients also had to have received dexamethasone (8 mg IV) after induction of anesthesia or sedation, followed by ondansetron (4 mg IV) before the end of surgery. Exclusion criteria were local anesthesia and missing data. For procedures less than 30 minutes in duration and for local anesthesia patients who transited through the PACU, if PONV was present, medications were given in the PACU.

In P1, a locally adapted protocol was used. This protocol was an algorithm-based on our previous database of PONV scores. We used a multivariate analysis of the early 2000s. Age, gender, history of PONV, and thyroid surgery were rated as major risks of PONV in our specific cancer teaching hospital. Depending on the score obtained, medication was administered incrementally, starting with no medication, droperidol at the end of surgery, or dexamethasone and droperidol during surgery, and finally, if symptoms were present in the PACU, ondansetron was given.

Patients were discharged after being assessed with a modified Aldrete score, including the before-discharge PONV intensity score. Possible adverse events, such as arrhythmia, hypotension, and allergy related to antiemetic medications were also checked.

We also extracted the incidence of PONV for different types of procedures and surgeries, as well as the effects of gender, age, and opioid requirements in P2; however, these extractions were not available in P1, except for opioid requirements, due to failure and shutdown of the old server.

Our new simplified protocol formally started in mid-2013; however, our database underwent a server migration in early 2014, therefore we judiciously skipped the 2013 and 2014 data because of probable loss of some data due to the migration. This also allowed some time for the anesthesia providers to adapt and assimilate the new protocol. Therefore, data were extracted from 2015 to 2018 (time of the study).

We verified each final result by a manual check of data extracted by the same query over a very short period (3 days) before extracting the targeted data for the broader period of time. Data were cleaned of redundancies and the missing data were calculated using Excel 2010 sheets.

Statistics

Prism V7 (Graphpad Software, San Diego, USA) and Microsoft Excel 2010 were used for statistical analysis. For comparison between periods, the patients were grouped as follows: no PONV (score 1), light PONV (score 2), heavy PONV (score 3, 4, and 5).

The Wilcoxon-Mann-Whitney and X2 for trend tests were used to compare data between and within periods, respectively. The type I error was set at $\alpha = 0.05$ (two-sided),

Results

From 1 January 2015 to 31 December 2018 (P2), 36,100 patients were screened. PONV scores were extracted from the Centricity anesthesia database using Crystal Report V8 software. We also had PONV scores for 27,602 patients for P1 (1 January 2007 to 31 December 2010); these scores had been extracted from our previous anesthesia database (Datex anesthesia®) by Archive Browser®. The mean completeness of the data was 94% in P2; this percentage was superior to the completeness in P1 (83%) ($p < 0.0001$).

The number of patients and the medication protocol used during both periods are presented in Figure 1. The administration of dexamethasone and ondansetron increased several fold ($p < 0.0001$). Overall, 18,080 patients in P2 had both dexamethasone and ondansetron (80% of those patients were considered to be eligible for the extended protocol). The demographic characteristics and durations of surgery are reported in Table 1 (for P2 only).

Upon admission to the PACU, the incidence of PONV (score 2 to 5) was 3% in P1 and 0.9% in P2 ($p < 0.0001$) (Table 2). No difference was found when comparing scores 1 and 2, P1 vs. P2 $p = 0.47$. Rescue medication was administered for 787 patients (2%) in P1 and 1418 patients in P2 (4%) ($p = 0.01$). No direct or putative adverse events related to antiemetic could be extracted in this cohort of patients.

No statistically significant difference was noticed in sedation scores between P1 and P2. The incidence of patients who had sedation scores above 1 was of 6.9% in P2 vs. 6% in P1 ($p = 0.2$).

No significant difference was noticed in the intensity of PONV scores when assessing the different types of surgery or procedures in P2 (Table 3). At PACU discharge, the incidence of no PONV (score 1) was 99 ± 0.5%.

The mean intraoperative morphine consumption was significantly less during P2 (3 ± 1.3 mg) than during P1 (6.9 ± 1.6 mg) ($p < 0.0001$). The mean PACU morphine consumption was significantly lower in P2 (2.6 ± 0.91 mg) than in P1 (11.6 ± 2.3 mg) ($p < 0.0001$). PONV scores higher than 2 were more frequent in the patients who received morphine than in the patients who had no morphine ($p = 0.0028$).

The intensity of the PONV score in P2 was significantly higher in women under 50 years old (8%) than in their male counterparts (2.2%) ($p < 0.0001$).

Discussion

The findings of this study show that expanding the indications of prevention of PONV from a ''locally-adapted PONV risk'' to a ''fit-for-most'' protocol improved the intensity of heavy PONV scores upon arrival in the PACU when compared with our historic data of previous years. However, while the amounts of administered antiemetic medications increased several folds, the intraoperative opioid consumption was decreased by 50%. The protocol reduced by half the absolute number of patients having severe nausea and vomiting, despite the increase (30%) in the total number of patients. Nevertheless, the need for rescue medications increased by 100%, which was mostly due to low-intensity PONV (score 2) since scores of 3 to 5 were significantly less common in this period. In addition, medications were not administered intraoperatively for sedation and procedures of less than 30 minutes or for local anesthesia, as directed by the new protocol. Other factors, such as increased attention by the nursing staff and improved medical education through a sustained quality assurance program, could also have played a part.

Overall, 80% of the patients apparently underwent a double treatment (dexamethasone followed by ondansetron); however, we can only indirectly confirm this 80% compliance because of the retrospective nature of the study. We also cannot interrogate our old database (P1); therefore, no comparative previous data about minimum putative compliance could be extracted.

In our new extended protocol, we administered dexamethasone and ondansetron in all anesthesia cases longer than 30 minutes, and we used droperidol as a rescue treatment in the PACU since potentially more cardiovascular effects, such QT prolongation, occur with droperidol than with ondansetron.[12] We therefore used droperidol for cases requiring additional PONV in the PACU as a rescue administration. Despite this ''fit-for-most'' strategy, a very small proportion of patients still had moderate to severe PONV scores. Nevertheless, the patients with very high PONV scores (incoercible vomiting) showed significantly decreased scores (tenfold). A recently published ''before and after'' study assessed the effect of the simplified algorithm in a restricted number of patients over two weeks.[13] Our study had a retrospective design and concerned all our patients in a much longer period in a real-life situation.

We believe that the use of a simplified algorithm, without calculating the local score,[14] had a better outcome for most patients regarding a high PONV score than was obtained with our historical group of patients whose preventive treatment administration was based on a locally adapted risk score. We acknowledge that this improvement might not totally be related to the change in the protocol and that other factors, such as the decrease in morphine consumption, might have played a part. However, we did not assess a cost-benefit or conduct a cost-effect analysis, and this could be considered a shortcoming. In addition, we were unable to detect any significant adverse effects related to the threefold increase in PONV medications. We also cannot exclude the potential effects of missing data in relation to the medications used for PONV, especially when a putative event might have been reported elsewhere or in another folder by mistake.

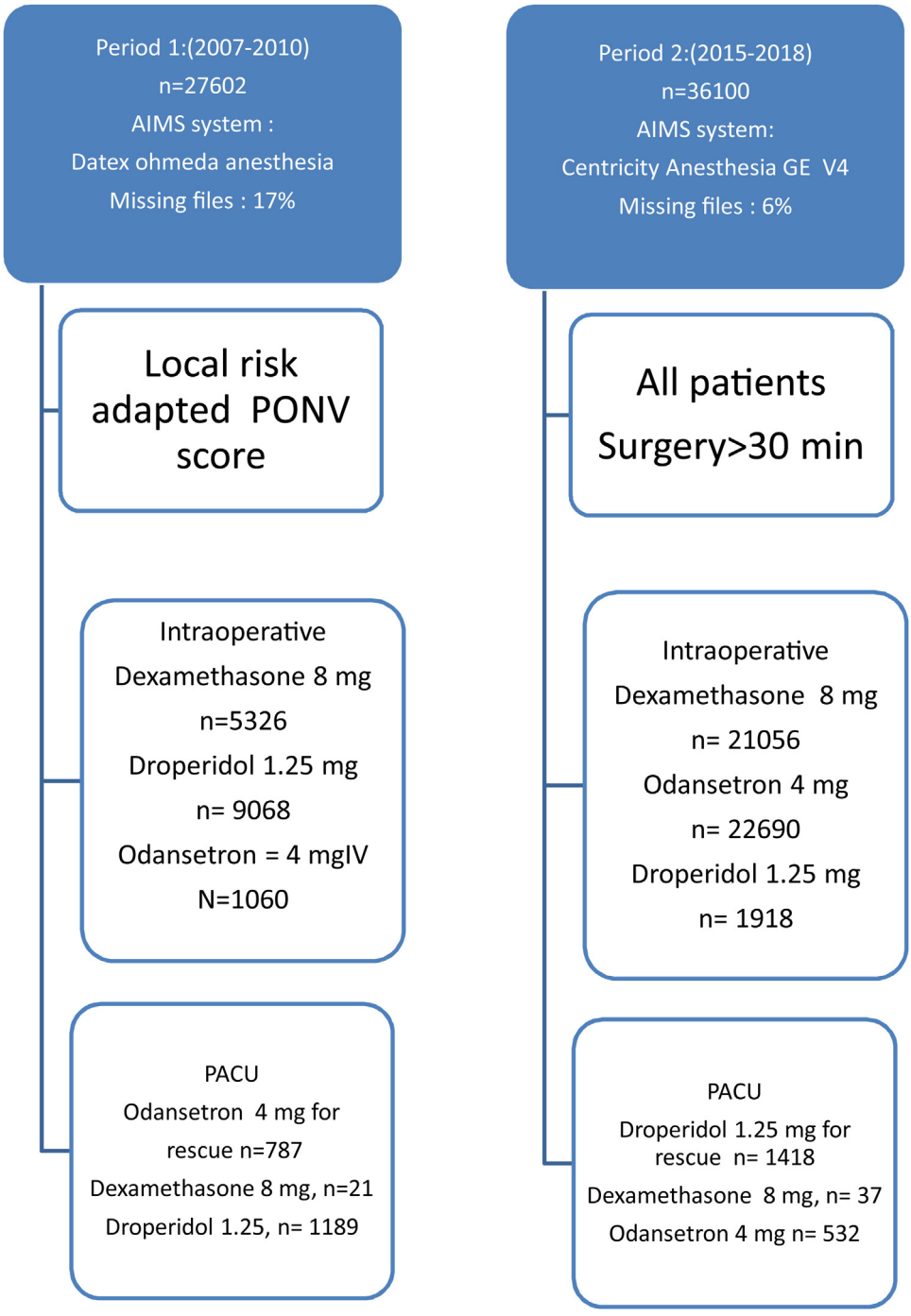


Figure 1 Number of patients and medication used in both periods.

Table 1 Gender ratio, weight, age, height, and duration of surgery (2015–2018).

Year	Number of anesthesia	Gender ratio F/M	Weight Kg (SD)	Age year (SD)	Height cm (SD)	Duration of surgery (SD)
2015	8590	69%	69.2 (15.8)	56 (14)	165 (9)	129 (108)
2016	8900	67%	69.9 (16.4)	57 (15)	166 (9)	146 (129)
2017	9306	67%	69.6 (16.3)	56 (15)	166 (10)	179 (153)
2018	9304	66%	69.6 (16.8)	57 (15)	166 (10)	180 (161)

Table 2 Comparison of Light and heavy intensity PONV score between P1 and P2 for intensity PONV score (3–4–5) P2 vs. P1. $p < 0.0001$, PONV score (1–2) P2 vs. P1.

Period	Score	1	2		3	4	5	% Missing data
P1	2007	4196	198	P1	68	29	2	32.4%
	2008	4908	228		92	26	14	20.7%
	2009	5708	158		87	36	3	10.7%
	2010	6360	141		63	28	5	13.9%
P2	2015	8527	314	P2*	56	23	1	5.5%
	2016	8295	353		59	19	1	5.7%
	2017	8485	280		43	14	0	5.2%
	2018	8551	253		41	17	2	4.9%

Table 3 Type of surgery or interventional procedures and the intensity of PONV in P2 (2015–2018) only.

Score	Surgery					Interventional				Not reported
	Gynecologial/ General surgery	Thyroid	Breast	ENT	Plastic and dermatology	Radiology	Endoscopy	Pediatrics	Brachytherapy	
1	3770	1000	6120	4050	2120	3120	2388	3188	1426	3045
2	248	37	423	115	93	159	98	13	24	134
3	43	4	45	16	9	28	22	1	5	26
4	18	3	17	4	4	15	9	3	0	8
5	01	0	0	00	1	1	0	0	0	1

ENT, Ear, Nose and Throat.

In addition, the average decrease of 3 mg of intraoperative morphine might have had its own effect on decreasing the intensity of PONV.

Another weakness of this study is the inability to report PONV scores at 24 hours, since our postoperative (Dx Care®) software is not connected to our intraoperative database (Centricity) and cannot be extracted in the same manner. However, we believe these 24-h PONV scores would not change significantly because treatments are given according to demand and are not given preemptively. The major risks for PONV include general anesthesia, morphine consumption, inhalational anesthesia, and type of surgery.[15–19] We have been decreasing opioid consumption over several years,[20] and this trend is ongoing.

Our preliminary goal after each new protocol is to decrease the incidence of PONV. However, since our institution conducts a significant number of surgeries, including gynecologic, breast, thyroid, and general surgeries, and yields, in theory, an incidence of PONV around 60%, we believe that switching to the simplified general algorithm did not overwhelmingly increase the cost, given the benefit of the decrease in the incidence of severe PONV. Nevertheless, because of the positive results, some savings have probably been secured because of the fewer number of patients having severe PONV, which is known to have expensive side effects, especially in ambulatory patients.

One point to note is that this assessment of nearly 63,000 patients over two periods would not have been possible without using our AIMS systems. However, once again, our AIMS system served as part of a quality assurance tool that allowed us to indirectly assess our new protocol.[6,7]

This study has other limitations, including its monocentric and retrospective nature. In addition, some data, such as all the demographic characteristics and types of surgery, were not available for P1 because the server was shut down in 2011. In addition, the 24-h postoperative scores are not stored on the same server and are not registered with the same software; therefore, they are not accessible by SQL extraction from the anesthetic software and require manual assessment. A last limitation was that the locally-risk-adapted PONV score could not be transcribed from our preoperative anesthetic evaluation to our current intraoperative anesthetic record software (Centricity anesthesia GE, USA). Consequently, we only have putative assumptions for P1, as the patients undergoing intraoperative treatments were high-risk patients according to our own local protocol. By contrast, in P2, this assumption would not be applicable as the indication for treatment included all patients except those having a surgery of less than 30 minutes.

Rescue injection in the PACU showed the efficiency of the protocol, since 99.5% of the patients were discharged with an intensity score of 1 for PONV. These positive findings are probably the maximum achievable when selecting those patients in whom an additional dose of droperidol was given without risking the synergic effect of QT prolongation due to the additional effect of ondansetron and droperidol.[11]

Conclusions

The change in our practice from adapted risk factors to a simplified ''fit-for-most'' algorithm was followed by a reduced intensity of severe PONV in the PACU in our population of cancer patients. We do not have enough data to

conclude that this new strategy was fully responsible for the reduction in heavy PONV, as uncertainty about other confounding factors, such as compliance, morphine consumption, and missing data, should also be considered. In addition, before generalizing this protocol, other factors should also be considered, including cost and side effects.[21] Overall, however, this study showed once again that AIMS systems can serve in quality assurance programs over decades, even if a major switch in equipment or clinical protocol is performed at some point.

Funding

Internal funding of Department of Anesthesia Gustave Roussy Institute. Villejuif France.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Sridharan K, Sivaramakrishnan G. Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: network meta-analysis of randomized clinical trials and trial sequential analysis. Int J Surg. 2019;69:1–12.
2. Ngo AL, Orhurhu V, Urits I, et al. Extended release granisetron: review of pharmacologic considerations and clinical role in the perioperative setting. Saudi J Anaesth. 2019;13:231–6.
3. Jeyabalan S, Thampi SM, Karuppusami R, Samuel K. Comparing the efficacy of aprepitant and ondansetron for the prevention of Postoperative Nausea and Vomiting (PONV): a double blinded, randomised control trial in patients undergoing breast and thyroid surgeries. Indian J Anaesth. 2019;63:289–94.
4. Hossain MM, Begum M, Hossain MM, et al. Efficacy of palonosetron as antiemetic prophylaxis for post operative patients. Mymensingh Med J. 2019;28:222–9.
5. de Morais LC, Sousa AM, Flora GF, Grigio TR, Guimaraes GMN, Ashmawi HA. Aprepitant as a fourth antiemetic prophylactic strategy in high-risk patients: a double-blind, randomized trial. Acta Anaesthesiol Scand. 2018;62:483–92.
6. Motamed C, Bourgain JL. Benefits and possible improvements of an anaesthesia information management system in a quality assurance programme. Br J Anaesth. 2014;113:885–6.
7. Motamed C, Bourgain JL. Postoperative nausea and vomiting in the post-anesthetic care unit, a 5-year survey of a quality assurance program in surgical cancer patients. Bull Cancer. 2015;102:405–10.
8. Apfelbaum JL, Silverstein JH, Chung FF, et al. Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. Anesthesiology. 2013;118:291–307.
9. Bailey P, White PF. Droperidol editorial: making a mountain out of a mole hill! Anesthesiology. 2003;99:760–1, author reply 1.
10. Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology. 2005;102:1094–100.
11. Charbit B, Alvarez JC, Dasque E, Abe E, Demolis JL, Funck-Brentano C. Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study. Anesthesiology. 2008;109:206–12.
12. Kolodzie K, Apfel CC. Nausea and vomiting after office-based anesthesia. Curr Opin Anaesthesiol. 2009;22:532–8.
13. Dewinter G, Staelens W, Veef E, Teunkens A, Van de Velde M, Rex S. Simplified algorithm for the prevention of postoperative nausea and vomiting: a before-and-after study. Br J Anaesth. 2018;120:156–63.
14. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693–700.
15. Apfel CC, Stoecklein K, Lipfert P. PONV: a problem of inhalational anaesthesia? Best Pract Res Clin Anaesthesiol. 2005;19:485–500.
16. Arif AS, Kaye AD, Frost E. Postoperative nausea and vomiting—a review. Middle East J Anaesthesiol. 2001;16:127–54.
17. Collins SJ, Robinson AL, Holland HF. A comparison between total intravenous anaesthesia using a propofol/alfentanil mixture and an inhalational technique for laparoscopic gynaecological sterilization. Eur J Anaesthesiol. 1996;13:33–7.
18. Camu F, Lauwers MH, Verbessem D. Incidence and aetiology of postoperative nausea and vomiting. Eur J Anaesthesiol. 1992;6:25–31.
19. Kenny GN. Risk factors for postoperative nausea and vomiting. Anaesthesia. 1994;49:6–10.
20. Motamed C, Bourgain JL. Trend of analgesic consumption and pain scores in the post anesthetic care unit (A 9-year survey in surgical cancer patients). Bull Cancer. 2011;9:E90–4.
21. Aubrun F, Ecoffey C, Benhamou D, et al. Perioperative pain and post-operative nausea and vomiting (PONV) management after day-case surgery: the SFAR-OPERA national study. Anaesth Crit Care Pain Med. 2019;38:223–9.

Brazilian Journal of Anesthesiology 2022;72(6): 768—773

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Changes in gap junction proteins Connexin30.2 and Connexin40 expression in the sinoatrial node of rats with dexmedetomidine-induced sinus bradycardia

Yong-Qiang Yin[a], **Yi Zhong**[b,*], **Yu Zhu**[a], **Lei Tian**[a]

[a] *Guizhou Medical University, Guiyang, China*
[b] *Affiliated Hospital of Guizhou Medical University, Department of Anesthesiology, Guiyang, China*

Received 17 September 2019; accepted 14 May 2022
Available online 23 May 2022

KEYWORDS
Autonomic nerve system;
Connexins;
Dexmedetomidine;
Sinus bradycardia

Abstract
Background: Dexmedetomidine (Dex) is widely used, and its most common side effect is bradycardia. The complete mechanism through which Dex induces bradycardia has not been elucidated. This research investigates the expression of gap junction proteins Connexin30.2 (Cx30.2) and Connexin40 (Cx40) within the sinoatrial node of rats with Dex-induced sinus bradycardia.
Methods: Eighty rats were randomly assigned to five groups. Saline was administered to rats in Group C. In the other four groups, the rats were administered Dex to induce bradycardia. In groups D_1 and D_2, the rats were administered Dex at a loading dose of 30 $\mu g.kg^{-1}$ and 100 $\mu g.kg^{-1}$ for 10 min, then at 15 $\mu g.kg^{-1}.h^{-1}$ and 50 $\mu g.kg^{-1}.h^{-1}$ for 120 min separately. The rats in group D_1A and D_2A were administered Dex in the same way as in group D_1 and D_2; however, immediately after the administration of the loading dose, 0.5 mg atropine was administered intravenously, and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min. The sinoatrial node was acquired after intravenous infusion was completed. Quantitative real-time polymerase chain reaction and western blot analyses were performed to measure mRNA and protein expression of Cx30.2 and Cx40, respectively.
Results: The expression of Cx30.2 increased, whereas the expression of Cx40 decreased within the sinoatrial node of rats with Dex-induced sinus bradycardia. Atropine reversed the effects of Dex on the expression of gap junction proteins.
Conclusion: Dex possibly altered the expression of gap junction proteins to slow down cardiac conduction velocity in the sinoatrial node.

* Corresponding author.
E-mail: 490173559@qq.com (Y. Zhong).

https://doi.org/10.1016/j.bjane.2022.05.004

Introduction

Dexmedetomidine (Dex) is widely used for sedation in intensive care units and anesthesia settings. Dex can decrease the level of catecholamine transmitters and increase acetylcholine in the heart. It has a significant inhibitory effect on the functions of the Sinoatrial (SA) and Atrioventricular (AV) nodes,[1] which can reduce heart rate, cause bradycardia and has the potential to induce cardiac arrest.[2,3] Atropine can reverse those cardiac effects.

The main function of cardiac connexins is the metabolic and electrical coupling among myocytes, which is the structural basis for maintaining electrical impulses and closely related to the electrophysiological properties of the unique cardiac conduction system.[4,5] Connexin 30.2 (Cx30.2) and connexin 40 (Cx40) are mainly expressed in the SA and AV nodes, which are essential to maintain normal function of the cardiac conduction system.[6,7] Cx40 has high electrical conductivity, which facilitates the rapid conduction of electrical impulses through cardiomyocytes, to increase the heart rate. However, Cx30.2 has the opposite effect.

We hypothesized that dexmedetomidine-induced bradycardia is caused by the change in Cx30.2 and Cx40 in the SA node of rats. This study determined the expression of Cx30.2 and Cx40 in the SA node of rats with Dex-induced sinus bradycardia, investigated if atropine can reverse the changes in expression, and elucidated the possible associated mechanism of action.

Methods

Animals and protocols

All protocols were approved by the Animal Care Welfare Committee of Guizhou Medical University (n° 1800454). Our study was performed in the laboratory of Guizhou Medical University, and the animals were provided by Guizhou Medical University. Rats were fed for one week in the laboratory to adapt to the new environment, light and dark alternated for 12 hours a day. Healthy adult Sprague-Dawley rats (n = 80) weighing 240—300 g were randomly divided into five groups according to a random number table. Rats with abnormal electrical-cardiac function were excluded. According to other studies,[8,9] combined with our pre-experiment, we chose different doses of Dex in our experiment. The rats in group C (control group) were administered normal saline at a loading dose of 60 $mL.kg^{-1}.h^{-1}$ for 10 min and then at 10 $mL.kg^{-1}.h^{-1}$ for 120 min. In group D_1, the rats were administered Dex at a loading dose of 30 $\mu g.kg^{-1}$ for 10 min and then at 15 $\mu g.kg^{-1}.h^{-1}$ for 120 min. The rats in group D_1A were administered Dex the same way as in group D_1; however, immediately after the administration of the loading dose of Dex, 0.5 mg atropine (Suicheng Pharmaceutical Co., Ltd., Henan, China) was administered intravenously and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min. In group D_2, the rats were administered Dex at a loading dose of 100 $\mu g.kg^{-1}$ for 10 min and then at 50 $\mu g.kg^{-1}.h^{-1}$ for 120 min. The rats in group D_2A were administered Dex in the same way as group D_2, but immediately after the administration of the loading dose of Dex, 0.5 mg atropine was administered intravenously and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min.

Experiments

Rats were anesthetized with sodium pentobarbital (50 $mg.kg^{-1}$, intraperitoneal injection). After the loss of righting reflexes, the animals were placed on their backs on a wooden board with their legs restrained by adhesive tape. Local anesthesia (0.5% lidocaine) was administered before femoral artery and vein catheterization. Small needle electrodes were inserted into the skin of the limbs and connected to the BL-420F information data acquisition and processing system (Chengdu Thaimeng software Co. Ltd., Chengdu, China) by crocodile clips to acquire standard lead II Electrocardiogram (ECG) data. The femoral artery was connected to the BL-420F by a polyvinyl chloride infusion extension tube to continuously monitor invasive arterial blood pressure. The femoral vein was connected to an infusion pump by an infusion extension tube to administer different drugs as per previously described procedures. The rats were administered continuous oxygen with oxygen flows of 2 $L.min^{-1}$ throughout the experiment, and SpO_2 was simultaneously monitored using a PM-9000 monitor (Mindraymedical international Co., Ltd., Shenzhen, China). During the experiment, the rats with Mean Arterial Pressure (MAP) < 70 mmHg, Heart Rate (HR) < 250 bpm after anesthesia, or ECG indicative of arrhythmia were excluded. The rats were divided into groups according to their original random numbers.

Isolation of the SA node

Thoracotomy was performed on the rats after anesthetizing the chest area with 0.5% lidocaine, and the heart was rapidly excised and immersed in ice-cold Tyrode's solution in order to stop the heartbeat. The sinus node tissue was isolated as previously described[5] after further pruning of the well-exposed crista terminalis. The superior vena cava, inferior vena cava, crista auricularis dextra, and sulcus terminalis were used as the location markers of the SA node. The sulcus terminalis was considered the center and was removed from the back along the long axis of the venous sinus. The position located at the lower left point parallel to the sulcus terminalis at a distance of 5 mm was then removed by eye scissors. The upper edge of the sinus node was determined by the transection from above the crista auricularis dextra to the back of the crista auricularis dextra, and the lower edge was determined by the transection of the ostium venae cavae inferiors. Finally, the long strip of sinus node tissue was exposed. All biopsies had an approximate volume of 1 × 2 mm^3, and there were 16 samples in each group. Eight tissue samples were stored in individual Eppendorf safe-lock tubes prefilled with 0.5 mL RNA at 4°C overnight followed by storage at -80°C until quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) analysis. The other eight samples were preserved at -80°C for western blot assays.

Time point monitoring

The BL-420F was used to monitor the HR and MAP of the rats throughout the experiment. HR and MAP were recorded at T_0 (just before Dex/saline infusion), T_1 (10 min after the beginning of Dex/saline infusion), T_2 (70 min after the

beginning of Dex/saline infusion), and T_3 (130 min after the beginning of Dex/saline infusion).

RNA extraction and qRT-PCR

We employed magnetic bead separation to obtain mRNA from the SA node according to the manufacturer's instructions (Invitrogen, USA), which was then reverse transcribed into cDNA using a first strand Cdna synthesis kit (Roche, Switzerland). A fluorescent quantitative kit (Light cycler 480 sybr green 1 master, Roche, Switzerland) was used to complete the amplification reaction. qRT-PCR was carried out using the Real-Time PCR Detection System (CFX96, Bio-Rad Laboratories, Inc. USA). All the experiments were performed in triplicate, and mRNA levels were standardized to that of Glyceraldehyde-Phosphate Dehydrogenase (GAPDH). We examined the melting curves for each reaction to ensure the amplification of a single PCR product. Relative gene expression was determined by the comparative C_T method. The primers used in the analysis are listed in Table 1.

Western blotting

Proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis on 8% tris-acetate gels before being transferred onto polyvinylidene difluoride membranes. After blocking with bovine serum albumin (5%), the membranes were incubated overnight at 4°C with rabbit polyclonal antibodies against mouse proteins Cx30.2 (1:1000; Abcam Trading Co., Ltd., Shanghai, China), Cx40 (1:2000; GeneTex Technologies Inc., USA), and GAPDH (1:8000; Abcam Trading Co., Ltd., Shanghai, China) as loading control. This was followed by incubation with goat anti-rabbit IgG secondary antibody (1:12000; Abcam Trading Co., Ltd., Shanghai, China) for 1h at 22 ± 2°C and washing of the membranes with tris-buffered saline containing tween 20. Reactive protein bands were detected using enhanced chemiluminescence and visualized using the Bio-Rad system. Bands from the resulting pictures were then quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Statistical analysis

Data were analyzed using SPSS 20.0 software and expressed as mean ± standard deviation. Statistical differences were assessed using one-way analysis of variance (ANOVA) and repeated measures analysis of variance. A p-value < 0.05 indicated statistical significance.

Results

Effects of Dex and Dex combined with atropine on HR in rats with sinus bradycardia

There were no significant differences in HR (beats/min) at T_1 (352 ± 40), T_2 (343 ± 42), and T_3 (335 ± 39) compared to HR at T_0 (350 ± 44) in group C ($p > 0.05$). HR was significantly lower at T_1 (244±25), T_2 (287 ± 29), and T_3 (262 ± 27) than at T_0 (355 ± 36) in groups D_1 ($p < 0.05$), whereas HR at T_2 was higher than at both T_1 and T_3 ($p < 0.05$). In group D_2, HR was lower at T_1 (212 ± 23), T_2 (215 ± 23), and T_3 (208 ± 23) than at T_0 (352 ± 38) ($p < 0.05$), and there was no difference in HR at T_1, T_2, and T_3 ($p > 0.05$). In group D_1A, HR was significantly lower at T_1 (241 ± 25) and at T_3 (315 ± 32) than at T_0 (350 ± 36) ($p < 0.05$), but no significant difference in HR was observed at T_2 (340 ± 35) ($p > 0.05$). HR was higher at T_2 and T_3 than at T_1 ($p < 0.05$). In groups D_2A, HR was significantly lower at T_1 (216 ± 22), T_2 (307 ± 31) and T_3 (286 ± 23) than at T_0 (361 ± 36) ($p < 0.05$), and HR was higher at T_2 and T_3 than at T_1 ($p > 0.05$). HR was significantly decreased at $T_{1\text{-}3}$ in groups D_1, D_2, and D_2A compared to group C ($p < 0.05$). Only the HR at T_1 in group D_1A was decreased compared to group C ($p < 0.05$) (Table 2).

Changes in the expression level of Cx30.2 and Cx40 within the SA node of rats with sinus bradycardia

The qRT-PCR and western blot analyses revealed that the expression of Cx30.2 was significantly increased in groups D_1 (mRNA, 2.75 ± 0.51; protein, 1.43 ± 0.18), D_2 (mRNA, 4.84 ± 0.83; protein, 2.40 ± 0.06), and D_2A (mRNA, 2.43 ± 0.23; protein, 1.43 ± 0.11) compared with group C (mRNA, 1.04 ± 0.03; protein, 1.00 ± 0.02) ($p < 0.05$), and was significantly higher in group D_2 than in group D_1 ($p < 0.05$). Moreover, mRNA and protein levels of Cx30.2 in groups D_1A (mRNA, 1.29 ± 0.30; protein, 1.09 ± 0.04) and D_2A were significantly decreased compared to those in the corresponding groups (groups D_1 and D_2, respectively) ($p < 0.05$), and was significantly higher in group D_2A than in group D_1A ($p < 0.05$). The qRT-PCR and western blotting results indicate that the mRNA and protein expression levels of Cx40 in groups D_1 (mRNA 0.63 ± 0.14; protein 0.73 ± 0.14) and D_2 (mRNA 0.34 ± 0.18; protein 0.56 ± 0.11) decreased compared to those in group C (mRNA, 1.11 ± 0.08; protein, 1.00 ± 0.04) ($p < 0.05$). The expression levels of Cx40 in Group D_2 were lower than those in group D_1 ($p < 0.05$). In addition, the expression levels of Cx40 in groups D_1A (mRNA, 1.08 ± 0.12; protein, 0.96 ± 0.07) and D_2A (mRNA, 0.96 ± 0.13, protein, 0.96 ± 0.13) were significantly increased compared to those in the

Table 1 Primers for the targeted genes.

Target gene	Primer sequence	Amplified length (bp)
GAPDH	Upstream primer- F: 5'TCTCTGCTCCTCCCTGTTC3' Downstream primer- R: 5' ACACCGACCTTCACCATCT3'	87
Cx30.2	Upstream primer- F: 5'AGCAGGAGGAGTTCGTGT3' Downstream primer- R: 5'ACAGCCAGAAGCGGTAGT 3'	96
Cx40	Upstream primer- F: 5′ACGTCTGCAGCATTGTCATC-3' Downstream primer- R: 5′CCCAGGTGGTAGAGTTCAGC-3′	147

Table 2 Changes in Heart Rate (HR) of rats with dexmedetomidine-induced sinus bradycardia.

Monitoring parameter	Group	T0	T1	T2	T3
HR (beats/min)	C	350 ± 44	352 ± 40	343 ± 42	335 ± 39
	D1	355 ± 36	244 ± 25[a,b]	287 ± 29[a,b,c]	262 ± 27[a,c]
	D1A	350 ± 36	241 ± 25[a,c]	340 ± 35[b]	315 ± 32[a,b]
	D2	352 ± 38	212 ± 23[a,c]	215 ± 23[a,c]	208 ± 23[a,c]
	D2A	361 ± 36	216 ± 22[a,c]	307 ± 31[a,b,c]	286 ± 23[a,b,c]

In group C (control group), rats were administered normal saline. In groups D_1 and D_1A rats were administered dexmedetomidine at a loading dose of 30 $\mu g.kg^{-1}$ for 10 min and then at 15 $\mu g.kg^{-1}.h^{-1}$ for 120 min. In groups D_2 and D_2A, rats were administered dexmedetomidine at a loading dose of 100 $\mu g.kg^{-1}$ for 10 min and then at 50 $\mu g.kg^{-1}.h^{-1}$ for 120 min. Moreover, in groups D1A and D2A, rats were administered atropine at a loading dose of 0.5 mg and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min. Compared to T_0.

[a] $p < 0.05$; compared to T_1.

[b] $p < 0.05$; compared to group C.

[c] $p < 0.05$. (Data are presented as mean ± standard deviation, n = 16 per group).

corresponding groups (groups D_1 and D_2, respectively) ($p < 0.05$) (Figs. 1 and 2).

Discussion

The heart is innervated by sympathetic and vagal nerves. Among the factors that influence the functions of SA and AV nodes, the autonomic nervous system plays the most important role.[10] A previous study reported that Dex, a highly selective α2-receptor agonist, caused heart rate alterations via the suppression of the activities of the peripheral and central sympathetic nerves, thereby inducing vagal-dominant conditions.[11] With the stimulation of α2-receptor binding in the locus coeruleus, Dex inhibits the release of neuronal norepinephrine and blocks the descending transmission of sympathetic nerve activity, thereby reducing adrenaline release from the adrenal medulla. In addition, Dex decreases sympathetic tone by inhibiting norepinephrine release from sympathetic terminals in the periphery, resulting in the reduction in blood pressure and HR.[12,13] In recent years, animal experiments have shown that Dex can directly activate the cardiac vagal nerve. Histocytological studies have also demonstrated the presence of α2-adrenergic receptors in the ambiguus nucleus, dorsal nucleus, and tractus solitarius nucleus of the medulla oblongata.[8,9] Sharp et al.[14] reported that Dex selectively decreased both GABAergic and glycinergic inhibitory input to the nucleus ambiguus and cardiac vagal neurons, with no significant effect on excitatory input. Decreasing inhibitory neurotransmission to cardiac vagal neurons results in an increase in the excitability of parasympathetic neurons that project to the

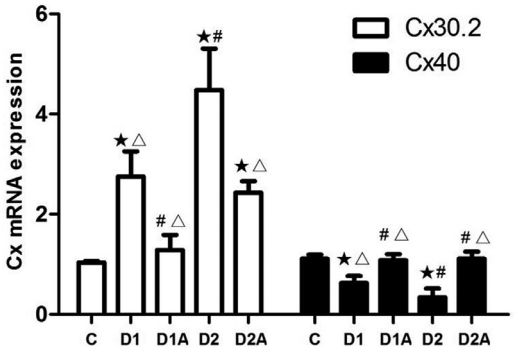
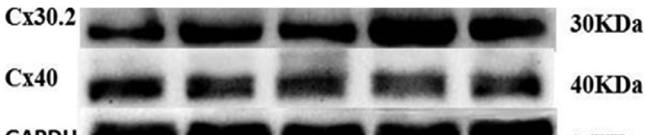


Figure 1 mRNA expression of Cx30.2 and Cx40 in rats with dexmedetomidine-induced sinus bradycardia. C (control group), the rats were administered normal saline. In groups D_1 and D_1A, the rats were administered Dex at a loading dose of 30 $\mu g.kg^{-1}$ for 10 min and then at 15 $\mu g.kg^{-1}.h^{-1}$ for 120 min. Groups D_2 and D_2A rats were administered Dex at a loading dose of 100 $\mu g.kg^{-1}$ for 10 min and then at 50 $\mu g.kg^{-1}.h^{-1}$ for 120 min. Moreover, the rats in groups D_1A and D_2A were administered atropine at a loading dose of 0.5 mg and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min. ★$p < 0.05$ vs. Group C, #$p < 0.05$ vs. Group D_1; △$p < 0.05$ vs. Group D_2. Data are presented as mean ± standard deviation, n = 8 per group).



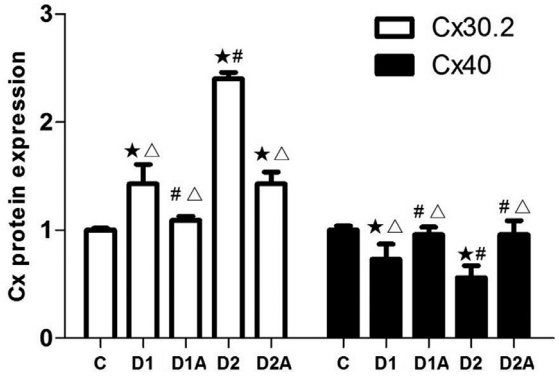


Figure 2 Protein expression of Cx30.2 and Cx40 in rats with dexmedetomidine-induced sinus bradycardia. In Group C, the rats were administered normal saline. The rats in groups D_1 and D_1A were administered Dex at a loading dose of 30 $\mu g.kg^{-1}$ for 10 min and then at 15 $\mu g.kg^{-1}.h^{-1}$ for 120 min. In groups D_2 and D_2A, the rats were administered Dex at a loading dose of 100 $\mu g.kg^{-1}$ for 10 min and then at 50 $\mu g.kg^{-1}.h^{-1}$ for 120 min. Moreover, in groups D_1A and D_2A, the rats were administered atropine at a loading dose of 0.5 mg and then at 0.5 $mg.kg^{-1}.h^{-1}$ for 120 min. ★$p < 0.05$ vs. Group C, #$p < 0.05$ vs. Group D_1; △$p < 0.05$ vs. Group D_2. Data are presented as mean ± standard deviation, n = 8 per group.

heart. Shimizu et al.[8,15] demonstrated that 100 $\mu g.kg^{-1}$ medetomidine (a racemic mixture of two stereoisomers, Dex and levomedetomidine, with Dex as the active enantiomer) activates the cardiac vagal nerve via the modulation of baroreflex control of the central nervous system.

A bradycardia rat model is considered to be successfully established if the HR decreases by > 30% and is stable for 30 min.[16] Shimizu et al.[8,9] demonstrated that both 10 and 100 $\mu g.kg^{-1}$ medetomidine significantly decreased norepinephrine levels in cardiac dialysis. Intravenous medetomidine (100 $\mu g.kg^{-1}$) significantly increased the cardiac dialysate acetylcholine concentrations both in rabbits and rats and had an effect equivalent to electrical vagal stimulation at 10 Hz (20 Hz electrical vagal stimulation may cause AV block or sinus arrest). We chose a loading dose of Dex (30 $\mu g.kg^{-1}$) as the low-dose group, which can just lead to HR decrease > 30% in rats. It is the threshold dose to make the model of sinus bradycardia successfully constructed. We chose a loading dose of Dex (100 $\mu g.kg^{-1}$) as the high-dose group. It is the threshold dose to make the HR decreased to a liminal value in rats, the heart rate did not decrease even as the drug dose increased.

