BJAN

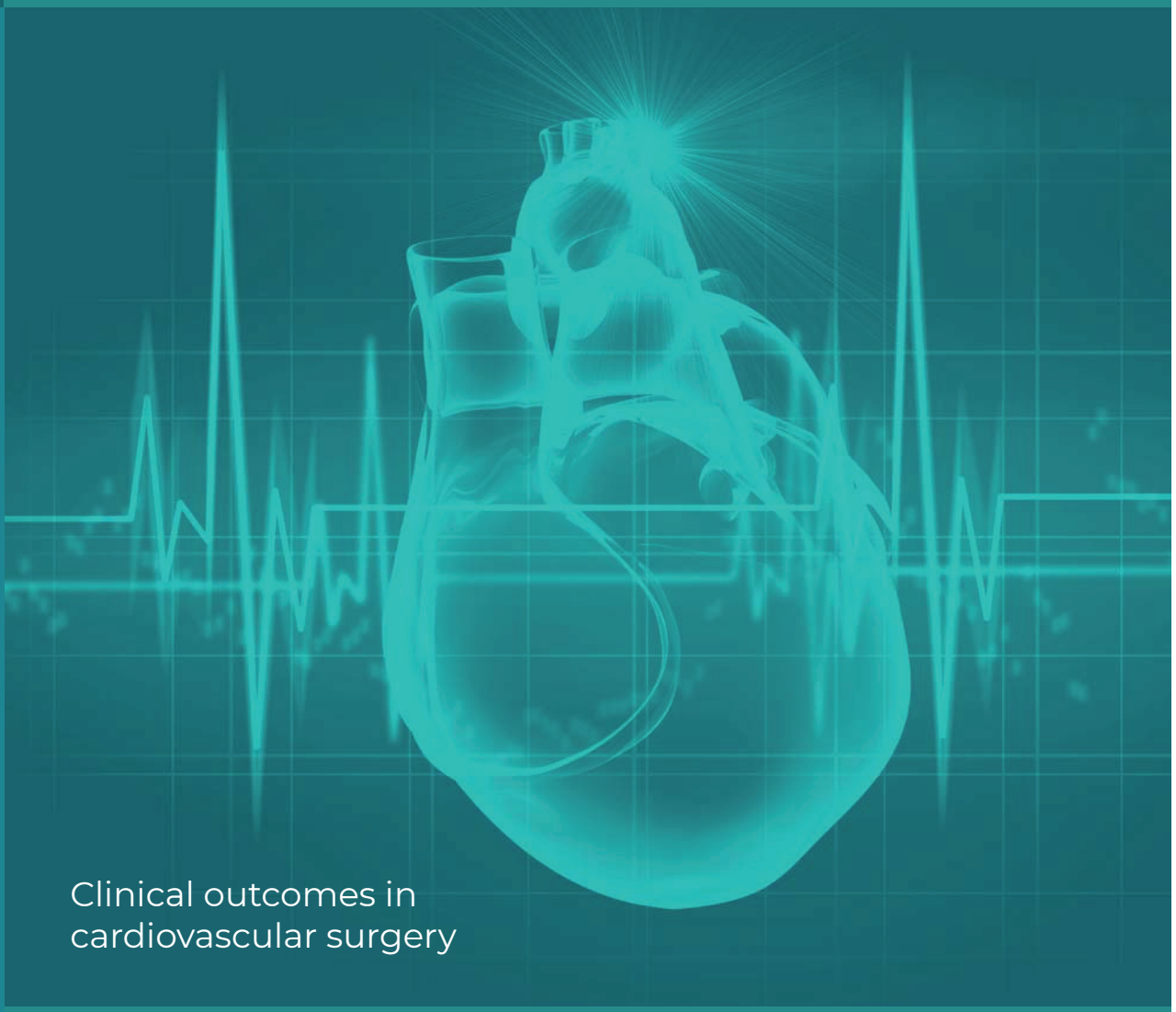
ELSEVIER

Vol. 74, N. 3 | May-June 2024 | ISSN 0104-0014

bjan-sba.org

BJAN
Brazilian Journal of Anesthesiology

Brazilian Journal of ANESTHESIOLOGY



Clinical outcomes in cardiovascular surgery

Brazilian Journal of Anesthesiology | Vol. 74 N. 3 | May/June 2024

SciELO

SBA Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

Editor-in-Chief
André Prato Schmidt - Universidade Federal do Rio Grande do Sul, Faculdade de Anestesia, Serviço de Anestesia e Medicina Perioperatória, Porto Alegre, RS, Brazil

Co-Editor
Rodrigo Leal Alves - Hospital São Rafael, Salvador, BA, Brazil

Associate Editors
Ana Maria Menezes Caetano - Universidade Federal de Pernambuco, Recife, PE, Brazil
Célio Gomes de Amorim - Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
Durval Campos Kraychete - Universidade Federal da Bahia, Salvador, BA, Brazil
Edmundo Pereira de Souza Neto - Centre Hospitalier de Montauban, Montauban, Tarn-et-Garonne, France
Eric Benedet Lineburger - Hospital São José, Criciúma, SC, Brazil
Florentino Fernandes Mendes - Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil
Gabriel Magalhães Nunes Guimarães - Universidade de Brasília, Brasília, DF, Brazil
Guilherme Antonio Moreira de Barros - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, Botucatu, SP, Brazil
João Manoel da Silva Júnior - Hospital do Servidor Público, São Paulo, SP, Brazil
José Otavio Costa Auler Junior - Faculdade de Medicina da Universidade de São Paulo São Paulo, SP, Brazil
Laís Helena Navarro e Lima - Queens University, Kinsgston, ON, Canada
Liana Maria Torres de Araújo Azi - Universidade Federal da Bahia, Salvador, BA, Brazil
Ligia Andrade da S. Telles Mathias - Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil
Lorena Ibiapina Mendes de Carvalho - Hospital Getúlio Vargas, Teresina, PI, Brazil
Luis Vicente Garcia - Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Luiz Guilherme Villares da Costa - Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
Luiz Marcelo Sá Malbouisson - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Luiz Marciano Cangiani - Hospital da Fundação Centro Médico Campinas, Campinas, SP, Brazil
Maria José Carvalho Carmona - Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Mariana Fontes Lima Neville - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Neuber Martins Fonseca - Faculdade de Medicina da Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
Norma Sueli Pinheiro Módolo - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, Botucatu, SP, Brazil
Oscar César Pires - Universidade de Taubaté, Taubaté, SP, Brazil
Paulo do Nascimento Junior - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, Botucatu, SP, Brazil
Priscilla Ferreira Neto Cardoso - Instituto da Criança HCFMUSP, São Paulo, SP, Brazil
Rodrigo Moreira e Lima - Queens University, Toronto, ON, Canada
Vanessa Henriques Carvalho - Universidade Estadual de Campinas, Campinas, SP, Brazil
Vinicius Caldeira Quintão - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Editorial Committee
Achal Dhir - London Health Sciences Centre, Western University, London, ON, Canada
Adrian Alvarez - Hospital Italiano de Buenos Aires, Buenos Aires, BA, Argentina
Adrian Gelb - University of California, San Francisco, CA, USA
Alexandra Rezende Assad - Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Alexis F. Turgeon - Université Laval, Québec, QC, Canada
Antônio Carlos Aguiar Brandão - Universidade do Vale do Sapucaí, Pouso Alegre, MG, Brazil
Ary Serpa Neto - Monash University, Melbourne, Australia
Bernd W. Böttiger - University Hospital of Cologne, Klinikum Köln, NW, Germany
Bobbie Jean Sweitzer - Northwestern Medicine, Chicago, IL, USA
Carlos Galhardo Júnior - Instituto Nacional de Cardiologia (INC/MS), Rio de Janeiro, RJ, Brasil
Carlos Manuel Correia Rodrigues de Almeida - Hospital CUF Viseu, Viseu, Beira Alta, Portugal
Catia Sousa Govêia - Universidade de Brasília, Brasília, DF, Brazil
Clarita Bandeira Margarido - Sunnybrook Health Sciences Care, Toronto, ON, Canada
Cláudia Marquez Simoes - Hospital Sírio Libanês, São Paulo, SP, Brazil
Claudia Regina Fernandes - Universidade Federal do Ceará, Fortaleza, CE, Brazil
Clovis Tadeu Bevilacqua Filho - Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
Clyde Matava - The Hospital for Sick Children, Toronto, ON, Canada
Cyril David Mazer - St. Michael's Hospital, Toronto, ON, Canada
dade de São Paulo, São Paulo, SP, Brazil
Daniel Cordovani - McMaster University, Hamilton, Canada
David Ferez - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Deborah Culley - Harvard University, Boston, MA, USA
Deepak K. Tempe - GB Pant Institute of Postgraduate Medical Education and Research, New Delhi, India
Edoardo Quareneghi - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, MI, Italy
Eduarda Schütz Martinelli - Toronto General Hospital, Toronto, ON, Canada
Eduardo Giroud Joaquim - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Eliane Cristina de Souza Soares - Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Emery Brown - Massachusetts Institute of Technology, Cambridge, MA, USA
Enrique A. Goytizolo - Hospital for Special Surgery (HSS), New York, NY, USA
Fabiana A. Penachi Bosco Ferreira - Universidade Federal de Goiás, Goiânia, GO, Brazil
Fábio Papa - University of Toronto, Toronto, ON, Canada
Federico Bilotta - Sapienza Università Di Roma, Roma, RM, Italy
Felipe Chiodini - Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Fernanda Bono Fukushima - Universidade Estadual Paulista, Botucatu, SP, Brazil
Fernando Abelha - Hospital de São João, Porto, Portugal
Filipe Nadir Caparica Santos - St. Michael's Hospital, Toronto, OK, Canada
Francisco A. Lobo - Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
Frederic Michard - MiCo, Consulting and Research, Denens, Switzerland
Getúlio Rodrigues de Oliveira Filho - Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
Gildásio de Oliveira Júnior - Alpert Medical School, Brown University, Providence, RI, USA
Giovanni Landoni - Vita-Salute San Raffaele University, Milano, LOM, Italy
Glauber Gouvêa - Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Glenio Bitencourt Mizubuti - Queen's University, Kingston, Canada
Gregory Hare - University of Toronto, Toronto, ON, Canada
Hazem Adel Ashmawi - Universidade de São Paulo, São Paulo, SP, Brazil
Ismar Lima Cavalcanti - Universidade Federal Fluminense, Niterói, RJ, Brazil
Jean-Jacques Rouby - Pierreand Marie Curie University, Paris, France
Jean-Louis Teboul - Paris-Sud University, Paris, France
Jean-Louis Vincent - Université Libre De Bruxelles, Bruxelles, Belgium
Jean-Michael Constantin - La Pitié Salpetriere Hospital, University Paris-Sorbonne, Paris, France
Joana Berger-Estilita - University of Bern, Bern, Switzerland
João Batista Santos Garcia - Universidade Federal do Maranhão, São Luís, MA, Brazil
João Paulo Jordão Pontes - Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
José Carlos Rodrigues Nascimento - Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil
Judymara Lauzi Gozzani - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Kurt Ruetzler - Cleveland Clinic, Cleveland, OH, USA
Laszlo Vutskits - Geneva University Hospitals, Geneve, GE, Switzerland
Leandro Gobbo Braz - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, Botucatu, SP, Brazil
Leonardo Henrique Cunha Ferraro - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Leopoldo Muniz da Silva - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, Botucatu, SP, Brazil
Luciana Paula Cadore Stefani - Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Luciano Gattinoni - University of Göttingen, Göttingen, Germany
Luis Antonio dos Santos Diego - Universidade Federal Fluminense, Niterói, RJ, Brazil
Luiz Fernando dos Reis Falcão - Universi
Luiz Guilherme Villares da Costa - Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
Luiz Marciano Cangiani - Hospital da Fundação Centro Medico Campinas, Campinas, SP, Brazil
Marcelo Gama de Abreu - University Hospital Carl Gustav Carus, Dresden, SN, Germany
Márcio Matsumoto - Hospital Sírio Libanês, São Paulo, SP, Brazil
Marcos Antônio Costa de Albuquerque - Universidade Federal de Sergipe, São Cristóvão, SE, Brazil
Marcos Francisco Vidal Melo - Harvard University, Boston, MA, USA
Maria Angela Tardelli - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Mariana Fontes Lima Neville - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Mário Jose da Conceição - Fundação Universidade Regional de Blumenau, Blumenau, SC, Brazil
Massimiliano Sorbello - AOU Policlinico Vittorio Emanuele, Catania, SIC, Italy
Matheus Fachini Vane - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Mônica Maria Siaulys - Hospital e Maternidade Santa Joana, São Paulo, SP, Brazil
Nádia Maria da Conceição Duarte - Universidade Federal de Pernambuco, Recife, PE, Brazil
Neuber Martins Fonseca - Faculdade de Medicina da Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
Nicola Disma - Istituto Giannina Gaslini, Genova, GE, Italy
Oscar Cesar Pires - Universidade de Taubate, Taubate, SP, Brazil
Paulo Alípio - Universidade Federal Fluminense, Niterói, RJ, Brazil
Pedro Amorim - Centro Hospitalar e Universitário do Porto, Porto, Portugal
Pedro Francisco Brandão - Universidade Federal do Espírito Santo, Vitória, ES, Brazil
Peter D. Slinger - University of Toronto, Toronto, ON, Canada
Philip Peng - University of Toronto, Toronto, ON, Canada
Plínio da Cunha Leal - Hospital São Domingos, São Luís, MA, Brazil
Priscilla Ferreira Neto Cardoso - Instituto da Criança HCFMUSP, São Paulo, SP, Brazil
Raffael Pereira Cezar Zamper - London Health Science Center, London, UK
Rajinder K. Mirakhur - Royal Hospital, Belfast, Northern Ireland, UK
Ricardo Antônio Guimarães Barbosa - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Ricardo Vieira Carlos - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Roberto Fumagalli - Università degli studi Milano Bicocca, Milano, MI, Italy
Rodrigo Lima - Queens University, Toronto, ON, Canada
Rogean Rodrigues Nunes - Centro de Ensino e Treinamento/SBA (Residência Medica) em Anestesiologia do Hospital Geral de Fortaleza, Fortaleza, CE, Brazil
Ronald Miller - University of California, San Francisco, CA, USA
Sara Lucia Ferreira Cavalcante - Hospital Geral do Inamps de Fortaleza, Fortaleza, CE, Brazil
Thais Cançado - Serviço de Anestesiologia de Campo Grande, Campo Grande, MS, Brazil
Thomas Engelhardt - Montreal Children's Hospital, Mcgill University, Montreal, Canada
Waynice Paula-Garcia - Universidade de São Paulo, São Paulo, SP, Brazil
Wolnei Caumo - Universidade do Rio Grande do Sul, Porto Alegre, RS, Brazil

Previous Editors-in-Chief
Oscar Vasconcellos Ribeiro (1951-1957)
Zairo Eira Garcia Vieira (1958-1964)
Bento Mário Villamil Gonçalves (1965-1979)
Masami Katayama (1980-1988)
Antônio Leite Oliva Filho (1989-1994)
Luiz Marciano Cangiani (1995-2003)
Judymara Lauzi Gozzani (2004-2009)
Mario José da Conceição (2010-2015)
Maria Angela Tardelli (2016-2018)
Maria José Carvalho Carmona (2019-2021)

Editorial Office
Managing Editor: Mel Ribeiro
Marketing Analyst: Thadeu de Moraes Carvalho
Librarian (BJAN): Marcelly Ramos
Librarian (SBA): Pedro Saldanha

The Brazilian Journal of Anesthesiology (BJAN) is the official journal of Sociedade Brasileira de Anestesiologia (SBA). The BJAN only accepts original articles for publication submitted and 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 Anesthesiology (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

© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. All rights reserved.

69°CBA

BRAZILIAN CONGRESS OF ANESTHESIOLOGY

The 69th Brazilian Congress of Anesthesiology is the official meeting of Brazilian anesthesiology and is set to take place in November in the capital of Minas Gerais state, Belo Horizonte. As Brazil's sixth-largest city, Belo Horizonte offers a blend of stunning scenery, top-level cuisine, and a vibrant cultural history.

November 13-16

MINAS CENTRO
BELO HORIZONTE, MG

Organization
Brazilian Society of Anesthesiology



We have invited the best professionals to CBA 2024, yourself included.

An up-to-date scientific program is being developed, and includes more than 20 international speakers and various activities.

- Albert Perrino
- Alexis Turgeon
- Burkhard Mackensen
- Carlos Galhardo
- Carolina Haylock-Loor
- Concezione Tommasino
- Emilia Guasch
- Federico Bilotta
- Freddy Espinoza
- Jean Michel Constantin
- Joana Berger-Estilita
- Konstantinos Alexopoulos
- Rodrigo Sosa Argaña
- Ronald L. Harter
- Ruth Landau
- Sayda Godínez
- Sonja Payne
- Vincent Bonhomme
- Daniela Filipescu
- Lawrence Tsen

MORE INFO: WWW.CBA2024.COM.BR

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

ISSN 0104-0014 • Volume 74 • Number 3 • May—June 2024

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.