A large number of studies have revealed that different types of gap junction channels have different conductance and that their ionic selectivity and permeation properties remain different.[7] In the cardiac conduction system, Cx40 and Cx43 have high unitary conductance, whereas Cx30.2 and Cx45 have low unitary conductance. It is now known that the SA and AV nodes are specialized tissues with slow impulse propagation that only express Cx30.2 (9 pS) and Cx45 (32 pS).[17] The co-expression of Cx30.2 and Cx40 within the AV node has been detected in mice. In addition, the homotypic gap junction channels formed by Cx40 have high unitary conductance (180 pS), whereas the Cx43/Cx45 heterotypic gap junctions formed by Cx30.2/Cx40 have relatively low unitary conductance (18 pS).[18] Significant changes in ECG and the indicators of the conduction function of the AV node have been reported in Cx30.2 and Cx40 gene-deficient mice.[17,19] Cx30.2, as an important marker of slow conduction, and Cx40, as an important marker of rapid conduction, contribute to the modulation of electrical impulse propagation in different areas of the AV node,[4,20] thereby maintaining normal AV conduction.

Compared to baseline HR, there was a reduction in the HR of rats in groups D_1 and D_2 by 31% and 40%, respectively, but neither AV block nor sinus arrest was observed. The MAP of the two experimental groups was significantly lower than that of the control group, and the expression levels of Cx30.2 in groups D_1 and D_2 were significantly higher than in group C. In addition, the expression levels of Cx40 in groups D_1 and D_2 were significantly lower than that in group C. Gap junctions are membrane channels that mediate the cell-to-cell movement of ions and small metabolites. In the heart, gap junctions play an important role in impulse conduction, and intercellular coupling disorders are an important cause of arrhythmia. The mechanism by which Dex influences the expression of Cx30.2 and the involvement of increased vagal activity have remained unknown.

The induction of vagal-dominant conditions by suppressing the activity of sympathetic nerve and directly increasing the activity of cardiac vagal nerve are widely recognized as the mechanisms by which Dex induces change in autonomic balance. We used atropine, a competitive and reversible antagonist of muscarinic acetylcholine receptors, to block M_2 receptors in the SA node. According to Jammes,[21] 0.5 mg atropine can completely block cholinergic neurotransmission in the heart of rats, thereby essentially relieving the inhibition of the vagus nerve on the heart. The results indicate that the expression of Cx30.2 was significantly reduced in groups D_1A and D_2A compared to groups D_1 and D_2, and the expression of Cx40 was significantly increased in groups D_1A and D_2A compared to groups D_1 and D_2. It can be inferred that the increased vagal activity may be one of the factors responsible for the changes in the levels of expression of Cx30.2 and Cx40 within the SA node in rats with Dex-induced sinus bradycardia. However, the HR in group D_2A was still significantly lower than that in group C, and the expression of Cx30.2 in group D_2A was significantly higher than that in group C. Based on our experimental results, we hypothesize that other mechanisms may be associated with the effect of high-dose Dex on the expression of Cx30.2,[22] and a further study is needed to identify the factors that are associated with the changes in the expression of Cx30.2.

Our study showed that bradycardia caused by prolonged (about 2h) Dex treatment may lead to changes in the expression of connexins in the SA node. In recent years, some studies have reported that Dex may cause cardiac arrest.[2,3] There is a study showing that changes of connexin expression in the heart can lead to abnormal conduction of electrical impulses, leading to arrhythmias and even sudden death.[23] The sinoatrial node is the main pacemaker of the heart, and its dysfunction may be more likely to cause arrhythmias. Considering the present findings, we suggest caution in the administration of Dex in patients with an impaired cardiac conduction system, especially those displaying SA node dysfunction. If Dex-related bradycardia occurs, atropine could be used to reduce the incidence of cardiac adverse events.

There were some limitations in our study. First of all, the cause of protein change in rats was not clear. Change of neurotransmitters in the sinoatrial node, or the direct effects of Dex on the sinoatrial node were all possible reasons. Secondly, in clinical anesthesia, although administration of Dex was in low dosage, the incidence of bradycardia was high. The purpose of our study was to observe the change in gap junction protein connexins in the sinoatrial node of bradycardia in rats. In order to ensure rats presented bradycardia, we choose relatively large doses of Dex. It is possible that the effects of Dex in humans could be somewhat different regarding the expression of the same proteins.

Conclusions

In summary, the expression of the low-conductive gap junction protein, Cx30.2, within the SA node was increased in rats with Dex-induced sinus bradycardia, and the expression of the high-conductive gap junction protein, Cx40, was decreased. The change in the expression of gap junction proteins, Cx30.2 and Cx40, is one of the causes of cardiac sinus bradycardia, and autonomic nervous activity is involved in the regulation of these proteins.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by Guizhou Provincial Natural Science Foundation ZK [2021]-433.

References

1. Ergul Y, Unsal S, Ozyilmaz I, et al. Electrocardiographic and electrophysiologic effects of dexmedetomidine on children. Pacing Clin Electrophysiol. 2015;38:682—7.
2. Takata K, Adachi YU, Suzuki K, et al. Dexmedetomidine-induced atrioventricular block followed by cardiac arrest during atrial pacing: A case report and review of the literature. J Anesth. 2014;28:116—20.
3. Zhang X, Schmidt U, Wain JC, et al. Bradycardia leading to asystole during dexmedetomidine infusion in an 18 year-old double-lung transplant recipient. J Clin Anesth. 2010;22:45—9.
4. Lo CW. Role of gap junctions in cardiac conduction and development: Insights from the connexin knockout mice. Circ Res. 2000;87:346—8.
5. Jansen JA, van Veen TA, de Bakker JM, et al. Cardiac connexins and impulse propagation. J Mol Cell Cardiol. 2010;48:76—82.
6. Munshi NV, McAnally J, Bezprozvannaya S, et al. Cx30.2 enhancer analysis identifies gata4 as a novel regulator of atrioventricular delay. Development. 2009;136:2665—74.
7. Kreuzberg MM, Sohl G, Kim JS, et al. Functional properties of mouse connexin30.2 expressed in the conduction system of the heart. Circ Res. 2005;96:1169—77.
8. Shimizu S, Akiyama T, Kawada T, et al. Medetomidine, an alpha (2)-adrenergic agonist, activates cardiac vagal nerve through modulation of baroreflex control. Circ J. 2012;76:152—9.
9. Kawada T, Akiyama T, Shimizu S, et al. Sympathetic afferent stimulation inhibits central vagal activation induced by intravenous medetomidine in rats. Acta Physiol. 2013;209:55—61.
10. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: An elegant interaction and emerging concepts. Cardiol Rev. 2010;18:275—84.
11. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382—94.
12. Snapir A, Posti J, Kentala E, et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. Anesthesiology. 2006;105:902—10.
13. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: A meta-analysis. Intensive Care Med. 2010;36:926—39.
14. Sharp DB, Wang X, Mendelowitz D. Dexmedetomidine decreases inhibitory but not excitatory neurotransmission to cardiac vagal neurons in the nucleus ambiguus. Brain Res. 2014;1574:1—5.
15. Shimizu S, Akiyama T, Kawada T, et al. Medetomidine suppresses cardiac and gastric sympathetic nerve activities but selectively activates cardiac vagus nerve. Circ J. 2014;78:1405—13.
16. Li Y, Fu X, Zhang Z, et al. Knockdown of cardiac kir3.1 gene with sirna can improve bradycardia in an experimental sinus bradycardia rat model. Mol Cell Biochem. 2017;429:103—11.
17. Kreuzberg MM, Schrickel JW, Ghanem A, et al. Connexin30.2 containing gap junction channels decelerate impulse propagation through the atrioventricular node. Proc Natl Acad. 2006;103:5959—64.
18. Stein M, van Veen TA, Remme CA, et al. Combined reduction of intercellular coupling and membrane excitability differentially affects transverse and longitudinal cardiac conduction. Cardiovasc Res. 2009;83:52—60.
19. Kirchhoff S, Nelles E, Hagendorff A, et al. Reduced cardiac conduction velocity and predisposition to arrhythmias in connexin40-deficient mice. Curr Biol. 1998;8:299—302.
20. Schrickel JW, Kreuzberg MM, Ghanem A, et al. Normal impulse propagation in the atrioventricular conduction system of cx30.2/cx40 double deficient mice. J Mol Cell Cardiol. 2009;46:644—52.
21. Jammes Y, Joulia F, Steinberg JG, et al. Endogenous adenosine release is involved in the control of heart rate in rats. Can J Physiol Pharmacol. 2015;93:667—75.
22. Monzen K, Nagai R, Komuro I. A role for bone morphogenetic protein signaling in cardiomyocyte differentiation. Trends Cardiovasc Med. 2002;12:263—9.
23. Severs NJ, Bruce AF, Dupont E, et al. RemodeUing of gap junctions and connexin expression in diseased myocardium. Cardiovasc Res. 2008;80:9—19.

Brazilian Journal of Anesthesiology 2022;72(6):774–779

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

An alternative approach for blocking the superior trunk of the brachial plexus evaluated by a single arm clinical trial

Thiago Nouer Frederico [a], **Rioko Kimiko Sakata** [a,*], **Luiz Fernando dos Reis Falcão** [a], **Paulo Cesár Castello Branco de Sousa** [a], **Fernanda Melhmann** [a], **Cesar Augusto Simões** [b], **Leonardo Henrique Cunha Ferraro** [a]

[a] *Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[b] *Universidade de São Paulo, São Paulo, SP, Brazil*

Received 5 June 2020; accepted 25 October 2020
Available online 17 February 2021

KEYWORDS
Ultrasonography;
Brachial plexus;
Nerve block

Abstract
Background: Interscalene brachial plexus block is associated with phrenic nerve paralysis. The objective of this study was to evaluate an alternative approach to interscalene brachial plexus blocks in terms of efficacy, grade of motor and sensory blockade, and phrenic nerve blockade.
Methods: The study was prospective and interventional. The ten living patients studied were 18 to 65 years old, ASA physical status I or II, and submitted to correction of rotator cuff injury. A superior trunk blockade was performed at the superior trunk below the omohyoid muscle, without blocking the phrenic nerve. The needle was advanced below the prevertebral layer until contacting the superior trunk. In order to guarantee the correct positioning of the needle tip, an intracluster pattern of the spread was visualized. The block was performed with 5 mL of 0.5% bupivacaine in ten patients. In the six cadavers, 5 mL of methylene blue was injected. Diaphragmatic excursion was assessed by ultrasonography of the ipsilateral hemidiaphragm. In three patients, pulmonary ventilation was evaluated with impedance tomography. Pain scores and analgesic consumption were assessed in the recovery room for 6 hours after the blockade.
Results: In the six cadavers, methylene blue didn't reach the phrenic nerve. Ten patients underwent arthroscopic surgery, and no clinically phrenic nerve paralysis was observed. No patient reported pain during the first 6 hours.
Conclusions: This study suggests that this new superior trunk approach to block the superior trunk may be an alternative technique to promote analgesia for shoulder surgery in patients with impaired respiratory function.

* Corresponding author.
E-mail: rsakata@unifesp.br (R.K. Sakata).

https://doi.org/10.1016/j.bjane.2020.10.015

Introduction

Interscalene Brachial Plexus Block (ISB) is the most commonly performed regional anesthesia technique for perioperative shoulder analgesia. This technique promotes the blockade of all fibers responsible for the innervation of the bone and muscular components of the shoulder, promoting effective postoperative analgesia. However, in the ISB, the local anesthetic is injected close to the phrenic, causing blocking of this nerve in practically 100% of cases when large volumes of local anesthetic are administered.[1] Therefore, ISB technique may be contraindicated in patients with limited pulmonary reserve or who do not tolerate a 25% reduction in lung capacity. Low volumes of local anesthetics have been used to allow phrenic nerve sparing. Despite the low-volume technique has reduced the incidence of hemi-diaphragmatic paralysis to 27–45%,[2–4] the incidence of phrenic nerve block is still high.

An alternative to ISB could be the superior trunk block and the sub-omohyoid suprascapular nerve block.[5,6] Some studies have shown that both techniques promote similar analgesic effect as the ISB for shoulder surgeries,[7,8] therefore, they may be substitutes for ISB to allow phrenic nerve sparing.[7]

However, recent studies have shown that those two techniques could compromise respiratory function through phrenic nerve block.[8,9] One hypothesis for this impairment of the respiratory function could be the endpoint of injection chosen by the authors. The most common anatomical variations are: C5 root emerging anterior to the anterior scalene muscle and following its path between the anterior scalene muscle and the sternocleidomastoid muscle until it reaches the remainder of the plexus in the supraclavicular area; C5 root emerging from its foramen, inside anterior scalene muscle, transfixing it and following its path between the anterior scalene muscle and the sternocleidomastoid muscle until finding the remainder of the plexus in the supraclavicular area; and C5 and C6 roots emerging from its foramens inside anterior scalene muscle and transfixing it to find the remainder of the plexus in the supraclavicular area (Figure 1). This variation keeps superior trunk structures nearer to the phrenic nerve for a longer pathway or delay the formation of the superior trunk. In this case, C5 reaches the remaining of brachial plexus only in the supraclavicular area because it might travel around the antero-lateral border of the anterior scalene muscle.

An intra-cluster injection in the superior trunk below the prevertebral layer of the deep cervical fascia in the supraclavicular area could limit the dispersion to the phrenic nerve without compromising analgesic effect for patients undergoing shoulder surgery.

The aim of this study was to evaluate the analgesic effect and the respiratory function after a block of the superior trunk in the area below the omohyoid muscle.

Methods

Study design: The study was prospective and a descriptive single-arm clinical trial.

Settings: The data of the patients were collected at the Hand and Upper Limb Surgery Section. The cadaver data were collected at the Service of Verification of Deaths.

Register: The study was registered at ClinicalTrials NCT03512990.

Ethical aspects

The study was performed after approval by the Ethics Committee (CEP 1350/2017; Adress: Rua Botucatu 740; Reference person: Miguel Roberto Jorge), and written informed consent was obtained from the participants. It was conducted according to ethical principles and the Declaration of Helsinki.

Inclusion and exclusion criteria

Participants

Ten living patients of both genders aged between 18 and 65 years, American Society of Anesthesiologists (ASA) physical status I or II, body mass index of less than 35 $kg.m^{-2}$ and were submitted to shoulder correction of rotator cuff injury, were included. Patients with cognitive impairment, infection at the blockade puncture site, coagulopathy, using anticoagulants, allergic to drugs, and pregnant were excluded from the study.

Interventions

Block technique

The patients were monitored with cardioscope, noninvasive arterial blood pressure and pulse oximetry.

The superior trunk blockade was performed with no sedation for better assessment of respiratory function. After antisepsis with chlorhexidine and local anesthesia with 1% lidocaine without epinephrine, a high-frequency linear transducer (M-Turbo R System, a 38×, 6–13 MHz, Fujifilm SonoSite Inc, Bothell, WA, USA) was used for the examination of the area. At the lower anterolateral side of the neck (posterior triangle), the brachial plexus was visualized in the scalene area. A careful examination of the region was carried out, identifying the transverse processes of the C7 and C6 roots. The transverse process of C7 has only a posterior tubercle while C6 has both tubercles. With these structures identified, it was possible to identify the roots of C5 and C6 and follow them until the moment they joined, forming the superior trunk. This junction usually occurs in the interscalene cleft, different anatomical variations of the C5 and C6 roots.

Once the superior trunk was identified, it was followed more distally until the supraclavicular area, below the omohyoid muscle, where it was possible to identify the suprascapular nerve outflow from the superior trunk.[10]

The injection was performed at the point where the superior trunk was positioned in the supraclavicular area, distally to the point where the suprascapular nerve leaves the superior trunk of the brachial plexus.

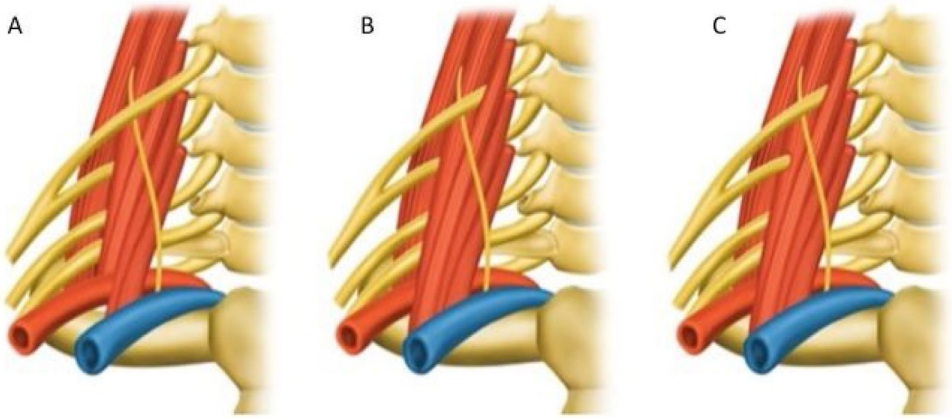


Figure 1 A, C5 root emerging anterior to the Anterior Scalene muscle and following its path between the Anterior Scalene Muscle and the Sternocleidomastoid muscle until it reachs the remainder of the plexus in the supraclavicular area. B, C5 root emerging from its foramen, inside Anterior Scalene muscle, transfixing it, and following its path between the Anterior Scalene Muscle and the Sternocleidomastoid muscle until finding the remainder of the plexus in the supraclavicular area. C, C5 and C6 roots emerging from its foramens inside Anterior Scalene muscle and transfixing it to find the remainder of the plexus in the supraclavicular area.

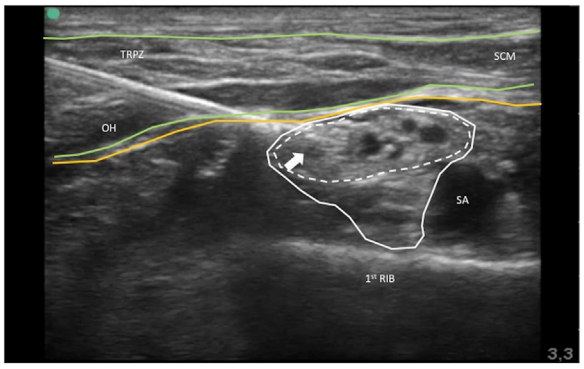


Figure 2 Final needle position, superior trunk intracluster/subparaneural: SA, Subclavian Artery; TRPZ, Trapezius muscle oh- omohyoid muscle; Green, Investing layer of deep cervical fascia; Orange, Pre-vertebral layer of deep cervical fascia; White, Brachial plexus; White dashed, Superior trunk; Solid arrow, Suprascapular nerve still inside brachial plexus sheath.

Block technique

The needle tip (Stimuplex A 50 mm, BBraun, Germany) was positioned deep into the prevertebral layer of the deep cervical fascia, preventing the needle tip from lying in the fascial plane between the investing layer of the deep cervical fascia and the prevertebral layer of deep cervical fascia. This is a loose fascial plane where the lymphatic chain and adipose brown fat are located and may allow easy dispersions towards the phrenic nerve. To ensure the correct position of the tip, an intra-cluster dispersion pattern of the local anesthetic was performed. At this site, 5 mL of 0.5% bupivacaine was injected into the patients (Figure 2).

General anesthesia

After the blockade and phrenic nerve evaluation, all patients underwent general anesthesia with 2 $\mu g.kg^{-1}$ of fentanyl, 2 $mg.kg^{-1}$ of propofol and 0.6 $mg.kg^{-1}$ of rocuronium. Anesthesia was maintained with sevoflurane. For postoperative analgesia, all patients received 2 g of dipyrone and 100 mg of ketoprofen at the end of the surgery. Postoperative analgesia was assessed in the recovery room by numerical scale and supplementary morphine for 6 hours after blockade.

Supplementary analgesia

All the patients could take 2 mg of morphine every 10 minutes as needed at the postanesthetic care room, before leaving the hospital.

Assessment

Analgesic effect

An anesthesiologist not involved in the block evaluated the nerve blocks. The modified Bromage scale[11] was used to assess motor function of the deltoid and biceps, muscles groups of the superior trunk. The sensory block was assessed using a pinprick test with a 25G hypodermic needle, a gauze, and alcohol. The thermal and painful sensitivities of the C5 and C6 dermatomes were examined. Blockade was considered positive when there was absence of thermal distinction, absence of pain to pinprick and motor function $\leq$ 2 by the modified Bromage scale. In the event of a failed block, an interscalene brachial plexus block with 5 mL of 0.5% bupivacaine at C7 level was performed.

Primary outcome was the analgesic effect, and the secondary outcome was the respiratory function.

Phrenic nerve block

The phrenic nerve block was assessed by ultrasound using the real-time movement of the ipsilateral diaphragm. Patients were asked to forcefully inhale through the nose in a sniffing fashion. The test was performed immediately before the block and at 30 minutes, 4 and 6-hours after blockade. The transducer was positioned at the midpoint of the clavicular lines and at the hemidiaphragm level on the ipsilateral side of the block. The movement of the diaphragm was evaluated with the patient in semi-seated position. Diaphragmatic excursion from baseline was measured in centimeters using the digital calipers. A decrease greater

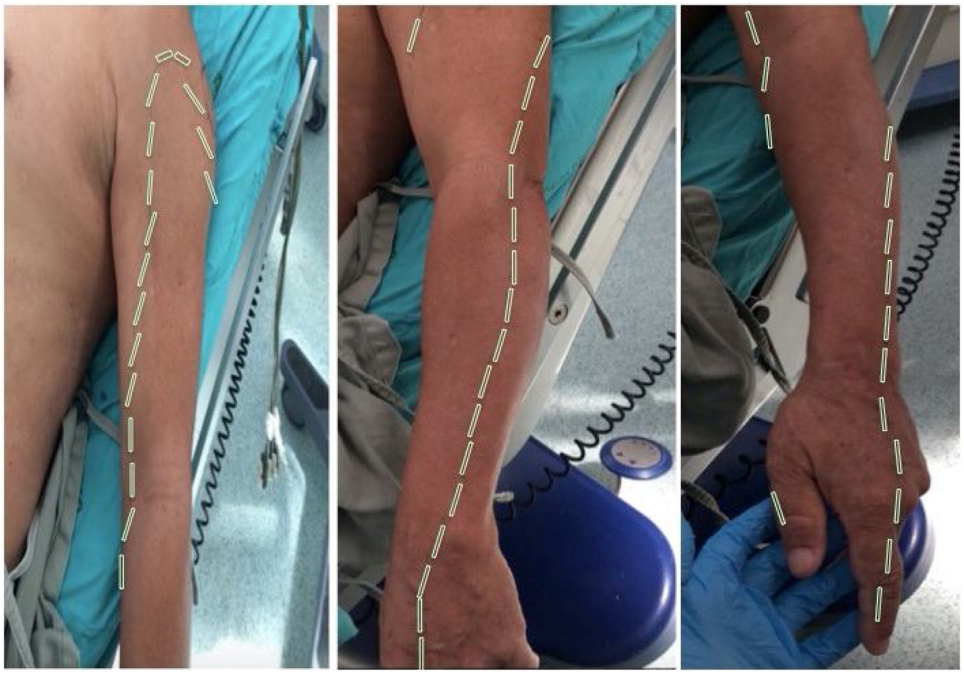


Figure 3 Area of sensory loss.

than 75% was considered hemidiaphragmatic paralysis.[12] In addition, in 3 cases, the evaluation of the respiratory function was performed using impedance tomography (Enlight 1800, Timpel Medical, Sao Paulo, SP, Brazil). This evaluation took place before the blockade, as well as 30 minutes and 4 hours after the blockade.

Cadaver dissection

Blocks were performed on six cadavers using the previously described technique, and only 5 mL of methylene blue was injected.

For the evaluation of the dispersion in cadavers, the cervical region was dissected, exposing the brachial plexus region from the interscalene cleft to the supraclavicular region.

Results

Clinical evaluation

Ten patients undergoing shoulder surgery due to rotator cuff injury received the selective superior trunk block. Participants data is in Table 1. In the evaluation of the blockade, all patients presented motor block of the biceps and deltoid muscles and experienced no pain to the pinprick in the C5 and C6 dermatomes (Figure 3).

No patient presented with phrenic nerve palsy when evaluated by diaphragm ultrasonography (Table 1). In addition, the three patients who were evaluated by impedance tomography showed no variation in the respiratory function.

All procedures occurred without complications. Regarding postoperative analgesia, no patient reported pain (score zero) until 6 hours after the blockade. They were discharged from the hospital without complications and didn't need hospital readmission.

Table 1 Demographic data and diaphragmatic excursion–median (IQR).

Age (years)	48.4 (21–68)
Gender.M / F, n (%)	7 (70) / 3 (30)
ASA,I / II, n (%)	6 (60) / 4 (40)
BMI (kg. m^{-2}) mean (±SD)	25.9 (± 4.2)
Operated side,R / L, n (%)	6 (60) / 4 (40)
Diaphragmatic excursion (cm)	
Baseline	4 (3,0 – 4,3)
30 min	3 (2,5 – 4,0)
4 h	4 (2,5 – 4,5)
6 h	4 (3,0 – 4,5)

M, Male; F, Female; R, Right; L, Left; ASA, American Society of Anesthesiologists physical status; BMI, Body Mass Index; IQR, Interquartile Range; SD, Standard Deviation.

Cadaver dissection

In all dissections, it was observed that methylene blue dispersed inside the brachial plexus but did not reach the phrenic nerve neither by cephalic dispersion nor by medial dispersion (Figure 4). In addition, in all cases, the contrast showed that the solution reached the suprascapular nerve as well.

Discussion

The findings of this study suggest that an intra-cluster injection into the superior trunk, right where suprascapular nerve

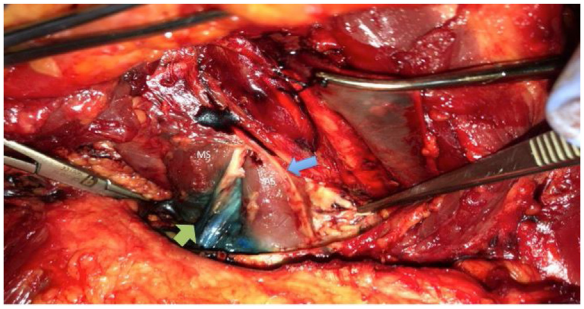


Figure 4 Brachial plexus dissection after methylene blue injection showed that methylene blue was restricted to the brachial plexus, without reaching the phrenic nerve. AS, Anterior Scalene Muscle; MS, Medium Scalene Muscle; Blue Arrow, Phrenic Nerve; Yellow arrow, Accessory nerve.

is branching off, deep to the omohyoid muscle, is an easy, reproducible technique and may be an alternative to a classic interscalene block.

This study shows that, by performing superior trunk block, it was possible to promote satisfactory analgesic effect for patients submitted to shoulder surgery, without compromising respiratory function.

Due to respiratory complications associated with interscalene blockade, new techniques have been studied to promote analgesic effect for shoulder surgeries. In 2014, Burckett-St. Laurent et al.[5] described the selective superior trunk block. This procedure targets the C5 and C6 components of the brachial plexus more distally after they unite into the superior trunk but before the suprascapular nerve branches off. However, the incidence of diaphragmatic involvement may be indirectly proportional to the distance from the nerve roots. Therefore, in this study, a more distal block was chosen, in the supraclavicular area, exactly where the suprascapular nerve is leaving the superior trunk. The results of this study suggest that this more distal approach may be as effective as the superior trunk block described by those authors, but with the potential to further decrease the chance of blocking the phrenic nerve.

Recently, Kim et al. (2019)[8] presented a study with 4.8% of phrenic paralysis with 15 mL of bupivacaine injected at the superior trunk. Renes (2009)[13] described a posterolateral supraclavicular nerve block was used as phrenic nerve sparing. This approach is less suitable for shoulder surgery because of reduced block effect to the suprascapular nerve.[8]

According to the anatomy, the superior trunk is preserved from the time that C5 and C6 join the same sheath, until the suprascapular nerve leaves the common sheath that surrounds the C5 and C6 neural structures. This takes place in the supraclavicular area where the suprascapular nerve starts its antero-posterior trajectory following the omohyoid to scapula.

Kim et al. (2019)[8] used the targeted level of insertion for the injection immediately before the branching point of the suprascapular nerve. We think that identifying the suprascapular nerve branching inside the same sheath is not the end of the superior trunk, but it is a nerve fascicle seen inside the trunk. Just after the suprascapular exits this sheath (in supraclavicular area) we can say that the superior trunk is over and blockade for the shoulder might fail. So, we propose a more distal approach to the superior trunk, outside the interscalene cleft, in the supraclavicular area where the first rib and the subclavian artery are visible.

In 2012, Siegenthaler et al.[6] described the blockage of the suprascapular nerve in the supraclavicular area, inferior to the belly of the omohyoid muscle. However, because of the proximity to the superior trunk, the fluid injected at this point was expected to reach some regions of the brachial plexus, which was recently been demonstrated in the cadaver study of Shembi et al. (2019).[9] The authors showed that 5 mL of contrast injected around the suprascapular nerve, below to the omohyoid muscle, reached the superior and middle trunk of the brachial plexus.

The study of Abdallah et al., (2020)[14] showed that suprascapular route consistently blocks the superior trunk and qualify it as an effective interscalene block alternative.

In addition, Shembi et al. (2019)[9] also demonstrated that in 20% of the cases, the dissections presented phrenic nerve involvement, suggesting a possible risk of diaphragmatic hemiparalysis with this technique. Despite the similar injection site to that of Sehmbi et al. (2019),[9] this study did not find the dispersion of contrast in the phrenic nerve in any of the dissections. We believe that the difference in results is due to the endpoint of the injection. Sehmbi et al. (2019)[9] performed the injection deep to the investing layer of deep cervical fascia, outside the prevertebral layer of deep cervical fascia (brachial plexus sheath), laterally within the inferior posterior triangle of the neck. At this point, the injection can be done in a loose fascial plane and may allow larger dispersions reaching the phrenic nerve. In our technique, it was performed as an intra-cluster injection in the superior trunk deep to the prevertebral layer of the deep cervical fascia which probably limited the dispersion of contrast to the phrenic nerve.

It is known that the brachial plexus sheath or axillary sheath is an extension of the prevertebral fascia that extends from the neck to the axilla. Therefore, it probably prevents the latero-medial spread at this level, keeping most of the injected fluid contained inside the brachial plexus sheath. Moreover, when the blockade is performed in the supraclavicular area, the injected fluid probably flows more easily distal than proximal, as the scalenes muscles make a constriction around the trunks, preventing the injected fluid from reaching the phrenic nerve through proximal (cranial) spread.[15–17]

A topic point of our study was to evaluate the same injection volume and location as the injection performed on the cadavers. It was observed that the injection of this volume using this technique was enough to promote satisfactory analgesic effect for the patients submitted to shoulder surgery, proving that the dispersion also reached the suprascapular nerve.

In addition, the non-impairment of the respiratory function of these patients was recorded, suggesting that this technique may be safe in patients with compromised respiratory function.

Therefore, new studies can evaluate if this technique could be used as an anesthetic technique for shoulder surgeries. In this case, it has to be considered that most the part of the skin around the shoulder is innervated by supraclavicular nerves (C3–C4) that come from the superficial cervical plexus and the nerve trajectory towards the

shoulder between the investing layer of the deep cervical fascia and the prevertebral layer of deep cervical fascia. The technique potentially spares those cutaneous branches. Therefore, light sedation is probably enough to tolerate this mild pain stimuli from arthroscopy portals, or better a local skin infiltration may be performed.

It was opted for 5 mL of methylene blue or local anesthetic because previous study has demonstrated that this volume is sufficient to promote analgesic effect for shoulder surgeries through the superior trunk block.[11]

In conclusion, this study demonstrates that a superior trunk block, below the omohyoid muscle may be an alternative technique to promote analgesic effect for shoulder surgery. Study limitations included lack of comparison with other techniques as well as a low number of participants.

Availability of data and material

With author and at Universidade Federal de São Paulo.

Funding Statement

Institutional.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Departmental.

References

1. Urmey WF, Talts KH, Sharrock NE. One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg. 1991;72:498–503.
2. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJ. Effect of local anaesthetic volume (20 vs. 5 mL) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. Br J Anaesth. 2008;101:549–56.
3. Stundner O, Meissnitzer M, Brummett CM, et al. Comparison of tissue distribution, phrenic nerve involvement, and epidural spread in standard- vs. low-volume ultrasound-guided interscalene plexus block using contrast magnetic resonance imaging: a randomized, controlled trial. Br J Anaesth. 2016;116:405–12.
4. Tran DQ, Elgueta MF, Aliste J, Finlayson RJ. Diaphragm-sparing nerve blocks for shoulder surgery. Reg Anesth Pain Med. 2017;42:32–8.
5. Burckett-St Laurent D, Chan V, Chin KJ. Refining the ultrasound-guided interscalene brachial plexus block: the superior trunk approach. Can J Anaesth. 2014;61:1098–102.
6. Siegenthaler A, Moriggl B, Mlekusch S, et al. Ultrasound-guided suprascapular nerve block, description of a novel supraclavicular approach. Reg Anesth Pain Med. 2012;37:325–8.
7. Hussain N, Goldar G, Ragina N, Banfield L, Laffey JG, Abdallah FW. Suprascapular and interscalene nerve block for shoulder surgery: a systematic review and meta-analysis. Anesthesiology. 2017;127:998–1013.
8. Kim DH, Lin Y, Beathe JC, et al. Superior Trunk Block: A Phrenic-sparing Alternative to the Interscalene Block: A Randomized Controlled Trial. Anesthesiology. 2019;131:521–33.
9. Sehmbi H, Johnson M, Dhir S. Ultrasound-guided subomohyoid suprascapular nerve block and phrenic nerve involvement: a cadaveric dye study. Reg Anesth Pain Med. 2019;44:561–4.
10. Lookman AA. Brachial plexus infiltration; single injection technique. Anaesthesia. 1958;13:5–18.
11. Falcão LF, Perez MV, de Castro I, Yamashita AM, Tardelli MA, Amaral JL. Minimum effective volume of 0.5% bupivacaine with epinephrine in ultrasound-guided interscalene brachial plexus block. Br J Anaesth. 2013;110:450–5.
12. Petrar SD, Seltenrich ME, Head SJ, Schwarz SK. Hemidiaphragmatic Paralysis Following Ultrasound-Guided Supraclavicular Versus Infraclavicular Brachial Plexus Blockade. A Randomized Clinical Trial. Reg Anesth Pain Med. 2015;40:133–8.
13. Renes SH, Spoormans HH, Gielen MJ, Rettig HC, van Geffen GJ. Hemidiaphragmatic paresis can be avoided in ultrasound-guided supraclavicular brachial plexus block. Reg Anesth Pain Med. 2009;34:595–9.
14. Abdallah FW, Wijeysundera DN, Laupacis A, et al. Subomohyoid Anterior Suprascapular Block versus Interscalene Block for Arthroscopic Shoulder Surgery: A Multicenter Randomized Trial. Anesthesiology. 2020;132:839–53.
15. Cornish PB, Leaper CJ, Hahn JL. The ''axillary tunnel'': an anatomic reappraisal of the limits and dynamics of spread during brachial plexus blockade. Anesth Analg. 2007;104:1288–91.
16. Franco CD, Rahman A, Voronov G, Kerns JM, Beck RJ, Buckenmaier CC3rd. Gross anatomy of the brachial plexus sheath in human cadavers. Reg Anesth Pain Med. 2008;33:64–9.
17. Nieuwveld D, Mojica V, Herrera AE, Pomés J, Prats A. Sala-Blanch. Medial approach of ultrasound-guided costoclavicular plexus block and its effects on regional perfussion. Rev Esp Anestesiol Reanim. 2017;64:198–205.

Brazilian Journal of Anesthesiology 2022;72(6): 780—789

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SYSTEMATIC REVIEW

Prone ventilation in intubated COVID-19 patients: a systematic review and meta-analysis

Ee Xin Chua[a], Zhen Zhe Wong[b], Mohd Shahnaz Hasan[a], Rafidah Atan[a], Nor'azim Mohd Yunos[a], Hing Wa Yip[a], Wan Yi Teoh[c], Mohd Afiq Syahmi Ramli[a], Ka Ting Ng [a,*]

[a] *Universiti Malaya, Faculty of Medicine, Department of Anesthesiology, Kuala Lumpur, Malaysia*
[b] *International Medical University, School of Medicine, Kuala Lumpur, Malaysia*
[c] *University of Liverpool, Faculty of Medicine, Liverpool L69 3BX, United Kingdom*

Received 12 November 2021; accepted 21 June 2022
Available online 7 July 2022

KEYWORDS
Acute respiratory distress syndrome;
COVID-19;
Intubation;
Prone position;
Supine position;
Ventilation

Abstract
Background: The efficacy and safety profiles of prone ventilation among intubated Coronavirus Disease 2019 (COVID-19) patients remain unclear. The primary objective was to examine the effect of prone ventilation on the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) in intubated COVID-19 patients.
Methods: Databases of MEDLINE, EMBASE and CENTRAL were systematically searched from inception until March 2021. Case reports and case series were excluded.
Results: Eleven studies (n = 606 patients) were eligible. Prone ventilation significantly improved PaO_2/FiO_2 ratio (studies: 8, n = 579, mean difference 46.75, 95% CI 33.35–60.15, $p < 0.00001$; evidence: very low) and peripheral oxygen saturation (SpO_2) (studies: 3, n = 432, mean difference 1.67, 95% CI 1.08–2.26, $p < 0.00001$; evidence: ow), but not the arterial partial pressure of carbon dioxide ($PaCO_2$) (studies: 5, n = 396, mean difference 2.45, 95% CI 2.39–7.30, $p = 0.32$; evidence: very low), mortality rate (studies: 1, n = 215, Odds Ratio 0.66, 95% CI 0.32–1.33, $p = 0.24$; evidence: very low), or number of patients discharged alive (studies: 1, n = 43, Odds Ratio 1.49, 95% CI 0.72–3.08, $p = 0.28$; evidence: very low).
Conclusion: Prone ventilation improved PaO_2/FiO_2 ratio and SpO_2 in intubated COVID-19 patients. Given the substantial heterogeneity and low level of evidence, more randomized- controlled trials are warranted to improve the certainty of evidence, and to examine the adverse events of prone ventilation.

This abstract was accepted for the top 200 e-poster presentation at the 17th World Congress of Anaesthesiologists (1–5th September 2021).
* Corresponding author.
E-mail: katingng1@gmail.com (K.T. Ng).

https://doi.org/10.1016/j.bjane.2022.06.007

Introduction

Severe pneumonia secondary to Coronavirus Disease 2019 (COVID-19) is associated with reduced peripheral oxygen saturation (SpO_2) of < 94%, low ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of < 300 mmHg, marked tachypnea (respiratory rate of > 30 breaths per minute), and lung infiltrates of > 50%.[1] Studies have reported that 15—30% of patients hospitalized for COVID-19 will develop severe pneumonia and hypoxemia,[1] many of which will require treatment in the intensive care unit.[2] In severe COVID-19 pneumonia, patients may progress to develop Acute Respiratory Distress Syndrome (ARDS),[2] and up to 88% of patients with COVID-19 in the intensive care unit require endotracheal intubation to maintain oxygenation.[3] Several observational studies reported that severe mechanically ventilated COVID-19 pneumonia patients were associated with high mortality of 27—31% in the intensive care unit.[3,4]

The application of the prone position during mechanical ventilation has been previously studied to improve oxygenation and reduce mortality in classical ARDS prior to the emergence of COVID-19.[5,6] At present, the World Health Organization (WHO) recommends the use of the prone position in patients with severe COVID-19 who require noninvasive ventilation based on the evidence of its benefit seen in classical ARDS.[7] A recent meta-analysis demonstrated that prone positioning improved oxygenation parameters (PaO_2/FiO_2 ratio and SpO_2) in awake spontaneously breathing COVID-19 patients.[8] However, the safety and efficacy profiles of prone ventilation in patients with severe COVID-19 requiring intubation remain unclear in the literature. Thus, a systematic review and meta-analysis is timely warranted to synthesize evidence on the use of prone ventilation in intubated COVID-19 patients before any recommendation can be made with certainty.

We hypothesized that prone ventilation improved oxygenation in intubated COVID-19 patients. The primary objective of this review was to examine the effect of prone ventilation on the PaO_2/FiO_2 ratio in intubated COVID-19 patients. Secondary objectives were to investigate the effects of prone ventilation on SpO_2, arterial partial pressure of carbon dioxide ($PaCO_2$), mortality rate, and number of patients discharged alive in intubated COVID-19 patients.

Methods

This review was conducted and reported according to the Cochrane Handbook for Systematic Reviews and Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), respectively.[9,10] The protocol of this review was published on PROSPERO (CRD42021241364) before the commencement of the literature search. Review questions were formulated using the Population, Intervention, Control, and Outcomes (PICO) approach, as shown in Supplemental Table E1. The primary outcome was the PaO_2/FiO_2 ratio after prone and supine ventilation. Secondary outcomes included SpO_2, $PaCO_2$, mortality rate, and number of patients discharged alive.

Databases of Ovid MEDLINE, Ovid EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched systematically from their inception until March 2021. The list of search items and strategy is presented in Supplemental Table E2. The inclusion criteria were any randomized-controlled trials or observational studies (retrospective or prospective) comparing prone and supine ventilation in adult (ages ≥ 18 years) intubated COVID-19 patients. The bibliography of the included studies was searched for any additional articles. Trial registries (clinicaltrials.gov and WHO International Clinical Trials Registry Platform Search Portal) were also searched for any ongoing studies. All case reports, case series, and editorials were excluded in this review.

The title-abstracts and full texts were screened according to the predefined inclusion and exclusion criteria by two authors (EC and ZW) independently. Any disagreement during the screening and selection of studies were resolved by consulting a third author (KN). The final list of included studies was agreed on by all the authors. Two authors (EC and ZW) extracted data independently using an online data extraction sheet. A third author (KN) cross-checked all the extracted data for any discrepancies. Any data that was presented in the form of median and interquartile range was converted to mean and standard deviation for data pooling.[11] The corresponding authors of the included studies were contacted at least twice if there was any unclear or missing data. In addition to the measured outcomes, other relevant data, namely authors, year of publication, sample size, age, duration of prone ventilation, enrollment criteria, and ventilation strategy were also extracted.

Two authors (EC and ZW) performed the risk of bias assessment for all the included studies independently, using the Newcastle-Ottawa Scale for non-randomized studies. It consists of three domains, namely selection, comparability, and outcome. Each domain was assessed using a star system with a maximum of 9 stars.[12] Studies with a total score of 7 or more were considered as low risk of bias. The certainty of evidence was assessed based on the risk of bias, inconsistency, imprecision, indirectness, and publication bias. A third author (KN) was consulted for any disagreement in the assessment of risk of bias and certainty of evidence for all the included studies.

The Review Manager software (version 5.4) was used for statistical meta-analysis. Dichotomous and continuous parameters were reported using Odds Ratio (OR) and Mean Difference (MD), respectively, with a Confidence Interval (CI) of 95%. Any p-value of < 0.05 was considered statistically significant. The I-square (I^2) test was used for assessment of statistical heterogeneity, with I^2 of < 40% categorized as low heterogeneity, I^2 of 40—60% as moderate heterogeneity, and I^2 of > 60% as substantial heterogeneity. In view of limited studies of small sample size with significant heterogeneity, a random-effect model was used for all the measured outcomes.

Results

Our search generated a total of 1722 articles and 41 articles were eligible for full text screening (Fig. 1). Twenty-eight studies were excluded after applying the inclusion and exclusion criteria, as listed in Supplemental Table E3. A total of 14 studies (a total of 658 patients) were included in this

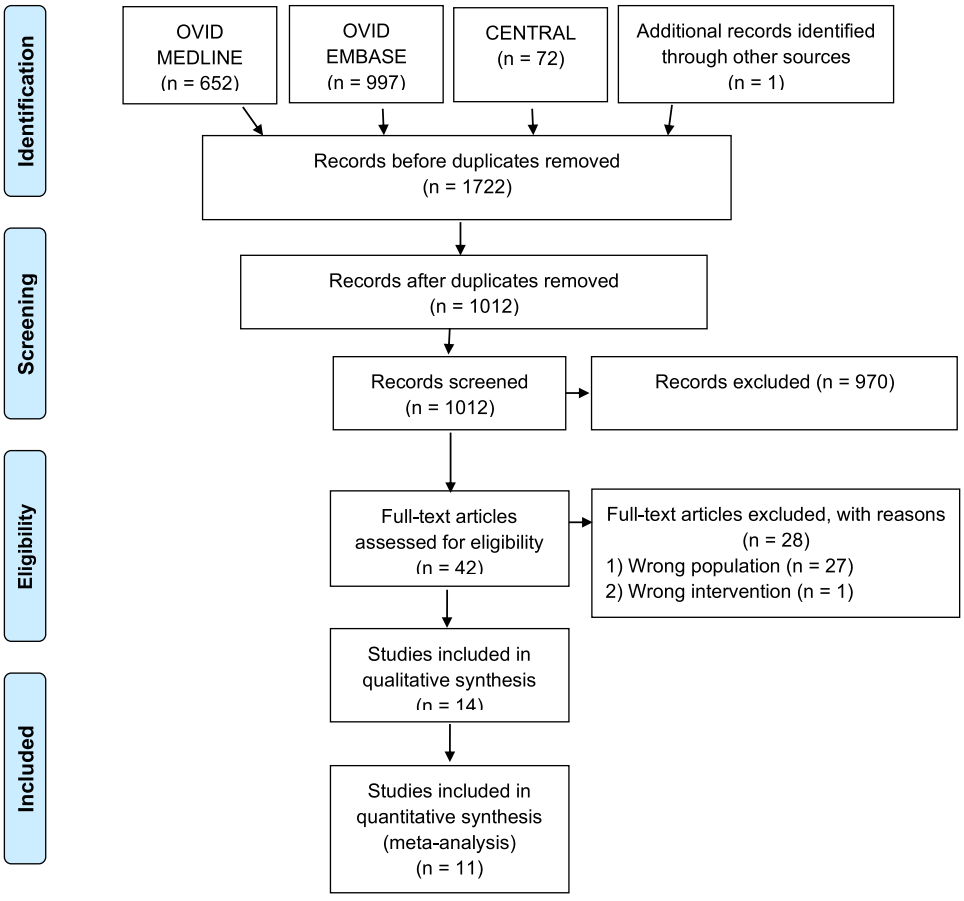


Figure 1 PRISMA flow diagram.

review. However, only eleven studies (a total of 606 patients) were included in quantitative meta-analysis, as three of the included studies did not report any of the outcomes of interest.[13-15] Search on trial registries did not identify any ongoing studies comparing prone and supine ventilation in intubated COVID-19 patients.

The clinical characteristics of our included studies are listed in Table 1. All 14 studies were single center cohort studies (6 prospective,[14,16-20] 8 retrospective[13,15,21-26]) Of all, only one study compared two separate cohorts of supine and prone ventilation in intubated COVID-19 patients.[25] The rest were crossover cohort studies, in which patients underwent both supine and prone ventilation regimens. The sample size varied from 9 to 261 patients in the included studies. The mean age and Body Mass Index (BMI) of patients ranged from 52.8 to 69.5 years and from 27.9 to 36.5 kg. m^{-2}, respectively. In terms of the settings of mechanical ventilation, the tidal volume varied across the included studies, ranging from 4 to 8 mL.kg^{-1} predicted body weight. The extrinsic Positive End-Expiratory Pressure (PEEP) used during mechanical ventilation also differed across the included studies. Most of our included studies used prolonged duration of prone ventilation per session, with the mean duration of prone ventilation ranging from 14.3 to 24 hours per session. The mean number of days of prone positioning ranged from 3.2 to 4.7 days across all the included studies.

The risk of bias assessment for all the included studies and PRISMA checklist are summarized in Supplemental Tables E4 and E5. Out of all included studies, eleven studies were considered as low risk of bias as they scored at least 7 out of 9 stars based on the domains of selection, comparability, and outcome in the Newcastle-Ottawa Scale.[13-15,17-19,21-23,25,26] Three studies were of high risk of bias as they had a total score < 7 due to potential bias in the comparability domain.[16,20,24] The summary of findings for all measured outcomes and certainty of evidence are outlined in Table 2 and Table 3.

Eight studies (n = 579 patients) examined the PaO_2/FiO_2 ratio after supine and prone ventilation.[16,17,19,21-24,26] Intubated COVID-19 patients who received prone ventilation had significantly higher mean PaO_2/FiO_2 ratio compared to the supine ventilation group (MD = 46.75, 95% CI 33.35 to 60.15, $p < 0.00001$; Fig. 2). However, the observed statistical heterogeneity was substantial (I^2 = 78%). The certainty of evidence was graded as very low due to the observational studies in nature, inconsistency, and publication bias.

Pooling of data from three studies (n = 432 patients) demonstrated that those with prone ventilation were associated with higher SpO_2 (MD = 1.67, 95% CI 1.08 to 2.26, $p < 0.00001$; I^2 = 0%; certainty of evidence: low, Suppementary Fig. E1).[18,20,26] Among all included studies, five of them (n = 396 patients) recorded the $PaCO_2$ after mechanical ventilation in the prone and supine position.[16,17,22,23,26] Our

Table 1 Clinical characteristics of included studies.

Author	Year	Design	Sample size	Country	Setting	Age (mean ± SD)	BMI (mean ± SD)	Criteria for enrolment	Criteria for stopping	Ventilation strategy		Mean duration of prone positioning per session (hours)	Mean number of days of prone positioning (days)
										Tidal volume (mL kg^{-1} predicted body weight)	Extrinsic PEEP (cmH_2O)		
Abou-Arab et al.	2020	Single center cohort study (prospective)	25	France	ICU	61.0 ± 5.5	30.0 ± 3.1	PaO_2/FiO_2 ratio < 150 mmHg for 12 hours despite LPV	–	< 6	–	16	–
Astua et al.	2020	Single center cohort study (prospective)	31	USA††	–	58.3 ± 1.7	27.9 ± 3.8	Moderate to severe ARDS (PaO_2/FiO_2 ratio ≤150 mmHg on FiO_2 ≥0.6 and PEEP ≥ 5 cm H_2O)	PaO_2/FiO_2 ratio > 200 for 8 hours supine	6 – 8	≥ 5	16	–
Berrill et al.	2020	Single center cohort study (retrospective)	34	UK	ICU	58.5 ± 11.1	31.0 ± 5.1	-	–	6 – 8	≥ 5 or 10	16.5	4.2
Clarke et al.	2021	Single center cohort study (prospective)	20	Ireland	ICU	52.8 ± 11.6	36.5 ± 10.7	Met the Berlin criteria for diagnosis of ARDS	–	< 8	–	16.4	–
Douglas et al.	2021	Single center cohort study (retrospective)	61	USA	ICU	56.7 ± 13.5	33.4 ± 8.9	Persistent severe hypoxemia (PaO_2/FiO_2 ratio < 150 mmHg, FiO_2 > 60% and PEEP > 10 cm H_2O) despite 2–6 hours stabilization with LPV in the assist-control mode applying PEEP according to the ARDS Network	FiO_2 < 0.6 with PEEP < 10 cm H_2O for ≥ 4 hours	< 8	> 10	24	–
Doussot et al.	2020	Single center cohort study (prospective)	67	France	ICU	67.5 ± 8.3	30.0 ± 6.1	Persistent PaO_2/FiO_2 ratio < 150 mmHg despite mechanical ventilation, sedation, and curarisation	–	–	–	16	4.7
Gleissman et al.	2021	Single center cohort study (retrospective)	44	Sweden	ICU	61.0 ± 13.0	-	-	-	6 – 8	-	14.3	3.2

Table 1 (*Continued*)

Author	Year	Design	Sample size	Country	Setting	Age (mean ± SD)	BMI (mean ± SD)	Criteria for enrolment	Criteria for stopping	Ventilation strategy		Mean duration of prone positioning per session (hours)	Mean number of days of prone positioning (days)
										Tidal volume ($mL\ kg^{-1}$ predicted body weight)	Extrinsic PEEP (cmH_2O)		
Khullar et al.	2020	Single center cohort study (retrospective)	23	USA	-	53.5 ± 13.0	32.3 ± 6.0	Met the Berlin definition for moderate-to-severe ARDS: PaO_2/FiO_2 ratio < 200 mmHg with PEEP ≥ 5 cm H_2O	–	4 – 6	≥ 5	16	–
Mittermaier et al.	2020	Single center cohort study (prospective)	9	Germany	ICU	62.0 ± 14.2	30.4 ± 6.5	PaO_2/FiO_2 ratio < 150 mmHg	–	–	–	15.4	–
Perier et al.	2020	Single center cohort study (prospective)	9	France	–	54.3 ± 8.7	32.8 ± 5.1	ARDS based on Berlin definition, within 72 hours of intubation	–	–	–	–	–
Sang et al.	2021	Single center cohort study (retrospective)	20	China	ICU	69.5 ± 9.5	-	Severe ARDS based on Berlin definition	–	6	5 – 15	–	–
Sharp et al.	2020	Single center cohort study (retrospective)	12	UK	ICU	56.5 ± 14.0	–	–	–	–	–	–	–
Shelhamer et al.	2020	Single center cohort study (retrospective)	261	USA	Wards; ICU	64.0 ± 13.4	31.6 ± 7.2	PaO_2/FiO_2 ratio < 150 mmHg, PEEP > 10 cm H_2O and FiO_2 > 0.6	–	–	>10	16	3.2
Weiss et al.	2020	Single center cohort study (retrospective)	42	USA	ICU	59.9 ± 13.4	34.2 ± 7.5	PaO_2/FiO_2 ratio of < 20 kPa with PEEP set ≥ 10 cm H_2O and FiO_2 ≥ 0.6.	PaO_2/FiO_2 ratio > 20 kPa in the supine position or if ECMO or palliative care was needed	6	≥10	16.3	3.7

SD, Standard Deviation; BMI, Body Mass Index; PEEP, Positive End-Expiratory Pressure; ICU, Intensive Care Unit; PaO_2/FiO_2 ratio, Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; LPV, Lung Protective Ventilation; USA, United States of America; ARDS, Acute Respiratory Distress Syndrome; FiO_2, Fraction of inspired Oxygen; UK, United Kingdom; ECMO, Extracorporeal Membrane Oxygenation.

Table 2 Summary of findings for primary and secondary outcomes.

N°	Outcomes	Trials	n	I^2(%)	Effect model	MD/OR (95% CI)	*p*-value
1	PaO_2/FiO_2 ratio	8	579	78	REM	46.75 (33.35, 60.15)	< 0.00001
2	$PaCO_2$	5	396	90	REM	2.45 (-2.39, 7.30)	0.32
3	SpO_2	3	432	0	REM	1.67 (1.08, 2.26)	< 0.00001
4	Mortality rate	1	261	-	REM	0.66 (0.32, 1.33)	0.24
5	Number of patients discharged alive	1	261	-	REM	1.49 (0.72, 3.08)	0.28

I^2, Heterogeneity; MD, Mean difference; OR, Odds Ratio; PaO_2/FiO_2 ratio, Ratio of Arterial Partial pressure of oxygen to fraction of inspired oxygen; REM, Random Effect Model; $PaCO_2$, Arterial Partial pressure of Carbon Dioxide; SpO_2, Peripheral Oxygen Saturation.

pooled data showed no significant difference in $PaCO_2$ between the prone and supine groups (MD = 2.45, 95% CI -2.39 to 7.30, p = 0.32; I^2 = 90%; certainty of evidence = very low, Supplementary Fig. E1). Of all included studies, only one study examined the mortality rate and number of patients discharged alive between the prone and supine groups.[25] No significant differences were reported in the outcomes of mortality (n = 261 patients, OR = 0.66, 95% CI 0.32 to 1.33, p = 0.24; certainty of evidence = very low, Supplementary Fig. E1) and number of patients discharged alive (n = 261 patients, OR = 1.49, 95% CI 0.72 to 3.08, p = 0.28; certainty of evidence: very low, Supplementary Fig. E1).

Discussion

To the best of our knowledge, this is the first systematic review that has summarized the evidence of prone ventilation in intubated COVID-19 patients during mechanical ventilation. Our systematic review and meta-analysis demonstrated that prone ventilation was associated with higher PaO_2/FiO_2 ratio and SpO_2 than supine ventilation in intubated COVID-19 patients. However, the level of evidence was graded as very low due to the nature of observational studies, inconsistency of substantial heterogeneity, and publication bias. Our findings were consistent with the systematic review and meta-analysis conducted by Munshi and colleagues,[5] which showed that prone positioning during mechanical ventilation in classical ARDS was associated with a significantly higher PaO_2/FiO_2 ratio on day 4 of intervention. Although most of our included studies reported the PaO_2/FiO_2 ratio on day 1 of intervention (during the first prone session),[16,17,22,23,26] it was suggested that the improvement in oxygenation parameters from prone ventilation was reproducible with repeated prone positioning.[27]

Prone ventilation has been widely used during the outbreak of COVID-19 pandemic. Several observational studies reported high frequency use of prone ventilation in intubated COVID-19 patients with ARDS, which ranged from 60% to 79%.[28-31] This phenomenon may be explained by a greater predominance of moderate-to-severe hypoxemia among patients with COVID-19 pneumonia, resulting in a drastic rise in the occupancy of intensive care units.[32] Moreover, the adaptation of prone ventilation in COVID-19-related ARDS may have derived from the intervention that had been proven to be beneficial in ARDS of other causes in previous studies.[29] The seminal PROSEVA trial, which showed significant reduction in mortality with prone positioning being applied early in the course of disease (< 24 h) for prolonged periods (> 16 h per session), was likely a fundamental contributing factor.[33,34]

In classical ARDS, the development of alveolar flooding with exudates and atelectasis due to inflammatory alveolar injury causes intrapulmonary shunting of blood and hypoxemia.[35] Prone ventilation is believed to reduce the compression on dorsal regions of alveoli by internal organs and ventral regions of the lungs, which occurs in the supine position due to gravity, and helps to even out the transpulmonary pressures across the different regions in the lungs.[27] The improved alveolar recruitment and ventilation-perfusion matching with more homogenous ventilation would benefit patients with severe COVID-19 pneumonia,[36] and impaired hypoxia-induced pulmonary vasoconstriction and higher incidence of intravascular thrombosis.[37] A diverse nature of severe COVID-19 pneumonia can contribute to a substantial degree of heterogeneity. Two recent large, multicenter prospective studies revealed that the form of lung injury in patients with COVID-19-related ARDS was similar to that of classical ARDS, which is characterized by reduced lung compliance and increased lung weight.[37,38] However, the nature of ARDS itself is a heterogenous syndrome,[39] thus severe COVID-19 induced ARDS patients may respond differently to the effect of prone ventilation.

In this review, most of our included studies recruited COVID-19 patients with PaO_2/FiO_2 ratio of < 100–150 mmHg,[16-19,21,22,26] which corresponded to moderate-to-severe ARDS as defined by the Berlin criteria.[40] The Berlin criteria, however, did not take lung compliance into consideration. In a study conducted by Puah and colleagues, COVID-19-related ARDS patients with high lung compliance (> 40 $mL.cm^{-1}$ H_2O) on the day of intubation showed significantly higher mortality rates.[41] Therefore, the great degree of heterogeneity in COVID-19-related ARDS among our included studies could have introduced bias to our findings. Future studies are warranted to examine the use of prone ventilation in a particular subgroup (severe, moderate, or mild) of COVID-19 ARDS patients.

Our included studies, with the exception of the study by Clarke and colleagues, did not report the duration of patients' illness from the onset of symptoms prior to intubation.[17] Moreover, it is unknown whether the patients in our included studies were subjected to early or late intervention. The variation in lung compliances in COVID-19 at different timings of intubation may have affected the efficacy of prone ventilation. Pandya and colleagues reported that COVID-19 patients with late intubation (> 1.26 days from time of presentation) had lower lung compliance as

Table 3 GRADE assessment of primary and secondary outcomes.

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	supine	Relative (95% CI)	Absolute (95% CI)		
PaO_2/FiO_2 ratio												
8	Observational studies	Not serious	Serious [a]	Not serious	Not serious	Publication bias strongly suspected [b]	324	255	–	MD **46.75 higher** (33.35 higher to 60.15 higher)	⊕◯◯◯ VERY LOW	
$PaCO_2$												
5	Observational studies	Not serious	Very serious [a]	Not serious	Not serious	Publication bias strongly suspected [b]	198	198	–	MD **2.45 higher** (2.39 lower to 7.3 higher)	⊕◯◯◯ VERY LOW	
SpO_2												
3	Observational studies	Not serious	Not serious	Not serious	Not serious	None	216	216	–	MD **1.67 higher** (1.08 higher to 2.26 higher)	⊕⊕◯◯ LOW	
Mortality rate												
1	Observational studies	Not serious	Not serious	Not serious	Serious [c]	None	48/62 (77.4%)	167/199 (83.9%)	**OR 0.66** (0.32 to 1.33)	**64 fewer per 1,000** (from 214 fewer to 35 more)	⊕◯◯◯ VERY LOW	
Number of patients discharged alive												
1	Observational studies	Not serious	Not serious	Not serious	Serious [c]	None	13/62 (21.0%)	30/199 (15.1%)	**OR 1.49** (0.72 to 3.08)	**58 more per 1,000** (from 37 fewer to 203 more)	⊕◯◯◯ VERY LOW	

CI, Confidence Interval; PaO_2/FiO_2 ratio, Ratio of Arterial Partial Pressure of Oxygen to Fraction of Inspired Oxygen; MD, Mean Difference; OR, Odds Ratio; $PaCO_2$, Arterial Partial Pressure of Carbon Dioxide; SpO_2, Peripheral Oxygen Saturation.

[a] Substantial heterogeneity $I^2 > 60\%$.

[b] Funnel plot is suggestive of publication bias.

[c] Total number of events less than 300.

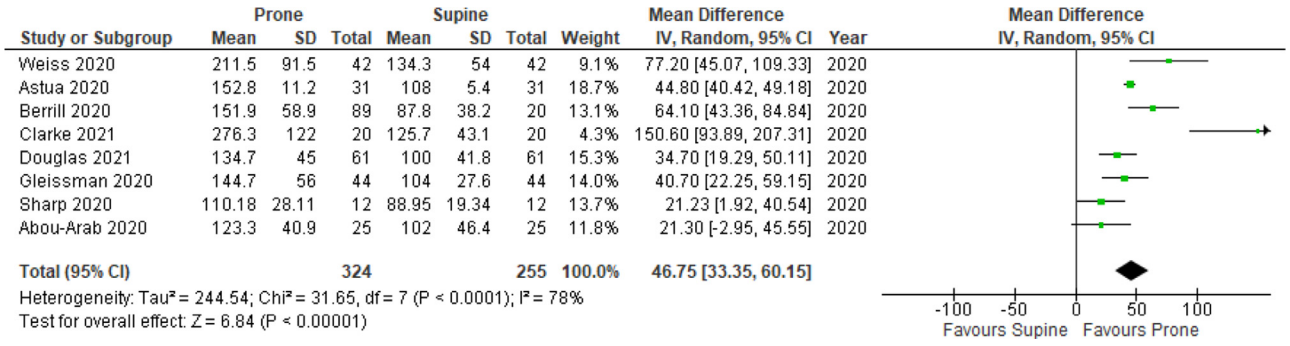


Figure 2 Forest plot of ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio).

compared to those who were intubated earlier.[42] Therefore, patients may have responded differently towards prone ventilation at different timepoints during the course of severe COVID-19-related ARDS, and this may have been another source of heterogeneity.

Scholten and colleagues suggested that the clinical benefit of prone positioning ventilation on mortality in ARDS may be related to the attenuation of ventilator-associated lung injury, which stems from the reduction of alveolar hyperinflation in the ventral regions of the lungs during prone ventilation.[43] In our review, however, there was no significant difference in mortality rate and number of patients discharged alive between the prone and supine groups, despite the similarities in ventilation strategy across our included studies. A significant number of patients in our included studies were obese with a mean BMI ranging from 27.9 to 36.5 $kg.m^{-2}$. A recent review revealed that obesity is associated with increased disease severity in COVID-19 pneumonia.[44] Ni and colleagues showed that obesity was significantly associated with reduced mortality in patients with classical ARDS.[45] Thus, our findings cannot be generalized to COVID-19 ARDS patients who are not obese, as obesity contributes to a significant disease burden for patients with multiple comorbidities. In addition, the majority of our included population were elderly patients (> 60 years old). Zhou and colleagues reported that the mortality rate of severe COVID-19 patients was significantly higher with an increased age group.[46] Nevertheless, our current findings are highly premature in view of the limited number of studies with small sample size.

The fall in $PaCO_2$ indicated an increased removal of carbon dioxide as a result of lung recruitment and reduced fraction of dead-space in patients with ARDS.[47] However, our review showed no significant improvement in $PaCO_2$ following the use of prone ventilation in COVID-19 patients. The $PaCO_2$ may decrease, remain unchanged or even increase, depending on the resultant effect of prone position on alveolar ventilation and minute ventilation (the ventilator setting of respiratory rate and tidal volume). Although prone position improves ventilation-perfusion matching in the lungs, it may also reduce chest wall compliance by restricting the movement of the anterior chest wall, and thus limiting carbon dioxide excretion.[48] Thus, the effect of prone ventilation on $PaCO_2$ in ARDS has been reported to be inconsistent.

There were several limitations in this review. One of the limitations was the lack of data from randomized controlled trials. Our included studies comprised only retrospective or prospective cohort studies, which contributed to methodological heterogeneity as well as to the low level of evidence. None of the studies reported the complications of both prone and supine ventilation (e.g., pressure ulcers and endotracheal tube obstruction) in COVID-19 patients. Thus, we were unable to assess the safety profile of prone and supine position in the mechanical ventilated COVID-19 patients in this review.

Conclusions

In this meta-analysis, prone ventilation improved PaO_2/FiO_2 ratio and SpO_2 in intubated COVID-19 patients. However, given the substantial heterogeneity and low level of evidence, more randomized controlled trials are warranted to improve the certainty of evidence, and to examine the adverse events of prone ventilation.

Conflicts of interest

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

We would like to thank Mr. Bryan Allan for proof-reading the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.06.007.

References

1. Attaway AH, Scheraga RG, Bhimraj A, et al. Severe covid-19 pneumonia: pathogenesis and clinical management. BMJ. 2021;372:n436.
2. Meng L, Qiu H, Wan L, et al. Intubation and ventilation amid the COVID-19 outbreak: Wuhan's experience. Anesthesiology. 2020;132:1317—32.

3. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region. Italy. JAMA. 2020;323:1574—81.
4. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and ventilator mortality among critically Ill adults with coronavirus disease 2019. Crit Care Med. 2020;48:e799—804.
5. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. Ann Am Thorac Soc. 2017;14:S280—8.
6. Mora-Arteaga JA, Bernal-Ramírez OJ, Rodríguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. Med Intensiva (Engl Ed). 2015;39:359—72.
7. WHO. COVID-19 Clinical management: living guidance. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. [Accessed 1 May 2021]
8. Cardona S, Downing J, Alfalasi R, et al. Intubation rate of patients with hypoxia due to COVID-19 treated with awake proning: a meta-analysis. Am J Emerg Med. 2021;43:88—96.
9. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell; 2019.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
11. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
12. Wells GA, Shea B, O'Connor D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 1 May 2021]
13. Khullar R, Shah S, Singh G, et al. Effects of prone ventilation on oxygenation, inflammation, and lung infiltrates in COVID-19 related acute respiratory distress syndrome: a retrospective cohort study. J Clin Med. 2020;9(12):4129.
14. Mittermaier M, Pickerodt P, Kurth F, et al. Evaluation of PEEP and prone positioning in early COVID-19 ARDS. EClinicalMedicine. 2020;28:100579.
15. Sang L, Zheng X, Zhao Z, et al. Lung recruitment, individualized PEEP, and prone position ventilation for COVID-19-associated severe ARDS: a single center observational study. Front Med (Lausanne). 2021;7:603943.
16. Astua AJ, Michaels EK, Michaels AJ. Proning During Pandemic: the rapid institution of a safe, transferable, and effective prone positioning program at Nychhc/elmhurst Hospital, a situationally resource limited facility, during the peak of the Covid 19 surge. Res Sq. 2020.
17. Clarke J, Geoghegan P, McEvoy N, et al. Prone positioning improves oxygenation and lung recruitment in patients with SARS-CoV-2 acute respiratory distress syndrome; a single centre cohort study of 20 consecutive patients. BMC Res Notes. 2021;14:20.
18. Doussot A, Ciceron F, Cerutti E, et al. Prone positioning for severe acute respiratory distress syndrome in COVID-19 patients by a dedicated team: a safe and pragmatic reallocation of medical and surgical work force in response to the outbreak. Ann Surg. 2020;272:e311—5.
19. Abou-Arab O, Haye G, Beyls C, et al. Hypoxemia and prone position in mechanically ventilated COVID-19 patients: a prospective cohort study. Can J Anaesth. 2020;68:262—3.
20. Perier F, Tuffet S, Maraffi T, et al. Effect of positive end-expiratory pressure and proning on ventilation and perfusion in COVID-19 acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;202:1713—7.
21. Berrill M. Evaluation of oxygenation in 129 proning sessions in 34 mechanically ventilated COVID-19 Patients. J Intensive Care Med. 2020;36:229—32.
22. Douglas IS, Rosenthal CA, Swanson DD, et al. Safety and outcomes of prolonged usual care prone position mechanical ventilation to treat acute coronavirus disease 2019 hypoxemic respiratory failure. Crit Care Med. 2021;49:490—502.
23. Gleissman H, Forsgren A, Andersson E, et al. Prone positioning in mechanically ventilated patients with severe acute respiratory distress syndrome and coronavirus disease 2019. Acta Anaesthesiol Scand. 2021;65:360—3.
24. Sharp T, Al-Faham Z, Brown M, et al. Prone position in covid-19: can we tackle rising dead space? J Intensive Care Soc. 2020;0:1—4.
25. Shelhamer M, Wesson PD, Solari IL, et al. Prone positioning in moderate to severe acute respiratory distress syndrome due to COVID-19: a cohort study and analysis of physiology. J Intensive Care Med. 2021;36:241—52.
26. Weiss TT, Cerda F, Scott JB, et al. Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study. Br J Anaesth. 2020;126:48—55.
27. Kallet RH. A Comprehensive review of prone position in ARDS. Respir Care. 2015;60:1660—87.
28. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46:2200—11.
29. Stilma W, van Meenen DMP, Valk CMA, et al. Incidence and practice of early prone positioning in invasively ventilated COVID-19 patients-insights from the PRoVENT-COVID observational study. J Clin Med. 2021;10:4783.
30. Langer T, Brioni M, Guzzardella A, et al. Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients. Crit Care. 2021;25:128.
31. and C-IGobotRN, Investigators tC-I. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47:60—73.
32. Camporota L, Sanderson B, Dixon A, et al. Outcomes in mechanically ventilated patients with hypoxaemic respiratory failure caused by COVID-19. Br J Anaesth. 2020;125:e480—3.
33. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159—68.
34. Sottile PD, Albert RK, Moss M. Prone positioning for nonintubated patients with COVID-19-potential dangers of extrapolation and intermediate outcome variables. JAMA Intern Med. 2022;182:622—3.
35. Sweeney RM, McAuley DF. Acute respiratory distress syndrome. Lancet. 2016;388:2416—30.
36. Santamarina MG, Boisier D, Contreras R, et al. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit Care. 2020;24:395.
37. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8:1201—8.
38. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763—70.
39. Wilson JG, Calfee CS. ARDS subphenotypes: understanding a heterogeneous syndrome. Crit Care. 2020;24:102.
40. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526—33.
41. Puah SH, Cove ME, Phua J, et al. Association between lung compliance phenotypes and mortality in COVID-19 patients with acute respiratory distress syndrome. Ann Acad Med Singap. 2021;50:686—94.

42. Pandya A, Kaur NA, Sacher D, et al. Ventilatory Mechanics in early vs late intubation in a cohort of coronavirus disease 2019 patients with ARDS. Chest. 2021;159:653—6.
43. Scholten EL, Beitler JR, Prisk GK, et al. Treatment of ARDS with prone positioning. Chest. 2017;151:215—24.
44. Chu Y, Yang J, Shi J, et al. Obesity is associated with increased severity of disease in COVID-19 pneumonia: a systematic review and meta-analysis. Eur J Med Res. 2020;25: 64.
45. Ni YN, Luo J, Yu H, et al. Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. Crit Care. 2017;21:36.
46. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054—62.
47. Vollenberg R, Matern P, Nowacki T, et al. Prone position in mechanically ventilated COVID-19 patients: a multicenter study. J Clin Med. 2021;10:1046.
48. Guerin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med. 2020;46:2385—96.

Brazilian Journal of Anesthesiology 2022;72(6):790–794

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

NARRATIVE REVIEW

Multidisciplinary management of idiopathic intracranial hypertension in pregnancy: case series and narrative review

Sara Alves [a,*], Natacha Sousa [b], Luísa Cardoso [b], Joana Alves [a]

[a] *Hospital de Braga, Anesthesiology Department, Braga, Portugal*
[b] *Hospital de Braga, Gynecology and Obstetrics Department, Braga, Portugal*

Received 25 August 2020; accepted 6 February 2021
Available online 20 March 2021

KEYWORDS
Idiopathic intracranial hypertension;
Pregnancy;
Cesarean section;
Labor analgesia;
Anesthesia

Abstract Idiopathic intracranial hypertension (IIH) is a neurological condition characterized by raised intracranial pressure of unknown etiology with normal cerebrospinal fluid (CSF) composition and no brain lesions. It occurs in pregnant patients at approximately the same frequency as in general population, but obstetric and anesthetic management of the pregnancy and labor remains controversial. In this article we provide a multidisciplinary review of the main aspects of IIH in pregnancy including treatment options, mode of delivery and anesthetic techniques. Additionally, we report three cases of pregnant women diagnosed with IIH between 2012 and 2019 in our institution.

Introduction

Idiopathic intracranial hypertension (IIH) is a neurological condition with a benign course characterized by raised intracranial pressure of unknown etiology. In these patients, the cerebrospinal fluid (CSF) composition is normal and brain lesions are absent.[1] It is a rare condition, with an estimated incidence of 0,9 per 100,000 population.[1] It occurs in pregnant patients at approximately the same rate as in general population.[1] During pregnancy it generally appears in the first half of gestation although IIH can appear in any trimester of pregnancy and pregnancy does not appear to alter the natural history of the disease.[1,2] A multidisciplinary evaluation of this patients during pregnancy and labor is essential. We will review the main aspects of IIH, including the obstetric and anesthetic considerations in the parturient with IIH, and report three cases that occurred in our institution between 2012 and 2019.

* Corresponding author.
E-mail: saraquelalves@hotmail.com (S. Alves).

https://doi.org/10.1016/j.bjane.2021.02.030

Table 1 Modified Dandy criteria for idiopathic intracranial hypertension.

Modified Dandy criteria for idiopathic intracranial hypertension
1. Signs and symptoms of increased intracranial pressure
2. Absence of localizing findings on neurologic examination
3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure
4. Awake and alert
No other cause of increased intracranial pressure present

Pathogenesis

The pathogenesis of IIH remains unclear but proposed etiologies suggest that it is caused by accumulation of CSF due to a defect in arachnoid villi reabsorption. An increased CSF production, cerebral edema, and abnormalities in cerebral blood flow (e.g. venous stenosis or venous hypertension) seem to be also involved.[2,3] Obesity may play a role through changes in sodium and water retention mechanisms, and also by increasing abdominal pressure which increases pleural and cardiac filling pressures, delaying venous return from brain resulting in increased intracranial venous pressure.[3–5]

Pregnancy was previously reported as an etiologic factor for IIH and the hyperestrogenemia, along with thrombophilia and hyperfibrinolysis, characteristic of pregnancy, were proposed as mechanisms that could promote or worsen IIH.[4] Nevertheless, this association was not clearly established.

Clinical presentation

The most frequent symptom of IIH is a generalized headache exacerbated with Valsalva maneuver and eye movement, being more severe in the morning. However, the features of headaches are variable and are not specific to IIH. It may be accompanied by photophobia, neck and back pain, nausea, vomiting, and tinnitus. Visual disturbances are common and IIH may present with diplopia, loss of acuity, or visual field.[4,5] The physical exam reveals papilledema, that is the hallmark sign of IIH, and it is usually bilateral and symmetric. Visual loss is the major morbidity in IIH and commonly gradual, but when its onset is abrupt and if intracranial hypertension is untreated it may cause permanent visual loss.[5]

Diagnosis

Idiopathic intracranial hypertension is a diagnosis of exclusion, so secondary causes must be excluded. The diagnosis is based according to Modified Dandy criteria for IIH (Table 1).[1,6]

Neuroimaging is required to exclude secondary causes of intracranial hypertension.[1,3] Magnetic Resonance Imaging (MRI) is safe and is the method of choice during pregnancy. When no structural or vascular lesion is identified it should be followed by lumbar puncture (LP).[5,7]

LP is an essential element to establish the diagnosis of IIH, defined as an opening CSF pressure above 25 mmHg. The evaluation of CSF contents must be normal to define IIH.[5,8] Ophthalmologic evaluation is imperative to evaluate the severity of optic nerve involvement and monitor response to treatment.[9]

Treatment

There are two major goals in treating IIH which are improvement of symptoms, predominantly headaches, and the preservation of vision. In general, pregnant women can be treated as nonpregnant adults, although with some considerations.[4,5]

Weight control is very important and a low-calorie diet should be started.[2] Considering that this approach can take some time to achieve effective outcomes and that excessive weight loss can induce adverse effects on the fetus (e.g. ketosis), other treatments should be tried simultaneously.[4,10]

Acetazolamide, a carbonic anhydrase inhibitor, reduces cerebrospinal fluid production and is the first line medical option for IIH in adults. However, its use in pregnant women remains controversial due to several reports of teratogenic effects in animals and a single case of a sacrococcygeal teratoma in humans. Food and Drug Administration classifies acetazolamide as a class C in pregnancy, even though there is a lack of adequate controlled studies in pregnant women and little clinical evidence that supports any adverse effects of this drug.[3] The use of other diuretics is usually not recommended during pregnancy because the lowering of maternal blood volume can reduce placental blood flow.[5,11,12] Corticosteroids should be reserved for acute visual loss situations.[3,5,13] Serial lumbar punctures can transiently relieve symptoms since CSF reforms within six hours. Furthermore, lumbar punctures can be painful, technically difficult in obese and pregnant women, and complicate with CSF leak or infection. Nonetheless, this is the preferable approach in many institutions during pregnancy.[2,5,13]

Surgical treatment is reserved for patients with severe progressive visual loss or persistent headache despite optimal medical therapy.[1] Optic nerve sheath fenestration option seems to be more beneficial to visual function, and lumboperitoneal or ventriculoperitoneal shunt can be technically difficult in pregnant women due to the gravid uterus.[5,14]

Management of pregnancy and labor

There is no indication to terminate a pregnancy in a woman diagnosed with IIH because gestation does not worsen the prognosis of IIH, neither affects perinatal outcome.[3,5]

Mode of delivery is often a controversial decision when a pregnant woman presents with IIH.[5,8]

Physiologic changes in pregnancy could change intracranial pressure. The increase in blood volume and cardiac output, combined with increased water and sodium retention, promote a progressive increment in cerebral blood flow, possibly causing cerebral edema. Despite this changes, CSF pressure is unaltered (7–15 mmHg) in normal pregnancy.

However, during the first and second stages of labor CSF pressure can rise to 39 and 71 mmHg, respectively.[1]

The concern is based on the theory that pushing efforts and uterine contractions increase blood pressure, cardiac output, and central venous pressure, consequently increasing CSF pressure. Nonetheless, an instrumented delivery – vacuum, forceps, or spatulas – is a good option to reduce maternal pushing efforts on the second stage of labor and thereby reducing the potential increase in CSF pressure.[5,8] IIH is not considered an indication for an elective cesarean delivery.[5,15]

Anesthetic considerations

Labor analgesia and cesarean anesthesia are a challenge to the anesthesiologist. The main goal is maintaining hemodynamic stability in order to control cerebral perfusion pressure and brain tissue oxygenation. Increases in intracranial pressures and abrupt decreases in mean arterial pressures must be avoided.