Editorial

844504 **Anemia and outcomes in cardiac surgery**
Luiz Guilherme V. da Costa, Fabio V. Papa, Gregory M.T. Hare, Marcello F. Salgado-Filho, Eric B. Lineburger, and André P. Schmidt

Original Investigations

744424 **The association of hemoglobin with postoperative delirium and atrial fibrillation after cardiac surgery: a retrospective sub-study**
Sinem Sari, Jack Brooker, Mateo Montalvo-Campana, Peter Shehata, Xuan Pu, Steven Insler, Kurt Ruetzler, Christopher A. Troianos, and Alparslan Turan

844501 **Apelin-13 reverses bupivacaine-induced cardiotoxicity: an experimental study**
Xixi Cai, Le Liu, Fangfang Xia, Thomas J. Papadimos, and Quanguang Wang

744471 **Cross-cultural adaptation and validation of the Iowa Satisfaction with Anesthesia Scale for use in Brazil: a cross-sectional study**
Nicole Morem Pilau Moritz, José Eduardo Moritz, Gabriel Oscar Cremona Parma, Franklin Dexter, and Jefferson Traebert

744453 **Evaluation of the relationship between the STOP-Bang score with oxygen reserve index and difficult airway: a prospective observational study**
Ilka D. Alp, Bengü G. Köksal, Keziban Bollucuoğlu, Gamze Küçükosman, Özcan Pişkin, Çağdaş Baytar, Rahşan D. Okyay, and Hilal Ayoğlu

744456 **Decreasing inconsistent alarms notifications: a pragmatic clinical trial in a post-anesthesia care unit**
Saullo Queiroz Silveira, Rafael Sousa Fava Nersessian, Arthur de Campos Vieira Abib, Leonardo Barbosa Santos, Fernando Nardy Bellicieri, Karen Kato Botelho, Helidea de Oliveira Lima, Renata Mazzoni de Queiroz, Gabriel Silva dos Anjos, Hermann dos Santos Fernandes, Glenio B. Mizubuti, Joaquim Edson Vieira, and Leopoldo Muniz da Silva

744423 **CYP2D6 isoenzyme and ABCB1 gene polymorphisms associated with postoperative nausea and vomiting in women undergoing laparoscopic cholecystectomy: a randomized trial**
Angela Henrique Silva Ribeiro, Estêvão Luiz Carvalho Braga, Nathalia de Araújo Gouveia Ferreira, Beni Olej, Nubia Verçosa, Leonardo dos Santos Antunes, and Ismar Lima Cavalcanti

744454 **Association of antimicrobial use and incidence of hospital-acquired pneumonia in critically ill trauma patients with pulmonary contusion: an observational study**
Estevão Bassi, Camila Trevizani Merighi, Carlos Issamu Tomizuka, Thais Guimarães, Fernando da Costa Ferreira Novo, Sergio Henrique Bastos Damous, Edivaldo Massazo Utiyama, and Luiz Marcelo Sá Malbouisson

744431 **Impact of withholding early antibiotic therapy in nonseptic surgical patients with suspected nosocomial infection: a retrospective cohort analysis**
Estevão Bassi, Bruno Martins Tomazini, Bárbara Vieira Carneiro, Amanda Rodrigues de Oliveira Siqueira, Sara Rodrigues de Oliveira Siqueira, Thais Guimarães, Fernando da Costa Ferreira Novo, Edivaldo Massazo Utiyama, Paolo Pelosi, and Luiz Marcelo Sá Malbouisson

844495 **Comparison of terbutaline and atosiban as tocolytic agents in intrauterine repair of myelomeningocele: a retrospective cohort study**
Shirley Andrade Santos, Fernando Souza Nani, Elaine Imaeda de Moura, Diogo Lima de Carvalho, Guilherme Jorge Mattos Miguel, Cristiane Maria Federicci Haddad, Joaquim Edson Vieira, Victor Bunduki, Mário Henrique Burlacchini de Carvalho, Rossana Pulcineli Vieira Francisco, Daniel Dante Cardeal, and Hermann dos Santos Fernandes

844502 **The effect of low dose intra-articular S(+) ketamine on osteoarthritis in rats: an experimental study**
Eugênio dos Santos Neto, Pedro Paulo de Alcantara Pedro, Maria do Socorro de Sousa Cartágenes, José Osvaldo Barbosa Neto, and João Batista Santos Garcia

Review Article

744446 **Does dexmedetomidine reduce the risk of acute kidney injury after cardiac surgery? A meta-analysis of randomized controlled trials**
Chunxiao Zhao, Shuo Liu, Huiquan Zhang, and Mengqi Gao

Letters to the Editor

744472 **The impact of early feeding on optimizing gastrointestinal recovery after cesarean section: a non-randomized, open-label, clinical trial**
Graziela Cyntia Silva Santos, Glaucevane da Silva Guedes, Alane Cabral Menezes de Oliveira, and Fabiana Andrea Moura

Brazilian Journal of Anesthesiology 2024;74(3): 844504



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Anemia and outcomes in cardiac surgery



In patients eligible for cardiac surgery, the prevalence of anemia ranges from 16% to 54%, with severe cases (hemoglobin < 10 g.dL^{-1}) affecting 5.5% of individuals. Perioperative anemia significantly elevates the risk of morbidity, mortality, and organic dysfunction.[1] Over recent decades, numerous studies have emerged to explore optimal blood transfusion strategies, determine the most effective transfusion triggers, and establish safe hemoglobin thresholds across diverse patient population.[2,3]

One of the most relevant studies in this context was the TRICC Trial,[4] a randomized clinical trial (RCT) involving 838 euvolemic patients. The study encompassed a diverse population with hemoglobin levels < 9 g.dL^{-1} within 72 hours of admission to the critical care unit. This groundbreaking work challenged the liberal transfusion logic in force at the time, comparing a restrictive transfusion trigger arm (hemoglobin < 7 g.dL^{-1}) to a liberal arm (hemoglobin < 10 g.dL^{-1}). The incidences of myocardial infarction and acute pulmonary edema were statistically lower in the restrictive group. The study concluded that a more restrictive transfusion strategy proved to be at least as effective, if not superior, to the liberal strategy in critically ill patients, except for mortality in the subgroup of patients with cardiovascular disease.

In 2016, Carson et al[3] published guidelines that revisited 31 RCTs, advocating for more restrictive transfusion trigger recommendations with hemoglobin levels < 7 g.dL^{-1} for the general population and 8 g.dL^{-1} for orthopedic patients, those undergoing cardiac surgery, and individuals with cardiovascular diseases.[5] However, the guidelines did not include patients with acute coronary syndromes and emphasized the need for additional research concerning patients with acute myocardial infarction.

In 2018, a systematic review comprising 37 RCTs investigated mortality as the primary outcome among individuals undergoing cardiac surgery.[6] This study concluded that hemoglobin levels between 7 and 8 g.dL^{-1} served as a safe transfusion trigger for the evaluated population compared to more liberal triggers. This approach also led to a reduction in the transfusion rate by 24%.

In 2018, another important noninferiority RCT (TRICS-III)[7] was published. This study compared a restrictive transfusion trigger (hemoglobin < 7.5 g.dL^{-1}) with a liberal trigger (hemoglobin < 9.5 g.dL^{-1} in the ICU or < 8.5 g.dL^{-1} in the ward) in patients undergoing cardiac surgery, particularly those with moderate and high risk of death. The primary outcome analyzed was a composite of overall mortality, acute myocardial infarction, stroke, or kidney disease requiring new-onset replacement therapy within six months post-surgery. The authors concluded that the restrictive strategy was noninferior to the liberal strategy group concerning the primary outcome.

In 2021, Ducrocq et al[8] conducted a noninferiority RCT in France and Spain, which was open-label and involved patients with acute myocardial infarction and hemoglobin levels ranging between 7 and 10 g.dL^{-1}. Patients were divided into two arms: the restrictive group had a transfusion trigger of hemoglobin < 8 g.dL^{-1} with a target between 8 and 11 g.dL^{-1}, while the liberal group had a transfusion trigger of hemoglobin < 10 g.dL^{-1} with a target above 11 g.dL^{-1}. The main objective of the study was a composite outcome of major cardiovascular complications (MACE), including death, stroke, recurrent acute myocardial infarction, or emergency revascularization. Once again, this study demonstrated the noninferiority of the restrictive group compared to the liberal group. However, an important limitation of this study was the wide lower margin of noninferiority, which could potentially encompass actual harm to patients. Additionally, the study had limited power to detect the superiority of one strategy over the other.

A recent meta-analysis from 2023,[9] which encompassed RCTs[10–12] enrolling patients with acute coronary syndrome, did not reveal a statistically significant difference between the liberal and restrictive strategies concerning outcomes such as mortality, acute myocardial infarction, revascularization, and the composite outcome of these events.

Similarly, in 2023, the Red Blood Cell Transfusion 2023 AABB International Guidelines[13] were published, reviewing 45 RCTs. These guidelines recommended a hemoglobin trigger of 7 g.dL^{-1} for hospitalized and stable patients,

https://doi.org/10.1016/j.bjane.2024.844504
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

7.5 g.dL^{-1} for patients undergoing cardiac surgery, and 8 g.dL^{-1} for orthopedic patients and those with previous cardiovascular comorbidities. However, there was a low level of evidence for transfusion recommendations in patients with acute myocardial infarction.

To address this issue, the MINT (Myocardial Ischemia and Transfusion) trial[14] was designed. This multicenter study aimed to shed light on the matter by enrolling patients with acute myocardial infarction. Participants were divided into two arms: one with a transfusion cutoff strategy of 7–8 g.dL^{-1} of hemoglobin, and another more liberal arm with a hemoglobin cutoff < 10 g.dL^{-1}. The primary outcome was a composite of recurrent acute myocardial infarction and death. The study found no statistical difference between the two arms. However, the authors expressed uncertainty about ruling out the harmful effects of the restrictive strategy. Subsequently, a Bayesian analysis was published, demonstrating the potential harm associated with the restrictive strategy in this population.[3]

Perioperative anemia may impact outcomes concerning multiple target organs, including the heart, kidneys, and central nervous system. Karkouti et al[2] addressed the association between anemia and the development of renal dysfunction, underscoring the significance of preoperative hemoglobin optimization in mitigating high mortality rates in cardiac surgery. Furthermore, red blood cell transfusions seem to be implicated in this outcome, attributed to factors such as the reduction in levels of 2,3-DPG, pro-inflammatory effects, leukocyte activation, and coagulation activation.[2]

Interestingly, in this issue of the *Brazilian Journal of Anesthesiology*, Sari et al[15] published an innovative retrospective subanalysis of the DECADE trial.[16] This study revealed no statistically significant association between various hemoglobin levels and delirium or atrial fibrillation in patients undergoing cardiac surgery. This conclusion was further supported by a robust Cox regression analysis, which was adjusted for clinically relevant variables.

Notably, there is an ongoing international multicenter randomized controlled trial focusing on transfusion thresholds in younger cardiac surgery patients. Known as TRICS-IV,[17] this open-label randomized controlled trial compares two commonly employed transfusion strategies in moderate to high-risk patients aged 65 years or younger who are undergoing cardiac surgery with cardiopulmonary bypass. It employs a superiority trial design and aims to enroll approximately 1,440 patients. The study tests the hypothesis that liberal transfusion is superior for younger patients undergoing cardiac surgery, based on previous evidence generated by subgroup analyses from the TRICS III trial.[7] The primary hypothesis suggests that maintaining a higher hemoglobin concentration for red blood cell transfusion (liberal transfusion strategy) will yield better outcomes compared to a restrictive strategy in terms of vital organ function (specifically the heart, brain, and kidneys) and lower mortality rates six months post-cardiac surgery. Hence, this study holds the potential to provide valuable new evidence in this field.

In summary, understanding key aspects of perioperative anemia is essential to guide professionals in making transfusion decisions in cardiac surgery. This entails considering the balance between risks and benefits, as well as the associated costs, with the ultimate goal of mitigating morbidity and mortality in this vulnerable population.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Loor G, Koch CG, Sabik JF, Li L, Blackstone EH. Implications and management of anemia in cardiac surgery: current state of knowledge. J Thorac Cardiovasc Surg. 2012;144:538–46.
2. Karkouti K, Wijeysundera DN, Beattie WS. Reducing Bleeding in Cardiac Surgery (RBC) Investigators. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation. 2008;117:478–84.
3. Khan MS, Spertus JA, Chan PS. Transfusion Strategy in Myocardial Infarction and Anemia. N Engl J Med. 2024;390:960–1.
4. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409–17.
5. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316:2025–35.
6. Carson JL, Stanworth SJ, Alexander JH, et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J. 2018;200:96–101.
7. Mazer CD, Whitlock RP, Fergusson DA, et al. Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery. N Engl J Med. 2018;379:1224–33.
8. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients with Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. JAMA. 2021;325:552–60.
9. Mistry N, Hare GMT, Shehata N, et al. Transfusion Thresholds for Acute Coronary Syndromes-Insights From the TRICS-III Randomized Controlled Trial, Systematic Review, and Meta-Analysis. J Am Heart Assoc. 2023;12:e028497.
10. Gonzalez-Juanatey JR, Lemesle G, Puymirat E, et al. One-Year Major Cardiovascular Events After Restrictive Versus Liberal Blood Transfusion Strategy in Patients with Acute Myocardial Infarction and Anemia: The REALITY Randomized Trial. Circulation. 2022;145:486–8.
11. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol. 2011;108:1108–11.
12. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013;165:964–971.e1.
13. Carson JL, Stanworth SJ, Guyatt G, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. JAMA. 2023;330:1892–902.
14. Carson JL, Brooks MM, Hébert PC, et al. Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. N Engl J Med. 2023;389:2446–56.
15. Sari S, Brooker J, Montalvo-Campana M, et al. The association of hemoglobin with postoperative delirium and atrial fibrillation after cardiac surgery: a retrospective sub-study. Braz J Anesthesiol. 2023. https://doi.org/10.1016/j.bjane.2023.02.003. Online ahead of print.
16. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet Lond Engl. 2020;396:177–85.

17. An International, Multi-centre, Randomized Controlled Trial to Assess Transfusion Thresholds in Younger Patients Undergoing Cardiac Surgery. Identifier NCT04754022. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT04754022 (accessed 2024-04-20).

Luiz Guilherme V. da Costa [a,*], Fabio V. Papa[b], Gregory M. T. Hare[b], Marcello F. Salgado-Filho[a], Eric B. Lineburger[c,d,e], André P. Schmidt[f,g,h,i,j,k]

[a] *Hospital Israelita Albert Einstein, Departamento de Anestesiologia, São Paulo, SP, Brazil*

[b] *University of Toronto, St. Michael's Hospital, Department of Anaesthesia, Toronto, Canada*

[c] *Hospital São José, Departamento de Anestesia e Tratamento da Dor, Criciúma, SC, Brazil*

[d] *Hospital São José, Centro de Pesquisa, Criciúma, SC, Brazil*

[e] *Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil*

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

[g] *Santa Casa de Porto Alegre, Serviço de Anestesia, Porto Alegre, RS, Brazil*

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

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

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

[k] *Programa de Pós-Graduação em Anestesiologia, Ciências Cirúrgicas e Medicina Perioperatória, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil.*

[*] Corresponding author.
E-mail: lgvc76@yahoo.com.br (L.G. Costa).

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

The association of hemoglobin with postoperative delirium and atrial fibrillation after cardiac surgery: a retrospective sub-study

Sinem Sari[a,b], Jack Brooker[a], Mateo Montalvo-Campana[a], Peter Shehata[c], Xuan Pu[d], Steven Insler[e], Kurt Ruetzler[a,c], Christopher A. Troianos[f], Alparslan Turan[a,c,*]

[a] *Cleveland Clinic, Anesthesiology Institute, Department of Outcomes Research, Cleveland, Ohio*
[b] *Adnan Menderes University, Department of General Anesthesiology, Aydın, Turkey*
[c] *Cleveland Clinic, Anesthesiology Institute, Department of General Anesthesiology, Cleveland, Ohio*
[d] *Cleveland Clinic, Department of Quantitative Health Sciences, Cleveland, Ohio*
[e] *Cleveland Clinic, Anesthesiology Institute, Department of Intensive Care & Resuscitation, Cleveland, Ohio*
[f] *Cleveland Clinic, Anesthesiology Institute, Cleveland, Ohio*

Received 2 May 2022; accepted 26 February 2023
Available online 8 March 2023

KEYWORDS
Anemia;
Delirium;
Atrial fibrillation;
General anesthesia;
Cardiac surgery

Abstract

Background: Most cardiac surgery patients experience postoperative anemia. Delirium and Atrial Fibrillation (AF) are common and independent predictors of morbidity and mortality. Few reports examine their association with postoperative anemia. This study aims to quantify the association between anemia and these outcomes in patients undergoing cardiac surgery.

Methods: This post-hoc analysis of the DECADE randomized controlled trial ran at six academic US hospitals. Patients aged 18—85 years with heart rate > 50 bpm undergoing cardiac surgery who had daily hemoglobin measurements in the first 5 Postoperative Days (POD) were included. Delirium was assessed twice daily with the Confusion Assessment Method for the ICU (CAM — ICU), preceded by the Richmond Agitation and Sedation Scale, with patients excluded from assessment if sedated. Patients had daily hemoglobin measurements, continuous cardiac monitoring plus twice-daily 12-lead electrocardiograms, up to POD4. AF was diagnosed by clinicians blinded to hemoglobin levels.

Results: Five hundred and eighty-five patients were included. Mean postoperative hemoglobin Hazard Ratio (HR): 0.99 (95% CI 0.83, 1.19; p = 0.94) per 1 g.dL^{-1} hemoglobin decrease. 197 (34%) developed AF, mainly on POD = 2.3. Estimated HR = 1.04 (95% CI 0.93, 1.17; p = 0.51) per 1 g.dL^{-1} hemoglobin decrease.

Conclusions: Most patients undergoing major cardiac surgery were anemic in the postoperative phase. AF and delirium occurred in 34% and 12% of patients, respectively, but neither were significantly correlated with postoperative hemoglobin.

* Corresponding Author.
E-mail: turana@ccf.org (A. Turan).

https://doi.org/10.1016/j.bjane.2023.02.003
0104-0014/© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Over 900,000 cardiac procedures are performed annually in the United States and with an ageing population this number is projected to rise considerably.[1] Delirium and Atrial Fibrillation (AF) are common complications of cardiac surgery with an incidence of up to 87% for delirium and 65% for AF.[2,3] Delirium is an acute onset of disturbed consciousness and cognitive ability, and is associated with an increased risk of death, Intensive Care Unit (ICU) length of stay, and hospital length of stay. Postulated mechanisms for the development of postoperative delirium include inflammation and hypoxia during the surgery itself as well as anesthetic and analgesia side effects (particularly volatile anesthetic gases and opioids).[4,5]

The incidence of anemia ranges from 5% to 75.8% in patients undergoing non-emergent surgical procedures with variation attributed to the particular study population and diagnostic criteria.[6-8] According to the World Health Organization (WHO) definition of anemia (< 13 g.dL^{-1} for males, $<$ 12 g.dL^{-1} for females), the incidence can be as high as 80 −90%.[9] Factors contributing to anemia include surgical blood loss, hemodilution from intravenous infusions and blunted postsurgical erythropoiesis due to inflammation.[10] Additionally, many surgical patients may have preoperative anemia due to nutritional deficiencies, hemorrhage in the case of trauma or due to chronic disease states.[10] Anemia leads to end organ dysfunction, presumably due to poor tissue perfusion arising from the reduced oxygen carrying capacity of blood when in the anemic state. Anemia is associated with poor postoperative outcomes including increased mortality, acute kidney injury, stroke, and infection.[11] The association between delirium and perioperative anemia is intuitive and biologically plausible, but presently the association remains unclear with relatively little published literature.