The anesthetic choice for IIH patients is complex and depends on balancing the risks and benefits of each available technique.[16,17] Although neuraxial anesthesia is contraindicated in patients with intracranial hypertension resulting from space occupying lesions due the risk of uncal herniation, in IIH patients there is a uniform swelling of the brain that prevents herniation, so neuraxial anesthesia can be used safely.[1,16,18,19] Spinal anesthesia will increase the volume of fluid in the subarachnoid space and epidural anesthesia will compress the dural sac, altering the compliance of spinal subarachnoid space.[20,21] There are case reports of successful use of both spinal and epidural anesthesia for cesarean delivery in IIH patients.[22–24]

Spinal anesthesia alone or combined with epidural has been used safely in IIH patients. It is crucial to use small volumes of local anesthetic and opioids in order to avoid an acute rise in intracranial pressure.[16] It allows CSF drainage and the use of small volumes of local anesthetic. The placement of a spinal catheter permits the monitoring of ICP.[25] The hypotension associated with spinal anesthesia reduces cerebral blood flow and cerebral perfusion pressure, therefore fluid load and vasoactive drugs should be available in order to minimize this risk. The anesthetist should closely monitor hemodynamic stability and neurological signs. An epidural catheter can be used with precaution due to the increase in epidural volume that will be transmitted to the subarachnoid space, increasing the intracranial pressure transiently. The rate of injection should be as slow as possible. Slowly incremental doses seem to be better tolerated than a high-volume dose.[21] Neurological, cardiovascular and respiratory monitoring should be prolonged in the next hours after the procedure.

General anesthesia in pregnancy is associated with several risks, including difficult airway, aspiration, awareness, and potential masking of neurological changes in IIH patients. In these patients, general anesthesia should also be avoided since laryngoscopy, intubation, inadequate depth of anesthesia, and extubation are associated with a significant raise in intracranial pressure.[16,18,20] If general anesthesia is necessary, it should be planned carefully to avoid intracranial pressure variations. In these cases, pharmacological choices are essential. Propofol is an intravenous induction agent that offers the advantage of decreasing cerebral blood flow, protecting the brain tissue.[18,21] The use of opioids is controversial and they should be carefully selected and titrated to avoid potential neonatal respiratory depression. Concerning neuromuscular blocking drugs, succinylcholine should be avoided for intubation because muscle fasciculations may raise intracranial pressure transiently.[18] The depth of anesthesia should be monitored. Extubation should be performed in a deep plain of anesthesia.[20,21] Mechanical ventilation should be carefully controlled with tight adjustment of carbon dioxide arterial pressure, in order to minimize its effects on cerebral blood flow.

Cases reports

Case 1

A 21-year-old multiparous woman at 18 weeks pregnant presented with frontal headache, nausea, and dizziness with 3 days of evolution. She was overweight, had a history of migraine, and smoking habits. On physical examination she had bilateral asymmetric papilledema but visual fields, acuity, and head MRI were normal. Diagnostic LP showed an opening pressure of 29 mmHg and a normal composition of CSF. In this LP 9 mL of CSF were drained. The severity of headache improved but she noted additional visual symptoms, like blurred vision. A second LP puncture was necessary in order to improve symptoms. After a multidisciplinary discussion, including obstetricians, neurologist, and anesthesiologist it was decided to terminate pregnancy at 38 weeks with an elective cesarean section to prevent acute relapse of intracranial hypertension. On presentation to the cesarean she was asymptomatic. Monitoring included pulse oximetry, electrocardiogram, noninvasive blood pressure, and urine output. A spinal anesthesia was selected. A 26G Quincke needle was used and 9 mg hyperbaric bupivacaine (5 mg.mL^{-1}) and 0.015 mg fentanyl were slowly injected. Multimodal analgesia was provided with 1000 mg intravenous paracetamol, 200 mg intravenous tramadol and 75 mg intramuscular diclofenac. The procedure was uneventful.

After delivery she had persistence of headache and intracranial hypertension symptoms, with no effect on visual fields, that were treated with acetazolamide 500 mg twice daily and two more CSF drainage with LP. With this approach there was a successful improvement of symptoms.

Case 2

A 30-year-old nulliparous, smoker, and obese woman with 18 weeks of gestation, presented at the emergency service with transient visual obscurations and tunnel vision with 3 weeks of duration but no headache. On physical examination she had bilateral papilledema but visual fields and acuity were normal with preserved hemodynamic stability. MRI revealed an empty sella turca image with enlargement of optic nerve dural sheaths. The first LP showed a CSF opening pressure of 47 mmHg with normal biochemical and cytological composition. At this stage, intracranial hypertension was managed with corticosteroids (methylprednisolone 250 mg once daily). The patient reported rapid improvement of

symptoms. After this episode, pregnancy was managed with a dietary weight control plan and four serial CSF drainages with lumbar punctures, showing a progressive decreasing opening CSF pressures. With this approach the patient noted an improvement of visual symptoms, with no headache history.

A cesarean section was scheduled in order to prevent intracranial hypertension exacerbations. On presentation for cesarean she was asymptomatic. Monitoring included pulse oximetry, electrocardiogram, noninvasive blood pressure and urine output. A spinal anesthesia was chosen. A 27G Quincke needle was used to withdraw passively 3 mL of CSF and then anesthesia was initiated with intrathecal 8 mg of hyperbaric bupivacaine (5 mg.mL^{-1}) and 0.002 mg sufentanil. The cesarean occurred uneventfully. Multimodal analgesia was provided with intramuscular diclofenac 75 mg. All symptoms and papilledema resolved on postpartum period, with no more treatment needed. No perinatal adverse outcomes were documented.

Case 3

A 27-year-old multiparous woman with excessive weight presented at the emergency service with a six-month history of holocranial headache that worsened at night with a refractory response to analgesia and progressive visual symptoms (visual obscurations and loss of vision on left eye hemicamp). Physical examination revealed altered visual fields and optic nerve atrophy, as well as a discrete decrease on right eye visual acuity. MRI showed a prominence of the suprasellar cistern and enlargement of optic and oculomotor nerve dural sheaths, changes of idiopathic intracranial hypertension. LP revealed an opening CSF pressure of 37 mmHg, and 30 mL were drained. Cytological and biochemical CSF analysis were normal. Acetazolamide 500 mg twice daily was started, with marked improvement of symptoms. In the meantime, the patient discovered that she was pregnant with 25 weeks of gestation. After a multidisciplinary discussion, it was decided to stop acetazolamide due to the potential teratogenic risks. Two serial LP were performed, showing opening pressures of 23 mmHg in both occasions.

Patient remained asymptomatic for the rest of the pregnancy and elective cesarean was scheduled at 39 weeks. On presentation for cesarean she was asymptomatic. An epidural anesthesia was used. The epidural space was located at the L3-4 interspace with the patient in lateral decubitus using an 18G Tuohy needle with loss-of-resistance to air. Anesthesia was provided through the epidural catheter with 75 mg ropivacaine (7.5 mg.mL^{-1}), and 0.01 mg sufentanil. A satisfactory level of block was achieved and cesarean occurred uneventful. Multimodal analgesia was provided with intravenous paracetamol 1000 mg and intramuscular diclofenac 75 mg. At the end of the surgery, the epidural catheter was removed. There were no symptoms, neurologic changes or other complications.

No fetal malformations were detected and no complications reported in perinatal period.

On maternal postpartum evaluation she reported only occasional mild headaches but visual fields remained altered and fundoscopy showed persistent optic nerve atrophy with no papilledema.

Discussion

The management of pregnancy and delivery in pregnant women with IIH is complex and controversial. Serial lumbar punctures can be part of the management of these patients and were the treatment of choice for the three cases presented in this article.

Although many review articles on IIH suggest that acetazolamide should be avoided in pregnancy, there is paucity of clinical evidence for this recommendation.[8,11] There was only a single case of sacrococcygeal teratoma reported in an infant of a mother treated with acetazolamide during first half of the pregnancy, in 1978.[26,27] There are no well-documented reports of adverse fetal effects of acetazolamide used during pregnancy. Therefore, it is important to promote a multidisciplinary approach involving neurologist and individualize each case, providing a careful risk-benefit assessment regarding the use of acetazolamide.[28,29] It might be considered if the risk of progressive visual loss outweighs potential risks.

Management of labor and mode of delivery are also controversial. In our report, all three cases underwent cesarean delivery based on the assumption that uterine contraction and bearing-down efforts during vaginal delivery could increase CSF pressure. However, studies suggest that IIH is not itself a specific indication for cesarean delivery.[5,15] The rise on CSF pressure is transient and vaginal deliveries have been reported with no adverse effects. Additionally, there is no evidence that either mode of delivery is superior in these patients, so the recommendation is that de decision should be based on obstetric indications and not dependent on the presence of IIH.[5,15]

The decision regarding the choice of the anesthetic technique for labor or cesarean should be individualized and discussed with the team because there are no published randomized controlled trials comparing the safety of neuraxial *versus* general anesthesia. The main goal is to avoid increase in ICP, using regional techniques or general anesthesia.

In 1979, Palop et al. reported two cases of lumbar epidural for labor analgesia in IIH patients.[30] Later, Perez Rodriguez reported the use of an epidural catheter for cesarean anesthesia and postoperative analgesia.[19] Moore and colleagues and Guerci et al. also reported cases of effective use of epidural anesthesia in IIH patients.[14,16] A successful use of combined spinal-epidural techniques was reported for Bedson and Plaat in IIH patient for cesarean.[23]

Intrathecal catheters are also an option for the management of these patients. Aly reported the use of an intrathecal catheter in labor analgesia and Moore et al. used an intrathecal catheter for cesarean anesthesia.[16,24]

In 2016, Gragasin and Chiarella reported a case of IIH in which the first option was an epidural catheter, but an unintended dural puncture occurred and an intrathecal catheter was inserted and used for labor analgesia, removal of CSF, and cesarean anesthesia.[25]

General anesthesia has also been reported as a safe option and it was the choice of Aboulish and colleagues for cesarean in a patient diagnosed with IIH.[31]

We report safe approaches to neuraxial techniques. Spinal anesthesia with or without LCR drainage can be performed using small volumes of local anesthetics and was

the technique of choice in two cases of our institution. In the third case, we decide to perform an epidural anesthesia using slow rate of injection in order to minimize the transmission of pressure to subarachnoid pressure.

Although we prefer neuraxial approach for IIH cases in our institution, there are reported cases of safe use of general anesthesia for cesarean in these patients.[21,31] General anesthesia in parturient have several risks of difficult airway, aspiration, and awareness. In cases of IIH, general anesthesia makes impossible to detect alterations on mental status that can be indicative of increasing ICP.

In conclusion, it is essential an antenatal multidisciplinary consultation to discuss the obstetric management and the anesthetic choice in order to promote an optimal and individualized approach to each case of IIH.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Karmaniolou I, Petropoulos G, Theodoraki K. Management of idiopathic intracranial hypertension in parturients: anesthetic considerations. Can J Anesth Can d'anesthésie. 2011;58:650.
2. Huna-Baron R, Kupersmith MJ. Idiopathic intracranial hypertension in pregnancy. J Neurol. 2002;249:1078–81.
3. Tang RA, Dorotheo EU, Schiffman JS, et al. Medical and surgical management of idiopathic intracranial hypertension in pregnancy. Curr Neurol Neurosci Rep. 2004;4:398–409.
4. Evans RW, Friedman DI. The management of pseudotumor cerebri during pregnancy. Headache. 2000;40:495–7.
5. Kesler A, Kupferminc M. Idiopathic intracranial hypertension and pregnancy. Clin Obstet Gynecol. 2013;56:389–96.
6. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013;81:1159–65.
7. Chung SM. Safety issues in magnetic resonance imaging. J Neuro-Ophthalmology. 2002;22:35–9.
8. Bagga R, Jain V, Das CP, et al. Choice of therapy and mode of delivery in idiopathic intracranial hypertension during pregnancy. Med Gen Med. 2005;7:42.
9. Wall M. Sensory visual testing in idiopathic intracranial hypertension: Measures sensitive to change. Neurology. 1990;40:1859.
10. Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2012;83:488–94.
11. Lee AG, Pless M, Falardeau J, et al. The use of acetazolamide in idiopathic intracranial hypertension during pregnancy. Am J Ophthalmol. 2005;139:855–9.
12. Falardeau J, Lobb BM, Golden S, et al. The use of acetazolamide during pregnancy in intracranial hypertension patients. J Neuro-Ophthalmology. 2013;33:9–12.
13. Corbett JJ, Thompson HS. The rational management of idiopathic intracranial hypertension. Arch Neurol. 1989;46:1049–51.
14. Guerci P, Vial F, McNelis U, et al. Neuraxial anesthesia in patients with intracranial hypertension or cerebrospinal fluid shunting systems: What should the anesthetist know? Minerva Anestesiol. 2014;80:1030–45.
15. Kuba G, Kroll P. Geburtsleitung und Indikationen zur Interruptio und Sectio caesarea bei Augenerkrankungen - eine Übersicht. Klin Monbl Augenheilkd. 1997;211:349–53.
16. Moore DM, Meela M, Kealy D, et al. An intrathecal catheter in a pregnant patient with idiopathic intracranial hypertension: analgesia, monitor and therapy? Int J Obstet Anesth. 2014;23:175–8.
17. Anson JA, Vaida S, Giampetro DM, et al. Anesthetic management of labor and delivery in patients with elevated intracranial pressure. Int J Obstet Anesth. 2015;24:147–60.
18. van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? J Neurol. 2002;249:129–37.
19. Pérez Rodríguez M, de Carlos Errea J, Dorronsoro Auzmendi M, et al. Hipertensión intracraneal idiopática: Cesárea con anestesia epidural tras normalización de la presión del líquido cefalorraquídeo. Rev Esp Anestesiol Reanim. 2013;60:594–6.
20. Leffert L. Neuraxial Anesthesia in Parturients with Intracranial Pathology. Anesthesiology. 2013;119:703–18.
21. Butala B, Shah V. Anaesthetic management of a case of idiopathic intracranial hypertension. Indian J Anaesth. 2013;57:401.
22. Heckathorn J, Cata JP, Barsoum S. Intrathecal anesthesia for cesarean delivery via a subarachnoid drain in a woman with benign intracranial hypertension. Int J Obstet Anesth. 2010;19:109–11.
23. Bedson CR, Plaar F, et al. Benign intracranial hypertension and anaesthesia for caesarean section. Int J Obstet Anesth. 1999;8:288–90.
24. Aly EE, Lawther BK. Anaesthetic management of uncontrolled idiopathic intracranial hypertension during labour and delivery using an intrathecal catheter. Anaesthesia. 2007;62:178–81.
25. Gragasin FS, Chiarella AB. Use of an Intrathecal Catheter for Analgesia Anesthesia, and Therapy in an Obstetric Patient with Pseudotumor Cerebri Syndrome. A case reports. 2016;6:160–2.
26. Worsham F, Beckman E, Mitchell C. Sacrococcygeal teratoma in a neonate: association with maternal use of acetazolamide. JAMA. 1978;240:251–2.
27. Havránek P, Hedlund H, Rubenson A, et al. Sacrococcygeal teratoma in Sweden between 1978 and 1989: Long-term functional results. J Pediatr Surg. 1992;27:916–8.
28. Al-Saleem AI, Al-Jobair AM. Possible association between acetazolamide administration during pregnancy and multiple congenital malformations. Drug Des Devel Ther. 2016;10:1471–6.
29. Holmes LB, Kawanishi H, Munoz A. Acetazolamide: maternal toxicity, pattern of malformations, and litter effect. Teratology. 1988;37:335–42.
30. Palop R, Choed-Amphai E, Miller R. Epidural anesthesia for delivery complicater by benign intracranial hypertension. New York City: Anesthesiology. 1979;50:159–60.
31. Abouleish E, Ali V, Tang R. Benign Intracranial hypertension and anesthesia for cesarean section. Anesthesiology. 1985;63:705–7.

Brazilian Journal of Anesthesiology 2022;72(6):795–812

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

NARRATIVE REVIEW

Clinical use of tranexamic acid: evidences and controversies

Maria J. Colomina [a,b,*], **Laura Contreras** [a], **Patricia Guilabert** [c], **Maylin Koo** [a,b], **Esther Méndez** [a], **Antoni Sabate** [a,b]

[a] *Bellvitge University Hospital, Department of Anaesthesia, Critical Care & Pain, Barcelona, Spain*
[b] *Barcelona University, Barcelona, Spain*
[c] *Universitat Autònoma de Barcelona, Vall d'Hebron University Hospital, Department of Anaesthesia, Critical Care & Pain, Barcelona, Spain*

Received 1 February 2021; accepted 8 August 2021
Available online 7 October 2021

KEYWORDS
Tranexamic acid;
Antifibrinolytics;
Liver surgery;
Cardiac surgery;
Subarachnoid hemorrhage;
Trauma;
Orthopedic surgery;
Obstetric hemorrhage

Abstract Tranexamic acid (TXA) significantly reduces blood loss in a wide range of surgical procedures and improves survival rates in obstetric and trauma patients with severe bleeding. Although it mainly acts as a fibrinolysis inhibitor, it also has an anti-inflammatory effect, and may help attenuate the systemic inflammatory response syndrome found in some cardiac surgery patients. However, the administration of high doses of TXA has been associated with seizures and other adverse effects that increase the cost of care, and the administration of TXA to reduce perioperative bleeding needs to be standardized.

Tranexamic acid is generally well tolerated, and most adverse reactions are considered mild or moderate. Severe events are rare in clinical trials, and literature reviews have shown tranexamic acid to be safe in several different surgical procedures. However, after many years of experience with TXA in various fields, such as orthopedic surgery, clinicians are now querying whether the dosage, route and interval of administration currently used and the methods used to control and analyze the antifibrinolytic mechanism of TXA are really optimal. These issues need to be evaluated and reviewed using the latest evidence to improve the safety and effectiveness of TXA in treating intracranial hemorrhage and bleeding in procedures such as liver transplantation, and cardiac, trauma and obstetric surgery.

* Corresponding author.
E-mails: mjcolomina@bellvitgehospital.cat, mjcolomina@gmail.com (M.J. Colomina).

https://doi.org/10.1016/j.bjane.2021.08.022

Introduction

Fibrinolysis is a process that remodels and degrades blood clots to restore vascular permeability. The fibrinolytic cascade starts simultaneously with hemostasis, and the clot forms when platelets bind to fibrinogen to form thrombin. This in turn will produce a fibrin mesh (clot retraction mediated by platelet integrin alpha II beta 3) that is stabilized by factor XIII and protected from fibrinolysis by plasminogen activator inhibitors (PAI-1), thrombin mediated fibrinolysis activation inhibitors (TAFI), and antiplasmin (alpha2-AP). These are found in the nucleus of the clot in a higher proportion than fibrinolytic components (plasminogen activators, urokinase-type plasminogen activator (u-PA), tissue-type plasminogen activator (t-PA), and the plasminogen substrate itself). However, the proportion of profibrinolytic factors is higher around the fibrin mesh, and they will therefore remodel the clot and ensure the permeability of the vessel, particularly in medium to small-caliber arteries. In patients with impaired hemostasis (bleeding or thrombosis), fibrinolysis may be overactivated, leading to bleeding.[1,2]

Tranexamic acid is a molecular analog of lysine that inhibits fibrinolysis by preventing the binding of plasminogen to fibrin.[2] Its preventive use has been studied in different surgical procedures, and it has proven effectiveness in reducing intraoperative bleeding. It is recommended in surgeries with an expected blood loss of more than 500 mL.[3]

TXA administration reduces mortality in bleeding trauma patients and in postpartum hemorrhage.[4,5] There is also evidence for TXA in other scenarios, such as cardiovascular surgery, patients with liver disease undergoing invasive surgery or procedures with risk of bleeding, and patients with acute hemorrhagic pathology; however, further studies are required before it can be routinely indicated. In vascular and urologic surgery, the use of TXA is still under investigation, although some randomized evidence in favor has already been published.[6,7]

In this narrative review of the latest scientific evidence and expert opinions, we address the issues surrounding the use of TXA in clinical situations in which it is recommended.

Methods

This narrative review is based on a bibliographic search carried out in the PubMed National Library for case-control studies, clinical practice guidelines and consensus documents published between 2000 and June 2020.

We used the Jadad scale to classify the case-control studies included in this review and select those that are most relevant for all patient populations and clinical settings. Jadad is a 5-point quality scale ranging from 0 (poor) to 5 (rigorous) based on 3 criteria: patient randomization, blinding, and case dropouts.[8] The studies are summarized in tables.

The initial manuscripts were selected by the authors (MJC, LC, PG, MK, EM, AS) and were then reviewed for inclusion by 2 of the authors, (MJC, AS), who eliminated articles with a score of 3 or lower on the Jadad Scale (poor quality).

This review does not aim to discuss all possible issues surrounding the use of TXA; instead, we focus on practical issues of efficacy and safety reported in each clinical context reviewed: orthopedic surgery and traumatology, liver disease and liver transplant, cardiac surgery, polytrauma patients, obstetric patients, and subarachnoid hemorrhage.

Discussion

Main concerns about tranexamic acid in orthopedic surgery and traumatology

i. Efficacy and safety of TXA in orthopedic surgery

TXA reduces transfusion rates by 25% in procedures such as primary knee[9] and hip[10] arthroplasty (Table 1). However, the latest efficacy reviews (Table 1), especially those related to thromboembolic events and renal complications, do not report safety outcomes.

Because individual comorbidities such as ischemic heart disease, history of stroke, peripheral vascular disease, thromboembolic disease, or vascular stent are not commonly reported, the meta-analysis of Fillingham et al.,[11] which included 78 randomized clinical trials, used an American Society of Anesthesiologists (ASA) physical status of III or greater as a proxy for the presence of comorbidities associated with an elevated risk of a thromboembolic event. Study populations in which more than 50% of patients were ASA III or higher were compared with populations in which more than 50% were ASA I or II. Because of limitations in the inclusion and exclusion criteria in randomized clinical trials (RCT), meta-regression was performed using ASA status as a proxy for patients at higher risk for arterial and venous thromboembolic events. The authors found that the administration of TXA did not increase the risk of thromboembolic disease in patients undergoing arthroplasty surgery, but the level of evidence is moderate.[11,12] The same authors published a clinical practice guideline in which they concluded that the effect of TXA was independent of the method of administration, the number of doses, the use of single or multiple doses, or administration before or after the incision. They also observed that 92% of the studies used a history of a thromboembolic event as the exclusion criterion, and noted that there is a paucity of randomized clinical trials on the risk of adverse effects of intravenous, topical and oral TXA in patients with a known history of VTE, MI, CVA, TIA, and/or vascular stenting, that no clinical trials have investigated specific risk factors, and that there is a paucity of randomized clinical trials on the risk of arterial thromboembolism. Taking these results into account, the authors' decision to consider TXA safe in this setting appears questionable.[13]

The Premier Perspective database, which includes 510 US hospitals, is based on notifications of total hip or knee arthroplasty in 872,416 patients from 2006 to 2012.[14] When stratifying according to age and comorbidity index, patients treated with TXA (compared to those not treated) presented a lower rate of thrombotic complications (0.6% vs 0.8%), acute renal failure (1.2% vs 1.6%), and combined complications (1.9% vs 2.6%). In another review,[15] the risk of venous thromboembolism was analyzed by reviewing 73 randomized controlled trials with 4,174 patients and 2,779 controls. The incidence of venous thromboembolism was

Table 1 Tranexamic acid in orthopedic surgery: meta-analysis.

Author (year) Type of study	Patients	Dosage	Blood loss Mean of difference (IC 95%)	Transfusion risk RR (IC 95%)	Adverse effects
Knee arthroplasty					
Fillingham et al.[9]	67 studies				Not described in article.
2018	> 9000 patients				In a safety meta-analysis (Fillingham YA,[11,13] 2018) TXA was only evaluated in primary knee arthroplasty
Meta-analysis					
		IV High doses (≥ 20 mg.kg^{-1} o > 1 g) vs control	-283,06 (-353,6; -219,7)	0,21 (0,15- 0,27)	
		IV low doses vs control	-272,29 (-397,42; -155,83)	0,35 (0,22-0,51)	
		Topical (> 1,5 g) vs control	-329,4 (-426,63; -240,21)	0,26 (0,15-0,4)	
		Topical (< 1,5 g) vs control	-266,32 (-341,69; -200,0)	0,25 (0,17 – 0,35)	
Hip arthroplasty					
Fillingham et al.[10]			16 RCT	31 RCT	Not described in article.
2018			1668 patients	2545 patients	In a safety meta-analysis (Fillingham YA,[11,13] 2018) ATX was only evaluated in primary hip arthroplasty
Meta-analysis					
		IV high doses (≥ 20 mg.kg^{-1} o > 1 g) vs control	**-332,54 (-430,22; -250,28)**	0,28 (0,2-0,38)	
		IV low doses vs control	**-313,72 (-414,95; -218,21)**	0,37 (0,26-0,5)	
		Topical (> 1,5 g) vs control	**-296,66 (-392,97; -200,82)**	0,29 (0,17-0,47)	
		Topical (< 1,5 g) vs control	**-363,75 (-733,03; -295,16) (NS)**	0,29 (0,12-0,58)	

Author (year) Type of study	Patients	Dosage	Intraoperative blood loss Mean of difference (IC 95%)	Total blood loss Mean of difference (IC 95%)	Transfusion risk RR (IC 95%)	Adverse effects
Spine surgery						
Lu VM[23]	6 RCT	10-30 mg.kg^{-1} initial bolus and	-124,11 (-207,15; -41,06)	-229,76 (-331,46; -128,06)	0,56 (0,29; 1,07)	4 patients with mild kidney function impairment
2018 Meta-analysis	937 patients	1 a 2 mg.kg^{-1}.h^{-1} perfusion				1 pulmonary embolism 1 deep venous thrombosis

IV, intravenous.

not significantly different from that of the controls (2.1% vs 2.0%).

ii. Dosage, timing and route of administration of TXA in orthopedic surgery

The meta-analysis by Fillingham et al.[9,10] stratified TXA according to dosage, and considered > 1 g or ≥ 20 mg.kg^{-1} for IV administration to be a high dose (the general dose is 15 mg.kg^{-1} body weight). (Table 1).

With regard to the timing of TXA administration to achieve maximum efficacy, the study by Tanaka et al.[16] concluded that in knee arthroplasty, 1 g of IV TXA administered preoperatively followed by a second dose (1 g) after removal of the hemostasis tourniquet significantly reduced blood loss without increasing the risk of thromboembolic complications. In primary hip arthroplasty, Imai et al.[17] recommend 1 g of IV TXA 10 minutes before surgery followed by a second dose 6 hours thereafter as an effective strategy for reducing blood loss. In general, IV administration of TXA is recommended before the surgical incision, but this recommendation has a moderate level of evidence because the studies that support it are inconclusive.[9,10,18–20]

In spinal surgery, the most frequently used doses are 10 to 30 mg.kg^{-1} as a loading dose prior to the surgical incision, followed by 1 to 2 mg.kg^{-1}.h^{-1} during surgery[21–23] (Table 1).

There are very few pharmacokinetic studies in TXA outside the setting of cardiac surgery, and the dosing regimens currently used are largely empirical. Unfortunately, none of these concentrations are based on any formal in vivo dose-response studies, and the corresponding therapeutic margin for TXA and its minimal therapeutic dose to inhibit fibrinolysis remain largely unknown.[24]

Results obtained from in vitro experiments may not accurately predict the effect in vivo. Picetti et al.[25] analyzed 21 pharmacodynamics studies of which 20 were *in vitro* and one was *in vivo*, and determined the drug plasma levels capable of reducing the activity of tissue plasminogen activator by 80% in vitro (10 mg.mL^{-1}), although other studies have not been able to verify these findings.[26] In the studies by Fillingham et al.,[9,10,18] topical, IV, and oral formulations of TXA were all superior to placebo in terms of reduced blood loss and transfusion risk, while no formulation was clearly superior when compared to each other. The use of repeated doses of oral, IV, topical TXA and higher doses of IV TXA did not significantly reduce blood loss or the risk of transfusion.

Topical administration of TXA may currently be considered as an alternative to the IV route in patients in whom the level of thrombotic risk is unknown, as it has the advantage of minimal systemic absorption and therefore less risk of complications.[12] Its effectiveness in reducing bleeding and transfusion is similar or slightly inferior than IV administration, but in the absence of thrombotic risk factors, IV administration is reasonable to achieve effective and reproducible plasma levels. However, it should be borne in mind that TXA has a dose-dependent cytotoxicity that affects wound re-epithelialization and can induce cell shedding. Therefore, bolus administration of topical TXA should not exceed a concentration of 5 to 10 mg.mL^{-1} and a concentration of TXA of 25 to 50 mg.mL^{-1} is recommended when moistening a surgical wound (the usual concentration in the vial is 100 mg.mL^{-1}).[27]

iii. Tranexamic acid and hip fracture

Although elderly patients can be candidates for primary hip arthroplasty, their clinical profile differs from other orthopedic patients. Efficacy and risk of complications is more uncertain than with elective orthopedic surgery, so the indication for TXA in hip fracture must be individualized. In a recent meta-analysis that included a total of 892 patients from 11 clinical studies, intravenous TXA reduced the risk of transfusion by 46%, with no increase in the risk of thromboembolic events; however, the quality of evidence is low.[28]

Various authors recommend taking an individualized, cautious approach when using TXA in this scenario.[29] Table 2 summarizes the different studies published on TXA in patients with hip fractures.

iv. Main recommendations for the use of TXA in orthopedic surgery

- Preoperative administration of TXA in primary hip and knee arthroplasty surgery is effective and safe.
- Topical administration of TXA is recommended as an alternative to intravenous (IV) TXA in orthopedic surgery patients in whom thrombotic risk data are unavailable.
- The indication of TXA in hip fracture should be individualized.

Tranexamic acid in patient with liver disease and liver transplantation

i. Efficacy and safety of TXA in liver disease and liver transplantation

Although patients with impaired liver function can present thrombocytopenia and a deficiency of factors produced in the liver (mainly V, VII, X, and fibrinogen), their ability to form thrombin is maintained by a high von Willebrand factor and factor VIII ratio. This, together with a low plasma concentration of natural anticoagulants (proteins C and S and antithrombin III), causes resistance to thrombomodulin that results in hypercoagulation and portal thrombosis, especially in patients with greater liver involvement (Child C and ascites). In this context, 2 situations can occur: hypofibrinolysis with an increase in PAI-1 and TAFI, especially in patients with hepatic decompensation due to infection/inflammation; and hyperfibrinolysis in patients with advanced but not decompensated liver involvement, probably due to low TAFI levels.[30]

In general, hyperfibrinolysis is usually found in patients scheduled for liver transplantation (LT); therefore, the profile of the patient awaiting LT differs slightly from that of the cirrhotic patient with inflammatory decompensation, and widely from that of the septic patient (with and without liver disease), who mainly presents hypofibrinolysis and a prothrombotic phenotype. However, despite clear signs of fibrinolysis on laboratory tests, the presence of clinical fibrinolysis (cause of bleeding) is rare.[31,32]

The detection of hyperfibrinolysis by laboratory tests has variable sensitivity and specificity, depending on the test

Table 2 Tranexamic acid in patients with hip fracture.[28]

Author (year)	RCT	Intervention: doses TXA	N patients (TXA vs Control)	Blood loss mL (SD mL) (TXA vs Control)	% Transfusion (TXA vs Control)	Adverse effects	Jadad[7]
Sadeghi 2007	Yes	15 mg.kg^{-1} IV bolus	32 35	960 (284) 1484 (374)	**37** **57**	No reported	**3**
Zufferey 2010	Yes	15 mg.kg^{-1} preoperatively IV bolus and repeat at 3 hours later	57 53	975 (741)[a] 1178 (912)[a]	**42** **60**	16% vascular adverse effects at 6 weeks in TXA group and 6% in placebo group	**3**
Vijay 2013	Yes	500 mg preoperatively IV bolus + infusion 1 mg.kg^{-1}.h^{-1} during surgery until end	45 45	39[b] (10) 91[b] (17,6)	**16** **40**	No reported	**4**
Emara 2014	Yes	- 1- 10 mg.kg^{-1} bolus preop + continuous infusion of 500 mg in 250 mL of SS with an infusion of 80 mL.h^{-1} until the end of surgery. - 1.5 g TXA in 100 mL SS - SS topic	IV 20 Topic 20 Control 20	640 (25) 625 (35) 1100 (30)	**5** **5** **35**	6 patients in TXA IV group (five cases of DVT and one case of stroke) versus 1 patient with DVT in the control group and no case in the topic TXA group	**3**
Lee 2015	NO	1 g IV bolus preoperatively	84 187	No reported	**6** **19**	There were no differences in mortality between both groups at 30 and 90 days.	**3**
Kang 2016	Yes	3 g in 100 mL SS topic through surgical deep drainage	([c]) 40 40	600 (53) 737 (62)	**45** **60**	No reported	**3**
Tengberg 2016	Yes	1 g IV bolus preop + IV infusion 3 g in 24 h	33 39	1526.6 (1012.7) 2100,4 (1152,6)	**81.8** **84.6**	90-day mortality was 27,2% in the TXA group compared to 10,2% (n = 4) in placebo group	**4**
Baruah 2016	NO	15 mg.kg^{-1} bolus IV 15 minutes before surgery	30 30	408,97 (106,35) 676,67 (87,88)	**90** **100**	No reported	
Watts 2017	Yes	2 doses of 15 mg.kg^{-1} in 100 mL SS IV prior to the incision and another at the end of the surgery	69 69	902 1205	**17** **26**	There were no differences in mortality between both groups at 30 and 90 days	**4**

RCT, Randomized control trial; SS, saline serum; SD, standard deviation; TXA, Tranexamic acid; IV, intravenous.
[a] Median (Interquartile Range).
[b] Deep drainage volumen.
[c] Only patients with hip fracture.

used and the population studied, and it is difficult to make comparisons given the heterogeneity of the patient populations included in the studies published so far. The reference test is euglobulin clot lysis time (ECLT), or alternatively the clot ratio at 60 minutes. In ECLT, clot lysis measured by viscoelastic techniques has excellent specificity but low sensitivity, with Rotem's FIBTEM obtaining the best result.[31]

During LT, between 50% and 70% of patients present hyperfibrinolysis during the anhepatic phase and reperfusion of the liver graft, presenting a profile characterized by elevated t-PA and low PAI-1 in the initial phases (hepatectomy and anhepatic), with a hatching of the t-PA in graft reperfusion that is attenuated and compensated by the sudden increase in PAI-1 at the end of the procedure. TAFI, plasminogen and alpha2-APE are maintained at low levels throughout the procedure.[32]

The main cause of massive bleeding in LT is hyperfibrinolysis, especially during graft reperfusion. This is associated with graft dysfunction and enhanced by the transfusion of prothrombotic factors (plasma, prothrombin complex) that stimulate hyperfibrinolysis and tissular hypoperfusion. Therefore, the prediction of hyperfibrinolysis is closely linked to the prediction of intraoperative bleeding. Hyperfibrinolysis in the reperfusion phase of liver transplantation is often a transient, self-limiting situation that resolves within 15 to 20 minutes. Despite the lack of clear evidence of an increased risk of hypercoagulability associated with the use of antifibrinolytics during LT, a significant number of case reports have described dramatic thrombotic events that are most likely associated with the administration of this class of drug. As a result, routine prophylactic administration of antifibrinolytics in patients undergoing LT cannot currently be recommended. Antifibrinolytic therapy (EACA or TXA) should only be considered in LT recipients with significant bleeding when hyperfibrinolysis is either suspected or confirmed by VET.[30] Steib et al.[33] determined that a maximum amplitude of less than 35 mm in the thromboelastogram was predictive of hyperfibrinolysis and bleeding. More recently, A10FIBTEM < 8 mm and A10EXTEM < 35 mm have been found to predict intraoperative bleeding.[34,35]

Liver transplantation invariably involves hypofibrinogenemia, so correction of fibrinolysis with active bleeding involves the administration of fibrinogen or cryoprecipitate at the same time as treatment with antibrinolytic drugs.[36] In our personal experience, intraoperative hyperfibrinolysis should be corrected with a TXA bolus of 1 to 2 g IV and fibrinogen with 2 to 4 g IV if A10EXTEM is < 15 mm or clotting time on FIBTEM is > 300 seconds. This dosage regimen is similar to that proposed by other authors.[30]

Given the uncertainty of whether prophylaxis with antifibrinolytics should be performed in patients with severely impaired liver function in surgical procedures or during liver transplantation, no clear recommendation can be made. Even if hyperfibrinolysis is a cause of bleeding, systematic intraoperative administration of antifibrinolytics is not recommended due to the risk of thrombosis, especially of the hepatic artery. Aprotinin was withdrawn from the market due to a tendency towards thrombosis and possible renal failure. Few randomized, double-blind studies have compared TXA prophylaxis with placebo; however, as different doses are used, a meta-analysis cannot be performed. Boylan used high doses,[37] Dalmau moderate doses,[38] and both demonstrated an important reduction in blood transfusion. In a comparative study in liver transplantation, antifibrinolytics, TXA and aprotinin showed the same efficacy when given prophylactically.[39] Regarding safety, a series of patients receiving prophylactic TXA did not show an increase in thrombotic phenomena relative to other series or to a group of untreated patients.[40] In contrast, venous thrombosis was higher in patients treated with aprotinin; however, after adjusting for risk, no differences were observed.[41]

ii. Main recommendations for the use of TXA in liver disease and liver transplantation.

- Although patients with impaired liver function may present coagulation factor deficiency, this status may be compensated, so it is important to evaluate a possible tendency towards hypercoagulation.
- The hemostatic profile of the liver transplant candidate is slightly different from that of the cirrhotic patient with inflammatory decompensation. Hyperfibrinolysis is detected in a higher proportion in patients scheduled for liver transplantation.
- Systematic antifibrinolytic prophylaxis cannot be recommended in patients with severe impairment of liver function or during liver transplantation.

Tranexamic acid in cardiac surgery, according to patient and type of surgery: special concerns

i. Patient and type of surgery: special concerns

Cardiac surgery (CS) is one of the specialties with the highest bleeding risk. The causes of coagulopathy after cardiopulmonary bypass (CPB) are multifactorial. Hemodilution and exposure to CPB circuits cause platelet destruction and thrombin generation, which increase fibrinolytic activity.[42–44] Furthermore, hypothermia and the administration of heparin and protamine also influence perioperative bleeding if the dosage is not correct. As fibrinolysis is an important cause of bleeding, antifibrinolytic drugs have been shown to be effective in reducing bleeding and the need for transfusion, and their use is now a Class I recommendation (level of evidence A) by the American Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists.[45]

TXA is indicated in all CS with and without CPB. It has been most widely studied in the context of coronary artery bypass surgery, although it has also been investigated in valve and ascending aortic surgery (Table 3).[42,46] Cardiac surgery patients have been one of the most widely studied populations in the context of TXA use, and the largest study, published by Myles et al.,[42] did not detect any TXA-induced thromboembolic complications.

ii. Dosage and interval of administration of TXA in cardiac surgery

Table 4 summarizes chronologically the different TXA regimens in CS.[42,47,48] In the study by Sigaut et al.,[48] 2 groups of patients receiving a TXA dose greater than 50 $mg.kg^{-1}$ and a lower dose were compared. No differences were found in the mortality, blood transfusion, and reinterventions to control bleeding.

Table 3 Tranexamic acid in cardiac surgery.