Postoperative AF is associated with increased in-hospital and long-term mortality, stroke, hospital length of stay and increased healthcare costs.[2,12,13] Possible mechanisms include myocardial inflammation, perioperative catecholamine release as part of the surgical stress response, mechanical injury, atrial dilation due to intraoperative volume overload and ischemia.[2,14-16] Given the possible role of atrial or global cardiac ischemia in the development of postoperative AF, there is a plausible link between perioperative anemia and postoperative AF. However, as with perioperative delirium, there is a lack of published evidence quantifying this link and current evidence is inconsistent.

This retrospective post-hoc analysis of a completed Randomized Controlled Trial (RCT) is designed to further quantify and characterize the association between perioperative anemia and the development of postoperative delirium and AF. Specifically, we tested the primary hypothesis that low hemoglobin levels are associated with postoperative delirium. Secondarily, we tested the hypothesis that low hemoglobin levels are associated with atrial fibrillation during the five postoperative days after cardiac surgery.

Methods

Study design and participants

This retrospective post-hoc analysis is a sub-study of the published DECADE trial (NCT02004613), which enrolled 798 participants at six academic centers in the United States.[17] Centers included three Cleveland Clinic centers including the main campus, Ohio State Wexner Medical Center, Northwestern University Medical Center, and UCLA Medical Center. The primary objective of the DECADE study was to assess the efficacy of dexmedetomidine in preventing AF and delirium in patients undergoing cardiac surgery. Patients aged 18−85 years who were scheduled for cardiac surgery with cardiopulmonary bypass and who had heart rates $\geq$ 50 beats per min were included.

Only patients in the DECADE trial treated in the Cleveland Clinic system were considered and only patients who had daily hemoglobin measurement after the surgery were enrolled in this analysis. Since 10 (1.7%) patients were missing on delirium and 2 (0.3%) patients missing on confounders after complete case analysis, we simply excluded them from our study population (Fig. 1). The study protocol and data utilization were approved by the Cleveland Clinic Foundation's Institutional Review Board.

Measurements

Patients in the cardiac ICU had continuous electrocardiographic monitoring. The diagnosis of atrial fibrillation in the cardiac ICU was made by clinicians masked to group allocation. Additionally, patients had twelve-lead Electrocardiograms (ECG) morning and evening for the first five postoperative days or until hospital discharge if sooner. A cardiologist or anesthesiologist masked to randomized group allocations diagnosed AF based upon the ECG. Atrial fibrillation was defined by: clinician diagnosis with documented arrhythmia lasting at least 5 min in monitored patients or the presence of arrhythmia on ECGs in unmonitored patients.

Delirium assessments were preceded by a Richmond Agitation and Sedation Scale to assess sedation.[18] Delirium was only assessed if Richmond Agitation and Sedation Scale scores were not −4 or −5, indicating insufficient alertness. Confusion Assessment Method for the ICU (CAM-ICU) evaluations were done in person by formally trained masked research physicians for the initial 5 postoperative days as long as patients remained hospitalized. Morning assessments were done before 10:00, and evening assessments after 17:00. Nurses, independent of research physicians' evaluation, also assessed CAM-ICU daily and described patients' mental status in their notes. Patients were considered to have had delirium if one or more CAM-ICU assessments by investigators or nurses were positive, or if there was clear indication of delirium in written nursing evaluations.

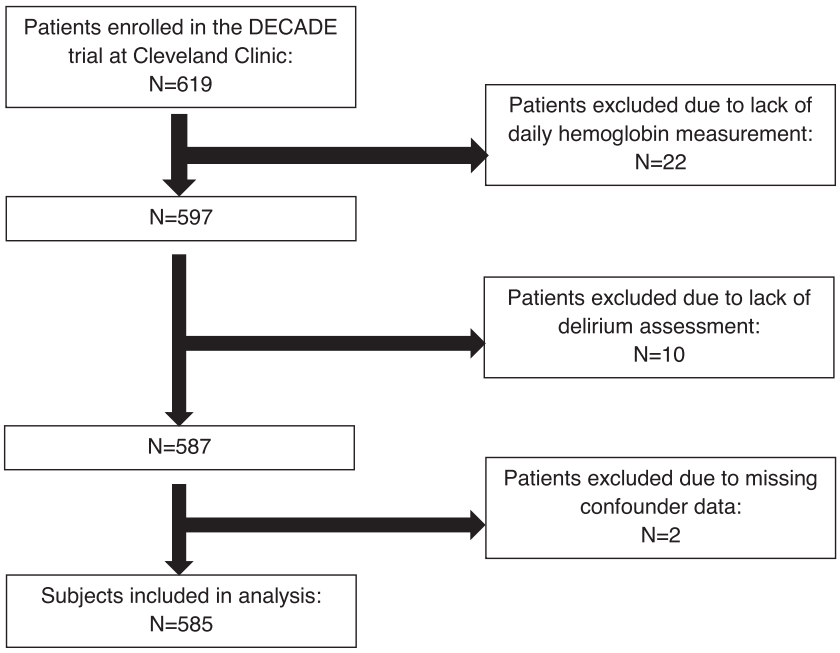


Figure 1 Description of the screening and subject selection process for this post-hoc analysis of the DECADE trial.

Exposure and confounders

Our exposure of interest was daily lowest hemoglobin from day of surgery until hospital discharge or postoperative day 4, whichever came first. Confounders were adjusted in all multivariable analyses including demographic, medical history, intraoperative and surgery characteristics (Table 1).

All the data was available in the original trial and only one medical history variable was obtained from our database.

Table 1 Baseline and demographic characteristics by postoperative lowest Hgb levels before event (n = 585).

Factor	< 8 g.dL^{-1} (n = 153)	8–11 g.dL^{-1} (n = 378)	≥ 11 g.dL^{-1} (n = 54)	ASD
Age, year	63 ± 11	63 ± 11	59 ± 11	0.36
Female	63 (41)	112 (30)	7 (13)	0.67
ASA physical status				0.06
I–III	30 (20)	76 (20)	12 (22)	
IV–V	123 (80)	302 (80)	42 (78)	
White	138 (90)	362 (96)	51 (94)	0.22
BMI, kg.m^{-2}	29 ± 10	29 ± 5	30 ± 10	0.15
Comorbidities				
History of stroke or TIA	14 (9.2)	12 (3.2)	3 (5.6)	0.25
Diabetes	49 (32)	74 (20)	5 (9.3)	0.59
Pulmonary disease	21 (14)	49 (13)	4 (7.4)	0.21
Kidney disease	25 (16)	23 (6.1)	4 (7.4)	0.33
Surgery duration, hour	6.2 [5.2, 7.5]	5.5 [4.7, 6.6]	4.9 [4.4, 5.8]	0.89
Surgical type				0.68
Valve/Aorta only	59 (39)	230 (61)	38 (70)	
CABG only	2 (1)	5 (1)	0 (0)	
CABG + Valve/Aorta	92 (60)	143 (38)	16 (30)	
Blood loss, mL	250 [0, 250]	250 [0, 250]	250 [0, 250]	0.09
Intraoperative RBC, mL	0 [0, 300]	0 [0, 0]	0 [0, 0]	0.61
RBC transfusion within postoperative 5 days, mL	350 [0, 700]	0 [0, 0]	0 [0, 0]	1.49

ASD, Absolute Standard Deviation; ASA physical status, American Society of Anesthesiologists physical status; BMI, Body Mass Index; TIA, Transitional Ischemic Attack; CABG, Coronary Artery Bypass Grafting; RBC, Red Blood Cell; Hgb, Hemoglobin.
Summary statistics are presented as mean ± SD (standard deviation), median [Q1, Q3], or n (%) by the lowest hemoglobin across postoperative days.
The ASD describes the difference of variables by groups. The higher the ASD, the more imbalanced it is.
Usually, ASD < 0.1 is considered as a good balance.

Statistical analysis

The association between postoperative hemoglobin and delirium was assessed using a multiple time-varying Cox proportional hazards model adjusting for all potential confounders in Table 1. The daily lowest hemoglobin measurement before onset of delirium was used as the time-varying exposure. We used a survival model to analyze the association between anemia and outcome to address the potential bias that can occur from the different follow-up times for each patient: patients who were discharged earlier or had earlier postoperative delirium had shorter exposure period than patients without the outcome.

The relationships between postoperative hemoglobin and atrial fibrillation were assessed in the Cox proportional hazard survival model in the same manner as in the primary analysis, adjusted for all confounders listed in Table 1.

The significance criterion was 0.05 for both primary and secondary analysis. SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA) was used for data retrieval and statistical analysis.

Power considerations

A *priori*

Of the 798 originally enrolled patients in the DECADE trial, only those treated at the primary study center were intended for inclusion (619). After participants were excluded due to missing hemoglobin measurements, outcomes, and confounders there was a residual sample of 585. The incidence of delirium was 15% and was simplified into a binary outcome. We simplified the power statement, treating delirium as a binary outcome, because the survival analysis planned is more powerful than logistic regression analysis assumed for the purpose of power assessment. We provided a power of 85% to detect an odds ratio of developing delirium 1.2 or greater for a one-unit increase in hemoglobin at the 0.05 significance level, assuming a normal distribution of hemoglobin with mean of 10 and standard deviation of 2 $mg.mL^{-1}$.

Post-hoc

Similar to a *priori* power calculation, delirium was simplified to a binary outcome and logistic regression was used to calculate power. With a sample size of 585, there was a power of over 0.9 to detect an odds ratio of 1.35 or greater with the observed delirium incidence of 0.13 and a normal distribution of hemoglobin with mean of 9.8 and standard deviation of 1.5 $mg.mL^{-1}$.

Results

Six-hundred nineteen Cleveland Clinic patients in the DECADE trial were considered for inclusion. After excluding patients with missing hemoglobin measurements, outcomes, and confounders, 585 patients were included in the final analysis (Fig. 1).

The baseline and confounder characteristics are listed in Table 1 by hemoglobin groups. On average, there were 4, 6, 3, 2, and 1 postoperative hemoglobin measurements from postoperative day 0 to postoperative day 4, respectively. Mean postoperative hemoglobin was 10 $g.dL^{-1}$ on postoperative day 0 and 1. Hemoglobin level was 9 $g.dL^{-1}$ from postoperative day 2 to postoperative day 4, inclusively. Patients whose mean hemoglobin was < 8 $g.dL^{-1}$ during the hospital stay had a median RBC transfusion (Q1, Q3) of 350 (0, 700) mL during the 5-day study period, while patients with mean hemoglobin ≥ 8 $g.dL^{-1}$ had a median RBC transfusion of 0 (0, 0) mL.

Postoperative delirium was present in 72 (12%) patients. Postoperative hemoglobin was not found to be significantly associated with delirium with an estimated Hazard Ratio (HR) of 0.99 (95% CI 0.83, 1.19; $p = 0.94$) associated with each 1 $g.dL^{-1}$ decrease in hemoglobin concentration (Table 2, Supplemental Table 2). This corresponds to 1% lower chance of experiencing delirium at next time point given the patient has not yet experienced the event.

One hundred ninety-seven patients (34%) developed atrial fibrillation with approximately 83% atrial fibrillation occurring during the first 3 postoperative days, primarily postoperative days 2 or 3. Postoperative atrial fibrillation was not found to be associated with hemoglobin level with an estimated HR of 1.04 (95% CI 0.93, 1.17; $p = 0.51$) with each 1 $g.dL^{-1}$ decrease in hemoglobin concentration (Table 2, Supplemental Table 3). This corresponds to a 4% higher chance of experiencing atrial fibrillation at the next time point given that the patient has not yet experienced the event.

No significant association between delirium and either intraoperative RBC transfusion volume or RBC transfusion volume within the first postoperative 5 days was found: estimated HR = 1.00 (95% CI 1.00, 1.001; $p = 0.22$) associated with each ml increase in intraoperative RBC transfusion and 1.00 (95% CI 1.00, 1.001; $p = 0.70$) associated with each ml increase in RBC transfusion within postoperative 5 days.

Additionally, there was no significant association between AF and intraoperative RBC transfusion amount ($p = 0.18$) or RBC transfusion amount within postoperative 5 days ($p = 0.79$).

Table 2 Association between hemoglobin and primary and secondary outcome (n = 585).

	HR associated with each $g.dL^{-1}$ decrease in Hgb (95% CI)[a]	*p*-value
Primary outcome		
Delirium	0.99 (0.83, 1.19)	0.94
Secondary outcome		
Atrial fibrillation	1.04 (0.93, 1.17)	0.51

HR, Hazard Ratio; Hgb, Hemoglobin; CI, Confidence Interval.

[a] The estimates were obtained from a time-varying covariate Cox-proportional hazards model with each corresponding outcome and daily hemoglobin concentration before the event/censoring time as the time-varying exposure, adjusting for confounders in Table 1.

Discussion

We did not find an association between low hemoglobin levels and either postoperative delirium or atrial fibrillation. Relatively little literature pertaining to postoperative delirium and anemia exists. Kunz et al., in a post-hoc analysis, included 183 patients undergoing a range of elective surgical procedures.[6] Ten out of 93 (10.9%) patients without postoperative anemia developed postoperative delirium. In the group with postoperative anemia, 28 (38.4%) out of 90 patients suffered postoperative delirium.[18] The difference from our results could be related to the type of surgeries included and/or the delirium assessment itself, which utilized a different tool, the Nursing Delirium Screening Scale. This tool, whilst validated, has been reported to have low sensitivity.[19] Combined with the lower frequency of delirium assessment compared to our study, it is possible that study design features can explain the difference in results between this study and that reported by Kunz et al.

A study of 415 patients aged over 65 years with hip fractures presenting for surgery found that hemoglobin less than 9.7 $mg.dL^{-1}$ was associated with delirium.[20] This level of anemia was examined as it is the level below which transfusion is generally considered in the locality of the study (The Netherlands). Assessment of delirium was done daily on the first 8 postoperative days using criteria from the Diagnostic and Statistical Manual 5 (DSM5) but a specific screening tool was not described. Higher levels of hemoglobin classified as anemic per WHO criteria were not assessed, so a definitive odds ratio for anemic and non-anemic patients cannot be compared to this study. The study included a more age-restricted study population which specifically excluded those who were anticipated to require ICU or coronary care unit placement. These factors, combined with a different surgical intervention, less frequent assessment of delirium (daily compared to twice daily in this study), and the lack of a validated assessment tool implies that a comparison of results with this study is not appropriate.

A prospective study of 472 patients undergoing major non-cardiac surgery using the CAM assessment (non-ICU equivalent of the assessment used in current study) found that preoperative hemoglobin < 13 $g.dL^{-1}$ was significantly associated with the incidence of postoperative delirium, however a correlation with postoperative anemia was not reported.[21] Patients included in this study were more than 65 years of age and the delirium assessment was performed only once per day during the first two postoperative days. The authors noted that intraoperative blood transfusion was the leading risk factor for the development of postoperative delirium, but the hemoglobin criteria for transfusions were not noted nor was the incidence of postoperative anemia.

A possible confounding factor is the impact of transfusion itself on the risk for delirium since those patients with more severe anemia are more likely to receive a greater volume of packed Red Blood Cells (RBC). No significant relationship between postoperative delirium and either the intraoperative RBC transfusion volume nor the volume of RBC transfused in the first five postoperative days was identified. The same was true of postoperative AF. This finding conflicts with the results of a secondary analysis of older patients undergoing major non-cardiac surgery.[21] However, this study found that postoperative delirium was only associated with transfusion volumes over 1 liter, which is significantly larger than transfusion volumes administered in our study population. Kwon and colleagues failed to find any correlation between intraoperative or early postoperative transfusion and delirium.[22] Transfusion does appear to be related to postoperative AF, possibly due to the effects of volume overload or inflammation.[23,24] The fact that no significant correlation between postoperative AF and transfusion volume in the intraoperative and early postoperative was identified in our study may be due to the generally low volumes of RBC administered in our patient sample.

Evidence linking postoperative atrial fibrillation with anemia is limited and conflicting. A systematic review and meta-analysis including 22 studies comprising 6098 patients identified multiple hematological abnormalities as established predictors of postoperative AF, however hemoglobin was not among them.[25] Another retrospective study of 1191 patients undergoing open cardiac surgery found that hemoglobin < 12.5 $g.dL^{-1}$ and hematocrit $< 35\%$ were associated with AF on univariate analysis, however on multivariate analysis, only hematocrit was significantly associated.[26] This study utilized a preoperative (48 hours before surgery) blood draw to assess anemia and excluded all patients with previously diagnosed atrial arrhythmias, but unlike this study, postoperative hemoglobin levels were not taken into consideration. Goldman reported that anemia (based on hematocrit $< 30\%$) is not a primary risk factor the development of AF in non-cardiac surgery.[27] This prospective study included 916 patients undergoing major non-cardiac surgery who were over 40 years of age and did not display a rhythm other than sinus rhythm during surgery. There are distinct differences in type of surgery and the assessment of both anemia and AF compared to our study.

Kim et al. evaluated 2627 patients undergoing catheter ablation for AF and found that pre-procedure anemia was independently predictive of the recurrence of AF, although post-procedure anemia was not considered.[28] We are not aware of additional studies examining the link between anemia and postoperative AF, however the plausible biological link between hypoxia (and thus, presumably, anemia) and postoperative AF has been discussed.[16] Studies have demonstrated that chronically hypoxic patients, such as those with obesity, Obstructive Sleep Apnea (OSA) or Chronic Obstructive Pulmonary Disease (COPD), have a higher incidence of postoperative AF.[29,30] The possibility that an adrenergic response to anemia is implicated in the development of postoperative AF has also been postulated.

Limitations of this study include its retrospective nature. Although the results did not demonstrate an association between anemia and either delirium or AF, the study design would not have been able to establish causation even if an association was demonstrated. Given the focus of interest in this study was major cardiac surgery requiring cardiopulmonary bypass, results may not be generalizable to other surgical procedures.[31]

Conclusion

This is the only study examining the association between postoperative hemoglobin, AF, and delirium in major cardiac surgery. Anemia was very common among patients

undergoing major cardiac surgery requiring cardiopulmonary bypass, with mean hemoglobin levels falling below WHO criteria for anemia throughout the period between surgery and POD4. Both delirium and atrial fibrillation were common in the postoperative phase. However, there was no significant association with postoperative hemoglobin and either delirium or AF identified.

Funding/Support

The study was funded by departmental funds. None of the authors has a personal financial interest related to this research.

Register number

Institutional Review Board (IRB): 21-399. This is a retrospective sub study of the DECADE trial (IRB 12-1379, NCT02004613).

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2023.02.003.

References

1. How Many Cardiac Surgeries Are Performed Each Year? – New Study by iData Research – iData Research [Internet]. [cited 2022 Jun 2]. Available from: https://idataresearch.com/over-900000-cardiac-surgeries-performed-every-year-in-the-united-states/.
2. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001;135:1061—73.
3. Demeure MJ, Fain MJ. The elderly surgical patient and postoperative delirium. J Am Coll Surg. 2006;203:752—7.
4. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci. 2007;62:420—6.
5. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth. 2009;103:i41—6. Suppl 1.
6. Kunz JV, Spies CD, Bichmann A, Sieg M, Mueller A. Postoperative anaemia might be a risk factor for postoperative delirium and prolonged hospital stay: A secondary analysis of a prospective cohort study. PLoS One. 2020;15:e0229325.
7. Haljamäe H, Stefánsson T, Wickström I. Preanesthetic evaluation of the female geriatric patient with hip fracture. Acta Anaesthesiol Scand. 1982;26:393—402.
8. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med. 2004;116:58—69. Suppl 7A(7 SUPPL. 1).
9. Gómez-Ramirez S, Jericó C, Muñoz M. Perioperative anemia: Prevalence, consequences, and pathophysiology. Transfus Apher Sci. 2019;58:369—74.
10. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015;102:1314—24.
11. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg. 1993;56:539—49.
12. Yadava M, Hughey AB, Crawford TC. Postoperative Atrial Fibrillation: Incidence, Mechanisms, and Clinical Correlates. Heart Fail Clin. 2016;12:299—308.
13. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004;43:742—8.
14. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation. 1996;94:390—7.
15. Tchervenkov CI, Wynands JE, Symes JF, Malcolm ID, Dobell ARC, Morin JE. Persistent atrial activity during cardioplegic arrest: a possible factor in the etiology of postoperative supraventricular tachyarrhythmias. Ann Thorac Surg. 1983;36:437—43.
16. Palin CA, Kailasam R, Hogue CW. Atrial fibrillation after cardiac surgery: pathophysiology and treatment. Semin Cardiothorac Vasc Anesth. 2004;8:175—83.
17. Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet. 2020;396:177—85.
18. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal Pv, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338—44.
19. Hargrave A, Bastiaens J, Bourgeois JA, Neuhaus J, Josephson SA, Chinn J, et al. Validation of a Nurse-Based Delirium-Screening Tool for Hospitalized Patients. Psychosomatics. 2017;58:594—603.
20. van der Zanden V, Beishuizen SJ, Scholtens RM, de Jonghe A, de Rooij SE, van Munster BC. The Effects of Blood Transfusion on Delirium Incidence. J Am Med Dir Assoc. 2016;17:748—53.
21. Behrends M, Depalma G, Sands L, Leung J. Association between intraoperative blood transfusions and early postoperative delirium in older adults. J Am Geriatr Soc. 2013;61:365—70.
22. Kwon YS, Kim JH, Lee JJ, Seo EM. The relationship between perioperative blood transfusion and postoperative delirium in patients undergoing spinal fusion surgery: Clinical Data Warehouse Analysis. Medicina (Kaunas). 2022;58:268.
23. Alameddine AK, Visintainer P, Alimov VK, Rousou JA. Blood transfusion and the risk of atrial fibrillation after cardiac surgery. J Card Surg. 2014;29:593—9.
24. Liu S, Li Z, Liu Z, Hu Z, Zheng G. Blood transfusion and risk of atrial fibrillation after coronary artery bypass graft surgery: A meta-analysis of cohort studies. Medicine. 2018;97:e9700.
25. Weymann A, Ali-Hasan-Al-Saegh S, Popov AF, Sabashnikov A, Mirhosseini SJ, Liu T, et al. Haematological indices as predictors of atrial fibrillation following isolated coronary artery bypass grafting, valvular surgery, or combined procedures: a systematic review with meta-analysis. Kardiol Pol. 2018;76:107—18.
26. Turkkolu ST, Selçuk E, Köksal C. Biochemical predictors of postoperative atrial fibrillation following cardiac surgery. BMC Cardiovasc Disord. 2021;21:167.
27. Goldman I. Supraventricular tachyarrhythmias in hospitalized adults after surgery. Clinical correlates in patients over 40 years of age after major noncardiac surgery. Chest. 1978;73:450—4.
28. Kim M, Hong M, Kim JY, Kim IS, Yu HT, Kim TH, et al. Clinical relationship between anemia and atrial fibrillation recurrence

after catheter ablation without genetic background. Int J Cardiol Heart Vasc. 2020;27:100507.
29. Yamashita K, Hu N, Ranjan R, Selzman CH, Dosdall DJ. Clinical risk factors for postoperative atrial fibrillation among patients after cardiac surgery. Thorac Cardiovasc Surg. 2019;67:107—16.
30. Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. Coron Artery Dis. 1996;7:475—8.
31. Chelazzi C, Villa G, de Gaudio AR. Postoperative atrial fibrillation. ISRN Cardiol. 2011;2011:203179.

Brazilian Journal of Anesthesiology 2024;74(3): 844501



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Apelin-13 reverses bupivacaine-induced cardiotoxicity: an experimental study



Xixi Cai [a], **Le Liu** [a], **Fangfang Xia** [a], **Thomas J. Papadimos** [b], **Quanguang Wang** [a,*]

[a] *The First Affiliated Hospital of Wenzhou Medical University, Department of Anesthesiology, Zhejiang Province, China*
[b] *The Ohio State University Wexner Medical Center, Department of Anesthesiology, Ohio, USA*

Received 4 September 2023; accepted 26 March 2024
Available online 5 April 2024

KEYWORDS
Apelin;
Bupivacaine;
Cardiotoxicity;
Protein kinase C;
Sodium channel

Abstract

Introduction: Cardiac arrest or arrhythmia caused by bupivacaine may be refractory to treatment. Apelin has been reported to directly increase the frequency of spontaneous activation and the propagation of action potentials, ultimately promoting cardiac contractility. This study aimed to investigate the effects of apelin-13 in reversing cardiac suppression induced by bupivacaine in rats.

Methods: A rat model of cardiac suppression was established by a 3-min continuous intravenous infusion of bupivacaine at the rate of 5 $mg.kg^{-1}.min^{-1}$, and serial doses of apelin-13 (50, 150 and 450 $\mu g.kg^{-1}$) were administered to rescue cardiac suppression to identify its dose-response relationship. We used F13A, an inhibitor of Angiotensin Receptor-Like 1 (APJ), and Protein Kinase C (PKC) inhibitor chelerythrine to reverse the effects of apelin-13. Moreover, the protein expressions of PKC, Nav1.5, and APJ in ventricular tissues were measured using Western blotting and immunofluorescence assay.

Results: Compared to the control rats, the rats subjected to continuous intravenous administration of bupivacaine had impaired hemodynamic stability. Administration of apelin-13, in a dose-dependent manner, significantly improved hemodynamic parameters in rats with bupivacaine-induced cardiac suppression ($p < 0.05$), and apelin-13 treatment also significantly upregulated the protein expressions of p-PKC and Nav1.5 ($p < 0.05$), these effects were abrogated by F13A or chelerythrine ($p < 0.05$).

Conclusion: Exogenous apelin-13, at least in part, activates the PKC signaling pathway through the apelin/APJ system to improve cardiac function in a rat model of bupivacaine-induced cardiac suppression.

© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author.
E-mail: quanguangwang@wzhospital.cn (Q. Wang).

https://doi.org/10.1016/j.bjane.2024.844501
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Bupivacaine, a long-acting and low-cost amide local anesthetic, is frequently used for conducting regional anesthesia; however bupivacaine can cause profound cardiac toxicities such as arrhythmia, hypotension and even cardiac arrest, as it may be accidentally injected or excessively absorbed into circulation, where the inhibition of the cardiac voltage-gated sodium channel is considered as the essential factor contributing to bupivacaine-induced cardiotoxicity.[1] Therefore, mitigating its cardiotoxicity is of vital concern to clinical anesthesiologists.

Apelin, the ligand of the Angiotensin Receptor-Like 1 (APJ), directly increases the frequency of spontaneous activation and the propagation of action potentials, and ultimately promotes cardiac contractility.[2,3] Its inotropic effect may be associated with an increase in the sodium current at more negative potentials, with implications in the transduction mechanisms that can lead to Protein Kinase C (PKC) activation,[4] something that, in turn, opens a window allowing to explore such a connection and how it could interfere with the deflagrated inherent mechanisms which lead to bupivacaine-induced toxicity. Therefore, apelin seems to be a promising target for therapeutic intervention in bupivacaine-induced cardiotoxicity.

Here, in a rat model of bupivacaine-induced cardiac suppression, we tested the hypothesis that apelin-13, the most abundant member of the apelin family, can mitigate bupivacaine-induced cardiotoxicity, and that PKC activation may be involved in its protective mechanism. With the aim of studying such condition, we chose to look for what were the implications of cardiotoxicity in the hemodynamics parameters, electrocardiographic waves, protein expression levels and in the immunofluorescence assay pattern.

Methods

Animals

The experimental protocols were approved by the Animal Ethics Committee of Wenzhou Medical University (No. wydw2016-0267, date of approval: May 25th, 2016), and the study was conducted in accordance with ARRIVE guidelines. The specific pathogen-free, 6—8 weeks old, 200—250 g, male Sprague-Dawley rats were purchased from the SLAC Laboratory Animal Company. After 1 week of adaptive feeding with free access to diet and water intake, the rats were randomized according to a random number table for further experiments.

Three different investigators were involved as follows for each animal: a first investigator, who was the only person aware of the treatment group allocation, performed the anesthesia and pharmacological interventions based on the randomization table. A second investigator was responsible for the hemodynamic and electrocardiographic (ECG) recordings, and the third investigator performed the Western blotting and immunofluorescence assay.

Animal preparation and monitoring

All rats were anesthetized with intraperitoneal administration of sodium pentobarbital 30 mg.kg^{-1} and ketamine 50 mg.kg^{-1}, and then placed on a warming pad in supine position to keep body temperature at 36—37 °C. The rats were then ventilated with a rodent ventilator in a volume-controlled mode (tidal volume 6 mL.kg^{-1}, 80 stroke/min). The carotid artery was cannulated using a PE50 catheter and connected to a pressure transducer to monitor hemodynamic parameters. Rats with a baseline blood pressure > 130/100 mmHg or < 110/70 mmHg were excluded. Another PE50 catheter was then inserted into the femoral vein and connected to a micro infusion pump (3500, Graseby, UK). Two biopotential leads were anchored subcutaneously over the right pectoral muscle and on the lower left side of the chest wall to record ECG parameters using a computer-based electrical physiology system. Data were collected after a 15-min stabilization period.

Establishment of bupivacaine-induced cardiac suppression in rats

We infused 15 mg.kg^{-1} bupivacaine via the right femoral vein with a micro infusion pump at 5 mg.kg^{-1}.min^{-1} for 3 min.[5] Bupivacaine-induced cardiac suppression was confirmed when the heart rate systolic Blood Pressure Product (RPP) was less than 30% of the baseline value.

Effect of apelin-13 in mitigating bupivacaine-induced cardiac suppression

Rats were randomized into five groups: Control group, Bupivacaine group (Bup group), bupivacaine + 50 μg.kg^{-1} apelin-13 group (Bup+Apln50 group), bupivacaine + 150 μg.kg^{-1} apelin-13 group (Bup+Apln150 group), and bupivacaine + 450 μg.kg^{-1} apelin-13 group (Bup+Apln450 group), with eight rats in each group. The bupivacaine-induced cardiac suppression model was developed in the Bup group, while the rats in the Control group were continuously infused with the same volume of Normal Saline (NS) alone, and an extra 0.1 mL NS was given via the jugular vein immediately after the end of the infusion to both groups. We administered 50, 150, and 450 μg.kg^{-1} apelin-13, dissolved in 0.1 mL NS, via the jugular vein immediately after the bupivacaine infusion in the Bup+Apln50, Bup+Apln150, and Bup+Apln450 groups, respectively.

Effects of F13A and chelerythrine on apelin-13 in mitigating bupivacaine-induced cardiac suppression in rats

Rats were divided into six groups: Bupivacaine group (Bup group), Bupivacaine + 150 μg.kg^{-1} apelin-13 group (Bup+Apln150 group), Bupivacaine + F13A group (Bup+F13A group), Bupivacaine + chelerythrine group (Bup+Chel group), Bupivacaine + 150 μg.kg^{-1} apelin-13 + F13A group (Bup+Apln150+F13A group), and Bupivacaine + 150 μg.kg^{-1} apelin-13 + chelerythrine group (Bup+Apln150+Chel group), with eight rats in each group. We administered 150 μg.kg^{-1} F13A and 5 mg.kg^{-1} chelerythrine through the jugular vein 15 min before bupivacaine infusion in the Bup+F13A and Bup

+Chel groups, and 0.1 mL NS was given immediately after the end of bupivacaine infusion.[6-8] The Bup+Apln150 group received intravenous administration of 150 μg.kg^{-1} apelin-13 immediately after the end of bupivacaine infusion, while the Bup+Apln150+F13A and Bup+Apln150+Chel groups were instead administered an additional 150 μg.kg^{-1} F13A and 5 mg.kg^{-1} chelerythrine 15 min before the bupivacaine infusion.

The initiation of the bupivacaine infusion was defined as time 0 min, and cardiac suppression was established at time 3 min. The hemodynamic and ECG parameters were recorded every five minutes for 30 min after bupivacaine infusion. Subsequently, the rats were sacrificed by anesthetic overdose, and their hearts were removed for protein measurements.

Western blotting

The tissues extracted from the left ventricular wall of eights rats in each group were lysed in 0.9 mL RIPA lysis buffer (No. 89900, ThermoFisher, China) and mixed with protease and phosphatase inhibitors for 15 min. The protein concentration was determined using a BCA protein assay kit (No. 23235, ThermoFisher, China). Each 1 mL protein mixture containing 15 μg protein and 200 μL 5$\times$ loading buffer was denatured by boiling at 100°C for 5 min. Each sample was separated using 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes by electrophoresis. The membranes were blocked in 5% non-fat dry milk for 2 h and incubated with specific primary antibodies against p-PKC (No. ab23513, Abcam, China), total PKC (No. ab32376, Abcam, China), Nav1.5 (No. ab187830, Abcam, China) and APJ (No. ab214369, Abcam, China) overnight (4 °C) and a secondary antibody for 2 h. The resulting band was established using an ECL detection kit with a Bio-Rad imager using GAPDH (Bioworld Technology, China) as an internal control.

Immunofluorescence assay

Heart tissues obtained from eights rats per group were embedded in OCT compound and frozen immediately in liquid nitrogen. We incubated 5 μm cardiac tissue sections with antibodies against p-PKC (1:100) and Nav1.5 (1:100) overnight at 4 °C. Then, membranes were incubated with secondary antibodies of FITC-conjugated goat anti-mouse IgG (1:200, No. 33207ES60, YEASEN, China) and TRITC-conjugated goat anti-rabbit IgG (1:200, No. 33109ES60, YEASEN, China) for 2 h at room temperature. After washing with phosphate-buffered saline, nuclei were stained with fluorescent dye 4′, 6-diamidino-2-phenylindole dihydrochloride for 5 min. Fluorescence was observed using a fluorescent microscope system (DP72, Olympus, Japan).

Sample size and statistical analysis

The sample size of n = 8 in each group for each set of the experiment was determined based on the sample size used in our previous study.[5] All statistical analyses were performed using SPSS version 13.0 software. The Shapiro-Wilk test was used for normal distribution test, and all continuous data that were normally distributed were expressed as mean $\pm$ Standard Deviation (SD). The overall differences in ECG and hemodynamic parameters within -15—0 min and 3—30 min period were respectively compared across time using two-way repeated measures analysis of variance (ANOVA). The paired *t*-test was used to compare repeatedly measured data among different timepoints within each group. Other outcomes were compared using one-way ANOVA followed by the Bonferroni post hoc method among groups. A value of $p < 0.05$ was considered significant.

Results

All animals completed the experiment, and eight rats in each group were included in the final analysis. The Shapiro-Wilk test revealed that all the variables were normally distributed.

Compared to data at -15 min and 0 min, the rats in the Bup group developed lower Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), RPP, and prolonged QRS and QT segment durations at 3-min ($p < 0.05$, Supplemental Table 1 and 2 in Supplemental File 1), suggesting the successful establishment of bupivacaine-induced cardiac suppression. Compared to the Bup group, the rats improved SBP, HR, RPP, QRS, QT segment duration and shortened duration required for recovering to 70% of baseline RPP in the Bup+Apln150 and Bup+Apln450 group, and DBP was increased only in the Bup+Apln150 group ($p < 0.05$). Compared to the Bup+Apln50 group, the rats in the Bup+Apln150 and Bup +Apln450 groups exhibited higher SBP, DBP, HR, RPP, shortened duration of QRS segment and duration required for recovering to 70% of baseline RPP in the 3—30 min interval ($p < 0.05$). DBP was increased, and QRS and QT segment durations were shortened in the 3—30 min period in the Bup+Apln450 group compared with the Bup+Apln150 group ($p < 0.05$, Fig. 1).