Author, year, Level of evidence (Jadad[8])	Patients and intervention groups	Objectives & Results	Comments
Myles PS et al.[42]	4631 adults' patients bypass coronary surgery	Objective 1º: Mortality and thrombotic complications during the first 30 days (p = 0.22):	Well-designed study with a very good sample size
(2017)	- 2320 Placebo	[•]386(16. 7%) Placebo	
RCT	- 2311 TXA.	[•]420 (18.1%) TXA	High doses (to 1 mL.kg^{-1} and 0,5 mL.kg^{-1}, according to Table S8 of the Supplemental material of Myles study 100 mg.kg^{-1}), significantly reduces bleeding (p = 0,026) and number of units transfused of blood products (p = 0.017)
Jadad 4	Initially 100 mg.kg^{-1} more than 30 min post anaesthesia induction	Objective 2º: Total number of blood products transfused during hospitalization (p < 0.001).	
	After, 50 mg.kg^{-1} due to the high incidence of seizures	[•]7994 Placebo [•]4331 TXA	The incidence of seizures is low in both groups.
		Re-intervention for major bleeding or cardiac tamponade (p = 0.001): [•]2.8% Placebo [•]1.4% TXA	
		Seizures (p = 0.002) [•]0.1% Placebo [•]0.7% TXA	
Sigaut et al.[48]	569 Adult's patients	Objective 1º: Incidence of transfusion up to 7 postoperative days (p = 0.3)	Well-designed study with correct size
(2014)	Coronary by-pass surgery	[•]180 low doses TXA	
RCT	- 284 low doses TXA	[•]170 high doses TXA	No differences in mortality or transfusion rate
Jadad 5	10 mg.kg^{-1} bolus +	Objective 2º: Blood products transfusion (p = 0.02)	
(level 1b)	1 mg.kg^{-1}.h^{-1} +	[•]4.1 ± 0.39 low doses TXA	Significant differences in blood loss, blood products transfused, and re-interventions for bleeding control
	1 mg.kg^{-1} priming OP	[•]2.5 ± 0.38 high doses TXA	
	- 285 high doses TXA	Blood loss first 24h (mL) (p = 0,01)	Incidence of seizures also low compared to other series reporting 3-7% of seizures
	30 mg.kg^{-1} bolus +	[•]820 ± 50.7 low doses TXA	
	16 mg.kg^{-1}.h^{-1} +	[•]590 ± 50.4 high doses TXA	
	2 mg.kg^{-1}priming OP	Re-surgical for bleeding (p = 0.03) [•]17 low doses TXA [•]14 high doses TXA	
		Seizures (p = 0.7) [•]2 low doses TXA	

Table 3 (*Continued*)

Author, year, Level of evidence (Jadad[8])	Patients and intervention groups	Objectives & Results	Comments
		[•]4 high doses TXA Mortality from day 0 to day 28 (p = 0.2) [•]14 low doses TXA [•]8 high doses TXA	
Kuiper et al.[47] (2019) Observational, prospective open cohort database Jadad 5	355 Adults Cardiac surgery - 204 blood products administration of and haemostatic medication according to medical criteria - 151 blood products administration of and ROTEM-guided haemostatic medication	1st Objective: Blood loss the day of the surgery (p < 0.001) [•]890 mL. Medical criteria [•]565 mL. Guided by ROTEM Use red blood cell transfusion and haemostatic medication. Decreased absolute risk of: [•]17% by red blood cell transfusion (p = 0.024) [•]12% for fresh frozen plasma (p = 0.019) [•]12% for fresh frozen plasma (p = 0.019) [•]4% by platelet transfusion (p = 0.582) In general, more TXA was administered but not more fibrinogen 2nd Objective: Re-surgical intervention for bleeding and mortality [•]No statistically significant difference In hospital stay [•]A mean of 4 days was reduced (p < 0.001) Economic costs [•]€4.8 million ($5.6 million) per year for the authors' hospital with about 1,000 procedures annually.	

RCT, Randomized control trial; OP, On-Pump coronary artery bypass surgery.

Table 4 Dosage regimens of tranexamic acid in cardiac surgery.

Author	Year	Loading dose	Maintenance dose	Dose in on-pump	Plasmatic concentration
Horrow et al.,[49] (1995)	1995	10 $mg.kg^{-1}$	1 $mg.kg^{-1}.h^{-1}$	No	
Fiechtner et al.,[50] (2001)	2001	10 $mg.kg^{-1}$	1 $mg.kg^{-1}.h^{-1}$	-	14-54 $mg.L^{-1}$
Dowd et al.,[51] (2002)	2002	12,5 $mg.kg^{-1}$	6,5 $mg.kg^{-1}.h^{-1}$	1 $mg.kg^{-1}$	52 $mg.L^{-1}$
Dowd et al.,[51] (2002)	2002	30 $mg.kg^{-1}$	16 $mg.kg^{-1}.h^{-1}$	2 $mg.kg^{-1}$	125 $mg.L^{-1}$
Fergusson (BART) et al.,[52] (2008)	2008	30 $mg.kg^{-1}$	16 $mg.kg^{-1}.h^{-1}$	2 $mg.kg^{-1}$	-
Sevilla Document (Leal-Noval et al., 2013)[53]	2013	30 $mg.kg^{-1}$	16 $mg.kg^{-1}.h^{-1}$	2 $mg.kg^{-1}$	-

Seizures in adult patients after CS are an independent predictor of permanent neurological damage and increase mortality by up to 29%.[54] The 2 main risk factors are open heart surgery, and especially advanced age. This latter could be due to the presence of vascular microembolisms that can cross the blood-brain barrier and can in themselves be epileptogenic. The TXA molecule, meanwhile, inhibits GABA-A receptors of the hippocampus and glycine receptors, causing an increase in neuronal excitability.[55–57]

The recommended TXA doses according to CS transfusion risk scales such as the Acta-Port Score[58,59] are:

1. Low risk of bleeding (Acta Port Score $\leq$ 19 with a transfusion prediction of between 5% and 69%): TXA bolus of 10 $mg.kg^{-1}$ prior to sternotomy + 1 $mg.kg^{-1}.h^{-1}$ perfusion throughout surgery. In this case, the dose is not adjusted for kidney failure.
2. High risk of bleeding (Acta Port Score $\geq$ 20 with a transfusion prediction of between 73% and 95%): TXA bolus of 30 $mg.kg^{-1}$ prior to sternotomy + 10 $mg.kg^{-1}.h^{-1}$ perfusion throughout surgery. The dose is adjusted according to glomerular filtrate levels (adapted from Jerath et al.[60]): $\geq$ 60 ($mL.min^{-1}$/ 1.73 m^2) - 10 ($mg.kg^{-1}.h^{-1}$); 30-60 ($mL.min^{-1}$/1.73 m^2) - 5 ($mg.kg^{-1}.h^{-1}$); < 30 ($mL.min^{-1}$/1.73 m^2) or dialysis - 3 ($mg.kg^{-1}.h^{-1}$).

iii. Main recommendations for the use of TXA in cardiac surgery

- Antifibrinolytic drugs have been shown to be extremely beneficial in cardiac surgery with CPB and are now recommended with a high level of evidence.
- TXA administration at doses higher than 50 $mg.kg^{-1}$ has failed to demonstrate a decrease in mortality, bleeding, or transfusion risk; instead, there is an increased risk of seizures.
- TXA is not generally considered necessary in CPB priming, but it is recommended to adjust the dose based on renal function, according to the serum creatinine level of each patient.

Tranexamic acid in the polytrauma patient: important questions

The CRASH-2 study, which showed a 14.5% reduction in 28-day mortality in the TXA group compared to 16% in the placebo group, has impacted TXA use in trauma patients.[4] A subsequent analysis derived from this study showed that patients treated with TXA within 1 hour of trauma had a 5.3% risk of mortality from bleeding compared to 7.7% in the placebo group. However, the risk of mortality from bleeding increased in patients treated more than 3 hours after the injury (4.4% vs 3.1%) (Table 5).[12]

Since publication of this study, many guidelines and scientific societies strongly recommend the administration of TXA. Early administration, at least within the first 3 hours of the trauma, is recommended.[61]

Despite its impact, the CRASH-2 study has important limitations that need to be considered: selection bias; the inclusion criteria make it impossible to determine the homogeneity of cohorts; there are no data on injury severity scores, presence of shock (lactate, base deficit) or fibrinolysis at admission; TXA did not reduce bleeding, and only 50% of study patients received blood transfusion; and there are no data on the number of cases requiring massive transfusion (MT) or the number of MT protocols used by the different hospitals.[62]

i. Is there evidence for starting administration of tranexamic acid in the out-of-hospital setting?

The CRASH study[4] is so far the only study providing a high degree of evidence for out-of-hospital administration. Stein et al.[63] performed a prospective study in 70 patients to evaluate changes in coagulation from on-scene administration of 1 g TXA to hospital admission. Patients treated with TXA showed higher FIBTEM (14 $\pm$ 5 vs. 11 $\pm$ 3.5; p = 0.010) and EXTEM (61 $\pm$ 6 vs. 50 $\pm$ 8; p < 0.001) values compared to the control group. The increase in D-dimer was significantly greater in the control group, indicating greater fibrinogen degradation (Table 5).

The prospective, multicenter Cal-PAT study[64] in 362 patients treated with prehospital TXA compared with 362 patients in a historical group showed a decrease in 28-day

Table 5 Tranexamic acid in polytraumatic patient.

Author (year) Type of study	Patients	Groups/Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad[5]
Moore et al.,[76] (2016) Descriptive Multicentric 2 Centres	Age ≥ 18 ISS > 15	3 Fibrinolysis phenotypes: - HF - Phy - SD	2540	- Define FL types - Define FL type predictors - FL relationship with mortality	HF (34%) SD (22%) Phy (14%) p < 0,0001	–	GCS of 3 in the SD and HF group may be a bias in mortality	(Not describe missing) No clinical trial
Raza et al.,[78] (2013) Prospective Observational Cohorts	Trauma Age > 15 Trauma Activation	- PAP ≤ 1500+LM < 15% normal - PAP > 1500+LM < 15% moderate (PAP only) - PAP > 1500+LM > 15% severe - PAP ≤ 1500+LM > 15% TEG only	288/325	-Prevalence and severity of FL -Sensitivity of ROTEM to detect FL -Association FL/ Tissue injury	Normal = 100 PAP only = 165 Severe = 15 TEG only = 8 90% of ISS > 24 PAP > 1500 and only 11.6% LM > 15%	-		(Describe missing) No clinical trial
CRASH-2[4] (2010) Prospective RCT Multicentric	Adult trauma (SAP < 90 mmHg and/or HR > 110) or bleeding risk at 8 h post-trauma	TXA Group Placebo Group	20211	Effect of early administration of TXA on survival, thrombotic lesions, and transfusion	Mortality TXA 14,5% vs 16 %; p 0.0035 RR 0.91 Vascular event TXA 1.7% vs 2 %; p 0.085	Any vascular occlusion (1.7% vs 2%; p = 0.084)	Lack of description of ISS and injuries of both groups	5

RCT, randomized control trial; FL, Fibrinolysis; HF, Hiperfibrinolisis; SD, *South Down* Fibrinolysis; PHY, Fibrinolysis physiological; GCS, Glasgow Coma Score; PAP, Plasmine anti-plasmine complex; LM, Lysis maxima; TEG, Thromboelastography; ISS, *Injury Severity Score*; SAP, Systolic arterial pressure; HR, heart rate.

mortality (3.66 vs. 8.3%). The difference in mortality was greatest in severely injured patients with ISS > 15 (6% vs. 15.5%).

These studies support prehospital administration of TXA, despite their design limitations. The randomized double-blind STAAMP study,[65] which evaluates the effect of prehospital TXA on 30-day mortality did not result in a significantly lower 30-day mortality, but it was safe and did not result in a higher incidence of thrombotic complications or adverse events.

ii. Should all multiple trauma patients receive TXA? Which trauma patients benefit the most from TXA treatment?

The first question is probably: in which kind of trauma is TXA is indicated? Should it be limited to severely bleeding, coagulopathic patients with hemodynamic compromise/shock? Or should the cyclist with an isolated tibial fracture also be included? Despite an increasing number of studies recommending liberal use, current guidelines recommend using TXA only for severe bleeding or in patients who are bleeding or at risk of significant hemorrhage that is (or at least might be) due to hyperfibrinolysis.[66] This raises the second question: Is TXA safe? There is growing concern about the possibility of thromboembolic complications.[24] In the military setting, TXA administration is an independent risk factor for VTE.[67–70] Additionally, statistical analysis ambiguities (more specifically, the interpretation of statistical tests), especially the upper limits of the confidence intervals in almost every study published by the *London School of Hygiene & Tropical Medicine*, may confound study findings.[24] The authors are aware of this problem. The results of CRASH-2, CRASH-3 and WOMAN were not reproducible in a modern hospital setting in developed countries with a high socioeconomic status.[71–74]

Nevertheless, 25% of patients present acute traumatic coagulopathy (ACT) on arrival at the hospital,[75] and the presence of fibrinolysis is also an aggravating factor for mortality.[75]

Moore et al.,[76] differentiated 3 phenotypes using thromboelastography in a study of 2.540 patients. Hyperfibrinolysis appeared in 18% of patients, and was associated with the highest mortality rate (34%), hypofibrinolysis was present in the 46% of patients and was associated with the second highest mortality rate (22%), and physiological fibrinolysis, found in 36% of patients, was associated with a 14% death rate. The authors[77] believe that an imbalance between the plasminogen activator inhibitor (PAI-I) and activator (tPA) could be the cause of hypofibrinolysis, and they question the use of TXA in these patients, suggesting that patients should be treated on the basis of thromboelastographic results, although more evidence is required (Table 5).[78]

Despite the progress in fibrinolysis phenotype diagnosing, empirical treatment with TXA within the first 3 hours after trauma is still recommended in mature trauma systems. Especially in patients with significant hemorrhage and systolic blood pressure less than 90 mmHg or heart rate higher than 110 beats /minute or who require any transfusion.[4]

iii. What is the ideal dosage and interval of TXA in trauma patients?

Grassin-Delyle et al.,[79] in a pharmacokinetic study in 73 trauma patients who received 1 g of intravenous TXA before arrival at the hospital, found that the plasma concentration on arrival at the hospital was 28.7 (21.85–38.5 [8.7–89.0]) μg.mL-1 and less than 20 μg.mL-1 (the lowest target concentration) in 21% of patients. The TAMPITI study[80] randomizes patients to receive placebo or 2 single IV boluses of TXA (4 g or 2 g), and the STAAMP[65] trial studies the effect of pre-hospital infusion of TXA, evaluating doses higher than 4 $mg.kg^{-1}$ in patients requiring transfusion.

iv. Is monitoring essential after TXA administration in trauma patients?

According to Moore et al.,[81] the empirical administration of TXA warrants careful evaluation, and the authors support its use within 2 hours of injury in severe trauma patients with a pattern of thromboelastogram-documented hyperfibrinolysis. When evaluating clot formation with thromboelastography, platelet-induced clot retraction may be interpreted as a false positive for hyperfibrinolysis, so some authors suggest measuring a sample in parallel with TXA to rule this out.[82]

v. Main recommendations for the use of TXA in trauma.

- In trauma patients with high suspicion of bleeding, TXA administration is recommended in the first 3 hours after the injury.
- Current evidence is limited to a recommendation of out-of-hospital administration of TXA.
- The ideal dosage and interval of administration of TXA in these patients has yet to be defined.

Tranexamic acid in the obstetric patient

Postpartum hemorrhage (PPH) is still the obstetric emergency with the highest maternal mortality. The overall incidence of PPH is estimated at between 6% to 11%, and that of severe PPH is between 1% and 3%.[83] According to the latest consensus guidelines published by NATA (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis), PPH is defined as blood loss of more than 500 mL in the first 24 hours, and severe PPH as blood loss of over 1000 mL.[83]

Up to 75% of PPH cases are caused by uterine atony,[84] which is why the use of uterotonics is recommended as the first line of treatment, with a 1A level of evidence.[83] However, only 6.4% of PPH-related deaths are due to uterine atony,[84] suggesting that other causes and treatments should be considered.

During placental delivery, degradation of fibrinogen and fibrin occurs together with an increase in the activation of plasminogen activators and fibrin degradation products due to activation of the fibrinolytic system, which is why TXA may be useful in cases of PPH that are not associated with uterine atony.[84,85]

i. Current evidence on the use of TXA in the obstetric patient.

A recent meta-analysis[84] analyzing the efficacy of preincisional TXA in caesarean section and the use of TXA after vaginal delivery, with uterotonic co-administration, showed a decrease in the incidence of bleeding, blood transfusion and additional medical interventions. Administration of prophylactic TXA for vaginal delivery also reduced bleeding.[86]

Table 6 Tranexamic acid in obstetrics' patients.

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad[5]
Novikova N[84]	Healthy women with low risk of bleeding by caesarean section or childbirth	Evaluates 12 RCT.	N: 3285	To determine the effectiveness and safety of TXA in preventing PPH compared to placebo, no treatment, or uterotonics	Decrease incidence of bleeding greater than 400-500 mL in vaginal delivery.	Nausea and vomiting were more frequent in TXA group.	Using the GRADE criteria, the risk of bias was assessed as moderate	
(2015)		9: Efficacy of pre incisional TXA in caesarean sections	Caesarea's: 2453		Decrease bleeding more than 1000 mL in caesarean sections.	Serious adverse effects could not be assessed by sample size		
Meta-analysis and Systematic review		3: Efficacy of TXA after vaginal delivery. In all RCTs, TXA was associated with uterotonics and compared with placebo or no treatment.	Deliveries: 832		Decrease bleeding, blood transfusion, and additional medical interventions.			
Mirghafourvand M[86]	Pregnant women with a single foetus at low risk of PPH	TXA group: 1 g of after delivery	N: 120	To assess the effect of TXA on postpartum vaginal bleeding in low risk of postpartum haemorrhage women	Bleeding as measured was significantly less in the TXA group.	2 cases had nausea and vomiting in TXA group and none in the control group, but the study is not powerful to assess adverse effects.	The size of the study is one of its biggest biases.	3
(2015)		Control: Placebo	TXA: 60			No thrombotic events.		
RCT double-blind			Control: 60					

Table 6 (*Continued*)

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad[5]
Sujata N[87]	Women undergoing elective or urgent caesarean section with high risk of PPH	TXA group: 10 mg.kg^{-1}	N: 60	To assess the effect of TXA in patients undergoing caesarean section with a high risk of PPH	TXA group required significantly less additional uterotonics.	TXA was safe for both and was not associated with a greater number of thrombogenic events, but the power of the study was insufficient to analyse the adverse effects.	The risk of bias is high because the study was not double-blind.	
(2016)		Control: Saline Serum	TXA: 30					
RCT		Both administered 10 minutes before the incision.	Control: 30					
WOMAN[5]	Women > 16 years old with clinical diagnosis of PPH after caesarean section or vaginal delivery	TXA group: 1 g, and a possible second dose after 30 minutes if bleeding was ongoing.	N: 20.021	To determine the effects of TXA on mortality, hysterectomy, and other complications in women with PPH	TXA did not decrease mortality from any cause or the incidence of hysterectomy.	There were no significant differences regarding the incidence of thromboembolic events, organ failure, or sepsis.	Regarding hysterectomy, in many cases the decision to perform a hysterectomy was already made before administering the drug.	5
(2017)		Control: Placebo.	TXA: 10,036		TXA decreased mortality from bleeding in patients who were administered in the first 3 hours postpartum.		Regarding mortality, in some cases it was so early after randomization that it should not be associated with AT use.	
RCT multi-centre, double blind			Control: 9,985		The TXA also significantly reduced the incidence of laparotomies to control bleeding.			

Table 6 (*Continued*)

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad[6]
Brenner A (Brenner et al., 2018)	WOMAN's study patients randomized in the first 3 hours postpartum.	TXA group: 1 g and a possible second dose after 30 minutes if bleeding was ongoing.	N: 14,923	To determine the effects of TXA on mortality and hysterectomy in women with PPH	TXA showed a significant decrease in death from bleeding, but not from hysterectomy.	No evaluated	This sub-analysis tries to avoid the biases discussed in the WOMAN study, but it has important statistical limitations.	5
WOMAN sub-analysis	Excluding hysterectomies and early deaths	Control: Placebo.	TXA: 7,518 Control: 7,405					
Sentilhes L[88]	Women in labour with vaginal delivery of a single expected child without increased risk of bleeding or thrombosis	TXA group: 1 g of TXA after delivery	N: 3,891	To know if the administration of prophylactically TXA in addition to oxytocin after delivery reduces the incidence of PPH	TXA decreased bleeding $\geq$ 500 mL, but not significantly (p = 0,07)	TXA was associated with an increased incidence of nausea and vomiting, but not increase the incidence of thromboembolic events at 3 months.	The importance of the difference between $\geq$ 500 mL and > 500 mL remains to be defined.	5
(2018)		Control: Placebo	TXA: 1,945		TXA decreased significantly bleeding > 500 mL, clinically significant PPH, and the use of additional uterotonics.			
RCT multi-centre, double blind			Control: 1,946					

RCT, Randomized control trial; TXA, Tranexamic acid; PPH, Postpartum Haemorrhage.

TXA after caesarean section with PPH risk reduced the need for uterotonics (Table 6).[87]

The WOMAN trial,[5] published in 2017, evaluated the efficacy of administration of TXA vs placebo in 20,021 patients with a clinical diagnosis of PPH. TXA reduced mortality from bleeding, but not all-cause mortality. However, as in other types of patients, mortality due to bleeding was reduced when the drug was administered within the first 3 hours postpartum, but not when it was administered after this window.[5] Hysterectomy was not reduced with TXA; however, many hysterectomies were indicated at the time PPH was diagnosed, so TXA did not affect this decision - a study weakness acknowledged by the authors.[5] In a recent study carried out in 15 French hospitals,[88] the administration of 1 g of TXA in the immediate postpartum period together with oxytocin decreased clinically significant PPH and the use of additional uterotonics (Table 6).[88]

Based on the foregoing evidence, after the administration of uterotonics and following diagnosis of PPH, the administration of 1 g IV TXA is recommended within the first 3 hours of delivery, repeating the dose after 30 minutes if necessary. This recommendation has a 1B level of evidence.[83]

However, in the case of caesarean section, the NATA consensus guidelines advise against the routine use of tranexamic acid to prevent PPH, reserving its use for cases of antepartum bleeding and in women at increased risk of PPH, and recommend administering TXA at doses of 0.5 to 1 g in addition to oxytocin in patients with high risk of PPH.[83] Despite the decrease in the incidence of bleeding greater than 500 mL after vaginal delivery shown in the study by Sentilhes et al.,[88] the prophylactic use of TXA in vaginal delivery is not currently recommended. In severe PPH, the NATA guidelines recommend goal-guided replacement using laboratory results or viscoelastic techniques (Table 6).[83]

ii. Main recommendations for the use of TXA in the obstetric patient.

- The use of prophylactic TXA in vaginal delivery is not currently recommended.
- TXA may be useful in postpartum hemorrhage (PPH) situations that are not associated with uterine atony.
- Once PPH has been diagnosed. After administration of uterotonics, 1 g of IV TXA is recommended within the first 3 hours of delivery, repeating the dose after 30 minutes if necessary. This recommendation has a high level of evidence.

Tranexamic acid in subarachnoid hemorrhage: evidence and controversies

Subarachnoid hemorrhage due to aneurysmal rupture occurs in relatively young patients (mean age 55 years).[89–91] A frequent complication of patients with SAH is rebleeding of the aneurysm itself, which occurs in the first 3 to 6 hours after SAH, and is the main cause of mortality and morbidity.[92–94] Early interventional treatment through coiling and/or clipping of the aneurysm fails to prevent most rebleeding that occurs in the early stages. Therefore, early medical treatment with antifibrinolytics could be indicated in these patients. However, although studies performed so far report a reduction in rebleeding, TXA did not improve morbidity and mortality, and the benefit of TXA in late cerebral ischemia is controversial.[89,91,93]

These studies, it should be noted, are heterogeneous in terms of drug, medication, dose, and final objectives.[95] The results of the ultra-early, short-term administration study are still pending.[96]

In view of the foregoing, routine administration of TXA is not indicated except in selected cases, and the best dosage and interval remain unclear.[92]

The most important studies performed in patients with intracranial hemorrhage - TICH-2[97] and CRASH-3[98] – show that functional status 90 days after intracerebral hemorrhage did not differ significantly between patients receiving TXA and those receiving placebo, despite a reduction in early deaths and serious adverse events. Treatment within 3 hours of injury reduces head injury-related death. TXA should be administered as soon as possible after injury. The CRASH-3[98] study reports that TXA is safe in patients with TBI.

i. Current evidence and controversies on the use of TXA in subarachnoid hemorrhage.

The current recommendations of the Neurocritical Care Society's Multidisciplinary Consensus Conference on management of SAH are[90]:

1) Early, short course with antifibrinolytic therapy before definitive treatment of the aneurysm (begun at the time of diagnosis and continued up to the point at which the aneurysm is secured, or at 72 hours post-ictus, whichever is shorter) (weak recommendation).
2) Do not start treatment 48 h after the event or extend it for more than 3 days when the risk of rebleeding has already decreased (Strong recommendation).

In addition, the authors suggest avoiding the use of antifibrinolytic therapy in patients with high thromboembolic risk, and closely monitoring for possible thromboembolic complications.

However, the authors of the 2013 European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage point out that there is currently no medical treatment that improves outcomes by reducing rebleeding (class 1, level A evidence), and further studies with ultra-early and short-term administration of TXA are needed.[95,96]

Considering all these data, and despite the different approaches put forward in the studies analyzed,[89,91,93] we believe that early treatment of the aneurysm either by endovascular technique (coiling) or by clipping is currently the treatment of choice and the mainstay of management in patients with subarachnoid hemorrhage due to aneurysmal rupture. However, rebleeding in the first few hours is a risk factor associated with high mortality. Starting treatment with TXA at the time of diagnosis and continuing it for the first 24 hours at most, or until the aneurysm is secured early, could provide protection against rebleeding, and prevent the ischemic complications associated with longer treatments.

ii. Main recommendations for the use of TXA in subarachnoid hemorrhage.

- A frequent complication of patients with subarachnoid hemorrhage (SAH) is rebleeding of the aneurysm itself. This occurs in the first 3 to 6 hours after SAH, and is the main cause of mortality and morbidity.
- Routine administration of TXA in SAH is not indicated, except in selected cases. The ideal dosage and interval is not clear.
- The recommendation of early treatment with TXA for the first 72 hours, before definitive treatment of the aneurysm, is weak.

Conclusion

We agree that the use of TXA provides benefits to improve patient outcomes during major bleeding. But, more quantitative studies are needed to evaluate the prophylactic use of TXA, optimal drug dosage, administration time as well as relevant safety aspects. Strong trials and subsequent meta-analyzes of such studies remain the pinnacle of reliable evidence. However, in the absence of such evidence, the anesthesiologist must evaluate the results reported in retrospective cohort studies with expert opinions of less scientific evidence. Still, we must use the full range of reliable, reproducible, and peer-reviewed data to increase our knowledge.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Holcomb JB. Multidisciplinary approach to the challenge of hemostasis. Anesth Analg. 2010;110:354–64.
2. Tengborn L, Blombäck M, Berntorp E. Tranexamic acid - An old drug still going strong and making a revival. Thromb Res. 2015;135:231–42.
3. Lloyd TD, Neal-Smith G, Fennelly J, et al. Peri-operative administration of tranexamic acid in lower limb arthroplasty: a multicentre, prospective cohort study. Anaesthesia. 2020;75:1050–8.
4. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32.
5. Shakur H, Roberts I, Fawole B, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.
6. Monaco F, Nardelli P, Pasin L, et al. Tranexamic acid in open aortic aneurysm surgery. A randomised clinical trial. Br J Anaesth. 2019;124:35–43.
7. Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. Cent European J Urol. 2018;71:72–7.
8. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
9. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. J Arthroplasty. 2018;33, 3090–8.e1.
10. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis. J Arthroplasty. 2018;33, 3083–9.e4.
11. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis. J Arthroplasty. 2018;33, 3070–82.e1.
12. Sheng Xu, Chen Jerry Yongqiang, Zheng Qishi, et al. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: A systematic review and network meta-analysis. Thromb Res. 2019;176:61–6.
13. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic Acid Use in Total Joint Arthroplasty: The Clinical Practice Guidelines Endorsed by the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. J Arthroplasty. 2018;33: 3065–9.
14. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ. 2014;349:g4829.
15. Franchini M, Mengoli C, Marietta M, et al. Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: a meta-analysis of randomised controlled trials. Blood Transfus. 2018;16:36–43.
16. Tanaka N, Sakahashi H, Sato E, et al. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br. 2001;83:702–5.
17. Imai N, Dohmae Y, Suda K, et al. Tranexamic Acid for Reduction of Blood Loss During Total Hip Arthroplasty. J Arthroplasty. 2012;27:1838–43.
18. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic acid in total joint arthroplasty: the endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. Reg Anesth Pain Med. 2019;44:7–11.
19. Saravanan R, Venkatraman R, Karthik K, et al. Efficacy of different doses and timing of tranexamic acid in major orthopedic surgeries: a randomized trial. Rev Bras Anestesiol. 2020;70:311–7.
20. Souza Neto E, Usandizaga G. Comparison of two doses of intra-articular tranexamic acid on postoperative bleeding in total knee arthroplasty: a randomized clinical trial. Rev Bras Anestesiol. 2020;70:318–24.
21. Colomina MJ, Koo M, Basora M, et al. Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial. Br J Anaesth. 2017;118:380–90.
22. Mosaad AA, Abd- MH, Abd-elazeem EM, et al. A Comparative Study between Prophylactic High Dose of Tranexamic Acid and Low Does Tranexamic Acid in Reducing Perioperative Blood Loss in Spine Surgery. J Clin Anesth. 2017;1:1–4.
23. Lu VM, Ho Y-T, Nambiar M, et al. The Perioperative Efficacy and Safety of Antifibrinolytics in Adult Spinal Fusion Surgery. Spine. 2018;43:E949–58.
24. Lier H, Maegele M, Shander A. Tranexamic Acid for Acute Hemorrhage: A Narrative Review of Landmark Studies and a Critical Reappraisal of Its Use Over the Last Decade. Anesth Analg. 2019;129:1574–84.
25. Picetti R, Shakur-Still H, Medcalf RL, et al. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood Coagul Fibrinolysis. 2019;30:1–10.
26. Yang QJ, Kluger M, Goryński K, et al. Comparing early liver graft function from heart beating and living-donors: A pilot study aiming to identify new biomarkers of liver injury. Biopharm Drug Dispos. 2017;38:326–39.

27. Eikebrokk TA, Vassmyr BS, Ausen K, et al. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. BJS Open. 2019;3:840–51.
28. Xiao C, Zhang S, Long N, et al. Is intravenous tranexamic acid effective and safe during hip fracture surgery? An updated meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg. 2019;139:893–902.
29. Heidet M. Tranexamic acid for acute traumatic hemorrhage in emergency medicine: why not, but…. Eur J Emerg Med. 2020;27:85–6.
30. Roullet S, Labrouche S, Mouton C, et al. Lysis Timer: a new sensitive tool to diagnose hyperfibrinolysis in liver transplantation. J Clin Pathol. 2019;72:58–65.
31. Abuelkasem E, Lu S, Tanaka K, et al. Comparison between thrombelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation. Br J Anaesth. 2016;116:507–12.
32. Bezinover D, Dirkmann D, Findlay J. Perioperative Coagulation Management in Liver Transplant Recipients. Transplantation. 2018;102:578–92.
33. Steib A, Gengenwin N, Freys G, et al. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. Br J Anaesth. 1994;73:645–8.
34. Blasi A, Sabate A, Beltran J, et al. Correlation between plasma fibrinogen and FIBTEM thromboelastometry during liver transplantation: a comprehensive assessment. Vox Sang. 2017;112:788–95.
35. Sabate A, Blasi A, Costa M, et al. Assessment of rotational thromboelastometry for the prediction of red blood cell requirements in orthotopic liver transplantation. Minerva Anestesiol. 2018;84:447–54.
36. Sabate A, Gutierrez R, Beltran J, et al. Impact of Preemptive Fibrinogen Concentrate on Transfusion Requirements in Liver Transplantation: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Transplant. 2016;16:2421–9.
37. Boylan JF, Klinck JR, Sandler AN, et al. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. Anesthesiology. 1996;85:1043–8, discussion 30A-31A.
38. Dalmau A, Sabaté A, Koo M, et al. Prophylactic use of Tranexamic Acid and Incidence of Arterial Thrombosis in Liver Transplantation. Anesth Analg. 2001;93:516.
39. Dalmau A, Sabaté A, Koo M, et al. The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: A comparative study. Liver Transplant. 2004;10:279–84.
40. Dalmau A, Sabaté A, Acosta F, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. Anesth Analg. 2000;91:29–34.
41. Warnaar N, Mallett SV, Klinck JR, et al. Aprotinin and the risk of thrombotic complications after liver transplantation: a retrospective analysis of 1492 patients. Liver Transpl. 2009;15:747–53.
42. Myles PS, Smith JA, Forbes A, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. N Engl J Med. 2017;376:136–48.
43. Yang QJ, Jerath A, Bies RR, et al. Pharmacokinetic modeling of tranexamic acid for patients undergoing cardiac surgery with normal renal function and model simulations for patients with renal impairment. Biopharm Drug Dispos. 2015;36:294–307.
44. Gerstein NS, Brierley JK, Windsor J, et al. Antifibrinolytic Agents in Cardiac and Noncardiac Surgery: A Comprehensive Overview and Update. J Cardiothorac Vasc Anesth. 2017;31:2183–205.
45. Society of Thoracic Surgeons Blood Conservation Guideline Task Force VA, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91:944–82.
46. Koster A, Faraoni D, Levy JH. Antifibrinolytic Therapy for Cardiac Surgery. Anesthesiology. 2015;123:214–21.
47. Kuiper GJAJM, van Egmond LT, Henskens YMC, et al. Shifts of Transfusion Demand in Cardiac Surgery After Implementation of Rotational Thromboelastometry-Guided Transfusion Protocols: Analysis of the HEROES-CS (HEmostasis Registry of patiEntS in Cardiac Surgery) Observational, Prospective Open Cohort Datab. J Cardiothorac Vasc Anesth. 2019;33:307–17.
48. Sigaut S, Tremey B, Ouattara A, et al. Comparison of Two Doses of Tranexamic Acid in Adults Undergoing Cardiac Surgery with Cardiopulmonary Bypass. Anesthesiology. 2014;120:590–600.
49. Horrow JC, Van Riper DF, Strong MD, et al. The dose-response relationship of tranexamic acid. Anesthesiology. 1995;82:383–92.
50. Fiechtner BK, Nuttall GA, Johnson ME, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. Anesth Analg. 2001;92:1131–6.
51. Dowd NP, Karski JM, Cheng DC, et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology. 2002;97:390–9.
52. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319–31.
53. Leal-Noval SR, Muñoz M, Asuero M, et al. The 2013 Seville Consensus Document on alternatives to allogenic blood transfusion. An update on the Seville Document. Med Intensiva. 2013;37:259–68.
54. Goldstone AB, Bronster DJ, Anyanwu AC, et al. Predictors and outcomes of seizures after cardiac surgery: a multivariable analysis of 2,578 patients. Ann Thorac Surg. 2011;91:514–8.
55. Sharma V, Katznelson R, Jerath A, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia. 2014;69:124–30.
56. Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. Can J Anaesth. 2012;59:6–13.
57. Takagi H, Ando T, Umemoto T. All-Literature Investigation of Cardiovascular Evidence (ALICE) group. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. J Cardiovasc Surg. 2017;58:633–41.
58. Klein AA, Collier T, Yeates J, et al. The ACTA PORT-score for predicting perioperative risk of blood transfusion for adult cardiac surgery. Br J Anaesth. 2017;119:394–401.
59. PORT score for PeriOperative Risk of blood Transfusion in cardiac surgery by ACTA. Available at: https://qxmd.com/calculate/calculator_436/PORT-score-for-PeriOperative-Risk-of-blood-Transfusion-in-cardiac-surgery-by-ACTA. [accesed 20 June 2020].
60. Jerath A, Yang QJ, Pang KS, et al. Tranexamic Acid Dosing for Cardiac Surgical Patients With Chronic Renal Dysfunction. Anesth Analg. 2018;127:1323–32.
61. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100.
62. Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg. 2013;74:1575–86.
63. Stein P, Studt J-D, Albrecht R, et al. The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients. Anesth Analg. 2018;126:522–9.
64. Neeki M, Dong F, Toy J, et al. Tranexamic Acid in Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study. West J Emerg Med. 2018;19:977–86.
65. Guyette FX, Brown JB, Zenati MS, STAAMP Study Group. Tranexamic Acid During Prehospital Transport in Patients at Risk for

Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surg. 2020;156:11–20.
66. Lier H, Shander A. Tranexamic acid: the king is dead, long live the king! Br J Anaesth. 2020;124:659–62.
67. Walker PF, Schobel S, Caruso JD, et al. Trauma Embolic Scoring System in military trauma: a sensitive predictor of venous thromboembolism. Trauma Surg Acute Care Open. 2019;4:e000367.
68. Howard JT, Stockinger ZT, Cap AP, et al. Military use of tranexamic acid in combat trauma: Does it matter? J Trauma Acute Care Surg. 2017;83:579–88.
69. Johnston LR, Rodriguez CJ, Elster EA, et al. Evaluation of Military Use of Tranexamic Acid and Associated Thromboembolic Events. JAMA Surg. 2018;153:169–75.
70. Adair KE, Patrick JD, Kliber EJ, et al. TXA (Tranexamic Acid) Risk Evaluation in Combat Casualties (TRECC). Trauma Surg Acute Care Open. 2020;5:e000353.
71. Benipal S, Santamarina JL, Vo L, et al. Mortality and Thrombosis in Injured Adults Receiving Tranexamic Acid in the Post-CRASH-2 Era. West J Emerg Med. 2019;20:443–53.
72. Gillissen A, Henriquez D, van den Akker T, et al. The effect of tranexamic acid on blood loss and maternal outcome in the treatment of persistent postpartum hemorrhage: A nationwide retrospective cohort study. PLoS One. 2017;12, e0187555.
73. Boutonnet M, Abback P, Le Saché F, et al. Tranexamic acid in severe trauma patients managed in a mature trauma care system. J Trauma Acute Care Surg. 2018;84:S54–62.
74. Hu W, Xin Y, Chen X, et al. Tranexamic Acid in Cerebral Hemorrhage: A Meta-Analysis and Systematic Review. CNS Drugs. 2019;33:327–36.
75. Bonet A, Madrazo Z, Koo M, et al. Thromboelastometric Profile and Acute Coagulopathy of the Polytraumatized Patient: Clinical and Prognostic Implications. Cir Esp. 2018;96:41–8.
76. Moore HB, Moore EE, Liras IN, et al. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients. J Am Coll Surg. 2016;222:347–55.
77. Moore EE, Moore HB, Gonzalez E, et al. Postinjury fibrinolysis shutdown. J Trauma Acute Care Surg. 2015;78:S65–9.
78. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost. 2013;11:307–14.
79. Grassin-Delyle S, Theusinger OM, Albrecht R, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. Anaesthesia. 2018;73:719–29.
80. Spinella PC, Thomas KA, Turnbull IR, TAMPITI Investigators. The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI): A Randomized, Double-Blind, Placebo-Controlled, Single-Center Trial. Front Immunol. 2020;11:2085.
81. Moore EE, Moore HB, Gonzalez E, et al. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. Transfusion. 2016;56:S110–4.
82. Longstaff C. Measuring fibrinolysis: from research to routine diagnostic assays. J Thromb Haemost. 2018;16:652–62.
83. Muñoz M, Stensballe J, Ducloy-Bouthors A-S, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019;17:112–36.
84. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2015:CD007872.
85. Ducloy-Bouthors AS, Duhamel A, Kipnis E, et al. Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial. Br J Anaesth. 2016;116:641–8.
86. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, et al. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol. 2015;55:53–8.
87. Sujata N, Tobin R, Kaur R, et al. Randomized controlled trial of tranexamic acid among parturients at increased risk for postpartum hemorrhage undergoing cesarean delivery. Int J Gynaecol Obstet. 2016;133:312–5.
88. Sentilhes L, Winer N, Azria E, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379:731–42.
89. Levy JH, Koster A, Quinones QJ, et al. Antifibrinolytic Therapy and Perioperative Considerations. Anesthesiology. 2018;128:657–70.
90. Le Roux P, Menon DK, Citerio G. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocritical Care. 2014;21:S1–26.
91. Starke RM, Kim GH, Fernandez A, et al. Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. Stroke. 2008;39.
92. Germans MR, Post R, Coert BA, et al. Ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA): study protocol for a randomized controlled trial. Trials. 2013;14:143.
93. Harrigan MR, Rajneesh KF, Ardelt AA, et al. Short-term antifibrinolytic therapy before early aneurysm treatment in subarachnoid hemorrhage: effects on rehemorrhage, cerebral ischemia, and hydrocephalus. Neurosurgery. 2010;67:935–9, discussion 939–940.
94. Hillman J, Fridriksson S, Nilsson O, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg. 2002;97:771–8.
95. Anker-Møller T, Troldborg A, Sunde N, et al. Evidence for the Use of Tranexamic Acid in Subarachnoid and Subdural Hemorrhage: A Systematic Review. Semin Thromb Hemost. 2017;43:750–8.
96. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35:93–112.
97. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391:2107–15.
98. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394:1713–23.