Compared to the Bup+Apln group, the Bup+Apln+F13A and Bup+Apln+Chel groups showed lower SBP, DBP, HR, and RPP. Additionally, the duration required for recovering to 70% of baseline RPP and QRS and QT segment durations in the 3—30 min interval were prolonged in the Bup+Apln+F13A group ($p < 0.05$, Fig. 2).

Compared to the Bup group, protein expression of p-PKC and Nav1.5 in the ventricular tissues of the Bup+Apln150 and Bup+Apln450 groups were upregulated, with Nav1.5 being more upregulated in the Bup+Apln450 group than in the Bup +Apln150 group ($p < 0.05$, Fig. 3). There were no significant differences in ventricular protein expressions of total PKC and APJ among Bup, Bup+Apln50, Bup+Apln150, and Bup +Apln450 groups ($p > 0.05$).

The fluorescence of p-PKC and Nav1.5 predominately accumulated around plasma membranes in rat ventricular cardiomyocytes from the Control group but displayed a relatively dispersive distribution in the Bup group. The membranous accumulation of fluorescence of p-PKC and Nav1.5 was more prominent in the Bup+Apln50, Bup+Apln150, and Bup +Apln450 groups than in the Bup group (Fig. 4).

There were no differences in expression of p-PKC, Nav1.5, PKC, and APJ among Bup+F13A, Bup+Chel, and Bup groups ($p > 0.05$). Compared to the Bup+Apln group, ventricular protein expression of p-PKC and Nav1.5, but not total PKC and APJ, were lower in rats from the Bup+Apln+F13A and Bup+Apln+Chel groups ($p < 0.05$, Fig. 3). Under

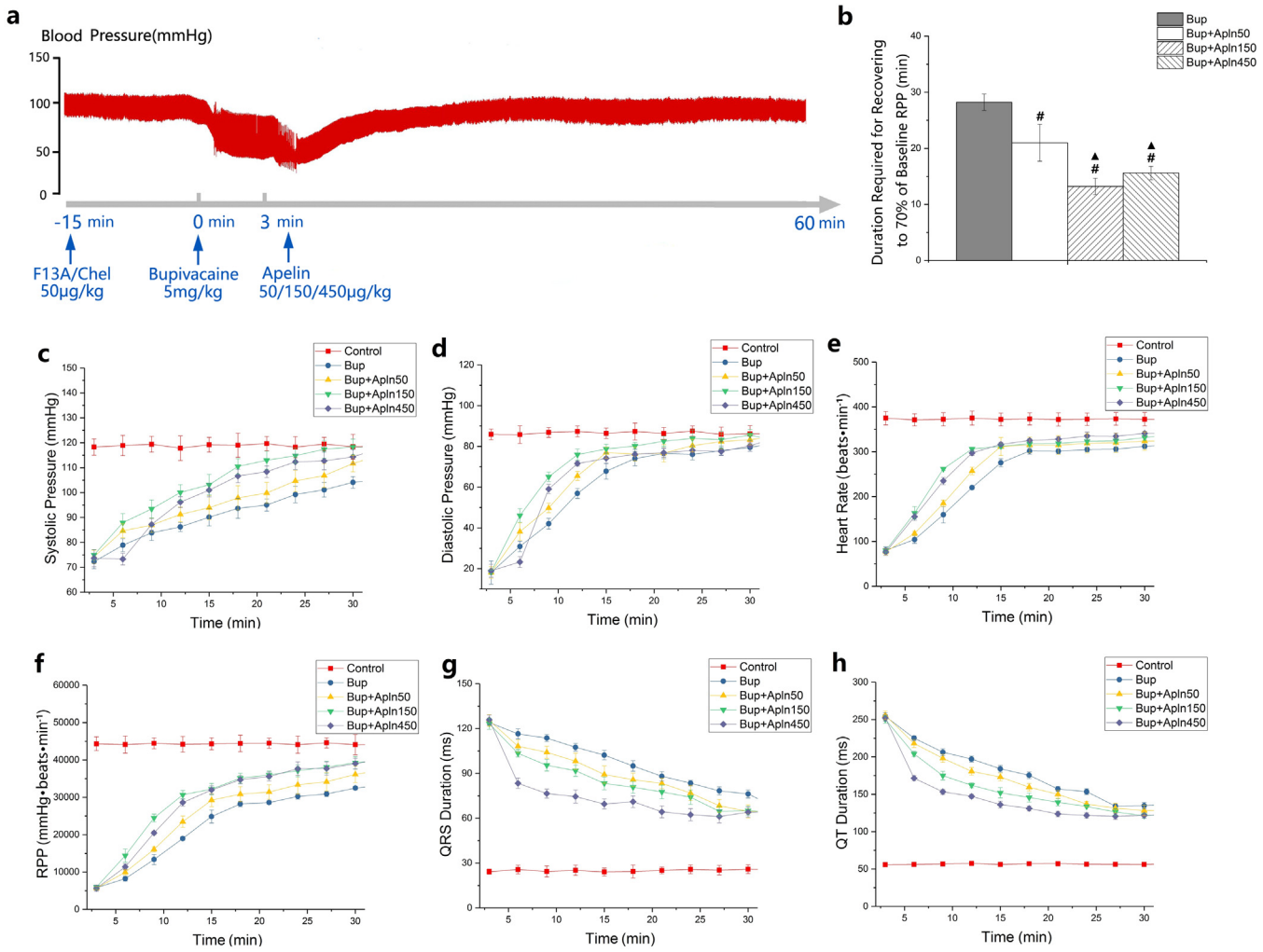


Figure 1 Effects of Apelin-13 on cardiac suppression induced by bupivacaine (3—30 min). The timeline of hemodynamics parameters (a), duration required for recovering to 70% of baseline RPP (b), systolic blood pressure (c), diastolic blood pressure (d), heart rate (e), RPP (f), QRS segment duration (g) and QT segment duration (h) of each group were plotted against time (3—30 min), and the initiation of bupivacaine infusion or normal saline was defined as time 0 min. Data were expressed as mean ± SD (n = 8). Continuous ECG and hemodynamic parameters in rats surviving at 30 min were compared across time by two-way repeated measures ANOVA. RPP, heart rate systolic blood pressure product. #$p < 0.05$ vs. Bup group, ▲$p < 0.05$ vs. Bup+Apln50 group.

immunocytochemistry assay, the membranous fluorescence of p-PKC and Nav1.5 in ventricular cardiomyocytes in the Bup+Apln+F13A and Bup+Apln+Chel groups was lower than in the Bup+Apln group (Fig. 5).

Discussion

The results of this study showed that the administration of apelin-13 tends to reduce bupivacaine-induced cardiac suppression in a dose-dependent manner, and these supposedly protective effects tend to be modified by both APJ inhibitor F13A and PKC inhibitor chelerythrine.

Arrhythmias rather than asystole appear to be more common with inadvertent intravenous administration of bupivacaine.[9] We established a rat model of cardiac suppression with continuous administration of bupivacaine for a relatively prolonged duration, and the total dose of bupivacaine was identical to the one we used to induce cardiac arrest in a previous study.[5] Here, the bupivacaine administration protocol in this study caused profound cardiac suppression in a short period, which was considered to be more compatible with the clinical scenarios. The QRS and QT segment duration on ECG, which represents the process of depolarization of the ventricle and the entire process of ventricular depolarization and repolarization, respectively, are closely related to sodium current. In our study, prolonged QRS and QT segments were demonstrated along with impaired hemodynamic stability, which supported the notion that sodium channel block serves as the predominate mechanism in bupivacaine-induced cardiotoxicity. It is probable that, within certain transduction mechanisms related to cellular sodium channel impairment triggered by bupivacaine-induced toxicity, the pathway induced by apelin-13 may interrupt the degeneration process. This interruption could result in a mitigated deleterious effect on the depolarization and repolarization patterns of the ECG, consequently ameliorating the contractile force and, consequently, influencing hemodynamic variables.

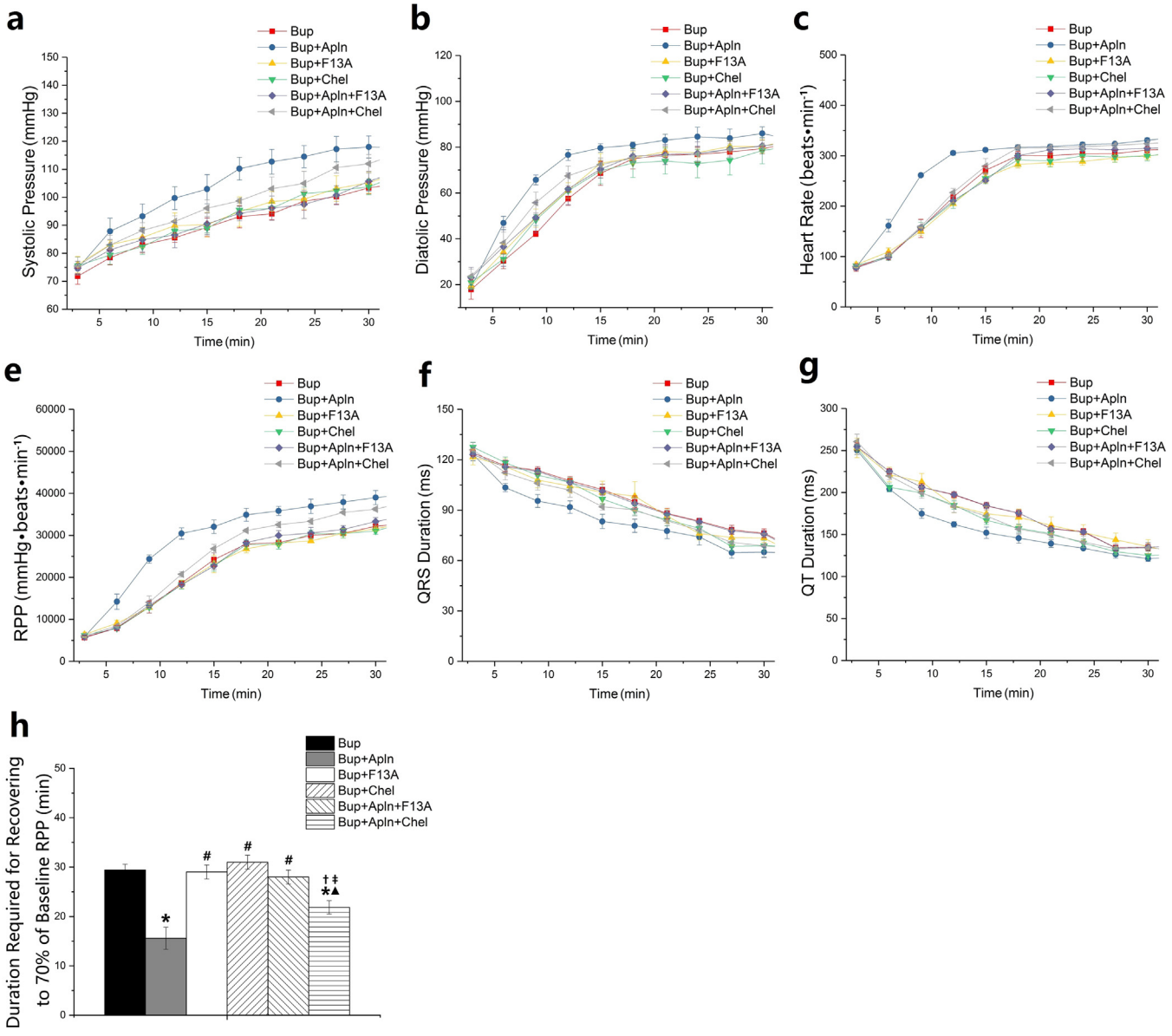


Figure 2 F13A and chelerythrine abolished the protective effects of apelin-13 on cardiac function in bupivacaine-treated rats (3−30 min). Systolic blood pressure (a), diastolic blood pressure (b), heart rate (c), RPP (d), QRS segment duration (e), QT segment duration (f) and duration required for recovering to 70% of baseline RPP (g) of each group were plotted against time (3−30 min). Data were expressed as mean ± SD (n = 8). Continuous ECG and hemodynamic parameters in rats surviving at 30 min were compared across time by two-way repeated measures ANOVA. RPP, heart rate systolic blood pressure product. * $p < 0.05$ vs. Bup group, # $p < 0.05$ vs. Bup+Apln group, ▲ $p < 0.05$ vs. Bup+F13A group, † $p < 0.05$ vs. Bup+Chel group, ‡ $p < 0.05$ vs. Bup+Apln+F13A.

Apelin, a ligand of the G protein-coupled receptor Angiotensin Receptor-Like 1 (APJ), is the most potent endogenous positive inotropic substance identified so far, yielding above 70% of the increase force observed with isoproterenol.[8] Apelin is unable to modulate L-type calcium current or voltage-activated potassium currents of ventricular myocytes. In contrast, apelin-13 has the beneficial effects of increasing sodium current amplitude and the "window" current of ventricle cardiomyocytes as well as shifting the mid-activation potential and facilitating channel opening at negative voltage. Thus, the increased intracellular sodium promotes the propagation of the action potential, contributing to the inotropic effects of apelin-13.[4] Our results showed that, along with improving hemodynamics, apelin-13 in varying doses may significantly allow recovery of the QRS and the QT segments that are both closely related to sodium current, thereby implying that apelin-13 modulated the sodium current in rats subjected to bupivacaine administration.

Apelin, through the APJ system, Increases Sodium-Hydrogen (NHE) activity, leading to intracellular alkalinization, and an increased myofilament sensitivity for calcium.[2] Also, via a PKC-dependent mechanism, apelin was reported to increase the sarcoplasmic reticulum Ca2+-ATPase and cause an increase in systolic [Ca2+]i, but a decrease in diastolic [Ca2+]i.[9] Changes in iNa amplitude and kinetics may modulate intracellular Na+ concentrations and the turnover of

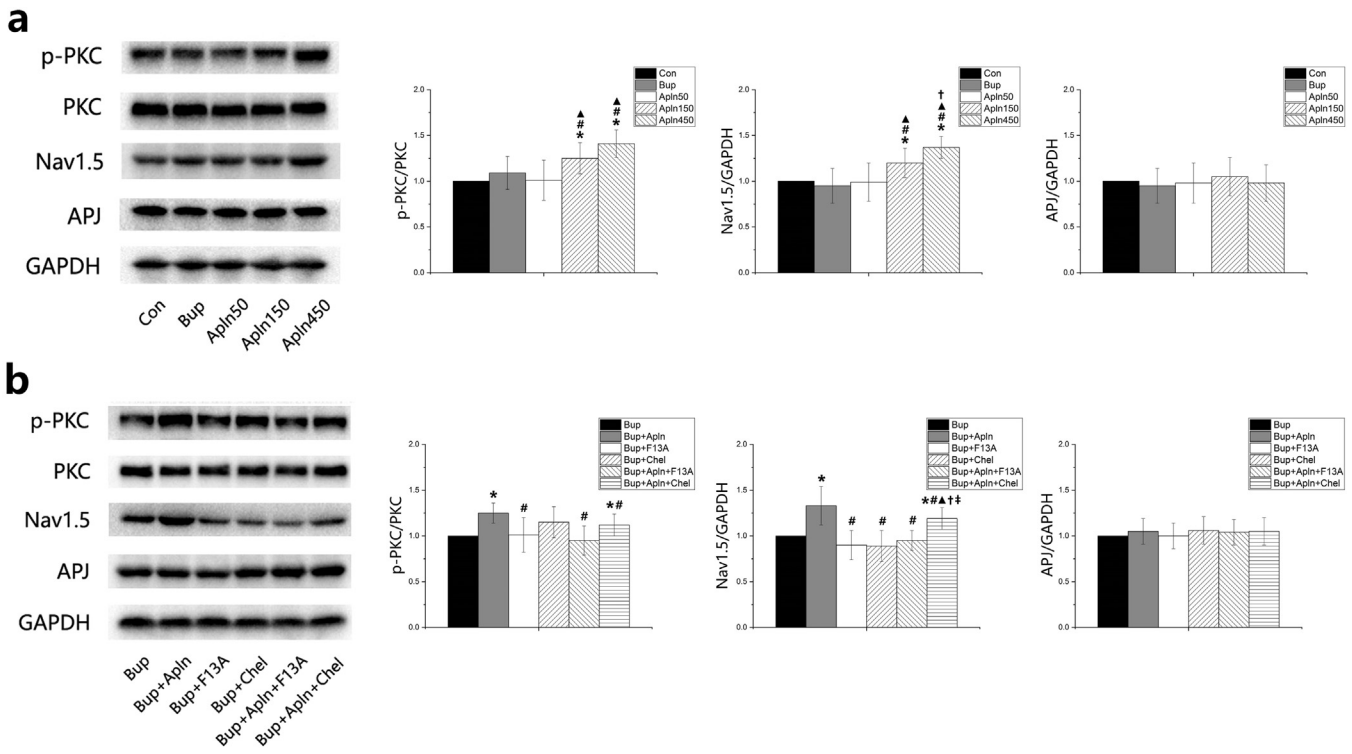


Figure 3 Apelin-13 increased p-PKC and Nav1.5 protein expressions as measured by Western Blotting. The protein expressions of p-PKC, PKC, Nav1.5 and APJ by Western blotting: (a) The dose-dependent manner of apelin-13 in increasing the ventricular expressions of p-PKC/PKC and Nav1.5 in bupivacaine-treated rats; (b) F13A and chelerythrine abolished the effects of apelin-13 on p-PKC and Nav1.5 protein expressions in bupivacaine-treated rats. Data were expressed as mean ± SD (n = 8). The relative protein expression in ventricular tissue was compared among groups by two-way repeated measures ANOVA. PKC, Protein Kinase C. * $p < 0.05$ vs. Control group, # $p < 0.05$ vs. Bup group, ▲ $p < 0.05$ vs. Bup+Apln50 group, † $p < 0.05$ vs. Bup+Apln150 group.

sodium-calcium exchangers thereby increasing intracellular calcium. Thus, modulation of sodium current by Apelin could play an essential role in its inotropic effect.[4] Mechanically, the APJ receptor when coupled to the G protein family member Gq protein can activate PKC, which is involved in cardiac excitability and electrical remodeling in a variety of cardiovascular diseases. Activation of PKC, but not PKA, is involved in the modulation of sodium current by apelin-13, since chelerythrine, the specific inhibitor of PKC, abolishes the increase in sodium current by apelin-13.[4] Here, our results

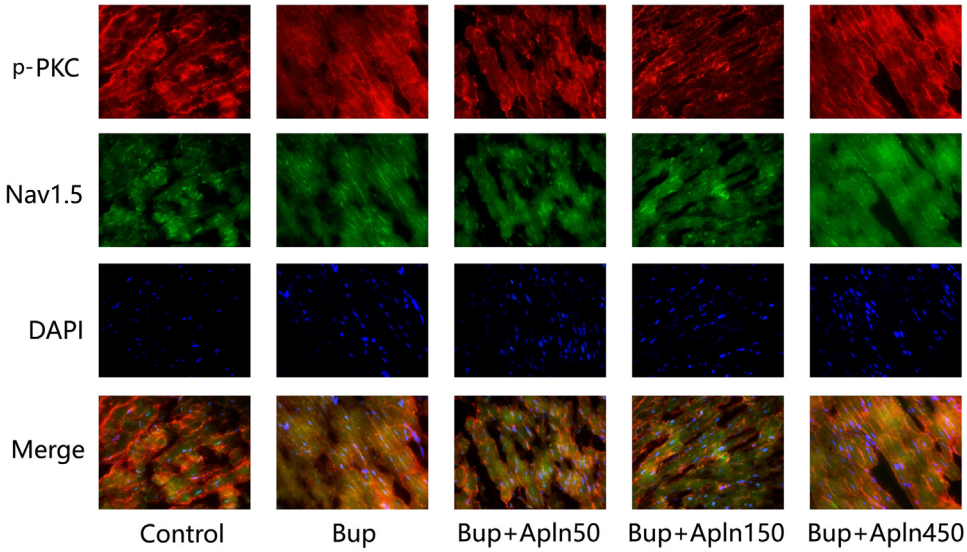


Figure 4 Apelin-13 increased p-PKC and Nav1.5 protein expression in bupivacaine-treated rats as measured by immunocytochemistry assay. PKC, Protein Kinase C.

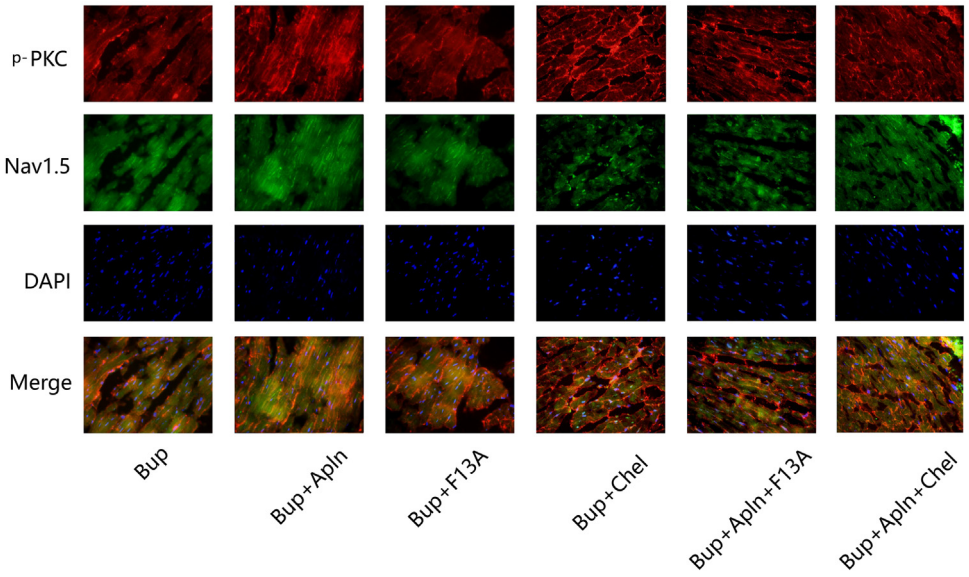


Figure 5 F13A and chelerythrine abolished the effects of apelin-13 on p-PKC and Nav1.5 protein expressions in bupivacaine-treated rats as measured by immunocytochemistry assay. PKC, Protein Kinase C.

indicate that PKC activation, as a downstream of the apelin/APJ system, may be involved in mitigating bupivacaine-induced cardiac suppression by apelin-13.

In our current study, 150 μg.kg^{-1} apelin-13 exerted a similar effect as the dose of 450 μg.kg^{-1} in attenuating bupivacaine-induced RPP reduction in rats; however, the larger dose caused transient SBP decline in the early stage. We assumed that the inotropic effect of apelin-13 prevailed over its vasodilatory effect when the dose was relatively low, but this was not so in rats receiving the higher dose of apelin-13. Several studies have been conducted to investigate the vasodilatory effect of apelin. The administration of apelin can lead to a rapid Nitric Oxide (NO)-dependent decrease in blood pressure and mean capillary filling pressure in rodent models,[10] and a NO clamp may significantly attenuate vasodilation induced by apelin. In vitro, apelin causes NO-dependent vasodilation in human mesenteric arteries and venoconstriction in endothelium-denuded human saphenous veins.[11,12] The inotropic and vasodilatory effects of apelin-13 make it a promising candidate for heart failure therapy. There is evidence that short-term infusion of apelin-13 causes direct peripheral and coronary vasodilatation, reduced cardiac preload and afterload, and increased cardiac output in patients with chronic heart failure.[13]

Several phosphorylation sites have been identified within the first intracellular linker loop of Nav1.5 consistent with direct regulation of Nav1.5 channel function by phosphorylation.[14] Since apelin-13 functioned on cardiomyocytes for a relatively short period, we previously surmised that apelin-13 and/or PKC activation would not alter the synthesis and recruitment of new channels. However, in our current study, apelin-13 treatment surprisingly increased the synthesis and recruitment of sodium channel protein in a dose-dependent manner, as evidenced in the upregulated expression of Nav1.5 demonstrated by Western blot and immunofluorescence assays.

There are some limitations in our study that need to be addressed. First, apelin appears to be rapidly cleared from the circulation with a short plasma half-life of no longer than 8 min,[8,15] but in this study we did not examine the benefit of the long-term administration of apelin-13. Second, using a specific inhibitor of PKC and APJ, we concluded that PKC might function as a vital protein following the binding of apelin-13 to APJ, but the exact mechanisms that may be involved in this process are still unclear and need further evaluation. Third, we did not measure NO expression or evaluate the inhibitory effect of the endothelial nitric oxide synthase inhibitor in apelin-13-treated rats; doing so may have assisted in the elucidation of potential mechanisms effecting a decrease in blood pressure. Finally, detailed in vitro data are needed to explore specific mechanisms.

Conclusion

Exogenous apelin-13, at least in part, activates the PKC signaling pathway through the apelin/APJ system to improve cardiac function in a rat model of bupivacaine-induced cardiac suppression.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This study was supported by the National Natural Science Foundation of China (Grant N° 81670219) and Science and Technology Bureau of Wenzhou City (N° Y2020161).

Data availability statement

Data are available from the authors upon reasonable request

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844501.

References

1. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. Reg Anesth Pain Med. 2002;27:556—61.
2. Farkasfalvi K, Stagg MA, Coppen SR, et al. Direct effects of apelin on cardiomyocyte contractility and electrophysiology. Biochem Biophys Res Commun. 2007;357:889—95.
3. Ashley EA, Powers J, Chen M, et al. The endogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. Cardiovasc Res. 2005;65:73—82.
4. Chamberland C, Barajas-Martinez H, Haufe V, et al. Modulation of canine cardiac sodium current by Apelin. J Mol Cell Cardiol. 2010;48:694—701.
5. Luo M, Yun X, Chen C, et al. Giving Priority to Lipid Administration Can Reduce Lung Injury Caused by Epinephrine in Bupivacaine-Induced Cardiac Depression. Reg Anesth Pain Med. 2016;41:469—76.
6. Tiani C, Garcia-Pras E, Mejias M, et al. Apelin signaling modulates splanchnic angiogenesis and portosystemic collateral vessel formation in rats with portal hypertension. J Hepatol. 2009;50:296—305.
7. Ustunel I, Acar N, Gemici B, et al. The effects of water immersion and restraint stress on the expressions of apelin, apelin receptor (APJR) and apoptosis rate in the rat heart. Acta Histochem. 2014;116:675—81.
8. Szokodi I, Tavi P, Foldes G, et al. Apelin, the novel endogenous ligand of the orphan receptor APJ, regulates cardiac contractility. Circ Res. 2002;91:434—40.
9. Wang C, Du JF, Wu F, et al. Apelin decreases the SR Ca2+ content but enhances the amplitude of [Ca2+]i transient and contractions during twitches in isolated rat cardiac myocytes. Am J Physiol Heart Circ Physiol. 2008;294:H2540—6.
10. Japp AG, Newby DE. The apelin-APJ system in heart failure: pathophysiologic relevance and therapeutic potential. Biochem Pharmacol. 2008;75:1882—92.
11. Katugampola SD, Maguire JJ, Matthewson SR, et al. [(125)I]-(Pyr(1))Apelin-13 is a novel radioligand for localizing the APJ orphan receptor in human and rat tissues with evidence for a vasoconstrictor role in man. Br J Pharmacol. 2001;132:1255—60.
12. Salcedo A, Garijo J, Monge L, et al. Apelin effects in human splanchnic arteries. Role of nitric oxide and prostanoids. Regul Pept. 2007;144:50—5.
13. Japp AG, Cruden NL, Barnes G, et al. Acute cardiovascular effects of apelin in humans: potential role in patients with chronic heart failure. Circulation. 2010;121:1818—27.
14. Marionneau C, Lichti CF, Lindenbaum P, et al. Mass spectrometry-based identification of native cardiac Nav1.5 channel alpha subunit phosphorylation sites. J Proteome Res. 2012;11:5994—6007.
15. Cheng CC, Weerateerangkul P, Lu YY, et al. Apelin regulates the electrophysiological characteristics of atrial myocytes. Eur J Clin Invest. 2013;43:34—40.

Brazilian Journal of Anesthesiology 2024;74(3): 744471



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Cross-cultural adaptation and validation of the Iowa Satisfaction with Anesthesia Scale for use in Brazil: a cross-sectional study*

Nicole Morem Pilau Moritz [a,b,*], **José Eduardo Moritz** [c], **Gabriel Oscar Cremona Parma** [a], **Franklin Dexter** [d], **Jefferson Traebert** [a]

[a] *Universidade do Sul de Santa Catarina, Programa de Pós-Graduação em Ciências da Saúde, Palhoça, SC, Brazil*
[b] *Hospital Universitário da Universidade Federal de Santa Catarina, Departamento de Anestesia, Florianópolis, SC, Brazil*
[c] *Ultralitho Centro Médico, Florianópolis, SC, Brazil*
[d] *University of Iowa, Department of Anesthesia, Iowa City, United States of America*

Received 23 July 2023; accepted 4 November 2023
Available online 10 November 2023

KEYWORDS
Ambulatory surgical procedures;
Anesthesia;
Conscious sedation;
Patient satisfaction;
Validation study

Abstract
Background: The Iowa Satisfaction with Anesthesia Scale (ISAS) was developed to assess the satisfaction of patients undergoing sedation with monitored anesthesia care. This study aimed to cross-culturally adapt the ISAS instrument and evaluate the acceptability, validity, and reliability of the proposed Brazilian version (ISAS-Br).
Methods: The cross-cultural adaptation process involved translation, synthesis, back-translation, expert committee review, pre-testing, and final review of the ISAS-Br. A cross-sectional study was conducted, involving 127 adult individuals undergoing ambulatory surgeries with moderate/deep sedation. The acceptability, reliability, and construct validity of the scale were assessed.
Results: The cross-cultural adaptation process did not require significant changes to the final version of the scale. The ISAS-Br demonstrated excellent acceptability, with a completion rate of 99% and an average completion time of 4.6 minutes. Exploratory factor analysis revealed three factors: emotional well-being, physical comfort, and anxiety relief, with respective composite reliability coefficient values of 0.874, 0.580, and 0.428. The test-retest reliability of the ISAS-Br, measured by the intraclass correlation coefficient, was 0.67 (95% confidence interval [95% CI] 0.42 to 0.83), and the Bland-Altman plot showed satisfactory agreement between the measurements.

*The research project for this study was submitted and approved by the Research Ethics Committees of the Federal University of Santa Catarina (CAEE 53334721.2.0000.0121) and the University of South Santa Catarina (CAEE 67752423.0.0000.0261).

* Corresponding author.
E-mail: nika_mp@yahoo.com.br (N.M. Moritz).

https://doi.org/10.1016/j.bjane.2023.11.001
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: The proposed Brazilian version of the ISAS underwent successful cross-cultural adaptation according to international standards. It demonstrated good acceptability and reliability, regarding the assessment of temporal stability. However, the ISAS-Br exhibited low internal consistency for some factors, indicating that this instrument lacks sensitivity to assess the satisfaction of deeply sedated patients. Further studies are necessary to explore the hypotheses raised based on the knowledge of its psychometric properties.
© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Satisfaction of patients with anesthesia and their perception of outcomes is a widely studied measure, becoming an important quality of care indicator.[1-8] To enhance the quality of care in ambulatory procedures, the American Society of Anesthesiologists created the concept of monitored anesthesia care (MAC) to differentiate sedation performed by a qualified anesthesia provider from that performed by other physicians.[9] In this scenario, comfort, safety, and full recovery are essential to achieve success at all stages of treatment.[10]

In this regard, Dexter et al.[11] developed a reliable and valid tool in American English known as the Iowa Satisfaction with Anesthesia Scale (ISAS). This instrument provides a better understanding of sedation outcomes from the patients' perspective and thereby improves their satisfaction with anesthesia. Anesthesia-specific satisfaction questionnaires encompass various dimensions of satisfaction, such as the relationship with the healthcare staff and access to information.[5,8,12] However, the ISAS questions specifically refer to the anesthesia experience itself, rather than to the perioperative period like other questionnaires,[13,14] making it a useful tool to gather information regarding satisfaction with different drugs and the quality of sedation.[11]

The ISAS scale consists of eleven questions that alternately assess negative and positive sensations to avoid acquiescence bias.[11] For each item, responses are given on a six-point Likert scale, and each response generates a score ranging from -3 to +3. The unweighted average of the eleven responses yields the total satisfaction score after reversing the scores of negative questions. Therefore, the higher the score, the greater the patient satisfaction.[11]

Since its publication in 1997, the ISAS has been adapted and validated with acceptable psychometric properties by Garcia et al.[15] for Spanish in Colombia and for French in France by Falempin et al.[16] In the literature, it is described as robust and highly acceptable, meeting the criteria of a questionnaire with good psychometric properties.[17,18] Several studies[4,19,20] have used this satisfaction scale, including in multicenter studies.[19,21]

As there is no specific Portuguese instrument in Brazil to assess the quality of sedation, the cross-cultural adaptation of the ISAS is expected to provide a useful tool for measuring satisfaction of Brazilian patients with anesthesia for ambulatory procedures. Furthermore, it may help to identify better anesthetic options in future studies. Therefore, the aim of this study was to perform a cross-cultural adaptation, evaluating the acceptability, validity, and reliability of the Brazilian version of ISAS.

Methods

The methodological approach of this study involved a first stage of cross-cultural adaptation of the ISAS[11] from its original English version and a second stage of assessing the psychometric properties of the proposed Brazilian version.

The research project for this study was submitted and approved by the Research Ethics Committees of the Federal University of Santa Catarina (Universidade Federal de Santa Catarina, CAEE 53334721.2.0000.0121) and the University of South Santa Catarina (Universidade do Sul de Santa Catarina, CAEE 67752423.0.0000.0261). All participants signed an informed consent form prior to participating in any of the stages. Permission was obtained from the authors of the original scale to conduct the study.

Cross-cultural adaptation stage

First, the original version of the ISAS was translated into Portuguese by three qualified and independent translators. Two translators without knowledge of the research's theoretical context, one being a Brazilian national fluent in English and the other an American fluent in Brazilian Portuguese. The third translator, a healthcare professional Brazilian native, fluent in English, with theoretical knowledge of the research. Based on the three versions, the researchers synthesized a Portuguese version, considering their common points and reviewing their discrepancies. This synthesized version was sent to two new independent and naïve on the construct translators to perform back-translations. One of them was a native English speaker living in Brazil, and the other was a linguistics specialist. The discrepancies between the translated versions, back-translations and the original were analyzed by a committee of experts, consisting of an anesthesiologist, two epidemiologists, a surgeon, and three medical students. A pre-final version, named ISAS-Br, was developed ensuring clarity, comprehensibility of the questions, as well as semantic, idiomatic, and conceptual equivalence, guaranteeing that the translated version retained the same content as the original version, considering the observations made by one of the authors of the original scale.

The pre-final version of ISAS-Br was used as a pre-test for ten adult Brazilian patients undergoing sedation for ambulatory procedures at the University Hospital of the Federal University of Santa Catarina (Hospital Universitário da Universidade Federal de Santa Catarina, HU-UFSC). The scale was presented preserving its original structure and sequence of the items. The objective was to identify comprehension problems, difficulties in understanding the meaning of each item, scale complexity and to inquire whether the

statements were related to satisfaction with anesthesia. The final version of ISAS-Br was proposed after the committee of experts reviewed the results of the pre-test.

Psychometric properties assessment stage

A cross-sectional epidemiological study was conducted with a minimum sample of 120 individuals, which corresponds to the appropriate proportion based on the scale items.[22] Data collection took place at HU-UFSC and two private clinics, all located in the city of Florianópolis/SC, Brazil, after obtaining authorization from each institution. It was conducted on specific, non-consecutive days at each institution, in accordance with the occurrence of procedures, until an adequate sample size was achieved. All eligible patients scheduled for procedures on these specific days were included.