Brazilian Journal of Anesthesiology 2022;72(6): 813—815

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Approach and anesthetic management for kidney transplantation in a patient with bilateral lung transplantation: case report

Sofia da Silva Ramos *, Ana Isabel Leite, Ana Eufrásio, Isabel Rute Vilhena, Raquel Inácio

Centro Hospitalar E. Universitário de Coimbra, E.P.E., Coimbra, Portugal

Received 1 November 2020; accepted 27 July 2021
Available online 17 November 2021

KEYWORDS
General anesthesia;
Clinical case;
Cystic fibrosis;
Lung transplantation;
Kidney transplantation

Abstract Lung transplantation is the last resort for end-stage lung disease treatment. Due to increased survival, lung recipients present an increased likelihood to be submitted to anesthesia and surgery. This case report describes a 23-year-old female patient with history of lung transplantation for cystic fibrosis, with multiple complications, and chronic kidney disease, and who underwent kidney transplantation under general anesthesia. Understanding the pathophysiology and changes related to immunosuppressive therapy is essential to anesthetic technique planning and safety, and for perioperative management. The success of both anesthesia and surgery requires a qualified multidisciplinary team due to the rarity of the clinical scenario and high incidence of associated morbidity and mortality.

Introduction

Lung Transplantation (LT) is a last-line therapy for lung failure. The lung graft outcome is conditioned by immediate complications, such as infections or acute rejections, or by late events, often related to immunosuppressive therapy.

Recently, a significant increase in post-transplant survival has been aimed at, therefore lung recipients are increasingly undergoing procedures that may or may not be related to lung transplant and which, depending on disease progression, may increase the likelihood of adverse events, and consequently make anesthesia management challenging.

The level of development of the pulmonary disorder and immunosuppressive therapy promote cardiovascular morbidity, progressive renal failure, and the involvement of multiple organs. Understanding pathophysiological changes is fundamental for planning anesthesia management, namely mechanical ventilation, fluid therapy, and analgesia.

The search in the medical literature revealed a clear shortage of cases reported, particularly of patients with lung transplantation submitted to other surgical interventions,[1,2] highlighting the relevance of our case report, particularly because it describes a surgical procedure associated with several peculiarities from the anesthesia and surgery point of view.

* Corresponding author.
E-mail: sofiasilvaramos.92@gmail.com (S. da Silva Ramos).

https://doi.org/10.1016/j.bjane.2021.07.041

Here we describe the anesthesia management of a patient scheduled for Kidney Transplantation (KT), under General Anesthesia (GA), with a history of bilateral LT.

Case report

We describe the case of a 23-year-old female patient, scheduled for living donor KT presenting history of bilateral LT due to CF, Chronic Kidney Disease (CKD) undergoing hemodialysis for nephropathic Cystinosis (CN), Diabetes Mellitus (DM) treated with low-weight insulin (American Society of Anesthesiologists physical status – ASA III). She had chronic pulmonary infection by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, pancreatic failure, and low bone mineral density. The LT had been performed 33 months before, and there were severe postoperative complications, such as Grade 3 primary graft dysfunction, need for extracorporeal membrane oxygenation, prolonged mechanical ventilation with temporary tracheostomy, heart failure with severe low Left Ventricle Ejection Fraction (LVEF) (< 20%), pericardial tamponade, dysphagia (requiring percutaneous endoscopic gastrostomy), and functional loss of the left lower limb resulting from compartment syndrome.

On the physical examination, lung auscultation revealed slight sound reduction at the left lung base, Body Mass Index (BMI) of 16 $kg.m^{-2}$, and a Central Venous Catheter (CVC) placed in the Internal Jugular (IJ). The Airway (AW) was not predicted difficult. Pre-hemodialysis investigation showed hemoglobin of 10.4 $g.dL^{-1}$, creatinine of 7.19 $mg.dL^{-1}$, potassium of 5.6 $mEq.L^{-1}$, and LVEF of 65%. Chest X-Ray and pulmonary function tests were normal.

The patient refused regional techniques. On the morning of the surgery, lorazepam 1.25 mg was administered orally, and corticosteroid and immunosuppressive therapy was maintained.

The patient was monitored according to American Society of Anesthesiologists standards, diuresis, bispectral index, neuromuscular function, and Central Venous Pressure (CVP). She was positioned on reverse Trendelenburg, given 4 mg dexamethasone, and GA was induced administering fentanyl, propofol/etomidate mixture, and rocuronium. Orotracheal intubation was achieved on the first attempt. Anesthesia was maintained using sevoflurane and rocuronium. Volume-controlled mechanical ventilation was started with Tidal Volume (TV) of 300 mL, RR of 12–13 breaths per minute, and positive end-expiratory pressure (PEEP) of 5–8 cmH_2O. Intravenous infusion of 0.9% saline solution at a rate of 100–200 $mL.h^{-1}$, and 125 mL of 20% mannitol were administered. Blood losses were 100 mL. Analgesia was performed administering paracetamol, tramadol, metamizole, and wound infiltration with 15 mL of 0.375% ropivacaine. The surgery lasted 150 minutes, was uneventful and the patient remained hemodynamically stable.

Postoperatively, the patient remained without complaints. Immunosuppressive therapy was adjusted according to the needs inherent to the KT. Patient diuresis remained above 1 $mL.Kg^{-1}.h^{-1}$ on the following days. The patient was discharged on the fifth day.

Discussion

The preanesthetic evaluation of these patients must consider the presence of pathophysiological peculiarities that impact pulmonary response to hemodynamic changes. It must include a comprehensive assessment of the function of the lung graft and all organs indirectly involved in post-transplant treatment. Commonly, patients undergoing LT are taking several medications that should be kept on the morning of surgery and resumed orally, as soon as possible.[1]

Ventilation and AW management may be challenged by the prolonged use of corticosteroids and the incidence of DM, which promote facial volume and cervical perimeter increase, and stiffness of the atlanto-occipital joint.[3] Dexamethasone was administered prior to induction to prevent laryngeal edema. A mixture of intravenous anesthetics was used for induction to combine the fast and effective anesthetic induction of propofol with the cardiovascular stability of etomidate. Delayed gastric emptying, present in 33% of these patients, increases the risk of pulmonary aspiration during anesthetic induction.[4] Orotracheal intubation should be performed gently to avoid surgical anastomosis trauma and tracheobronchial stimuli. Reduced lung graft functional reserve, unpredictable cardiovascular response, adverse effects of immunosuppressive therapy and its interference with anesthetic drugs can impact the perioperative period.[1] Whenever possible, invasive monitoring techniques should be avoided due to the infection risk.[1]

Hypotension after induction, resulting from the depressant effect of anesthetic agents and the distension of the ventilated lungs, should not be corrected with liberal fluid therapy due to the risk of volume overload, mainly in patients with kidney disorder.[1]

The anesthetic technique must consider cardiovascular and respiratory risks related to orotracheal intubation and mechanical ventilation, and the susceptibility of the lung graft to fluid overload due to the absence of lymphatic drainage. We chose to use a 0.9% saline solution because of the risk of worsening hyperkalemia in a patient with CKD. Every single anesthesia technique can be used on a completely compensated patient.[1] However, regional anesthesia techniques should be favored, as they do not promote a bronchoconstrictor effect, they do not affect mucociliary clearance, and are associated with less hemodynamic fluctuations. The neuraxial approach may be difficult due to the presence of osteoporotic vertebrae and the risk of bleeding secondary to coagulopathy. Epidural analgesia is associated with a reduction in postoperative cardiovascular and pulmonary complications and, when compared with systemic opioids, it reduces respiratory muscle fatigue, and improves bronchial secretion clearance. The combination of GA and epidural block is safe; however, thoracic epidurals should be used with prudence, as the reduction in intercostal muscle strength resulting from the blockade should be avoided in patients with pulmonary disorders. The peripheral regional approach is well tolerated, excluding the brachial plexus block for the potential for paralysis of the phrenic nerve can compromise the ventilatory function in patients with a greater dependence on normal diaphragm muscle functioning.[1]

Anesthetic maintenance can be performed with halogenated or intravenous anesthetics and short-acting opioids.

Usually, this combination is well tolerated and prevents large fluctuations in hemodynamic parameters. Nitrous oxide is not recommended due to the risk of underlying pneumothorax, emphysematous lung or intestinal distension.[1]

Generalized muscle atrophy, particularly noticeable in the patient reported here, can modify the duration of neuromuscular blockade, delaying the recovery of spontaneous breathing, and consequently neuromuscular blockade should be monitored. Electrolyte imbalances, drug interactions, changes in metabolism disorders, and volume of distribution are factors that also contribute to the unpredictable duration of the neuromuscular blockade.

Bilateral LT generally does not show significant differences in lung compliance, which facilitates mechanical ventilation. However, airway resistance may be increased, resulting in high Peak Inspiratory Pressures (PIP). In these patients, using TV < 7 mL.kg^{-1} of ideal weight and PEEP between 5 and 8 cmH_2O may be associated with improvement in gas exchange and a lower incidence of postoperative pulmonary dysfunction. Plateau pressure between 20 —25 cmH_2O and PIP up to 30—35 cmH_2O are recommended to avoid trauma to the bronchial anastomosis and alveoli. In chronic stable hypercapnic asymptomatic recipients, minute ventilation should be adjusted to avoid hypocapnia.[1,2]

Postoperative pain control is extremely important, as insufficient analgesia precludes coughing and secretion clearance, facilitating atelectasis and respiratory infections. Non-steroidal anti-inflammatory drugs should be avoided due to possible nephrotoxicity. Opioids should be administered with caution, due to the risk of respiratory depression and moderate cough reflex inhibition. Due to its lower respiratory depressant potential, tramadol may be a reasonable alternative. Paravertebral, transverse abdominis plane, or rectus abdominis sheath blocks are safe options.

Optimizing hemodynamic, pulmonary, and metabolic parameters is critical for the favorable surgical outcome.

The absence of guidelines for the anesthetic management of these patients, due to the paucity of publications in the medical literature, motivated the comprehensive research on pathophysiology, and the preparation of a customized plan for the anesthesia and surgery. We hope that this case report will help as an adjuvant in future anesthetic management of lung transplant patients undergoing surgical procedures that may or may not be a new transplant.

Conclusion

Currently, LT is the last-line therapy for chronic pulmonary disorders. Patients with a functioning lung graft can tolerate GA without severe complications. However, a pathologically compromised graft is associated with an increased risk of postoperative respiratory failure. Other factors may contribute to increase morbidity and mortality in these patients, such as cardiovascular disorders, DM, and the unpredictable risk of infection.

Due to their greater frailty, transplant patients require greater care and surveillance by the anesthesiologist. Anesthetic management must include perioperative measures to protect the lung graft, particularly regarding mechanical ventilation, to adequately manage medication of chronic use to avoid the risk of rejection, organ failure or infection.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Feltracco P, Falasco G, Barbieri S, Milevoj M, Serra E, Ori C. Anesthetic considerations for nontransplant procedures in lung transplant patients. J Clin Anesth. 2011;23:508—16.
2. Seo M, Kim WJ, Choi I-C. Anesthesia for non-pulmonary surgical intervention following lung transplantation — two cases report. Korean J Anesthesiol. 2014;66:322—6.
3. Hogan K, Rusy D, Springman SR. Difficult laryngoscopy, and diabetes mellitus. Anesth Analg. 1988;67:1162—5.
4. Paul S, Escareno CE, Clancy K, Jaklitsch MT, Bueno R, Lautz DB. Gastrointestinal complications after lung transplantation. J Heart Lung Transplant. 2009;28:475—9.

Brazilian Journal of Anesthesiology 2022;72(6): 816—818

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Anesthesia strategy for factor X deficiency coagulopathy: case report

Carla Isabel Ferreira *, Fábio Costa, Ana Rita Arantes, Graça Horta, Elsa Soares, Filipa Félix

Hospital de Braga, Serviço de Anestesiologia, Braga, Portugal

Received 12 January 2021; accepted 8 August 2021
Available online 17 November 2021

KEYWORDS
Factor X;
Anesthesia;
Management

Abstract Factor X deficiency ranks among the rarest coagulopathies and has a variable presentation spectrum. We intend to present a proposal for anesthesia protocol for individuals with the coagulopathy. The excision of an ovarian neoplasm was proposed for a 26-year-old, female, ASA II patient, with congenital Factor X deficiency. Physical examination and lab tests were normal, except for Prothrombin Time (PT) 22.1s (VR: 8—14s), International Normalized Ratio (INR) 1.99 (VR: 0.8—1.2) and Activated Partial Thromboplastin Time (aPTT) 41.4s (VR: 25—37s). We concluded that a history of bleeding should always be investigated, along with a pre-anesthetic coagulation study.

Introduction

Blood coagulation occurs due to the sequence of physical, biochemical, and cellular reactions in a series of phases, culminating in the formation of a platelet and fibrin plug at the site of vascular injury, and continuity of activated procoagulant substances at the injury site. Given that the concept of "coagulation cascade" describes only a set of chemical reactions that lead to the formation of a clot, it does not fully explain hemostatic events *in vivo*.[1]

Factor X (FX), or Stuart-Prower Factor, is a vitamin K-dependent plasma glycoprotein synthesized in the liver, and plays an essential role in the coagulation cascade, as it is activated either by the extrinsic pathway (Tissue Factor FVIIa), or by the intrinsic pathway (FXIa and FVIIIa), and is the first enzyme in the common pathway of thrombin formation.[2]

Congenital FX deficiency is an autosomal recessive disease with an incidence of 1:1000000. Total or partial FX deficiency causes an impairment of clot formation, leading to a hemorrhagic condition that presents with hemorrhagic symptoms of variable severity.[2]

The diagnosis of this disorder is based on the measurement of functional FX activity (FX:C) and FX plasma antigen (FX:Ag) levels by immunoassay, Prothrombin Time (PT), and Activated Partial Thromboplastin Time (aPTT).[2] It is important to check for vitamin K deficiency or an acquired deficiency, more often seen in elderly patients, as part of the differential diagnosis.[3]

* Corresponding author.
E-mail: carlaisabelferreira18@gmail.com (C.I. Ferreira).

https://doi.org/10.1016/j.bjane.2021.08.024

The classification of the deficiency is based on the results of immunological and functional assays: the parallel reduction of FX and FX:Ag indicates Type I deficiency, usually caused by a defect in glycoprotein synthesis or in the abolition of protein secretion. The discrepancy between low FX:C and normal FX:Ag indicates Type II deficiency, that is, a normal or minimally reduced release of non-functioning FX.

FX deficiency can be mild, moderate, or severe. Mild FX deficiency (FX:C 6—10 IU.dL^{-1}) is characterized by easy bruising and/or menorrhagia and is usually diagnosed during routine laboratory testing or by a family history. In moderate FX deficiency (FX:C 1—5 IU.dL^{-1}), hemorrhage occurs with trauma or surgical aggression, and is therefore usually diagnosed after the hemostatic challenge has occurred. Severe FX deficiency (FX:C < 1 IU.dL^{-1}) may appear in neonates (e.g., central nervous system hemorrhage or umbilical stump) and tends to exhibit the most severe phenotype.[3]

From a clinical point of view, as this is a very heterogeneous bleeding disorder, measuring FX:C based on PT prolongation and aPTT suffices for the correct diagnosis of FX deficiency, but not to predict clinical phenotype, particularly in patients with moderate or mild impairments, as the presentation can range from severe to completely absent symptoms.[2]

In the past, bleeding episodes in patients with FX deficiency were treated with Prothrombin Complex Concentrate (PCC) or Fresh Frozen Plasma (FFP). However, the concentrations of FX in FFP are low and, therefore, large volumes are required to achieve FX replacement, and there may be a risk of overloading the circulatory volume. Other adverse events associated with FFP are allergic reactions, thromboembolic complications, and transfusion-related lung injury. PCC contains factors II, IX, X, and some factor VII, so it also presents a risk of thromboembolic complications.[3]

Therefore, current guidelines recommend using single factor concentrates when available for patients with rare bleeding disorders. Thus, Plasma-Derived FX concentrate (pdFX) is approved for on-demand and prophylactic treatment of bleeding episodes, as well as for perioperative management for patients with hereditary FX deficiency. However, it may not be available at all hospitals.[4]

The present case report aims to describe the anesthetic and perioperative management of patients with FX deficiency, presenting suggestions for strategies in the perioperative care of surgical patients with this rare coagulopathy.

Case report

A planned excision of an ovarium neoplasm was proposed for a 26-year-old, female, ASA (AMerican Society of Anesthesiologists) physical status II patient, with a personal history of non-stratified Factor X deficiency without immuno-hemotherapy follow-up. The diagnosis was made at 7 years of age, during a pre-anesthetic consult, by lab tests with increased TP and aPTT, leading to the diagnosis of congenital FX deficiency by gene sequencing, given there was no history of family hemorrhage events. There was no history of previous surgeries, despite the proposal of amygdalotomy, that was not performed due to risk of hemorrhage inherent to surgery on a patient with coagulopathy. The physical exam was uneventful, and the patient weighed 56 kg and measured 159 cm. Preoperative lab tests revealed hemoglobin of 13.9 g.dL^{-1} (VR: 12—15 g.dL^{-1}); hematocrit of 39.4% (VR: 34.7—46.0%); 162,000 platelets (VR: 150,000—440,000); TP 22.1s (VR: 8—14s); International Normalized Ratio (INR) of 1.99 (VR: 0.8-1.2), and aPTT of 41.4s (VR: 25-37s).

On the day of the surgery, based on the orientation of the immunohemotherapy specialist, before anesthesia induction, 600 mL of frozen fresh plasma and 1 g of tranexamic acid were administered at the initial intraoperative stage. Two units of red blood cells had been reserved and immunotherapy was alerted that massive transfusion protocol would be triggered if necessary. Two large caliber peripheral venous accesses (16G) were put in place on each one of the upper limbs.

We performed balanced general anesthesia, maintenance with 2% sevoflurane and monitoring with electrocardiogram, pulse oximetry, noninvasive blood pressure, capnography, anesthesia depth monitoring, and diuresis.

A laparoscopic approach was decided to decrease surgical aggression and to decrease risk of bleeding. During surgery, a total of 300 mL of Plasma Lyte was infused. To prevent nausea and vomiting, 4 mg of dexamethasone and 4 mg of ondansetron were administered and also, 1,000 mg of paracetamol and 100 mg of tramadol for postoperative analgesia. Surgical procedure time was 1 hour and 30 minutes with approximate blood loss of 200—300 mL.

Anesthesia and surgery were uneventful. The postanesthesia care unit stay was satisfactory during immediate postoperative follow-up. During the initial 12 postoperative hours, 1 g of tranexamic acid was administered, aimed at avoiding late postoperative bleeding. The patient remained in the hospital for 72 hours after surgery for hemorrhage surveillance.

Although the diagnosis of XF deficiency was confirmed, we were unaware of baseline levels; the *a posteriori* measurement result was 7.8% (VR: 70—120%).

Discussion

In rare hemorrhagic disorders, the major challenge is to maintain homeostasis during a surgical procedure, as there are constant blood losses with consumption and loss of the insufficient factor. Information available on the anesthetic and perioperative handling of FX deficiency seems limited, as the patient population is relatively small.

The present case describes a patient with FX deficiency proposed for programmed excision of an ovarian neoplasm. To optimize the outcome and minimize the risk of bleeding, a multidisciplinary approach with replacement of FX levels through FFP, a minimally invasive surgical approach, and longer-than-usual hospital stay for bleeding surveillance were used. Based on the result of the FX levels in the postoperative period and on the clinical evaluation of the patient, we considered that the patient presented a mild FX deficit. However, whatever the phenotype classification, FX levels must be restored when patients with this deficiency undergo a surgical procedure, as they are at risk of severe postoperative hemorrhage.[3,4]

The importance of the pre-anesthetic evaluation that led to the diagnosis of the deficiency in this patient, reached prior to the hemostatic challenge posed by tonsillectomy, is

also noteworthy. If such an assessment had not occurred, there could have been serious consequences.

According to the current literature, some suggestions of anesthetic strategy and available therapeutic alternatives are proposed for the perioperative approach of factor X deficiency coagulopathy, namely: 1) Plasma-derived FX concentrate, approved in the United States and Europe, for the treatment and prophylaxis of bleeding episodes and for perioperative management of patients with hereditary FX deficiency. The prophylactic dose of 25 IU.kg^{-1} is safe and effective, being administered 2—3 times a week, as its half-life is 29.4 hours. In addition, pdFX can be administered at higher doses to support perioperative management in patients with mild to severe deficiency[3,4]; 2) Fresh Frozen Plasma 15—20 mL.kg^{-1} in the immediate preoperative period, followed by postoperative maintenance of daily FFP transfusion (5 mL.kg^{-1}) for one week, may be sufficient to prevent bleeding complications after an elective abdominal surgical procedure[2-4]; 3) Prothrombin Complex Concentrate 15 to 20 IU.Kg^{-1} in the immediate preoperative period followed by postoperative maintenance of 10 to 15 IU.Kg^{-1} daily transfusion. Due to possible thromboembolic complications, FIX and D-Dimer levels should be monitored mainly in long-term treatments.[2,4] To treat hemorrhagic events in patients with severe deficiency, 20 to 30 IU.kg^{-1} should be administered once a day, which can be changed according to the type of hemorrhage and residual FX activity; 4) Epidural anesthesia is not recommended and is contraindicated in patients with factor X deficiency, unless prophylactic therapy with FFP is administered[5]; 5) Subarachnoid block is safer than epidural anesthesia in patients with coagulopathies[5]; 6) Use of antifibrinolytic drugs with tranexamic acid, desmopressin and fibrin glue[2,4]; and 7) Choice of minimally invasive surgical techniques such as laparoscopy.

Therefore, our case report underscored changes in the anesthesia and perioperative approach for a laparoscopy procedure with minor risk of hemorrhage, but that due to the rare deficiency, made the patient a hemostatic challenge. We also intend to alert toward existing hemorrhage disorders in patients without a personal or family history of hemorrhage, and to the importance of pre-anesthetic coagulation investigation and, also to the importance of investigating FX deficiency in the event of prolonged PT and aPTT of unknown cause.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Ferreira CN, Sousa MO, Dusse LMS, Carvalho MG. O novo modelo da cascata de coagulação baseado nas superfícies celulares e suas implicações A cell-based model of coagulation and its implications. Rev Bras Hematol Hemoter. 2010;32:416—21.
2. Menegatti M, Peyvandi F. Factor X deficiency. Semin Thromb Hemost. 2009;35:407—15.
3. Shapiro A. Plasma-derived human factor X concentrate for on-demand and perioperative treatment in factor X-deficient patients: pharmacology, pharmacokinetics, efficacy, and safety. Expert Opin Drug Metab Toxicol. 2017;13:97—104.
4. Escobar MA, Auerswald G, Austin S, Huang JN, Norton M, Millar CM. Experience of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency undergoing surgery. Haemophilia. 2016;22:713—20.
5. Módolo NSP, De Azevedo VLF, Santos PSS, Rosa ML, Corvino DR, Castro Alves LJS. Anesthetic strategy for Cesarean Section in a patient with factor XI deficiency. Case report. Rev Bras Anestesiol. 2010;60:176—80.

Brazilian Journal of Anesthesiology 2022;72(6):819–822

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Immunoadsorption therapy for a meningococcemia patient with myocarditis, adrenal hemorrhage, and purpura fulminans: a case report

Nihal Akcay *, **Hasan Serdar Kihtir**, **Guner Ozcelik**, **Ulkem Kocoglu Barlas**, **Mey Talip Petmezci**, **Esra Sevketoglu**

University of the Health Sciences, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Pediatric Intensive Care Unit, Istanbul, Turkey

Received 23 November 2020; accepted 27 June 2021
Available online 17 July 2021

KEYWORDS
Myocarditis;
Purpura Fulminans;
Plasmapheresis;
Waterhouse-Friderichsen Syndrome

Abstract *Neisseria meningitidis*, also known as meningococcus, is a relatively uncommon cause of invasive infection, but when it occurs, it is frequently severe and potentially life-threatening. A ten-year-old female patient developed a purpuric rash with fever. Upon arrival to the pediatric intensive care department, she was unconscious and in a poor general condition. We combined treatment with antibiotics, volume resuscitation, hydrocortisone, and CytoSorb® therapy resulted in a stabilization of hemodynamics, as well as control of hyperinflammation. We observed a significant decrease in vasopressor dosage in this patient.

Introduction

Neisseria meningitidis (meningococcus) infections are a particular threat since they may cause epidemics and pandemics, rather than sporadic or endemic transmission. Around 12 serological groups have been identified among *N. meningitidis* strains, but more than 90% of infections are caused by A, B, C, Y, and W group isolates. Identification of *N. meningitidis* serogroups that predominate in a given country is vital for the development of local vaccination strategies. The clinical presentation of *N. meningitidis* is similar to the case of other bacterial neuroinfections. A common, but not pathognomonic sign of meningococcal septicemia is purpuric rash. The rash and adrenal hemorrhage (Waterhouse-Friderichsen syndrome) can be observed in fulminant infections, especially in children.[1] CytoSorb® (CytoSorbents Europe, Berlin, Germany) is a promising new extracorporeal cytokine hemoadsorption therapy that can modulate the cytokine storm during sepsis. Here we present a case of severe meningococcemia that was successfully

* Corresponding author.
E-mail: drnihalakcay@gmail.com (N. Akcay).

https://doi.org/10.1016/j.bjane.2021.06.021

treated with CytoSorb® hemadsorption therapy in the pediatric intensive care unit.

Case description

A ten-year-old female patient was admitted to our emergency clinic with purpuric rash and confusion. Her immunization status was appropriate to her age, and her previous medical history was unremarkable. She had vomiting, rash, fever, and stomachache, all started two hours before admission. She was given fluid replacement therapy and ceftriaxone of 50 $mg.kg^{-1}$ IV (intravenous) in the emergency department with a pre-diagnosis of meningococcemia. She had an ecimotic lesion on her hand where she had a peripheral venous line and this lesion progressed through her arm after the antibiotic treatment. She was then transferred to our pediatric intensive care unit since she was hypotensive despite fluid replacement. When she was admitted, she was unconscious and in a poor general condition. Her Glasgow Coma Score was 7 (E: 2, V: 1, M: 4), blood pressure was 91/75 (82) mmHg, heart rate was 140/min, the body temperature was 37.5 °C, respiratory rate was 24/min, SpO_2 was 88, capillary refill time was 5 seconds, and the pupillary light reflex was positive in both eyes. She had many petechial and purpuric lesions on her trunk and legs as well as an ecimotic lesion beginning from her hand, leading towards her shoulder. She had signs of meningeal irritation in the form of neck stiffness, positive Kernig's, and Brudzinski's sign. Other physical exam findings did not show a pathologic sign. The patient was intubated due to her worsening clinical condition and put on invasive mechanical ventilation. PRISM score was 20, Predicted mortality was 22.2%; PELOD 9 and Predicted mortality were 66%. Laboratory test results showed: urea 46 $mg.dL^{-1}$, creatinine 0.74 $mg.dL^{-1}$, glucose 176 $mg.dL^{-1}$, proBNP 23,500 $ng.L^{-1}$, hemoglobin 10.2 $g.dL^{-1}$, leukocyte 16,990/mm^3, thrombocyte 120,000/uL, prothrombin time 19.4 seconds, INR 1.64, activated partial thromboplastin time 44.7 seconds. Blood gas analysis: pH 7.34, pCO_2 45.7 mmHg, lactate 4.5 $mmol.L^{-1}$, and bicarbonate 23.8 $mmol.L^{-1}$. The other laboratory parameters were in normal ranges. Adrenaline infusion was initiated because she was hypotensive and poor peripheral perfusion despite isotonic boluses (20 $mL.kg^{-1}$ twice). Vancomycin (60 $mg.kg^{-1}.day^{-1}$ divided into 4 doses) and ceftriaxone (100 $mg.kg^{-1}.day^{-1}$ divided into 2 doses) treatments were initiated. Control thrombocyte and INR levels were 42,000/uL and 2, respectively. After insertion of the central venous line and hemodialysis catheters, therapeutic plasma exchange was initiated. Her ejection fraction was 15% on echocardiography and therefore milrinone infusion of 0.5 $mcg.kg^{-1}.min^{-1}$ was added and PiCCO (Pulsion Medical Systems, Munich, Germany) (Pulse index Continuous Cardiac Output) monitorization was applied. Adrenaline and noradrenaline infusions were titrated up to 0.5 $mcg.kg^{-1}.min^{-1}$ according to blood pressure and PiCCO parameters. Hydrocortisone was added on as shock-dose treatment since the patient's inotropic agent needs to increase. Hemodialysis with coexisting use of CytoSorb® cytokine trapping filter was initiated since she was anuric. Inotropic agent need of the patient decreased after the use of CytoSorb® filter. Cytokine trapping filter was used twice in 24 hours and there was an absolute decrease in inotrope need. Therapeutic plasma exchange was continued daily. She was free of inotropes on the third day of her hospitalization and her ejection fraction rose to 40% on echocardiography. The abdominal ultrasonography showed adrenal hemorrhage (Fig. 1). Immediate laboratory and clinical response were achieved (Table 1) after 3 days of hemodialysis and CytoSorb® therapy. Meningococcal type B was isolated from the blood specimen of the patient. Therapeutic plasma exchange was performed for five days and then stopped since her thrombocyte levels reached 100,000/uL and the patient was extubated. Hydrocortisone was decreased to maintenance dose gradually. After the patient's need for intensive care was over, she was transferred to the ward on the 11th day of her treatment.

The written informed consent to publication was obtained from the parents on behalf of the patient.

Discussion

We, herein, described a 10-year-old girl who presented with severe septic shock associated with Neisseria meningitidis type B. Neisseria meningitidis is one of the most important bacterial infections that shows off as meningitis and/or septicemia. The predominant feature in some children is cardiovascular collapse leading to septic shock with Neisseria meningitidis. High concentrations of IL-6, IL-8, TNF, IL-1, and endotoxins are seen in meningococcal shock. Overproduction of nitric oxide lowers arterial blood pressure due to vasodilation and impairs cardiac contractility. A most severe form of meningococcemic septic shock is named purpura fulminans and it is associated with a large number of bacteria in the bloodstream.[2] Hemodynamic stabilization is the mainstay of therapy in pediatric septic shock. Resuscitation in septic shock can be rapidly achieved by restoration of perfusion by administration of intravenous fluid, inotropic support, and vasopressor drugs. It is of utmost importance to maintain the appropriate mean arterial pressure level.[2–4]

We used norepinephrine and epinephrine to stabilize mean arterial pressure as our patient had myocardial dysfunction and avoided fast fluid resuscitation. Milrinone was added to support cardiac contractility. We initiated early antibiotic treatment.

Hemadsorption is an adjunctive therapy to reduce elevated cytokine levels. CytoSorb® has been designed to remove multiple inflammatory mediators from the bloodstream in a size range of approximately 10–55 kD. Moreover, CytoSorb® results in rapid hemodynamic stabilization and increased survival, particularly if initiated within 24 hours.[5] We used hemadsorption in our patient with an indication of a severe septic shock.

We observed a significant decrease in vasopressor dosage in this patient. Notably, this patient who was given CytoSorb® therapy < 48 hours after onset of septic shock, survived and we obtained a reduction in all biomarker levels (procalcitonin, C-reactive protein, and serum lactate) after CytoSorb® therapy.

In this patient with meningococcemia, the combined treatment with antibiotic therapy, volume resuscitation, hydrocortisone, and CytoSorb® therapy resulted in a stabilization of hemodynamics, as well as a well-controlled

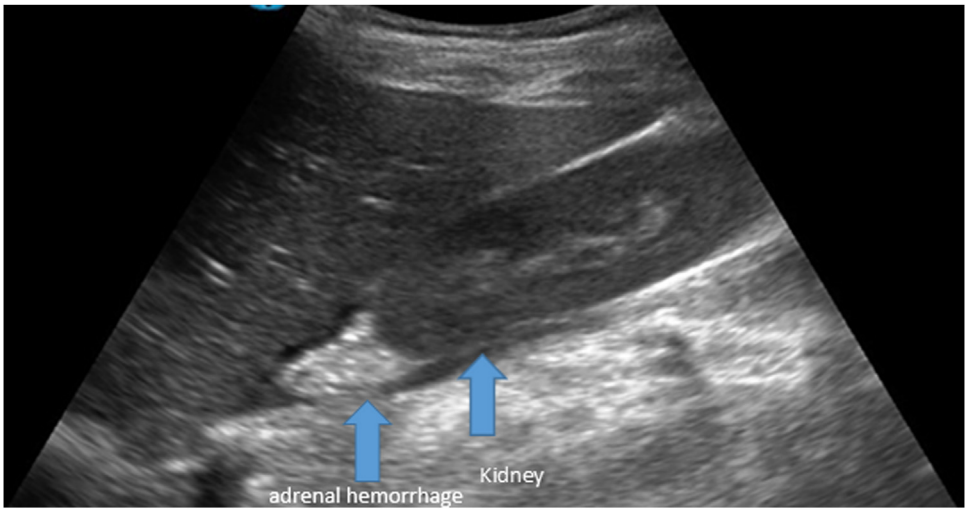


Figure 1 The image of the adrenal hemorrhage that was detected on the abdominal ultrasonography.

Table 1 Changes in biochemical, hematological, and hemodynamic parameters after the CytoSorb®.

CytoSorb® hemadsorption	Before CytoSorb® administration	12th hour	24th hour	72nd hour
WBC (per μL)	16,990	16,920	26,010	32,990
Platelet (per μL)	120	126	72	59
CRP ($mg.L^{-1}$)	136.8	99.2	32.3	14.7
Procalcitonin ($ng.mL^{-1}$)	52.73	17.9	8.76	1.02
Urea ($mg.dL^{-1}$)	46	31	23	43
Creatinine ($mg.dL^{-1}$)	0.74	0.52	0.49	0.25
AST ($U.L^{-1}$)	35	28	25	23
ALT ($U.L^{-1}$)	14	17	15	29
Fibrinogen ($mg.dL^{-1}$)	352	305	364	258
INR	1.64	1.28	1.59	1.09
APTT (s)	44.7	49.1	38.9	31.4
PT (s)	19.4	15.2	18.9	13
D, dimer ($\mu g\ FEU.mL^{-1}$)	7.17	2.85	1.23	0.46
PELOD	7	3	2	2
$ScvO_2$ (%)	58	75	78	76
Lactate ($mmol.L^{-1}$)	8.1	2.2	1.3	1.1
EF (%)	15	22	28	42
VIS	77.5	9.5	9.5	2.5
Adrenaline dose ($\mu g.kg^{-1}.min^{-1}$)	0.50	0.07	0.07	–
Noradrenaline dose ($\mu g.kg^{-1}.min^{-1}$)	0.20	–	–	–
Milrinone dose ($\mu g.kg^{-1}.min^{-1}$)	0.75	0.25	0.25	0.25
BP (mmHg)	93/46	115/74	103/63	104/74
CVP (mmHg)	10	11	9	11
CI ($L.min^{-1}.m^{-2}$)	3,57	3,82	3,88	3,99
GEDVI ($mL.kg^{-1}$)	357	302	395	516
EVLWI ($mL.kg^{-1}$)	15	9	13	10
SVRI ($dyne.sec.m^2/cm^5$)	820	1140	1316	1744

CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; PT, prothrombin time; PELOD, pediatric logistic organ dysfunction; EF, ejection fraction; VIS, vasoactive-inotropic score; BP, blood pressure; CVP, central venous pressure; CI, cardiac index; GEDVI, global end-diastolic volume index; ELWI, extravascular lung water index; SVRI, systemic vascular resistance index.
(VIS [vasoactive inotropic score]: dopamine dose ($\mu g.kg^{-1}.min^{-1}$) + dobutamine dose ($\mu g.kg^{-1}.min^{-1}$) + 100 x adrenaline dose ($\mu g.kg^{-1}.min^{-1}$) + 100 x noradrenaline dose ($\mu g.kg^{-1}.min^{-1}$) + 10 x milrinone dose ($\mu g.kg^{-1}.min^{-1}$) + 10.000 x vasopressin dose ($U.kg^{-1}.min^{-1}$).

hyperinflammation. In our opinion, the use of CytoSorb® helped to take the severe hyper inflammation in septic shock under control and presumably, helped the patient to overcome the acute phase by early intervention. We can also

predict that CytoSorb® was safe and easy to use in combination with hemodialysis.

Conclusion

To our knowledge, this is the first report on the successful use of hemoadsorption for cytokine removal therapy in a pediatric patient with meningococcal septic shock and Waterhouse-Friderichsen Syndrome. It enables a rapid and clear stabilization in hemodynamics as well as a reduction in catecholamine need and a decrease in lactate.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010;10:32–42.
2. Siddiqui JA, Ameer MA, Gulick PG. Meningococcemia. [Updated 2020 Oct 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534849/
3. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S526–42.
4. Hilarius KWE, Skippen PW, Kissoon N. Early Recognition and Emergency Treatment of Sepsis and Septic Shock in Children. Pediatr Emerg Care. 2020;36:101–6.
5. Kogelmann K, Jarczak D, Scheller M, et al. Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care. 2017;21:74.

Brazilian Journal of Anesthesiology 2022;72(6): 823—825

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Perioperative administration of recombinant activated factor VII in a Glanzmann's thrombasthenia patient with platelet refractoriness: case report

Flora Margarida Barra Bisinotto [a,b,*], Laura Bisinotto Martins [a,c], Giovanini Pires de Camargos [d], Marcelo de Paula Bianco [e]

[a] CET/SBA Integrado de Uberaba, Uberaba, MG, Brazil
[b] Universidade Federal do Triângulo Mineiro (UFTM), Disciplina de Anestesiologia, Uberaba, MG, Brazil
[c] Hospital Regional Jose Alencar, Uberaba, MG, Brazil
[d] Universidade de Uberaba, Faculdade de Medicina, Uberaba, MG, Brazil
[e] Universidade de Uberaba, Uberaba, MG, Brazil

Received 27 February 2021; accepted 11 September 2021
Available online 28 November 2021

KEYWORDS
Surgery;
Prostatectomy;
Dental extraction;
Disorders;
Hematological;
Activated recombinant factor VII

Abstract Glanzmann's Trombasthenia (GT) is a genetic disorder, that develops with a tendency toward bleeding and is characterized by the absence or decrease in platelet aggregation. Surgical bleeding may be difficult to control. Platelet transfusion is the main treatment, albeit refractoriness can occur. We describe the case of a patient with GTand platelet refractoriness, who was submitted to radical prostatectomy and dental extraction. The perioperative treatment with apheresis platelet concentrate and activated recombinant factor seven allowed the procedures to be performed uneventfully. We discuss the complexity of the case and the treatment option.

Introduction

Glanzmann's Thrombasthenia (GT) is a rare autosomal recessive hemorrhagic disorder (1:1,000,000), characterized by the absence or decrease of platelet aggregation, with normal platelet count and morphology. It was first described by a Swiss pediatrician, Edward Glanzmann in 1918, as a "Hemorrhagic Hereditary Thrombasthenia".[1] Platelet dysfunction is caused by quantitative and/or qualitative defects in platelet integrins αIIbβ3 (formerly known as Gycoprotein [GP] — IIb-/IIIa), which are receptors on the surface of platelets that mediate the final step of platelet aggregation.[1,2] Clinically, GT develops with a tendency toward mucocutaneous bleeding throughout life. Post-trauma and post-operative bleeding can be remarkably severe. No specific treatment is available. Platelet transfusion is a beneficial measure, but in many patients, its effectiveness is reduced by the development of alloimmunization that can occur after recurrent transfusions,[1,2] thus the use of recombinant activated factor VII (rFVIIa) becomes a feasible

* Corresponding author.
E-mail: florabisinotto@gmail.com (F.M. Bisinotto).

https://doi.org/10.1016/j.bjane.2021.09.021

alternative. This case report describes the perioperative management of a patient with GT who underwent surgical procedures with potential risk of hemorrhage. The present report is relevant because GT is a rare disorder with scarce perioperative management data available and it poses difficulty in conducting randomized clinical trials.

Case report

A 62-year-old male patient, 85 kg, diagnosed with GT in childhood, was scheduled for open radical prostatectomy and surgical tooth extraction. At the time of GT diagnosis, the patient referred frequent episodes of epistaxis and the condition progressed to gingival bleeding and chronic anemia. Regarding family history, the patient referred two sisters with diagnosis of GT. In his past anesthetic history, at 12-years of age he underwent surgical repair of a knee fracture that required blood transfusions. Three months before the current presentation, he underwent a prostate biopsy complicated with hemorrhagic shock, although preoperatively he received platelet transfusion. He was taking tranexamic acid. Laboratory tests showed normal red blood cell count, 176 $\times$ 103 mm^{-3} platelets and normal blood clotting tests. Optimization for the scheduled surgeries was performed by the hematologist and consisted of the administration of one unit of apheresis platelets and rFVIIa at a dosage of 350 KUI (82.0 $\mu g.kg^{-1}$), both one hour before surgery. Intraoperatively the same dosage of rFVIIa was administered every two hours. Monitoring consisted of pulse oximetry, ECG tracing, capnography, and invasive blood pressure after radial artery cannulation. Balanced general anesthesia was performed, using sevoflurane inhalation combined with target-controlled infusion of remifentanil. The duration of the surgical procedures was 4 hours, with estimated blood loss of approximately 500 mL. The procedure was uneventful, and the patient was extubated and sent to the ICU. He received platelet concentrate every 12 hours for 6 days and rFVIIa (350 KUI) every 3 hours on the first postoperative day (PO), then every 4 hours on the second PO, every 6 hours on the third PO, every 8 hours on the fourth PO, and every 12 hours on the fifth PO, followed by tranexamic acid until hospital discharge, on the seventh PO. The patient presented hematuria, anemia, and platelet transfusion reaction as postoperative complications.

Discussion

The case illustrates the management for preventing hemorrhagic complications in surgical patients with GT. Prophylactic or therapeutic platelet transfusion is the standard perioperative treatment for patients with GT. However, repeated transfusions can elicit alloimmunization to Human Leukocyte Antigens (HLA) and/or to GP IIb and IIIa, causing platelet transfusion refractoriness and future transfusions ineffective. This occurred for the patient described here and was evident in the prostate biopsy procedure, which was complicated with hemorrhagic shock, as he showed refractoriness to prophylactic platelet transfusion. Thus, rFVIIa represents an alternative for bleeding prevention and treatment during surgery or other invasive procedures. Some studies suggest that rFVIIa can be effective, with no safety concern for patients with GT showing platelet antibodies and/or platelet refractoriness and would be the most effective alternative.[2] The case reported enabled us to perform two procedures with high risk of hemorrhage, such as radical prostatectomy and surgical tooth extraction. GT is the most frequent hereditary disorder of the platelet αIIbβ3 integrin receptor complex. When there is platelet activation, αIIbβ3 shows an inside out response to signaling and shifts its configuration from resting to the active state, that is required for the binding of fibrinogen and other ligand proteins.[1,2] Although rare, GT has a worldwide distribution. The first manifestations are in childhood, rarely in adolescence. The analysis of a registry of 187 patients with GT, shows that in 85% of the patients the disorder started before 14 years of age, and the mean onset age was 5.6 years.[2] Bleeding is mainly mucocutaneous in nature with hematomas, petechiae and bruises after minimal trauma. Some patients have only small hematomas, others often show potentially fatal hemorrhages. Gingival bleeding and epistaxis are frequent and can be difficult to control with local measures and require transfusions. Menorrhagia occurs in almost all girls, and child delivery is associated with risk of severe or even fatal hemorrhage.

Although, by definition, all patients with GT have complete absence of platelet aggregation, the underlying biochemical abnormality varies from one relative to another. As a result of these differences, GT is classified into 3 types according to the levels of αIIbβ3 protein on the platelet surface. Approximately 75% of GT patients are classified as type 1 (0—5% of αIIbβ3); type II (5—20% of αIIbβ3) occurs in 15% of patients; and around 10% of patients are classified as type III (variant type, above 20% of αIIbβ3).[2] The diagnosis of GT is often overlooked, since GT has clinical and laboratory features in common with other platelet disorders. Ordering appropriate laboratory tests is essential. Normal platelet count values do not rule out GT, as generally the test shows values within normal range in patients with GT. Complete blood count may reveal iron deficiency. Prothrombin time and activated partial thromboplastin are normal. However, bleeding time will be prolonged, although it is not recommended as a diagnostic tool, due to lack of standardization, trauma associated to the test and low positive predictive value. There are multiple more specific and dedicated laboratory tests, such as light transmission aggregometry, the gold standard for diagnosing platelet function;[3] Platelet Function Analyzer (PFA), a highly sensitive test for diagnosing GT; flow cytometry and molecular analysis of the ITG2B and ITGB3 genes.[1] The rarity of GT makes it difficult to carry out controlled clinical trials. Thus, case reports enable acknowledging the best options for the management of these patients. Therapeutic options for treating bleeding in patients with GT are very limited. Bleeding episodes can be treated with local measures and antifibrinolytics. Platelet transfusion is the standard of care if bleeding can be controlled with these conservative measures. It is also the standard prophylaxis in surgical patients, but it is estimated that nearly 50% of patients develop antiplatelet antibodies,[2] resulting in accelerated platelet destruction and transfusion failure. To mitigate these risks, ideally single-donor platelets with compatible Leukocyte Antigen (HLA) and apheresis platelets with reduced leukocytes should be used, as was performed in this case. rFVIIa represents a viable alternative to overcome the platelet refractoriness issue. The exact hemostatic mechanism of rFVIIa is unclear. rFVIIa is known to play a fundamental role in

the coagulation cascade starting the process. Hemostatic doses of rFVIIa seem to bind to the surface of activated platelets and thus increase local thrombin generation and adhesion of GP IIb and IIIa deficient platelets. With enough thrombin formation, there is the creation of a hemostatic plug of stable fibrin.[1,2] Duman et al.[4] showed a case of a child with GT who had bleeding during an adenoidectomy and was satisfactorily treated with rFVIIa. Conversely to the present case, rFVIIa was used for treatment and not for prophylaxis of hemorrhagic events. A study by Poon[5] analyzing rFVIIa efficacy in patients with GT, with or without platelet refractoriness, submitted to surgery or not, reported the use of a mean dose of 80 μg.kg^{-1}, at 2-hour intervals for bleeding episodes and surgical procedures. Although there is a difference in the management related to the extension of the surgery, rFVIIa is indicated for both minor and major procedures, as reported in the present case. In the postoperative period, the frequency of administration is decreased as adequate hemostasis is attained, and antifibrinolytic administration can be started. The association of antifibrinolytic with rFVIIa should be avoided because of the risk of thrombosis. Dental procedures present a risk to patients with GT, and often must be done in a hospital setting. In the case here reported, performing the prostatectomy and the dental extraction during the same procedure proved to be understandable due to the risk and high cost of carrying out each procedure separately. Administration of rFVIIa is associated with potential risks of thromboembolic events and allergic reactions, therefore, care must be taken to comply with administration guidelines.

Conclusion

GT is a rare disease and can present a major challenge during the management of invasive or surgical procedures, due to scarce expertise on the disease or the lack of adequate preparation of the patient. The management plan by the surgical team together with the hematologist is crucial to prevent potentially fatal complications. In the case presented, the administration of rFVIIa as a hemostatic alternative therapy was considered effective and with an appropriate safety profile.

Informed consent

Written informed consent for publication of this article was obtained from the patient.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Solh T, Botsford A, Solh M. Glanzmann's thrombasthenia: pathogenesis, diagnosis, and current and emerging treatment options. J Blood Med. 2015;6:219—27.
2. Poon MC, Di Minno G, D'Oiron R, et al. New insights into the treatment of Glanzmann thrombasthenia. Transfus Med Rev. 2016;30:92—9.
3. Poon MC, D'Oiron R. Alloimmunization in congenital deficiencies of platelet surface glycoproteins: focus on Glanzmann's thrombasthenia and Bernard Soulier's Syndrome. Semin Thromb Hemost. 2018;44:604—14.
4. Duman EN, Saylan S, Cekic B. Conduta no perioperatório de paciente pediátrico com trombastenia de Glanzmann durante adenoidectomia. Rev Bras Anestesiol. 2012;62:548—53.
5. Poon MC. The use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia. Thromb Haemost. 2021;121:332—40.

Brazilian Journal of Anesthesiology 2022;72(6):826–828

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Neuraxial block anesthetic technique in a patient with SCN8A encephalopathy: case report

Eric Guimarães Machado [a,*], **Isis da Rocha Costa Billé** [a], **Mariana Moraes Pereira das Neves Araújo** [b,c], **José Francisco Nunes Pereira das Neves** [b], **Gilson Lorena Maués** [b], **Marco Felipe Bouzada Marcos** [d], **Fernando de Paiva Araújo** [b,c]

[a] *Santa Casa de Misericórdia de Juiz de Fora, Serviço de Anestesiologia, Juiz de Fora, MG, Brazil*
[b] *Hospital Monte Sinai, Serviço de Anestesiologia, Juiz de Fora, MG, Brazil*
[c] *Hospital Universitário de Universidade Federal de Juiz de Fora (UFJF), Serviço de Anestesiologia, Juiz de Fora, MG, Brazil*
[d] *Hospital Escola Luiz Gioseffi Jannuzzi, Valença, RJ, Brazil*

Received 17 June 2020; accepted 26 August 2020
Available online 4 February 2021

KEYWORDS
Encefalopatias;
Raquianestesia;
Canais de Sódio

Abstract Mutations in SCN8A gene lead to changes in sodium channels in the brain, which are correlated with severe epileptic syndrome. Due to the rarity, there are few studies that support anesthesia in that population. The present study aims to report alternatives to inhalation anesthesia at epileptic encephalopathy.
Case report: Male, 4 years old, with SCN8A encephalopathy with surgical indication of orchidopexy. Neuroaxis block was performed and dexmedetomidine was used as a pre-anesthetic and sedation. The anestheticsurgical act was uneventful.
Conclusion: The association of neuraxial block and dexmedetomidine proved to be a viable alternative for surgery in patients with SCN8A encephalopathy.

Introduction

Mutations on gene SCN8A lead to changes in voltage-dependent sodium channels in the brain that have recently been associated with severe epileptic syndrome, although a well-defined clinical presentation is still being investigated. SCN8A encephalopathy is a rare syndrome with

* Corresponding author.
E-mail: ericgmac@hotmail.com (E.G. Machado).

https://doi.org/10.1016/j.bjane.2020.08.013

onset in childhood, described by the presence of recurrent drug-resistant seizures, developmental delay, and frequent epileptiform activity on the Electroencephalogram (EEG).[1,2]

Given the disease is rare, there are no studies in the literature favoring a particular anesthesia management for these patients. According to Pal et al.,[3] mice with SCN8A gene mutations are more sensitive to sevoflurane and isoflurane, inhalation agents commonly used in pediatric anesthesia. Thus, the present case report aimed to describe alternatives to the use of inhalation anesthesia in this group of individuals.

Case report

Consent to report the case with educational purposes was authorized and signed by the family. The patient was a 4-year-old male, 16 kg, candidate for orchidopexy and circumcision. The patient presented SCN8A encephalopathy with major developmental and behavioral impairment and was being followed-up at Instituto Estadual do Cérebro Paulo Niemeyer (Rio de Janeiro, RJ) for 2 years, with the diagnosis confirmed by whole exome sequencing in 2014 (the only case confirmed of the syndrome in Brazil to date). The patient was on regular use of oxcarbamazepine 6% (600 mg.day^{-1}), sodium divalproate (375 mg.day^{-1}) and cannabidiol (144 mg.day^{-1}). Despite using anticonvulsant medication, the patient had countless daily episodes of seizures. Physical examination was unremarkable and complementary tests within normal values.

Dexmedetomidine (2 μg.Kg^{-1} by nasal route) was administered as preanesthetic medication, 30 minutes before entering the operating room. At that time, the patient presented a short-duration seizure episode that repeated during positioning on the operating table. In the operating room, the patient was monitored with electrocardiogram, pulse oximetry and noninvasive blood pressure. After venous cannulation with 22G catheter, hydration with sodium chloride solution 0.9% was started. Sedation was maintained with continuous intravenous infusion of dexmedetomidine (1.0 μg.Kg^{-1}.h^{-1}) and the patient received O_2 supplement by nasal catheter (3 L.min^{-1}). With the patient in the sitting position, spinal anesthesia was performed with a single puncture using a pediatric Quincke 25G type needle and administration of 10 mg of 0.5% hyperbaric bupivacaine.

The anesthetic-surgical procedure was uneventful. At the end, the patient was sent to the Postanesthetic Recovery Unit (PACU), placed under the same intraoperative monitoring and no new seizure episodes were observed. He was discharged from the PACU 120 minutes after admission, presenting score of 10 on the modified Aldrete scale. Hospital discharge was on the postoperative day 1.

Discussion

Epilepsy is a common pediatric neurological disorder, and drug-resistant epilepsies are present in 30% of cases. Such severe forms include epileptic encephalopathies, responsible for several sequelae and cognitive and behavioral impairment. SCN8A encephalopathy is a recently described epileptic encephalopathy, caused by mutations on the SCN8A gene that codifies the sodium channel Nav1.6.[1]

SCN8A encephalopathy was first identified in 2012 and only 140 cases have been diagnosed since. Most individuals affected present drug-resistant seizures and inconsistent response to conventional anticonvulsants.[1]

Although developmental delay may start from birth in a child presenting SCN8A encephalopathy, in many cases, development is normal before seizures begin. The most common clinical presentations are intellectual impairment (varying from mild, moderate to severe) and motor abnormalities, which include hypotonia, ataxia, dystonia, hyperreflexia, and choreoathetoses. (1) Severe cognitive, motor, and behavioral impairment can be observed, as the condition progresses. (2) Sudden death during seizure has been reported in five individuals. Most patients reported in the literature were in the first two decades of life.[1] In the case reported, the child presented motor delay and important cognitive impairment.

There are reports in the literature showing that mice with gene SCN8A mutations assessed by EEG monitoring were more sensitive to volatile anesthetics (sevoflurane and isoflurane). Despite not increasing emergence and awakening time, in vivo exposure resulted increased theta wave activity on EEG, which correlates with general anesthesia depth.[3] There are no reports in the literature to date describing the anesthetic management of patients with SCN8A encephalopathy. Thus, pursuing anesthetic alternatives for these patients is required. In the present report, we chose to use neuraxial block associated with dexmedetomidine as pre-anesthetic medication and intraoperative sedation.

In pediatrics, spinal anesthesia remains controversial as the first-choice technique and its use have been limited to specialized pediatric surgery centers. However, the literature provides a rationale concerning safety of the technique.[4] The main limitation of the technique is the limited duration of the blocks in children, that can be overcome by associating adjuvant drugs such as clonidine, morphine, epinephrine, neostigmine,[4] and even intravenous dexmedetomidine.[5]

In the present case, the drug used for spinal anesthesia was 0.5% hyperbaric bupivacaine. Bupivacaine is a local anesthetic and, as such, blocks the sodium channel at axons reversibly, preventing spread of stimulus. Despite the patientś syndrome presented altered sodium channels, no adverse reactions were observed by using neuraxial local anesthetic, and the child responded to the technique within what is expected in individuals without SCN8A syndrome.

Dexmedetomidine is an α-2 agonist class drug and is used in pediatric patients as pre-anesthetic medication for intraoperative sedation and as an adjuvant drug in postoperative pain management.[5] Although there are no studies to support using the drug both in SCN8A encephalopathy or in the pediatric population in general, in the present case report, its use provided satisfactory results and no adverse effects.

Conclusion

The association of neuraxial block and dexmedetomidine as pre-anesthetic medication and intraoperative sedation proved to be a feasible alternative for surgeries below the diaphragm for patients with SCN8A encephalopathy.

Although the mutation found in this syndrome is on sodium channel blockers, using a local anesthetic – such as, in this case, bupivacaine – yielded the expected response, like that in other individuals in the same age group. Plus, dexmedetomidine proved to be efficient in promoting sedation during the procedure.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Meisler MH, Helman G, Hammer MF, et al. SCN8A encephalopathy: Research progress and prospects. Epilepsia. 2016;57:1027–35.
2. Malcolmson J, Kleyner R, Tegay D, et al. SCN8A mutation in a child presentingwith seizures and developmental delays. Cold Spring Harb Mol Case Stud. 2016;2:a001073.
3. Pal D, Jones JM, Wisidagamage S, Meisler MH, Mashour GA. Reduced Nav1.6 Sodium channel activity in mice increases in vivo sensitivity to volatile anesthetics. PLoS One. 2015;10:e0134960.
4. Gupta A, Saha U. Spinal anesthesia in children: A review. J Anaesthesiol Clin Pharmacol. 2014;30:10–8.
5. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015;115:171–82.

Brazilian Journal of Anesthesiology 2022;72(6): 829—831

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SHORT COMMUNICATION

Non-reactive mydriasis after rocuronium infusion in patients with COVID-19: a case series

Flávia Assis Fernandes [a], João Paulo Jordão Pontes [a,b,*], Celso Eduardo Rezende Borges [b], Erika Lopes Honorato [c], Sanzio Dupim Soares [d], Norma Sueli Pinheiro Módolo [e], Laís Helena Navarro e Lima [e,f]

[a] *Hospital Mater Dei Santa Genoveva de Uberlândia, Departamento de Anestesiologia, Uberlândia, MG, Brazil*
[b] *Uberlândia Medical Center, Departamento de Anestesiologia, Uberlândia, MG, Brazil*
[c] *Uberlândia Medical Center, Departamento de Neurologia, Uberlândia, Uberlândia, MG, Brazil*
[d] *Uberlândia Medical Center, Departamento de Terapia Intensiva, Uberlândia, MG, Brazil*
[e] *Universidade Estadual Paulista (UNESP), Departamento de Anestesiologia, Botucatu, SP, Brazil*
[f] *Queens University, Department of Anesthesia and Perioperative Care, Kingston, Canada*

Received 18 February 2022; accepted 28 May 2022
Available online 8 June 2022

Introduction

The routine use of Neuromuscular Blocking Agents (NMBAs) in patients under mechanical ventilation due to Acute Respiratory Distress Syndrome (ARDS) still causes debate. Although NMBA infusion improves oxygenation in moderately severe ARDS, its effect on mortality is contentious, as most studies have assessed infusions of only 48-hour duration and with cisatracurium.[1] Currently, 88% of patients with Coronavirus Disease 2019 (COVID-19)-related ARDS under mechanical ventilation need an NMBA infusion to optimize oxygenation and ventilation. In contrast, only 22% of patients with "classic ARDS" need an NMBA for the same purpose.[2]

NMBAs are hydrophilic polar molecules that cannot normally cross the Blood-Brain Barrier (BBB).[3] However, NMBAs can impair cholinergic transmission in the Central Nervous System (CNS), producing autonomic dysfunction, excitotoxicity, seizures, and neuronal death, when the BBB becomes permeable due to pathological conditions.[3] Accordingly, mydriasis has been reported due to prolonged NMBA infusions in patients with disrupted BBB caused by severe systemic inflammation,[4] and in patients with immature BBB function.[5,6] Causes of mydriasis include parasympathetic nervous system block, sympathetic nervous system hyperstimulation, cerebral vascular injuries, and brain death.[7]

Non-reactive dilated pupils might represent an important warning sign for neurological complications, especially in unconscious mechanically ventilated patients when a more comprehensive neurological physical exam might not be possible. After obtaining written consent from patients or patients' relatives for reporting and publication, we describe three cases of mechanically ventilated COVID-19 patients with mydriasis who received continuous rocuronium infusion for respiratory parameter optimization.

Case 1

A previously hypertensive 50-kg, 65-year-old female patient (former smoker) was admitted to an Intensive Care Unit (ICU) with respiratory failure due to COVID-19 and underwent orotracheal intubation after 17 days of symptoms. The patient was sedated with ketamine 0.2 $mg.kg^{-1}.h^{-1}$, fentanyl 50 $mcg.h^{-1}$, and midazolam 5 $mg.h^{-1}$. A continuous infusion of rocuronium (15 $mg.h^{-1}$) was started due to

* Corresponding author.
E-mail: pontesjpj@gmail.com (J.P. Pontes).

https://doi.org/10.1016/j.bjane.2022.05.007

ventilator asynchrony after 1-week of mechanical ventilation. She presented with fixed mydriasis not responding to light after 48 h of rocuronium infusion. Laboratory tests did not show any changes that could justify the change in the pupillary pattern. Likewise, no structural changes were observed on Computed Tomography (CT) of the head. Rocuronium was discontinued, leading to complete regression of the pupillary pattern 24 h after the discontinuation. The patient was discharged from the hospital without neurological sequelae 42 days after the fixed mydriasis episode.

Case 2

A 69-kg, 71-year-old male patient with a history of hypertension, diabetes, and dementia was admitted to an ICU with respiratory failure due to COVID-19 and intubated 12 days after the onset of symptoms. He was sedated with ketamine 0.2 $mg.kg^{-1}.h^{-1}$, propofol $mg.kg^{-1}.h^{-1}$, and dexmedetomidine 0.5 $mcg.kg^{-1}.h^{-1}$. Continuous infusion of 20 $mg.h^{-1}$ rocuronium was started after 3 days of tracheal intubation to improve ventilator synchrony. Bilateral mydriasis was observed in 48 h. Laboratory tests showed anemia, elevated inflammatory markers, and acute renal failure (serum creatinine: 1.8 $mg.dL^{-1}$). An urgent head CT scan showed no structural changes. Due to the suspicion of rocuronium-induced mydriasis, the drug was discontinued. In 12 h, an isochoric, medium, and reactive pupillary pattern was observed. Although the patient regained consciousness 1 week after the mydriasis episode, he died 9 days later due to sepsis caused by bacterial pneumonia.

Case 3

A previously hypertensive 95-kg, 49-year-old male patient was admitted to an ICU with respiratory failure due to COVID-19 and intubated 10 days after the onset of symptoms. The patient was receiving ketamine 0.3 $mg.kg^{-1}.h^{-1}$, midazolam 5 $mg.h^{-1}$, fentanyl 2 $mcg.kg^{-1}.h^{-1}$, and rocuronium 25 $mg.h^{-1}$ in a continuous infusion. Anisocoria, followed by fixed 7-mm mydriasis, developed in 48 h after rocuronium infusion (Fig. 1; Supplemental Video 1). A head CT scan was unremarkable. Clinical measures for neuroprotection were initiated. Clinically, the patient had non-dialytic acute renal failure (serum creatinine: 3.7 $mg.dL^{-1}$) without electrolyte disturbances. Therefore, rocuronium-induced mydriasis was suspected. The pupillary pattern returned to normal after 36 h of rocuronium infusion discontinuation. The patient died 5 days after the mydriasis episode due to sepsis caused by bacterial pneumonia.

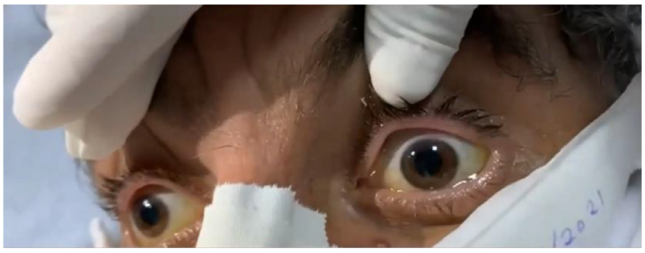


Figure 1 Anisocoric pupils after continuous rocuronium infusion.

In all three cases, the patients received antibiotic therapy, daily dexamethasone, and thromboprophylaxis with therapeutic doses of enoxaparin.

Discussion

In addition to being a hydrophilic molecule, rocuronium has a molecular weight of 610 Da, exceeding the normal permeability limit of the BBB of 450 Da.[6] However, situations of BBB integrity loss can facilitate the access of rocuronium to the CNS.[8] COVID-19 is associated with the release of a storm of pro-inflammatory cytokines, generating systemic inflammation and increased endothelial permeability. The spike protein of SARS-CoV-2 can destabilize the BBB by reducing tight-junction resistance and expression of metalloproteinases that ultimately facilitate neuroinflammation and might be the explanation for the neurological manifestations after COVID-19.[9] The three patients mentioned in this report had severe systemic manifestations with a high probability of affecting the BBB integrity, which would facilitate the effects of rocuronium on the CNS.

Fixed mydriasis episodes have already been reported in neonates after high doses of rocuronium,[5,6] suggesting the passage of the drug to the CNS due to the immaturity of the BBB. Fixed mydriasis has also been reported in patients with ARDS undergoing Extracorporeal Membrane Oxygenation (ECMO) therapy under continuous infusion of rocuronium.[4] NMBAs can act as antagonists in different cerebral nicotinic receptors despite an association among NMBA excitatory effects, such as seizures, due to the increase in intracellular calcium.[3] Therefore, drugs with anticholinergic effects might present paradoxical CNS effects, depending on the agent, concentration, and subtype of the respective receptor.[8] The pupillary diameter at rest represents a balance between the two systems: stimulation of the Sympathetic autonomic Nervous System (SNS) dilates the pupil, and Parasympathetic autonomic Nervous System (PNS) stimulation contracts it. Therefore, SNS activation or PNS inhibition causes mydriasis.[7] Furthermore, other factors, such as local or systemic administration of medications, can change pupil diameter.[7] Regarding the autonomic balance of the pupillary reflex, NMBAs seem to preferentially inhibit cholinergic transmission, causing mydriasis.[4-6,8]

Upon sudden-onset fixed mydriasis in comatose patients, the diagnosis causing this sign should be promptly investigated, as it is generally a life-threatening sign.[7] Therefore, CNS insults, such as cerebral edema, brainstem ischemia/infarction, or hemorrhage, must be immediately recognized and treated. Arterial and venous thrombosis is a common manifestation in patients with COVID-19, requiring antithrombotic prophylaxis. Nevertheless, this approach is not without risks since hemorrhagic complications, including bleeding into the CNS, might occur. All patients in this report were immediately assessed with a head CT to rule out structural causes amenable to surgical or clinical treatment. Additionally, causes such as pharmacological PNS inhibition (i.e., with atropine), excessive sympathetic activity (overdose of sympathomimetics or high doses of vasoactive amines), hypothermia, barbiturate overdose, and hypermagnesemia, among other causes, should also be ruled out.[7] The patients in this report were normothermic and were not

using vasoactive sympathomimetic amines at mydriasis presentation. Furthermore, they were neither receiving antimuscarinic drugs nor had electrolyte disturbances. Ketamine infusion has been associated with bilateral light-responsive mydriasis; however, when given in higher doses than our patients received and in repeated bolus.[10] Moreover, all our patients presented with a fixed mydriasis pattern, which differs from the pattern of ketamine.

In line with other case reports,[4,5] the time association between rocuronium suspension and pupillary reflex recovery, in addition to the evidence in animal experiments,[3] indicate the CNS effect of this drug. Additionally, Langley et al.[6] demonstrated reversal of mydriasis in neonates submitted to anesthesia with rocuronium immediately after the infusion of sugammadex, a specific reversal agent of this NMBA. In all cases, the patients had been on high doses of rocuronium in continuous infusion and had some reason for loss of integrity of the BBB in common.[4-6] Another important point refers to the probably higher rocuronium plasma level in patients 2 and 3 owing to altered creatinine clearance. Interestingly, similar case reports with other nondepolarizing NMBAs, such as atracurium and vecuronium, suggest a "pharmacological class" mydriatic effect in patients with impaired BBB.[8]

In summary, a mydriatic and hyporesponsive pupillary pattern is associated with poor neurological prognosis. Therefore, knowing the medications that can interfere with or even mimic neurological injury is essential for the adequate management of critically ill patients. Thus, continuous rocuronium infusion should be considered as a differential diagnosis in a patient who develops bilateral fixed mydriasis simultaneous to widespread NMBA use due to the COVID-19 pandemic.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2022.05.007.

References

1. Welhengama C, Hall A, Hunter JM. Neuromuscular blocking drugs in the critically ill. BJA Educ. 2021;21:258—63.
2. Grasselli G, Cattaneo E, Florio G, et al. Mechanical ventilation parameters in critically ill COVID-19 patients: a scoping review. Crit Care. 2021;25:115.
3. Cardone C, Szenohradszky J, Yost S, et al. Activation of brain acetylcholine receptors by neuromuscular blocking drugs. A possible mechanism of neurotoxicity. Anesthesiology. 1994;80:1155—61. discussion 29A.
4. He H, Yu Z, Zhang J, et al. Bilateral dilated nonreactive pupils secondary to rocuronium infusion in an ARDS patient treated with ECMO therapy: a case report. Med (Baltim). 2020;99:e21819.
5. Joyce C, Greenwald BM, Han P. Bilateral dilated nonreactive pupils in a neonate after surgery. A A Case Rep. 2016;6:286—7.
6. Langley RJ, McFadzean J, McCormack J. The presumed central nervous system effects of rocuronium in a neonate and its reversal with sugammadex. Paediatr Anaesth. 2016;26:109—11.
7. Thomas PD. The differential diagnosis of fixed dilated pupils: a case report and review. *Crit* Care Resusc. 2000;2:34—7.
8. Schmidt JE, Tamburro RF, Hoffman GM. Dilated nonreactive pupils secondary to neuromuscular blockade. Anesthesiology. 2000;92:1476—80.
9. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood—brain barrier. Neurobiol Dis. 2020;146:105131.
10. Vide S, Costa CM, Gambus PL, et al. Effects of ketamine on pupillary reflex dilation: a case report. A A Pract. 2018;10:39—41.

Brazilian Journal of Anesthesiology 2022;72(6): 832—833

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CLINICAL IMAGES

Improving the success rate of intravenous cannulation

Anthony M.H. Ho, Gregory Klar, Glenio Bitencourt Mizubuti *

Department of Anesthesiology and Perioperative Medicine, Queen's University, Kingston, Ontario, Canada

Received 31 March 2022; accepted 21 May 2022
Available online 1 June 2022

First attempt intravenous (IV) cannulation success rate by anesthesiologists is 50.9—79.7%.[1,2] Cannulation starts with the needle puncturing the vein at an angle (Fig. 1a). The needle-cannula combo is then advanced further so that the cannula tip is completely within the vein before it can be advanced. During this advancement, if the incident angle of the needle has not been reduced, the tip may puncture the back wall of the vein (Fig. 1a) and become interstitial. Bending the needle slightly (Fig. 2)[3] facilitates parallel needle advancement (Fig. 1b).

Instead of parallel advancement, we suggest a slight upward tilt (Fig. 1c) to create an arrowhead-shaped tip that has the least chance of puncturing the upper/lower vein

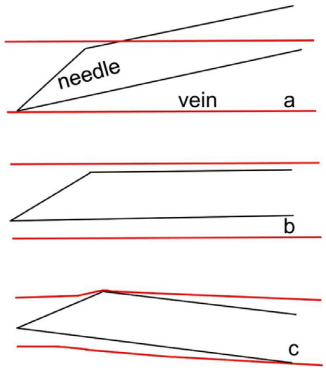


Figure 1 (a) The advancing tip of the needle of the IV cannula can go through the opposite (i.e., posterior) wall of the vein if the incident angle is not adjusted to nearly zero after the initial blood flashback. (b) The advancing tip of the needle is parallel to the vein, avoiding double-puncture, but the safety margin is small as any unsuspected downward tilt will lead to double-puncture. (c) A slight upward tilt of the needle provides the least chance of an inadvertent downward bias, and since the receding side of the bevel does not penetrate, it is the safest, even if the vein is slightly smaller than the IV needle-cannula set.

Figure 2 The IV needle-cannula shield (a) can be used to bend the set by a few degrees (b) while maintaining sterility.

* Corresponding author.
E-mail: Gleniomizubuti@hotmail.com (G.B. Mizubuti).

https://doi.org/10.1016/j.bjane.2022.05.005

wall. The receding edge of the bevel has little chance of puncturing the vein wall.

Fig. 1c illustrates the situation in which the vein is slightly smaller than the cannula. Here, the challenge is not so much entering the vein since the metal needle tip is tapered. The key is not to double-puncture the vein during advancement. This chance is reduced if there is a small upward tilt of the needle tip (Fig. 1c), made possible by the aforementioned pre-bending of the needle-cannula set (Fig. 2).

Financial support

Departmental and institutional resources. No external funding was acquired for the current work.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Bensghir M, Chkoura K, Mounir K, et al. Peripheral intravenous access in the operating room: characteristics and predictors of difficulty. Ann Fr Anesth Reanim. 2012;31:600—4.
2. Angles E, Robin F, Moal B, et al. Pre-operative peripheral intravenous cannula insertion failure at the first attempt in adults. Development of the VENSCORE predictive scale and identification of risk factors. J Clin Anesth. 2021;75:110435.
3. Solomowitz BH. Intravenous cannulation: a different approach. Anesth Prog. 1993;40:20—2.

Brazilian Journal of Anesthesiology 2022;72(6): 834—835

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CLINICAL IMAGES

Anatomy variation of brachial plexus trunks during supraclavicular nerve block: clinical image

Vendhan Ramanujam *, Patrick Van Kirk

Warren Alpert Medical School of Brown University/Rhode Island Hospital, Department of Anesthesiology, Providence, Rhode Island, USA

Received 31 May 2022; accepted 24 June 2022
Available online 6 July 2022

For successful ultrasound-guided peripheral nerve block, recognition of anatomy of interest either as normal or abnormal is vital. We report the image of anatomical variation of brachial plexus at supraclavicular level in a 28-year-old healthy male with no significant medical history and no prior neck surgery, injury, or radiation exposure who came for wrist surgery. A caudal tilt towards ipsilateral lung during supraclavicular ultrasound scanning revealed the presence of superior and middle trucks, superior and medial to subclavian artery respectively rather than being situated lateral to artery along with inferior trunk (Fig. 1). Anomalies of brachial plexus have usually been reported in interscalene region.[1] Rarely a single trunk abnormality has been reported in supraclavicular region.[2] Thus, our report of images of deviation of two trunks are clinically compelling. When there are alterations in signaling between mesenchymal and neuronal growth cones or circulatory factors at time of development of brachial plexus such abnormalities can

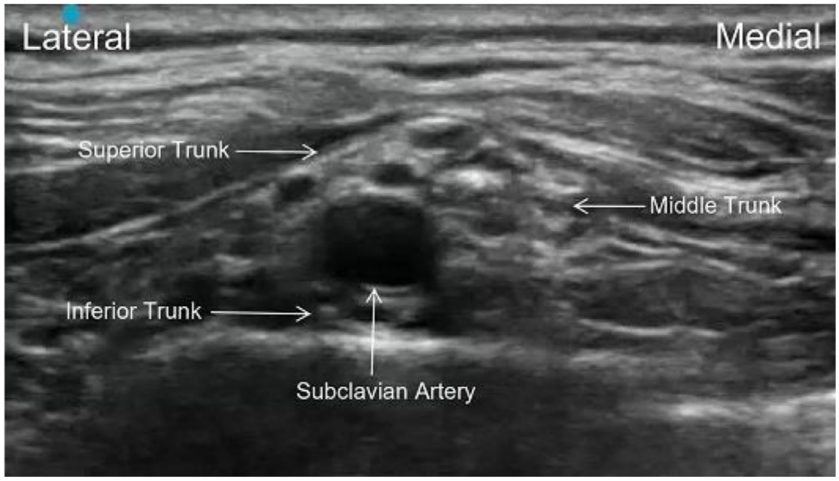


Figure 1 Brachial plexus anomaly at supraclavicular level with superior and middle trunks superior and medial to subclavian artery, respectively.

* Corresponding author
E-mail: vendhan_ramanujam@brown.edu (V. Ramanujam).

https://doi.org/10.1016/j.bjane.2022.06.009

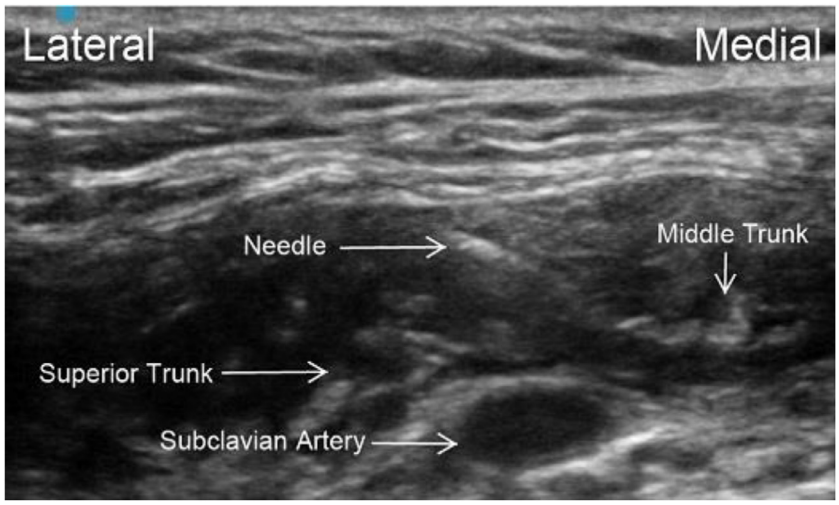


Figure 2 Targeted blocking of superior and middle trunks.

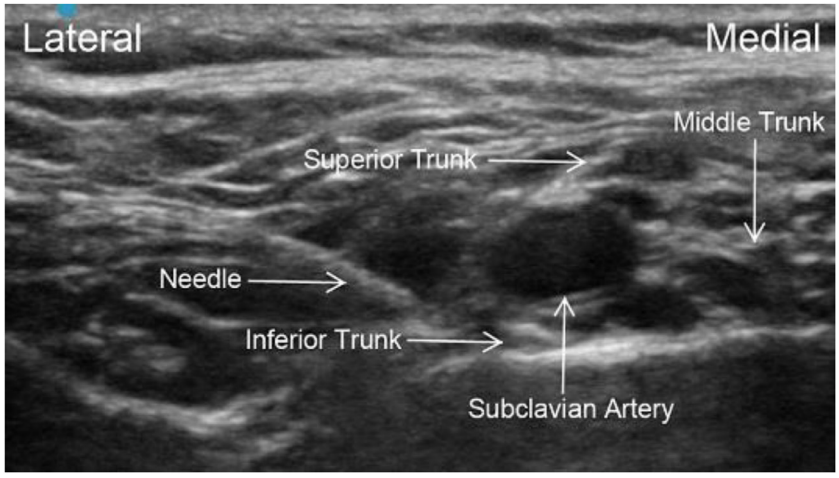


Figure 3 Targeted blocking of inferior trunk.

occur.[3] The anomaly recognition allowed us to individually block the trunks and achieve a successful surgical anesthesia (Figs. 2 and 3). In conclusion, anatomical variation of brachial plexus can happen, and use of ultrasound helps identifying them to safely and successfully administer the block.

Conflicts of interest

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Kessler J, Gray AT. Sonography of scalene muscle anomalies for brachial plexus block. Reg Anesth Pain Med. 2007;32:172—3.
2. Chin KJ, Niazi A, Chan V. Anomalous brachial plexus anatomy in the supraclavicular region detected by ultrasound. Anesth Analg. 2008;107:729—31.
3. Padur AA, Kumar N, Shanthakumar SR, Shetty SD, Prabhu GS, Patil J. Unusual and unique variant branches of lateral cord of brachial plexus and its clinical implications – A cadaveric study. J Clin Diagn Res. 2016;10:AC01—4.

Brazilian Journal of Anesthesiology 2022;72(6): 836–838

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Does adding lateral femoral cutaneous nerve block improves the analgesia of pericapsular nerve group block in the fractured hip surgeries?*

Dear Editor,

Patients undergoing surgery for fractured hip often are elderly with comorbidities, hence pain management remains a challenge. The current literature has suggested that Ultrasound-Guided (USG) Pericapsular Nerve Group block (PENG block) is a safe and effective analgesic technique in such patients.[1] Most hip surgeries require lateral incision, which involves the cutaneous supply by the branches of the Lateral Femoral Cutaneous Nerve (LFCN). Case reports have shown that blocking the LFCN may provide an additional advantage to the PENG block in terms of quality and duration of analgesia.[2,3] However, supportive literature based on detailed scientific study was lacking. Hence, we conducted a prospective, double blinded, randomized study to compare PENG block with a combination of PENG block and LFCN block for efficacy of analgesia in fractured hip surgery.

After approval from the hospital ethical Committee and Registration with Trial Registry (CTRI), a prospective randomized trial was done at a teaching industrial hospital from April 2021 to December 2021. After informed written consent, 60 patients were randomized into two equal groups: Group P (PENG block, n = 30) and Group PL (PENG block +LFCN block, n = 30). Patients of both sexes aged 18–80 years with severe pain due to hip fracture were included. Patients who refused to participate, having severe cardiovascular disease, contraindication for regional anesthesia, history of hip surgery within three months, and having difficulty in communication due to hearing loss were excluded from the study. Patients were assessed for pain by the Numeric Rating Score (NRS) where 0 = no pain and 10 = most severe pain. Patients with NRS < 5 at rest were excluded from the study. Patients who were non-compliant to the study protocol during the study period were also excluded from analysis. In both groups, ultrasound guided PENG block was performed with a curvilinear low-frequency ultrasound probe (2–5 MHz) in the supine position (Fig. 1 A and B). In group P, 30 mL 0.5% ropivacaine and 8 mg dexamethasone was injected, and in group PL, a 30 mL mixture of 0.5% ropivacaine + 8 mg dexamethasone was prepared and a 25 mL mixture was injected, and the remaining 5 mL drug was used for LFCN block. In group PL, to block the LFCN, a high frequency ultrasound transducer/probe (6–13 MHz) was used (Fig. 1 C and D).