Patients undergoing sedation (MAC) by an anesthesiologist for any ambulatory procedures were selected. The included patients were Brazilian, literate, and over 18 years of age. Patients undergoing ophthalmic surgery were only included if their postoperative vision was not compromised, allowing them to individually respond to the scale. Individuals diagnosed with any degree of cognitive dysfunction, mental illness, or neurological disease were excluded.

The sedation was conducted at the discretion of the anesthesiologist and the decision to perform local anesthesia was made by the surgeon. The procedure would start once the patient ceased to respond to verbal commands. After the procedure, patients were transferred to the postanesthesia recovery room. Subsequently, at least one hour after their admission to the recovery room, with the patients fully alert and conscious, the attending nurse handed the instructions and ISAS-Br questionnaire to them and stepped away to allow the patients to respond to it comfortably and individually. All professionals involved signed a consent form to acknowledge the research and were not involved with the research. The assistant anesthesiologist only prescribed medication if necessary.

The scale was also completed a second time, through an electronic form, sent on the day following the procedure. This sample corresponded to 20% of the total sample of patients, randomly selected for test-retest analysis purposes. Sociodemographic data were collected through interviews and data regarding preanesthetic consultation, type and time of procedure, and the American Society of Anesthesiologists (ASA) physical status were obtained from the patient's medical records.

Statistical analysis was performed using the Jamovi v.2.3.9 program. Qualitative data were presented as absolute and relative numbers. Quantitative variables were presented as means and standard deviations (SD).

The acceptability of ISAS-Br was assessed by response rates and completion time. Exploratory factor analysis (EFA) is a statistical method rooted in the premise that correlations between variables arise from a shared underlying factor. In the context of patient-reported outcomes, these constructs represent the meaningful dimensions that influence how patients perceive and answer the individual items within a questionnaire. Thus, EFA was used to determine construct validity, evaluating the dimensional structure of the instrument and item adequacy. Initially, two methods were employed to determine if the data could be subjected to factor analysis: the Kaiser-Meyer-Olkin (KMO) criterion and Bartlett's test of sphericity. For interpreting KMO indices, values greater than 0.5 are considered acceptable. The Bartlett's test of sphericity values with significance levels ($p < 0.05$) indicate that the matrix is factorable. The parallel analysis method was used to determine the number of factors to be retained, and the maximum likelihood method with varimax rotation for proper factor extraction.

Reliability was assessed through internal consistency and scale stability. Values above 0.6 for the composite reliability coefficient were considered acceptable. Scale stability was determined through test-retest analysis. Values above 0.7 for the intraclass correlation coefficient (ICC) were considered indicative of a strong correlation. However, a high correlation does not necessarily imply that there is good agreement between two methods. So, a Bland-Altman plot was used for a more detailed analysis of the agreement between the test and retest. The adopted level of statistical significance was 5% ($p < 0.05$).

Results

The cross-cultural adaptation of ISAS followed international protocols, with most items having similar translations.[23,24] The only item that showed discrepancies was item 11 ("I hurt"), which was translated as "Doeu" and "Me machuquei". The committee decided that, to maintain the original emotional meaning, as discussed with the scale author, "Eu sofri" would be more appropriate. The back-translations remained consistent with the original scale, except for this final item, which was appropriately back-translated as "I suffered". Thus, the pre-final version was formed and applied to ten patients as a pre-test. All participants found it easy to respond to, objective, accessible, and understood well the items, and they believed that the items were correlated with the construct of satisfaction with anesthesia. After this process, in the final review, the proposed Brazilian version (ISAS-Br) was approved by the committee without the need for adjustments, as presented in Figure 1.

ISAS-Br was administered to 128 patients to assess its psychometric properties. The sociodemographic and anesthesia-related characteristics are described in Table 1. The participants' ages ranged from 21 to 80 years, with a mean of 47 years (SD = 13.5). The mean procedure duration was 45 minutes (SD = 35.89), ranging from 10 to 170 minutes.

The mean total score of ISAS-Br was 2.59 (SD = 0.54) with a range of -0.27 to 3.0. Table 2 shows the responses for each item. Ceiling and floor effects were observed in all items, with little response variability, with item 7 showing the highest variation and items 8 and 10 showing the lowest. All patients who reported thermal discomfort mentioned feeling cold. Regarding acceptability, 127 out of 128 participants (99%) answered the ISAS-Br completely, with a mean completion time of 4.6 minutes (SD = 2.34).

Regarding construct validity, the Kaiser-Meyer-Olkin measure of 0.63 and the Bartlett's test of sphericity with $p < 0.001$ indicated that the data matrix could be factorized. EFA was conducted, and it was determined, based on parallel analysis, to retain three factors (see scree plot in Fig. 2). These factors collectively accounted for 39.84% of the total variance. Factor 1, related to emotional well-being,

Cada afirmação da pesquisa descreve uma sensação que você possa ter tido **durante** sua anestesia.

Para cada item, por favor, marque a resposta que melhor descreve como você se sentiu.

Se você não sentiu o que está descrito na afirmação, marque alguma das respostas de discordância: discordo totalmente, discordo moderadamente ou discordo um pouco.

Se você sentiu o que está descrito na afirmação, marque alguma das respostas de concordância: concordo totalmente, concordo moderadamente ou concordo um pouco.

Não há respostas certas ou erradas.

Marque uma resposta apenas para cada item. Faça isso colocando um X na opção de resposta que melhor dá sua opinião sobre o item.

Ninguém deve ajudá-lo a preencher a pesquisa. Só você deve ler a pesquisa e marcar as respostas que parecem melhor se adequar.

Por favor, não tenha pressa. Queremos que suas respostas sejam precisas.

1. Vomitei ou tive vontade de vomitar.

☐ Discordo totalmente

☐ Discordo moderadamente

☐ Discordo um pouco

☐ Concordo um pouco

☐ Concordo moderadamente

☐ Concordo totalmente

(mesmas opções de respostas da afirmação 1 nas afirmativas de 2 a 11)

2. Gostaria de receber a mesma anestesia novamente.
3. Senti coceira.
4. Eu me senti relaxado(a).
5. Senti dor.
6. Eu me senti seguro(a).
7. Senti muito frio ou muito calor.
8. Fiquei satisfeito(a) com meus cuidados anestésicos.
9. Senti dor durante a cirurgia.
10. Eu me senti bem.
11. Eu sofri.

The Iowa Satisfaction with Anesthesia Scale is copyrighted (Franklin Dexter and the University of Iowa Research Foundation).

Figure 1 Final version of ISAS-Br.

contributed 19.65%, factor 2, associated with physical comfort, contributed 12.90%, and the final factor, addressing anxiety/fear relief, contributed 7.29%. The factor loadings of the items on each factor are described in Table 3.

Regarding scale reliability, the values of composite reliability indicators were 0.874, 0.580, and 0.428 for factors 1, 2, and 3 respectively, calculated considering the factor loadings of each item. In Figure 3, the temporal stability of the ISAS-Br, with 25 participants, is assessed through two plots, illustrating the ICC (Fig. 3A) and Bland-Altman (Fig. 3B) analysis. ICC value was 0.67 (95% CI 0.42 to 0.83), indicating a moderate to substantial correlation with statistical significance between test scores and retest scores. Bland-Altman plot analysis demonstrated satisfactory agreement between measurements.

Discussion

The American ISAS[11] scale has already been validated in Spanish[15] and French,[16] demonstrating adequate psychometric

Table 1 Description of the cross-cultural adaptation study sample of the ISAS-Br (n = 127).

Characteristics	n	(%)
Age		
18–59 years	99	78
> 60 years	28	22
Gender		
Female	56	44
Male	71	56
Skin color (n = 124)		
White	103	83
Non-white	21	17
Education[a]		
Incomplete elementary/middle education	27	21
Complete elementary/middle education or higher	100	79
ASA physical status (n = 125)		
I	51	41
II	72	58
III	2	2
Surgical specialties		
Dermatology	17	13
General surgery	19	15
Gynecology	5	4
Ophthalmology	6	5
Plastic surgery	23	18
Urology	57	45
Healthcare system		
Public	64	50
Private	63	50
History of previous anesthesia		
No	18	14
Yes	109	86
Sedative medication		
Alfentanil, midazolam, ketamine	1	1
Fentanyl, midazolam	6	5
Fentanyl, midazolam, clonidine	1	1
Fentanyl, midazolam, dexmedetomidine	1	1
Midazolam, sufentanil	1	1
Propofol	18	14
Propofol, alfentanil	5	4
Propofol, alfentanil, midazolam	1	1
Propofol, dexmedetomidine	13	10
Propofol, dexmedetomidine, ketamine	1	1
Propofol, fentanyl	40	31
Propofol, fentanyl, ketamine	1	1
Propofol, fentanyl, dexmedetomidine	10	8
Propofol, fentanyl, midazolam	23	18
Propofol, midazolam	1	1
Propofol, midazolam, dexmedetomidine	1	1
Propofol, midazolam, dexmedetomidine, ketamine	1	1
Propofol, midazolam, sufentanil	2	2

[a] Over four years of study.

properties for assessing anesthesia satisfaction. Being the only scale designed for MAC and aimed at providing accurate information about satisfaction with anesthetics, the present study sought to perform its cross-cultural adaptation, thus proposing the ISAS-Br. It followed all the steps determined by internationally accepted methodology,[23,24] resulting in a version that maintained the original meaning of the scale, even resembling the translations in languages of the same Latin origin, such as French and Spanish.[15,16]

The psychometric properties of the ISAS-Br were analyzed in a sample of 127 patients, which represents an adequate sample size according to the literature.[22] The demographic characteristics were similar to those of the original American, French, and Spanish versions.[11,15,16] However, it is noteworthy that 21% of the participants in the ISAS-Br study did not complete elementary education. This implies a low education level, potentially affecting scale interpretation, as patients responded unassisted. Conversely, the healthcare professionals involved, including the anesthetist, surgeon, and nurse responsible for questionnaire distribution, were not part of the research. They were aware that the questionnaire focused on medication evaluation rather than their own work, minimizing potential bias.

The average time to complete the scale was around five minutes, like the original and Spanish versions and slightly longer than the French version.[11,15,16] This demonstrated good acceptability, in addition to a 99% response rate.

The average score found was 2.59 (SD = 0.54), higher and with a lower SD than those found by Dexter et al.[11] (2.1, SD = 0.87), Falempin et al.[16] (2.2, SD = 0.7), Garcia et al.[15] (2.27, SD = 0.83), and Candiotti et al. (2.0, SD = 0.97).[19] This finding can be explained by the low incidence of negative sensations related to anesthesia, particularly intraoperative pain, which increases discrimination in satisfaction among patients. Additionally, a floor-ceiling effect[25] was observed in all items, especially regarding items 8 and 10, which are related to satisfaction and well-being. This response pattern was also evidenced in Falempin et al's study.[16] However, the French version obtained greater response variability compared to the ISAS-Br. This can be explained by the anesthetic depth, as in the present sample the patients expected (sought) deep sedation for their surgery, having been unconscious for parts of the anesthetic, reducing discrimination with the ISAS-Br. Hence, an alternative hypothesis emerges about cultural influence. Many patients in this study strongly agreed with the positive scale items, even while also reporting adverse events. They might have associated negative sensations, particularly pain, with the surgical procedure rather than anesthesia.

The EFA of the Brazilian version revealed three factors explaining satisfaction with moderate/deep sedation. The first factor, linked to emotional support, had "feeling good" with the highest factor loading. "Feeling pain" was the item that made the greatest contribution to the second factor, which was associated with physical comfort. Itchiness and thermal discomfort had minimal factor loadings. This suggests that pain, hurt, and even nausea/vomiting, although associated with physical sensations, are influenced by emotional factors, and may impact satisfaction more than itchiness and feeling cold. Despite their very low contributions to overall satisfaction, items 3 and 7, which are related to potential drug side effects, provide important information

Table 2 Proportion of responses for each item of the ISAS-Br (n = 127).

	Agree very much n (%)	Agree moderately n (%)	Agree slightly n (%)	Disagree slightly n (%)	Disagree moderately n (%)	Disagree very much n (%)	Means subscore
1. I threw up or felt like throwing*	4 (3.1)	0 (0)	1 (0.8)	1 (0.8)	2 (1.6)	119 (93.7)	2.83
3. I itched*	6 (4.7)	0 (0)	6 (4.7)	2 (1.6)	-	113 (89.0)	2.50
5. I felt pain*	4 (3.1)	4 (3.1)	7 (5.5)	1 (0.8)	3 (2.4)	108 (85.1)	2.39
7. I was too cold or hot*	13 (10.2)	8 (6.3)	17 (13.4)	1 (0.8)	4 (3.1)	84 (66.2)	1.49
9. I felt pain during surgery*	5 (3.9)	–	6 (4.7)	–	1 (0.8)	115 (90.6)	2.57
11. I hurt*	4 (3.1)	–	1 (0.8)	1 (0.8)	2 (1.6)	119 (93.7)	2.75

	Disagree very much n (%)	Disagree moderately n (%)	Disagree slightly n (%)	Agree slightly n (%)	Agree moderately n (%)	Agree very much n (%)	Means subscore
2. I would want to have the same anesthetic again	4 (3.1)	-	3 (2.4)	5 (3.9)	3 (2.4)	112 (88.2)	2.61
4. I felt relaxed	2 (1.6)	2 (1.6)	3 (2.4)	1 (0.8)	3 (2.4)	116 (91.2)	2.69
6. I felt safe	1 (0.8)	–	–	3 (2.4)	5 (3.9)	118 (92.9)	2.87
8. I was satisfied with my anesthetic care	2 (1.6)	–	1 (0.8)	–	1 (0.8)	123 (96.8)	2.87
10. I felt good	1 (0.8)	–	–	1 (0.8)	3 (2.4)	122 (96.0)	2.75

Items 1, 3, 5, 7, 9, 11 are negative/dissatisfaction (order of responses presented in reverse). The Iowa Satisfaction with Anesthesia Scale is copyrighted (Franklin Dexter and the University of Iowa Research Foundation).

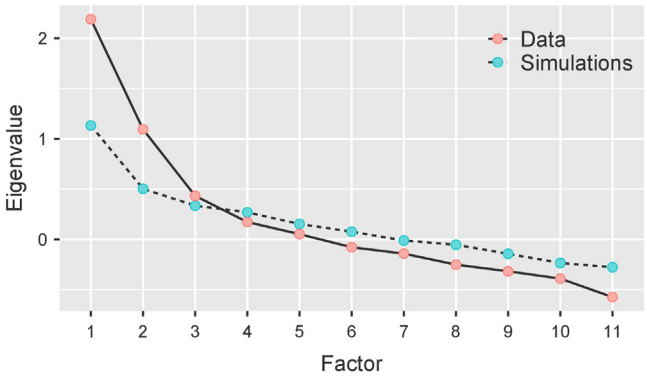


Figure 2 The scree plot displays the eigenvalues generated by the parallel analysis method in the exploratory factor analysis. This method, considered more accurate than others, compared the eigenvalues from the pilot sample (data) with those generated from a random sample of the same size (simulations). The goal is to identify the point at which the observed eigenvalues significantly deviate from the mean eigenvalues of random data. Only eigenvalues greater than those generated in the random sample were retained, indicating the extraction of three factors.

that should be considered, as the instrument is associated with satisfaction with anesthetics. The third factor, possibly linked to anxiety/fear relief, explains questions 2 and 4 about receiving the same anesthesia again and feeling relaxed.

Although the Cronbach's alpha coefficient is widely used for assessing internal consistency, the composite reliability has been presented as a more robust indicator of precision than alpha. This is because, in the computation of composite reliability, the factorial weights of the items can vary, whereas in the alpha coefficient the item loadings are fixed to be equal.[26] Therefore, this indicator was chosen to assess the internal consistency of each factor in this scale due to variations in item contributions to the satisfaction with anesthesia construct. The emotional well-being factor had high internal consistency, while physical comfort factors and anxiety/fear relief had lower internal consistency.

The results of the test-retest, which yielded an ICC value of 0.67, along with the interpretation of the Bland-Altman plot, demonstrated statistical significance and good stability of the scale. These findings are consistent with the ICC results reported by Dexter et al.[11] (0.74), Falempin et al.[16] (0.74), and Garcia et al.[15] (0.71). In a Canadian study, Fung et al.[20] found a lower ICC (0.57) in a sample of patients undergoing ophthalmic procedures. Considering that the administration time of the scale influences patient recall,[27] the ISAS-Br was administered within the recommended timeframe and repeated (retest) on the day following the procedure.

Although the ISAS aims to assess anesthetic agents, it is complex due to multidimensional satisfaction,[6] making it challenging for patients to distinguish medication effects from anesthesiology care. Furthermore, according to Capuzzo et al.[12] and Fung and Cohen,[28] emotional aspects impact anesthesia satisfaction more than negative sensations. The ISAS strongly depends on pain and there is a paradoxical relationship between pain and patient satisfaction,[29] the findings in this study and the difficulty in transforming satisfaction into something objective are understandable. Nonetheless, the ISAS is an interesting tool, more for its ability to identify potential factors of dissatisfaction and its sensitivity to intervention than for its structure.[21]

Another important aspect to highlight is that due to procedure-related anxiety, some patients request a deeper level of sedation, which can positively influence their level of satisfaction. In this study, the procedure would start after the patient stopped responding to verbal commands, indicating moderate to deep sedation.[30] However, the deeper the level of sedation and the higher the doses of sedatives, the lower the ability to distinguish sensations related to drugs during the procedure, affecting the face validity of the ISAS since this instrument measures satisfaction with anesthetics.

Table 3 Factor loadings from the exploratory factor analysis of ISAS-Br after extraction using the maximum likelihood method with varimax rotation and composite reliability indices for each factor.