After 30 minutes of completion of the block NRS was assessed for pain during rest and movement by passively lifting the Limb 15° above the resting level by an observer who was unaware about the groups. After that, patients were positioned in the sitting position for spinal anesthesia, and Ease of Spinal Positioning (EOSP) was assessed using a four-point scale (0 = unable to position, 1 = patient had pain or abnormal posturing, 2 = discomfort or require support for positioning, 3 = optimal). Patients who were unable to position (score = 0) were given additional analgesic (ketamine 10–20 mg + fentanyl 10–20 μg) and were excluded from the study. All the patients were given standard spinal anesthesia with a mixture of 1.4 mL 0.5% bupivacaine and 0.4 mL (20 μg) fentanyl. Postoperative analgesia was continued with Injection paracetamol 1 g every 8 hours and Injection tramadol 50 mg intravenously when pain was > 3 on NRS. Patients were assessed at intervals of 4, 6, 8, 10, 12, 24 hours. The primary objective was to compare the Numeric Pain Scores (NRS) during rest and movement. Secondary objectives were to compare Ease of Spinal Positioning (EOSP), duration of analgesia (first request to rescue analgesia with tramadol), and total tramadol consumption in 24 hours.

The results were analyzed using statistical software (MedCalc version 20.0). Normally distributed data (represented as Mean ± SD) was assessed using the Student's *t*-test. Non-normally distributed data and ordinal data were represented as median & Interquartile Range (IQR) and assessed using the Mann-Whitney U-test. A p-value < 0.05 was considered significant.

All 60 patients completed the study. Our results showed no significant difference in NRS at rest or on movement in group P and group PL at all-time points of 4, 6, 8, 12, and 24 hours ($p > 0.05$). The first request to rescue analgesia (duration of block) was significantly longer in group PL, mean (SD)

* Presentation at a meeting: As a poster at National Conference of Indian Society of Anaesthesiologists 2021. IRB number: # Anaesth/00-01/2021 [18.01.21]. Clinical trial registration number: CTRI Number CTRI/2021/04/032822 [Registered on: 15/04/2021] - Trial Registered Prospectively.

https://doi.org/10.1016/j.bjane.2022.06.005

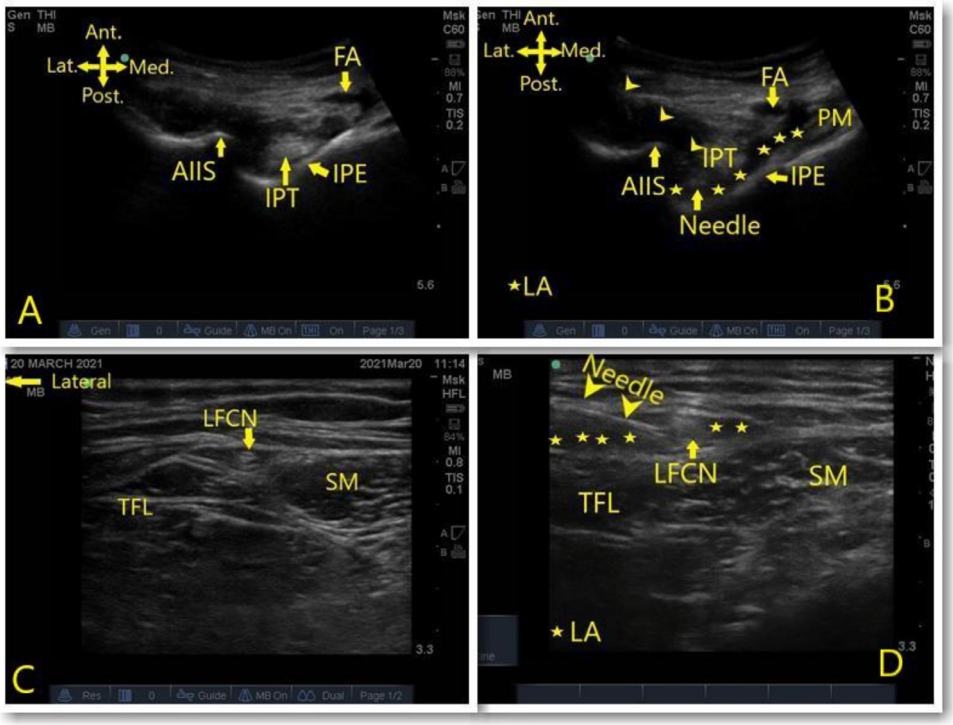


Figure 1 (A) Sonoanatomy of PENG block, (B) Block needle entry from lateral to medial in an in-plane approach and the needle tip between the psoas tendon anteriorly and the pubic ramus posteriorly, (C) Sonoanatomy of LFCN block showing LFCN at the lateral margin of sartorius muscle, (D) Block needle entry from lateral to medial and spread of local anesthetic around the LFCN nerve. AIIS, Anterior Inferior Iliac Spine; IPE, Iliopubic Eminence; IPT, Iliopsoas Muscle Tendon; PM, Pectineus Muscle; FA, Femoral Artery; LFCN, Lateral Femoral Cutaneous Nerve; TFL, Tensor Fasciae Latae; SM, Sartorius Muscle (SM), LA, Local Anesthetic; Ant., Anterior; Post., Posterior; Lat., Lateral; Med., Medial.

15.26 (4.25) h, than in group P, 10.9 (3.17) h ($p < 0.0001$). Tramadol consumption, median (IQR) in 24 hours, was significantly higher in group P 75 (150–50) mg than in group PL 50 (50–50) mg ($p = 0.012$). The EOSP score, median (IQR), was not significantly different in group P 3 (3–2) and group PL 3 (3–2) ($p = 0.83$).

PENG block is a novel ultrasound guided technique which has been used successfully to improve Ease of Spinal Positioning (EOSP).[1,4] Morrison et al. have reviewed the usefulness of PENG block and found it very effective.[5] In our study, we observed significant improvement in NRS after block ($p < 0.00001$) and EOSP in both groups.

Two previously published case reports found that addition of LFCN was more effective in providing postoperative analgesia for hip surgery.[2,3] In our study we observed that addition of LFCN improved the duration of request to first rescue analgesia and 24 hours tramadol consumption. We also conducted subgroup analysis of patients with either lateral or posterolateral incision. However, the difference was not statistically significant ($p = 0.31$).

The novelty of the present study was that there has been no such comparative study yet published. However, there were a few limitations in our study, Firstly, sensory testing was not done for LFCN. The study was also not adequately powered to detect a significant difference influenced by site of incision.

To conclude, combining LFCN block with PENG block improves the duration of analgesia and reduces the requirement of rescue analgesics.

Conflicts of interest

The authors declare no have conflicts of interest.

References

1. Giron-Arango L, Peng PWH, Chin KJ, Brull R, Perlas A. Pericapsular Nerve Group (PENG) block for hip fracture. Reg Anesth Pain Med. 2018;43:859–63.
2. Thallaj A. Combined PENG and LFCN blocks for postoperative analgesia in hip surgery-A case report. Saudi J Anaesth. 2019;13:381–3.
3. Roy R, Agarwal G, Pradhan C, Kuanar D. Total postoperative analgesia for hip surgeries, PENG block with LFCN block. Reg Anesth Pain Med. 2019;44:684.
4. Sahoo RK, Jadon A, Sharma SK, Peng PW. Peri-capsular nerve group block provides excellent analgesia in hip fractures and positioning for spinal anesthesia: A prospective cohort study. Indian J Anaesth. 2020;64:898–900.
5. Morrison C, Brown B, Lin DY, Jaarsma R, Kroon H. Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review. Reg Anesth Pain Med. 2021;46:169–75.

Ashok Jadon [a,*], Surabhi Srivastawa [a], Apoorva Bakshi [a], Rajendra K. Sahoo [b], Bhupendra K. Singh [a], Neelam Sinha[a]

[a] *Tata Motors Hospital, Telco Colony, Department of Anesthesia & Pain Relief Service, Jamshedpur, Jharkhand, India*

[b] *Kalinga Institute of Medical Sciences, India, and Morphological Madrid Research Centre (MoMaRC), Department of Anaesthesiology and Pain Management, Madrid, Spain*

[*] Corresponding author.
E-mail: jadona@rediffmail.com (A. Jadon).
Received 19 February 2022; accepted 15 June 2022
Available online 4 July 2022

Brazilian Journal of Anesthesiology 2022;72(6): 839—840

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Immersive virtual reality on a pregnant patient during an elective orthopedic surgery

Dear Editor,

We recently used immersive virtual reality on a 21-week pregnant patient scheduled for an elective anterior cruciate ligament repair as a sedation-sparing technique. She had no major comorbidities and no past surgical history. Some readers might find useful insights reading this letter and further research could come as a result. Immersive Virtual Reality (IVR) is an amazing alternative candidate during anesthesia practice when a nonpharmacological approach for anxiolysis, unique patient experience, adjuvant analgesia, and procedural amnesia are desired.

In the recent literature, exciting results across different patient populations explored the ease to use, the

Figure 1 An immersive virtual reality headset generated tridimensional computerized footage with immersive songs.

https://doi.org/10.1016/j.bjane.2022.07.002

noninvasiveness characteristics, the analgesic, and the anxiety-relieving benefits of this technology.[1,2] Moreover, there is a positive public perception of the gadget and its application in healthcare as more people understand its use in other daily activities.[3]

Pharmacological sedation and its overdosage come with risks, especially in the pregnant population. As such, oversedation increases upper airway obstruction risks and can cause significant hemodynamic changes. Indeed, the most common mechanism encompassing 21% of the closed claims database in monitored anesthesia care is respiratory depression due to relative or absolute sedation overdose.[4] Besides, there is a widespread belief that sedatives can adversely affect their yet-to-be-born children and emerges as a challenge to providers.

Accordingly, after we conducted neuraxial and peripheral nerve blocks under no sedation per the patient's request, the IVR headset was provided. The technology generated (Fig. 1) tridimensional computerized footage with immersive songs. The diopter adjustment created a better tridimensional experience as reported by the patient. Using a touchscreen remote wired to the headset, the patient determined the scenario, volume, and other parameters. We performed periodic satisfaction assessments feeling confident the technology was positively impacting her care given the feedback received. Total IVR exposure lasted for approximately 2 hours. No adverse or unexpected events were observed. Discharge happened on the same day from the Post Anesthesia Care Unit (PACU) with optimal pain control and patient satisfaction with the technology. She stated that she would undergo the same experience if another procedure should be done under the same conditions. Important to note is the lack of a standardized satisfaction assessment scale applied to Virtual Reality under these circumstances. It limited our objective measurement of the patient's contentment. Plus, due to time restrictions, we made no outpatient assessment. Thus, all the feedback given was nonstandardized and subjectively appraised. Despite these constraints, the use of the technology, the feasibility, and the level of patient satisfaction match literature findings.[2]

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2022.07.002.

References

1. Hoffman H, Chambers G, Meyer W, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. Ann Behav Med. 2011;41:183—91.
2. Indovina P, Barone D, Gallo L, Chirico A, De Pietro G, Giordano A. Virtual reality as a distraction intervention to relieve pain and distress during medical procedures. Clin J Pain. 2018;34:858—77.
3. Keller M, Park H, Cunningham M, Fouladian J, Chen M, Spiegel B. Public perceptions regarding use of virtual reality in health care: a social media content analysis using facebook. J Med Internet Res. 2017;19:e419.
4. Bhananker SM, Posner KL, Cheney FW, Caplan RA, Lee LA, Domino KB. Injury and liability associated with monitored anesthesia care. Anesthesiology. 2006;104:228—34.

Ramon Magalhães Mendonça Vilela [a,*], Enrique Goytizolo [b], Florentino Fernandes Mendes[a]

[a] *Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil*
[b] *Hospital for Special Surgery, New York, United States of America*

[*] Corresponding author.
E-mail: ramonmmvilela@gmail.com (R.M. Vilela).
Received 11 May 2022; accepted 1 July 2022
Available online 15 July 2022

Brazilian Journal of Anesthesiology 2022;72(6): 841—842

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Comparison of incidence of emergence delirium in pediatric patients with three different techniques of general anesthesia using sevoflurane and propofol: a randomized controlled trial

Dear Editor,

In 1960, Eckenhoff first identified Emergence Delirium (ED), also known as Emergence Agitation (EA), a phenomenon observed at the time of recovery from General Anesthesia (GA).[1] It is characterized by a dissociative state of consciousness, causing behavioral disturbances. Incidence of ED in the general population ranges from 5% to 30%, but its incidence varies from 2% to 80% in the pediatric population, more so in children in the age group of 2—8 years. The cause of ED appears to be multifactorial in origin. Use of volatile anesthetics, prolonged duration and type of surgery, pain, and rapid emergence are some factors known to increase its incidence.

There is literature suggesting the influence of GA techniques in the incidence of ED. Total Intravenous Anesthesia (TIVA) is proven to have the least ED incidence than other methods. However, TIVA carries certain disadvantages like requiring intravenous (IV) access for administration, infusion pumps designed to deliver TIVA and their high cost, known allergies to propofol, etc.[2] The use of only inhalation technique is also not free from disadvantages like difficulty in administration by mask, the need of higher concentration of agents, operation theatre environment pollution, high cost, higher incidence of malignant hyperthermia in susceptible individuals, and increased incidence of ED in pediatrics.[3] We studied the technique of combination of inhalational and intravenous agents to overcome the disadvantages of both the techniques and take advantage of their benefits. Our study aimed to find and compare the incidence of ED in pediatric patients of 2 to 10 years of age while using three different anesthetic techniques with sevoflurane and/or propofol.

We conducted the study after approval from the Institute's Ethical Committee AIIMS Jodhpur and registered under the Clinical Trial Registry India (CTRI/2018/05/014064) before enrolling the patients. This was a parallel, double-blinded, randomized, controlled trial. Seventy-five pediatric patients of ages 2 to 10 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled for elective laparoscopic surgery of 1—4 hours duration under GA were enrolled. Patients who did not give consent, assigned for elective surgery under regional anesthesia, with hepatic impairment and renal insufficiency, with active upper respiratory tract infection, with a history of previous psychiatric or congenital neurological disease, on drugs like antipsychotic drugs, antiepileptics which would influence the outcome were excluded from the study. The patients were divided into three groups of 25 each by a computer-generated random number table, and allocation concealment was done by Sequential Numbered Opaque Sealed Envelope as:

Group A, anesthesia was induced with oxygen (FiO_2 0.50), air, and sevoflurane (increasing concentration up to 8%) via face mask and was maintained with sevoflurane (1—1.2 MAC).

Group B, anesthesia was induced with a bolus injection of 3 $mg.kg^{-1}$ propofol and was maintained with sevoflurane, oxygen (FiO_2 0.50), and air.[4]

Group C, anesthesia was induced with a bolus injection of 3 $mg.kg^{-1}$ propofol and was maintained with oxygen (FiO_2 0.50), air, and continuous infusion of 100—400 $mcg.kg^{-1}.min^{-1}$ propofol.[5]

Premedication was given to the patient as per the Institute's protocol with IV midazolam (20 $mcg.kg^{-1}$) 30 minutes before surgery. After adequate preoxygenation with 100% oxygen, 0.25 $mg.kg^{-1}$ IV lidocaine and 2 $mcg.kg^{-1}$ fentanyl were given to all patients during anesthesia induction. The attending anesthesiologist was given a sealed envelope with instructions for including the patients in different study groups.

After adequate mask ventilation, a standard dose of a muscle relaxant atracurium was administered and patients were intubated. Supplementary doses of fentanyl (1 $mcg.kg^{-1}$) were given every hour from the initial dose until the completion of the procedure or the patient's requirement as assessed by the attending anesthesiologist for all the patients. In addition, all patients received IV paracetamol 10—15 $mg.kg^{-1}$ before extubating. Neuromuscular blockade was reversed with standard doses of IV neostigmine and glycopyrrolate.

Emergence reactions and severity of pain at extubation and in PACU were recorded at intervals of 5 min for 20 minutes by another anesthesiologist as per the PAED scale & FLACC scale respectively, who was blinded to the technique

https://doi.org/10.1016/j.bjane.2022.05.002

Table 1 Comparison of number and percentage of children with ED and pain at emergence in the three groups of children undergoing different techniques of GA.

		Groups			
		A	B	C	*p*-value
Emergence Delirium n (%)	Absent	14 (56)	21 (84)	23 (92)	0.006
	Present	11 (44)	4 (16)	2 (8)	

ED, Emergence Delirium; GA, General Anesthesia; Groups: A, Anesthesia induced and maintained with sevoflurane; B, Anesthesia induced with propofol and maintained with sevoflurane; and C, TIVA.

used for anesthesia. The PAED score of > 12 was considered as ED, and a FLACC score of > 4 was considered as moderate pain and requiring intervention.

The cumulative incidence of ED was 44%, 16%, and 8% in groups A, B, and C, respectively (Table 1). The mean age of children presenting with ED was found to be less than 4 years, and 87% of ED patients experienced pain. By using time-to-event analysis, as compared to Group A, a significantly lower risk of ED was seen in Group B ($p = 0.003$) and Group C ($p < 0.001$). No difference was seen in groups B and C ($p = 0.133$).

Many studies suggest that ED following sevoflurane and desflurane is probably due to rapid emergence from anesthesia by these agents due to their low blood solubility or due to pain at emergence. The reason could also be the rapidity of induction by sevoflurane, leading to biochemical, physiological, or structural changes in the brain cells, which later manifest as delirium in the postoperative period.[3]

ED not only increases duration of PACU stay but also can cause physical, mental, and psychological trauma to the patient as well as to the parents. There is increased occupancy of PACU beds and resource utilization in the form of drug usage and the number of nursing staff for monitoring and restraining patients.

Though the incidence of ED in Group B is 8% higher than in Group C, the difference is not statistically significant. On the other hand, the incidence of ED in Group B is 18% lower than in Group A, and this difference is statistically significant. Group C, i.e. TIVA, carries certain disadvantages like requiring IV access for administration, infusion pumps designed to deliver TIVA and their high cost, known allergies to propofol, etc. preclude its use. Thus, the combination technique may be recommended over TIVA.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Eckenhoff JE, Kneale DH. Dripps RD. The incidence and etiology of postanesthetic excitement a clinical survey. Anesth J Am Soc Anesthesiol. 1961;22:667–73.
2. Chandler J, Myers D, Mehta D, et al. Emergence delirium in children: A randomized trial to compare total intravenous anesthesia with propofol and remifentanil to inhalational sevoflurane anesthesia. Paediatr Anaesth. 2013;23:309–15.
3. Singh R, Sood N, Chatterji C, Kharbanda M, Mahajan V. Comparative evaluation of incidence of emergence agitation and postoperative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia. Indian J Anaesth. 2012;56:156.
4. Wells LT, Rasch DK. Emergence "delirium" after sevoflurane anesthesia: a paranoid delusion? Anesth Analg. 1999;88:1308–10.
5. Uezono S, Goto T, Terui K, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. Anesth Analg. 2000;91:563–6.

Deepak Modi[a], Shilpa Goyal [a,*], Nikhil Kothari[a], Ankur Sharma [b], Rakesh Kumar[a], Swati Chhabra [a], Akhil Goel [c], Pradeep Bhatia[a]

[a] *All India Institute of Medical Sciences (AIIMS) Jodhpur, Department of Anaesthesiology and Critical Care, Rajasthan, India*
[b] *All India Institute of Medical Sciences (AIIMS) Jodhpur, Department of Trauma & Emergency (Anaesthesiology), Rajasthan, India*
[c] *All India Institute of Medical Sciences (AIIMS) Jodhpur, Department of Community Medicine and Family Medicine, Rajasthan, India*

[*] Corresponding author.
E-mail: drshilpagoyal@yahoo.com (S. Goyal).

Received 1 February 2021; accepted 10 May 2022
Available online 20 May 2022

Brazilian Journal of Anesthesiology 2022;72(6): 843—844

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Letter to the Editor commenting on "Efficacy of serratus anterior plane block versus thoracic paravertebral block for postoperative analgesia after breast cancer surgery: a randomized trial"

Dear Editor,

We have read with very great interest the study published by Arora S et al.: "Efficacy of serratus anterior plane block versus thoracic paravertebral block for postoperative analgesia after breast cancer surgery: a randomized trial", especially for the attention paid to the key points in the management of breast surgery: postoperative analgesia optimization, incidence of postoperative nausea and vomiting reduction, prevention of the onset of chronic pain and functional impotence.[1]

Traditionally, radical oncologic breast surgery has been performed under general anesthesia. Many regional anesthetic techniques have been described in literature, including Thoracic Epidural Paravertebral Block (TPVB), Intercostal Nerve Blocks, Brachial Plexus Blocks, and Trunk Nerve Blocks as Pectoral Nerve Block 1-2 (PECS1, PECS2), Erector Spinae Plane Block (ESP), and Serratus Anterior Plane block (SAP).[2]

Research on this topic is abundant, but there is a shortage of comparative studies among regional techniques combined one another associated with general anesthesia.[3]

Routinely, in our Centers we use combinations of peripheral/neuraxial blocks associated with sedation or general anesthesia, which guarantees a total coverage also in the axillary area.[4]

Particularly, we manage to use PECS2 block to cover muscles, axilla, and lateral cutaneous branches of intercostal nerves (reliable from T2 to T4), SAP block to cover lateral cutaneous branches from T4 to T7, and parasternal block (or transversus thoracic muscle plane block) to cover anterior cutaneous branches. Lastly, the skin of the breast, breast gland, and nipple are supplied by the second to sixth intercostal nerves (T2—T6), which are adequately blocked with TPVB. Regarding ESP block, it provides analgesia in the territories innervated by the anterior branches of the spinal nerves and can achieve an anesthetic plane in the territories innervated by the dorsal branches of the spinal nerves.

Indeed, TPVB is the first choice, a safe and reliable method under ultrasound guidance. Rather than complications (bleeding, epidural spread, pneumothorax), it is the anthropometric characteristics of the patient (a paravertebral space > 5.5 cm deep) that preclude its use.

These alternatives are effective and easy to perform in real working condition.

Our observation when adopting the same techniques even in less expert hands such as those of the residents is that, with the same quality of the procedure and correct execution, PECS and SAP blocks are easier to execute and can be performed with the patient under sedation or asleep and ventilated so as to avoid the emotional component that often prejudices the mere execution of anesthesiology procedures, while ESP must be performed in a sitting position and therefore the patient's emotionality, perhaps the technical difficulties may affect the actual quality of the block and above all the discomfort of the patient (sensation of widening of the fascial planes and at least two punctures on the back).

ESP and PECS/SAP are also superimposable as a benefit to the vision of the surgeons who perform the procedure in the operating room and then follow up the patients.

If the surgical procedure foresees greater anatomical involvement the choice falls on the peridural management for better repeatability, for better coverage of more anatomical metameres, and so less possible uncovered and painful surgical areas in the postoperative period.

In short, depending on the type of breast surgery and the time of the surgical list, opting for the peridural in larger surgical frameworks and adding a block on the more scarified territory remains a winning option; TPVB and ESP are excellent choices even on large surgical territories, but the multi-sectorial nature of the territory to be analyzed and anesthetized obliges more injections and therefore discomfort for the patient, both in favor of the peridural and in favor of the management of the PECS and SAP blocks, which are simpler both in terms of execution, even with a single puncture on the periarticular shoulder tissue, and of surgical outcome.

Arora's study concerns American Society of Anesthesiologists physical Status (ASA) I—II patients, excluding elderly, obese and other categories of frail patients, for whom it may be desirable to avoid general anesthesia. A combination of several locoregional techniques would guarantee surgical anesthesia compared to one alone.

These regional anesthesia techniques can be done under the ever-growing constraints in time. We are of the opinion that their combination, far from delaying it, could lead to a time gain by acting on the nerve pathways at different levels, reaching the anesthetic plane first.

https://doi.org/10.1016/j.bjane.2022.05.001

Improved pain control combined with reduced opioid consumption and reduced complications, such as vomiting, ensures a speed recovery after surgery, with less time spent in recovery rooms and ordinary hospital stays, with obvious economic benefits.

There is also the potential benefit concerning the relationship between multimodal anesthesia techniques and the lower incidence of tumor recurrence which, despite the lack of strong evidence in the literature, still represents a hot topic and could further endorse regional anesthesia techniques in this clinical scenario.[5]

We believe that elective breast surgery anesthesia might be tailored to the patient's needs as much as to the surgical approach, and we deem appropriate for the anesthesiologist to be able to master as many techniques as possible in order to obtain the best result for the patient.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Arora S, Ovung R, Bharti N, Yaddanapudi S, Singh G. Efficacy of serratus anterior plane block versus thoracic paravertebral block for postoperative analgesia after breast cancer surgery – a randomized trial. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.09.017. Epub ahead of print.
2. Woodworth GE, Ivie RMJ, Nelson SM, Walker CM, Maniker RB. Perioperative Breast Analgesia: A Qualitative Review of Anatomy and Regional Techniques. Reg Anesth Pain Med. 2017;42:609—31.
3. Jacobs A, Lemoine A, Joshi GP, Van de Velde M, Bonnet F. PROSPECT Working Group collaborators#. PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2020;75:664—73.
4. Santonastaso DP, DE Chiara A, Bagaphou CT, et al. Erector spinae plane block associated to serratus anterior plane block for awake radical mastectomy in a patient with extreme obesity. Minerva Anestesiol. 2021;87:734—6.
5. Sessler DI, Riedel B. Anesthesia and Cancer Recurrence: context for divergent study outcomes. Anesthesiology. 2019;130:3—5.

Matteo Zappaterra [a,1], Alessio Cittadini [b,1], Andrea Sica [b,1,*], Domenico Pietro Santonastaso [b,1], Vanni Agnoletti [b,1]

[a] *Anesthesia and Intensive Care Unit, AUSL Romagna, Santa Maria delle Croci Hospital, Ravenna, Italy*
[b] *Anesthesia and Intensive Care Unit, AUSL Romagna, M. Bufalini Hospital, Cesena, Italy*

[*] Corresponding author.
E-mail: andrea.sica@auslromagna.it (A. Sica).
Received 27 November 2021; accepted 10 May 2022
Available online 18 May 2022

[1] All authors contributed equally to the work.

Brazilian Journal of Anesthesiology 2022;72(6): 845—847

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Risk factors for prolonged ventilation in patients undergoing endovascular treatment of unruptured intracranial aneurysm: a retrospective cohort study

Dear Editor,

The perioperative management of unruptured intracranial aneurysms represents a challenge for anesthesiologists. In recent years, endovascular treatment has emerged as a safe option for these patients, but the literature regarding intraoperative management is scarce.[1] Standard of care requires absolute immobility, which can be obtained with general anesthesia and muscle paralysis. However, general anesthesia is not free of complications as the hemodynamic alterations related to intubation and laryngoscopy can also represent a risk to aneurysm integrity.[1]

Recently, Hurtado et al.[1] suggested the use of a second generation Supraglottic Airway Device (SAD) for endovascular treatment of unruptured intracranial aneurysms, showing it could represent a feasible alternative to endotracheal intubation in selected patients. While SADs have been proposed for several endovascular scenarios[2—4] and may be associated with a reduced hemodynamic response compared to laryngoscopy,[2] their benefits should be weighed against potential risks associated with the prolonged use of these devices, which include oropharyngeal edema and pneumonia.[5,6] The identification of patients at risk for prolonged mechanical[7] ventilation may be useful when choosing the appropriate airway device. The aim of this study was to identify risk factors for prolonged ventilation in patients undergoing endovascular treatment of unruptured intracranial aneurysm.

A retrospective cohort study was conducted, and the study protocol was in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee for Clinical Research of the Padova University Hospital (Chairman: Dr. Sergi, reference: AOP/0042595;16/07/2020). Informed consent was waived due to the retrospective nature of the study.

A retrospective review of the records of patients admitted to our teaching Hospital (University Hospital of Padua, Italy) undergoing endovascular treatment of unruptured intracranial aneurysms from April 1st, 2014, to May 30th, 2020 was performed.

We included only adult patients and therefore we did not include patients under 18 years of age.

The following data was collected: demographic information such as age (years), sex, American Society of Anesthesiologists Physical Status (ASA-PS) and data related to the aneurysm (aneurysm size, aspect ratio, dome/neck ratio, aneurysm location and type: saccular vs. fusiform), data related to the procedure (duration and type: coiling, assisted coiling, vessel occlusion, flow diverter), and need for prolonged ventilation identified by Intensive Care Unit (ICU) admission.

An a priori sample size was not calculated. Data for each continuous variable was analyzed for normal distribution using the Shapiro-Wilk test. Results for continuous variables with normal distributions were expressed as mean and standard deviation values; those with non-normal distributions were expressed as median and interquartile range values. Analysis of data with a normal or a non-normal distribution was performed using the two-tailed Student's *t*-test and the Mann-Whitney *U* test, respectively. The results for analyses of categorical variables were reported as percentages and were compared among groups using the Chi-Square test or the Fisher's exact test as appropriate. To determine the relationships between the dependent categorical variable (need for prolonged ventilation) and one or more independent categorical variables (need for prolonged ventilation predictors), we performed a multiple logistic regression analysis to calculate Odds Ratios (ORs) with 95% Confidence Intervals (95% CIs); to avoid overfitting, only variables with a *p*-value lower than 0.05 on univariate regression analysis were included in the multivariable logistic regression.

The Receiving Operator Curve (ROC) was performed on identified variables to show their robustness, with best cut-off points for prediction determined using the Youden index.

A total of 102 consecutive patients were included in our analysis. Eight of these patients (7.8%) required prolonged mechanical ventilation and were admitted to the ICU, while all the others were discharged from the Post-Anesthesia Care Unit to the neurosurgical ward on the same day of the angiographic procedure.

Characteristics of included patients are shown in Table 1, there was no missing data. Univariate analysis identified aneurysm location and procedure duration as risk factors for prolonged ventilation. Multiple logistic regression then confirmed duration as a significant predictor (OR = 1.04, 95% CI 1.02—1.05, *p*-value = 0.004). The ROC for procedure

https://doi.org/10.1016/j.bjane.2022.03.005

Table 1 Table showing characteristics of patients requiring prolonged ventilation (ICU admission group) and of patients not requiring prolonged ventilation (ward admission group).

	ICU admission (n = 8)	Ward admission (n = 94)	*p*-value
Patients' characteristics			
Age	49 (47–62.75)	55 (48–66)	0.525
Sex (Female) (%)	7 (87.5%)	72 (76.6%)	0.478
ASA-PS	2.5 (2–3)	2 (2–3)	0.381
Aneurysm characteristics			
Aneurysm dimension (mm)	7 (5.75–9)	7 (5–10.75)	0.940
Dome neck ratio	1.57 (1.19–1.68)	1.52 (1.22–1.85)	0.755
Aspect ratio	1.44 (1.41–1.60)	1.42 (1.16–2.05)	0.842
Sacciform (%)	7 (87.5%)	84 (89.4%)	0.870
Aneurysm location			
Anterior cerebral artery	0 (0.0%)	2 (2.1%)	0.038*
Middle cerebral artery	0 (0.0%)	5 (5.3%)	
Anterior communicating artery	1 (12.5%)	12 (12.8%)	
Posterior cerebral artery	1 (12.5%)	0 (0.0%)	
Basilar artery	0 (0.0%)	12 (12.8%)	
Internal carotid artery	6 (75.0%)	52 (55.3%)	
Pericallosal artery	0 (0.0%)	5 (5.3%)	
Vertebral artery	0 (0.0%)	6 (6.4%)	
Procedure characteristics			
Procedure length	185 (166.25–216.25)	120 (90–160)	0.002*
Procedure			
Assisted coiling	1 (12.5%)	21	0.717
Coiling	1 (12.5%)	16	
Flow diverter	6 (75.0%)	52	
Occlusion	0 (0.0%)	5 (5.3%)	

duration identified this variable as a good predictor for prolonged ventilation requiring ICU admission, with an area under the curve of 0.830 (95% CI 0.723–0.937) and best threshold identified at 137 minutes (Fig. 1).

Our study shows that endovascular treatment of unruptured aneurysms has a low rate of complications and confirms that a SAD approach is potentially feasible, considering the low percentage of patients requiring prolonged mechanical ventilation after the intervention.

Interestingly, the analyzed patient and aneurysm characteristics were not associated with prolonged ventilation requiring ICU admission, while procedure duration had a strong relationship. A possible explanation is that duration represents an indirect index of complexity and relates to the technical difficulty in completing the procedure. We identified 137 minutes as the best threshold, however, given the monocentric nature of the study, this threshold may be subject to variation across different centers.

As SAD in these procedures is conditional to the duration of the intervention, we suggest that technically complex procedures, potentially requiring longer operative times, may be safer to perform with endotracheal intubation. When the procedure is technically less complex and therefore duration is predicted to be short, SAD can be considered as an effective alternative.

Our study presents some limitations that need to be discussed. The first and main limitation is related to the retrospective and single center design of our study. Given the nature of the study, we cannot determine causality but only correlation among variables and future prospective studies are necessary to further investigate this topic. Secondly, we recognize that the sample size of our study is small and could

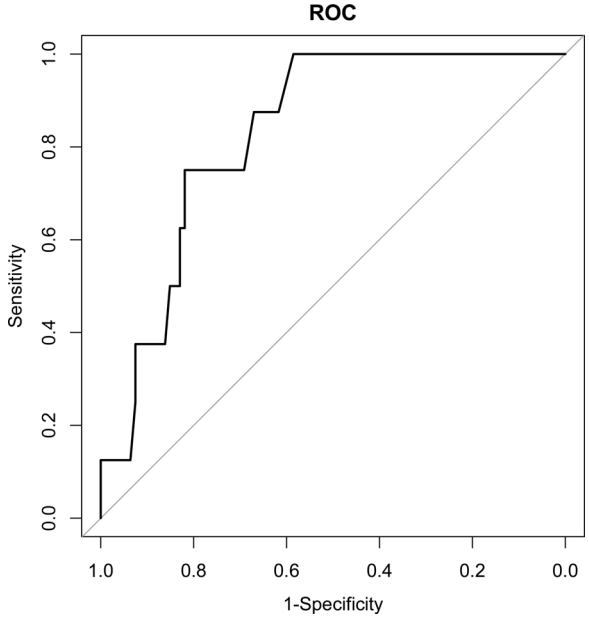


Figure 1 Need for ICU admission ROC curve (variable: procedure length). The ROC curve plots the true positive rate against the false positive rate at all procedure length values. The diagonal dotted line represents the reference line (AUC = 0.500).

be insufficient to detect all potentially relevant risk factors for prolonged mechanical ventilation.

We can conclude that procedure duration has a strong relationship with postoperative need for prolonged mechanical ventilation. In this framework, SADs could be considered as feasible for most patients undergoing endovascular treatment for unruptured intracranial aneurysms. However, for complex and time-consuming procedures, in our opinion endotracheal intubation has to be preferred given the risk of prolonged ventilation. Future prospective and multicentric studies are advisable to advance knowledge on this topic.

Fundings

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Hurtado P, Garcia-Orellana M, Amaro S, et al. Use of second generation supraglottic airway device for endovascular treatment of unruptured intracranial aneurysms: a retrospective cohort. Braz J Anesthesiol. 2021;26:S0104—0014(21)00165—2. https://doi.org/10.1016/j.bjane.2021.04.008.
2. Wood ML, Forrest ET. The haemodynamic response to the insertion of the laryngeal mask airway: a comparison with laryngoscopy and tracheal intubation. Acta Anaesthesiol Scand. 1994;38:510—3.
3. De Cassai A, Andreatta G, Gabrieli JD, Causin F, Boscolo A, Navalesi P, et al. Supraglottic airway device in acute ischemic stroke undergoing mechanical thrombectomy: is it feasible? World Neurosurg. 2020;139:179—81.
4. Golshevsky J, Cormack J. Laryngeal mask airway device during coiling of unruptured cerebral aneurysms. J Clin Neurosci. 2009;16:104—5.
5. Cook TM, Lee G, Nolan JP. The ProSeal laryngeal mask airway: a review of the literature. Can J Anaesth. 2005;52:739—60.
6. Munari M, Franzoi F, Sergi M, et al. Extensively drug-resistant and multidrug-resistant gram-negative pathogens in the neurocritical intensive care unit. Acta Neurochir (Wien). 2020. https://doi.org/10.1007/s00701-020-04611-3.
7. Munari M, De Cassai A, Sandei L, et al. Optimizing post anesthesia care unit admission after elective craniotomy for brain tumors: a cohort study. Acta Neurochir (Wien). 2021. https://doi.org/10.1007/s00701-021-04732-3.

Alessandro De Cassai [a,*], Federico Geraldini [a], Giacomo Cester[b], Sabrina Calandra[c], Massimiliano Caravello[a], Francesco Causin [b], Marina Munari[a]

[a] *University Hospital of Padova, Anesthesia and Intensive Care Unit, Padova, Italy*
[b] *University Hospital of Padova, Neuroradiology Unit, Padova, Italy*
[c] *University of Padova, Section of Anesthesiology and Intensive Care, Department of Medicine – DIMED, Padova, Italy*

[*] Corresponding author:
E-mail: alessandro.decassai@aopd.veneto.it (A. De Cassai).
Received 7 May 2021; accepted 12 March 2022
Available online 22 March 2022

Thank you, reviewers, for contributing to the BJAN's quality.

Your hard work is essential to our journal.

Ahmed Alshewered
Airton Bagatini
Alexandra Assad
Alexandre Martucci
Ana Maria Menezes Caetano
Breno Lima
Bruno Besen
Carlos Galhardo
Carlos Rodrigues Almeida
Catia Sousa Goveia
Clarissa Mendanha
Craig Slater
Cristiane Tavares
Daniel Kim
Daniel Negrini Medeiros
Daniel Perin
Deise Martins Rosa
Diogo Bruggemann da Conceição
Domingos Cicarelli
Durval Kraychete
Eder Reis
Eduarda Schütz Martinelli
Emiliana Mello
Enrique Aramburu Goytizolo
Eva Marquez Flores
Fabio De Vasconcelos Papa
Fatima Carneiro Fernandes
Florentino Fernandes Mendes
Gabriel Magalhaes Nunes Guimaraes
German Soto
Getulio R. de Oliveira Filho
Gilberto Braulio
Giorgio Pretto
Gisele Gribel
Glauber Gouvea
Guilherme Campos
Gustavo Ayala de Sa
Haili Zhu
Hugo Ribeiro
Isabela Sirtoli
Jairo Alberto Dussan-Sarria
Jijian Zheng
Joao Batista Santos Garcia
João M Silva-Jr
João Paulo Jordão Pontes
Josenilia Gomes
Kiyonobu Nishikawa
Leandro Da Costa Lane Valiengo
Leopoldo Muniz da Silva
Liana Maria Tôrres de Araújo Azi
Ligia Mathias
Lorena Ibiapina Mendes de Carvalho
Luc Vanlinthout
Luis Vicente Garcia
Luiz Marcelo Malbouisson
Marcelo Vaz Perez
Marcio Matsumoto
Maria Angela Tardelli
Maria Beatriz Duarte Gavião
María Fernanda Ramírez
Mariana Fontes Lima
Mariana Fragão-Marques
Mario da Conceição
Matheus Vane
Miriam Menezes
Mohamed Daffalla A. Gismalla
Nádia Maria da Conceição Duarte
Neuber Martins Fonseca
Paul H. Quax
Pauline Maciel August
Paulo Alipio Germano-Filho
Pedro Ferro Lima Menezes
Pedro Hilton Andrade Filho
Plínio da Cunha Leal
Raffael Zamper
Rodrigo Leal Alves
Rodrigo Lima
Rodrigo Pegado
Sergio Marques Borghi
Stefano Malaguti Ferreira
Thiago Gomes
Thiago Ramos Grigio
Tiago Manuel Horta Reis da Silva
Ursula Guirro
V. O. Ajuzieogu
Victor Sampaio de Almeida
Vinicius Caldeira Quintao
Virender K. Mohan
Waynice Paula-Garcia

BJAN

Brazilian Journal of Anesthesiology

Contact us

editor.bjan@sbahq.org www.bjan-sba.org +55 21 979 770 024