	Factor			
	1 Emotional well-being factors	2 Physical comfort	3 Anxiety/ Fear relief	Singularity
Item 10	0.95			0.09
Item 6	0.83			0.31
Item 8	0.74			0.29
Item 5		0.75		0.43
Item 9		0.69		0.47
Item 11		0.45		0.80
Item 1		0.33		0.87
Item 3		0.16		0.97
Item 7		0.14		0.97
Item 4			0.61	0.61
Item 2			0.43	0.81
Composite reliability	0.874	0.580	0.428	

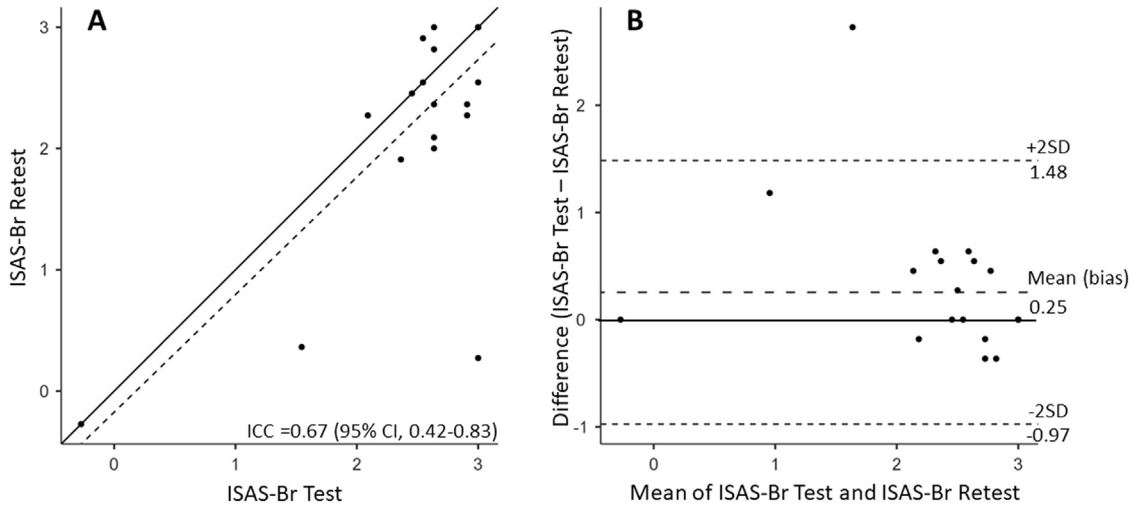


Figure 3 These two plots illustrate the temporal stability of ISAS-Br (n = 25). (3A) ICC is shown in a scatter plot with retest and test scores. Most data points are close to the identity line, randomly scattered around it. This suggests that the test and retest measurements have good correlation. (3B) Bland-Altman plot displaying the relationship between the test vs retest bias (y axis: difference between values from test and retest for each individual) and the theoretical real value (x axis: mean value from test and retest for each individual). The points clustered around the bias line (mean difference = 0.25, p = 0.054), within the limits of agreement (-0.97 to 1.48), indicate that the test and retest measurements have good agreement and consistency. Both plots show that there is no significant systematic bias between them since there is low vertical dispersion and no apparent patterns.

Among the limitations of this study is the non-continuous sampling, which could introduce selection bias. Positively, this sample included different populations, from two private clinics and one public university hospital, increasing its heterogeneity. The high mean score of the ISAS-Br together with the limited response variability also represents a limitation for some statistical tests, particularly those related to variance. These limitations require caution in the analysis of the presented results, and further studies in different populations are recommended to confirm the hypotheses raised in the discussion regarding different sedatives, anesthetic depth, and cultural aspects.

In conclusion, this study successfully adapted the ISAS for the Brazilian context to measure satisfaction with anesthesia from the patient's perspective. The ISAS-Br demonstrated high acceptability and good temporal stability. However, it exhibited limited internal consistency for certain factors, indicating that this instrument lacks sensitivity to assess the satisfaction of deeply sedated patients. Understanding its psychometric properties encourages further research to explore its full potential as an instrument. Likewise, its availability enables researchers to expand their knowledge of patient perceptions with different anesthetic medications and their combinations.

Conflicts of interest

The Iowa Satisfaction with Anesthesia Scale is copyright Franklin Dexter and the University of Iowa Research Foundation. Dr. Dexter receives no funds personally other than his salary and allowable expense reimbursements from the University of Iowa and has tenure with no incentive program. He and his family have no financial holdings in any company related to his work, other than indirectly through mutual funds for retirement. Income from the Division of Management Consulting work including use of the Iowa Satisfaction with Anesthesia Scale is used to fund Division research. A list of all the Division's consults is available in Dr. Dexter's posted curriculum vitae at https://FranklinDexter.net/Contact_Info.htm.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Fleisher LA. Quality anesthesia medicine measures, patients decide. Anesthesiology. 2018;129:1063–9.
2. Chin J, Mcgrath M, Lokken E, Upegui CD, Prager S, Micks E. Ketamine compared with fentanyl for surgical abortion: a randomized controlled trial. Obs Gynecol. 2022;140:461–9.
3. Heidegger T, Husemann Y, Nuebling M, et al. Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmaking among six hospitals in Switzerland and Austria. Br J Anaesth. 2002;89:863–72.
4. Heidegger T, Saal D, Nübling M. Patient satisfaction with anaesthesia - part 1: satisfaction as part of outcome – and what satisfies patients. Anaesthesia. 2013;68:1165–72.
5. Nübling M, Saal D, Heidegger T. Patient satisfaction with anaesthesia – part 2: construction and quality assessment of questionnaires. Anaesthesia. 2013;68:1173–8.
6. Schiff JH, Fornaschon AS, Frankenhauser S, Schiff M, Snyder-Ramos SA, Martin E, et al. The Heidelberg Peri-anaesthetic Questionnaire – development of a new refined psychometric questionnaire. Anaesthesia. 2008;63:1096–104.

7. Williams MR, Ward D, Carlson D, et al. Evaluating patient-centered outcomes in clinical trials of procedural sedation, part 1 efficacy: sedation consortium on endpoints and procedures for treatment, education, and research recommendations. Anesth Analg. 2017;124:821—30.
8. Williams MR, McKeown A, Dexter F, et al. Efficacy outcome measures for procedural sedation clinical trials in adults: an ACTTION systematic review. Anesth Analg. 2016;122:152—70.
9. American Society of Anesthesiologists. Distinguishing monitored anesthesia care ("MAC") from moderate sedation/analgesia (conscious sedation) [Internet]. www.asahq.org [last update 2018 Oct 17; cited 2021 Sep 7]. Available at: https://www.asahq.org/standards-and-guidelines/statement-on-distinguishing-monitored-anesthesia-care-from-moderate-sedation-analgesia.
10. Hobaika A, Diniz M, Castro C. Cuidados anestésicos monitorados em anestesia ambulatorial. Rev Med Minas Gerais. 2005;15:37—40.
11. Dexter F, Aker J, Wright W. Development of a measure of patient satisfaction with monitored anesthesia care. Anesthesiology. 1997;87:865—73.
12. Capuzzo M, Landi F, Bassani A, Grassi L, Volta CA, Alvisi R. Emotional and interpersonal factors are most important for patient satisfaction with anaesthesia. Acta Anaesthesiol Scand. 2005;49:735—42.
13. Caljouw MAA, Van Beuzekom M, Boer F. Patient's satisfaction with perioperative care: development, validation, and application of a questionnaire. Br J Anaesth. 2008;100:637—44.
14. Auquier P, Pernoud N, Bruder N, Simeoni MC, Auffray JP, Colavolpe C, et al. Development and validation of a perioperative satisfaction questionnaire. Anesthesiology. 2005;102:1116—23.
15. García LFJ, Capera ADR. Validation to spanish of the Iowa Satisfaction with Anesthesia Scale (ISAS) for monitored anesthesia care in ophthalmic surgery. Rev Colomb Anestesiol. 2014;42:272—80.
16. Falempin A-S, Pereira B, Gonnu-Levallois S, et al. Transcultural validation of a french version of the Iowa Satisfaction with Anesthesia Scale (ISAS-F). Can J Anesth. 2020;67:541—9.
17. Barnett S, Alagar R, Grocott M, Giannaris S, Dick J, Moonesinghe S. Patient-satisfaction measures in anesthesia. Anesthesiology. 2013;119:452—78.
18. Chanthong P, Abrishami A, Wong J, Herrera F, Chung F. Systematic review of questionnaires measuring patient satisfaction in ambulatory anesthesia. Anesthesiology. 2009;110:1061—7.
19. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. Anesth Analg. 2010;110:47—56.
20. Fung D, Cohen M, Stewart S, Davies A. Can the Iowa satisfaction with anesthesia scale be used to measure patient satisfaction with cataract care under topical local anesthesia and monitored sedation at a community hospital? Anesth Analg. 2005;100:1637—43.
21. Dexter F, Candiotti KA. Multicenter assessment of the iowa satisfaction with anesthesia scale, an instrument that measures patient satisfaction with monitored anesthesia care. Anesth Analg. 2011;113:364—8.
22. Anthoine E, Moret L, Regnault A, Sbille V, Hardouin JB. Sample size used to validate a scale: a review of publications on newly - developed patient reported outcomes measures. Health Qual Life Outcomes. 2014;12:1—10.
23. Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Heal. 2005;8:94—104.
24. Mokkink LB, Prinsen CA, Patrick D, et al. COSMIN study design checklist for patient-reported outcome measurement instruments [Internet]. COSMIN 2019 [cited 2021 Sep 7]. Available on: https://www.cosmin.nl/wp-content/uploads/COSMIN-study-designing-checklist_final.pdf.
25. Terwee CB, Bot SDM, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60:34—42.
26. Valentini F, Damásio BF. Average variance extracted and composite reliability: reliability coefficients. Psicol Teor Pesqui. 2016;32:1—7.
27. Chadha RM, Dexter F, Brull SJ. Lack of recall after sedation for cataract surgery and its effect on the validity of measuring patient satisfaction. Korean J Anesthesiol. 2020;73:319—25.
28. Fung D, Cohen M. What do outpatient value most in their anesthesia care. Can J Anaesth. 2001;48:12—9.
29. Capuzzo M, Alvisi R. Is it possible to measure and improve patient satisfaction with anesthesia? Anesth Clin. 2008;26:613—26.
30. American Society of Anesthesiologists. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia [Internet]. www.asahq.org [last update 2019 Oct 23; cited 2021 Sep 7]. Available at: https://www.asahq.org/standards-and-guidelines/statement-on-continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedation-analgesia.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Evaluation of the relationship between the STOP-Bang score with oxygen reserve index and difficult airway: a prospective observational study

Ilka D. Alp, Bengü G. Köksal *, Keziban Bollucuoğlu, Gamze Küçükosman, Özcan Pişkin, Çağdaş Baytar, Rahşan D. Okyay, Hilal Ayoğlu

Zonguldak Bülent Ecevit University Medical School, Department of Anesthesiology and Reanimation, Zonguldak, Turkey

Received 15 March 2023; accepted 21 July 2023
Available online 28 July 2023

KEYWORDS
Airway management;
General anesthesia;
Hypoxia;
Obstructive sleep apnea;
Oxygen reserve index

Abstract

Background: Patients diagnosed with Obstructive Sleep Apnea (OSA) syndrome have a tendency towards hypoventilation, hypoxia, and hypercarbia in the perioperative period. This study hypothesized that the Oxygen Reserve Index (ORi) could predict possible hypoxia and determine difficult airways in patients at risk for OSA, as determined by the STOP-Bang questionnaire.

Methods: This prospective study included adult patients undergoing elective surgery under general anesthesia with endotracheal intubation, divided into two groups: low risk (0–2 points) and high risk (3–8 points) based on their STOP-Bang questionnaire results. The primary outcome measure was the highest ORi value reached during preoxygenation and the time to reach this value. Data were recorded at four time points: before preoxygenation (T1), end of preoxygenation (T2), end of mask ventilation (T3), and end of intubation (T4), as well as partial oxygen pressure values in T1, T2, and T4. The secondary outcome measures were the grading scale for mask ventilation, Cormack-Lehane score, tonsil dimensions, use of a stylet, and application of the burp maneuver during intubation.

Results: In the high-risk group, preoperative peripheral oxygen saturation values, the highest ORi value reached in preoxygenation, and ORi values at T3 and T4 times were lower, and the time to reach the highest ORi value was longer ($p < 0.05$).

Conclusion: Using ORi in patients with OSA may be useful in evaluating oxygenation, and since difficult airway is more common, ORi monitoring will better manage possible hypoxic conditions.

© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by recurrent episodes of upper airway obstruction during sleep,

* Corresponding author:
E-mail: bengukoksal@gmail.com (B.G. Köksal).

https://doi.org/10.1016/j.bjane.2023.07.010
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

accompanied by sleep fragmentation, hypoxemia, and arterial oxygen desaturation. Although OSA patients tend to be obese, non-obese patients can also have OSA. In obese patients, increased adipose tissue in the neck predisposes to airway narrowing, while in patients with normal body weight, tonsillar hypertrophy or craniofacial skeletal abnormalities predispose to narrowing or closure of the airway.[1] Since most patients are not diagnosed with OSA in the preoperative period, any patient undergoing elective surgery may present with OSA symptoms or signs.[2] Recognizing these patients prevents complications that may develop in the perioperative process or early intervention. The increased frequency of difficult mask ventilation and difficult intubation in patients with OSA makes preoperative evaluation and appropriate preparation crucial.[3]

Several questionnaires have been developed for diagnosing OSA syndrome. These questionnaires screen patients at risk for OSA and direct them toward polysomnography, which provides a definitive diagnosis. The STOP-Bang questionnaire is preferred due to its ease of application, speed, and practicality. Studies comparing the questionnaire with polysomnographic tests have shown high sensitivity, especially in high-risk groups.[4,5]

The Oxygen Reserve Index (ORi^{TM}) is a noninvasive and continuous measurement parameter used to assess real-time oxygen reserve status at a Partial pressure of Oxygen (PaO_2) in the mild hyperoxia range of approximately 100−200 mmHg. ORi is measured by applying a sensor to the finger and varies in the range of 0.00−1.00, depending on the oxygenation reserve status.[6] Additionally, ORi allows clinicians to accurately assess the patient's oxygenation status without arterial blood gas administration, preventing unnecessary and unexpected hypoxia.[7]

Based on these findings, this study hypothesizes that ORi can be used to predict possible hypoxia and determine difficult airways in patients at risk for OSA, as determined by the STOP-Bang questionnaire.

Methods

Ethical approval

This prospective observational study was conducted at Zonguldak Bülent Ecevit University Health Training and Research Center, Zonguldak, from January 2021 to June 2022 after obtaining approval from the faculty ethics committee (ethical approval No. 2020-22/16) and written consent from the patients. The principles of the Declaration of Helsinki and the STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) guidelines were followed when reporting this study. This study was registered at Clinicaltrials.gov (NCT05640856).

Participants

The study included 72 patients aged 18−65 in the American Society of Anesthesiologists (ASA) I−III risk group intubated under general anesthesia and undergoing elective surgery. Patients previously diagnosed with OSA syndrome before preoperative evaluation, as well as those diagnosed with asthma, chronic obstructive pulmonary disease, heart failure or coronary artery disease, morbid obesity (Body Mass Index – BMI > 45 $kg.m^{-2}$), alcohol or drug addiction, pregnant or lactating women, and those allergic to the drugs to be administered, were excluded from the study.

Procedures and patient management

The patients in the study were divided into two groups: Group L, low risk (0−2 points), and Group H, high risk (3−8 points), according to their STOP-Bang score. Patients were monitored using electrocardiography and noninvasive blood pressure as they were taken to the operating room. A Rainbow® Sensor (Masimo Corp., Irvine, CA, USA) was applied to the fourth finger on the arm without a blood pressure cuff and covered with a light shielding sheath to measure ORi and Peripheral Oxygen Saturation (SpO_2). This sensor was imaged using Root® with the Radical-7® instrument (Masimo Corp.). A bilateral cerebral oximetry (NIRS) sensor was also attached to the patient's forehead.

In patients who were not premedicated, a 20G arterial cannula was inserted in the arm to which the ORi probe was not attached, and preoperative blood gas was measured at the bedside. Patients were then informed about preoxygenation, and it was applied for 3 min with 6 L. min^{-1} 100% oxygen using a properly fitted mask without leakage.

Patients who could not cooperate with preoxygenation and whose expiratory oxygen concentration (FeO_2) did not exceed 80% were excluded from the study. After 3 min, anesthesia was induced using 1 $mg.kg^{-1}$ lidocaine, 2−2.5 $mg.kg^{-1}$ propofol, and 1 $mcg.kg^{-1}$ fentanyl. Mask ventilation was graded using the Han scale[8] (Grade 1: Ventilated by mask, Grade 2: Ventilated by mask with oral airway, Grade 3: Difficult to ventilate (insufficient, unstable, requiring two assistants, significant gas leakage despite appropriate mask etc.), Grade 4: Unable to ventilate (with/without neuromuscular blockade). A mask grade > 2 was defined as difficult mask ventilation. Mask ventilation was continued for 120 seconds after administration of 0.6 $mg.kg^{-1}$ rocuronium, and at the end of this period (T3), Endotracheal Intubation (ETI) was performed (T4). The same blinded physician performed mask ventilation and intubation. Tonsil size was evaluated according to the Brodsky[9] scale, classifed as; grade 0 Tonsils within the tonsillar fossa; Grade 1 Tonsils just outside of the tonsillar fossa and occupy ≤ 25% of the oropharyngeal width; Grade 2 Tonsils occupy 26−50% of the oropharyngeal width; Grade 3 Tonsils occupy 51−75% of the oropharyngeal width; Grade 4 Tonsils occupy > 75% of the oropharyngeal width and the patient's Cormack-Lehane (CML) score was assessed during laryngoscopy. The time from the beginning of the laryngoscopy to the insertion of the endotracheal tube between the vocal cords was noted as the apnea time. Arterial blood gas samples were taken simultaneously with intubation. The standard difficult intubation protocol was applied to all patients in the study. After the first intubation attempt, in cases where the vocal cords could not be seen with laryngoscopy (CML score III and IV), intubation was attempted using the stylet and/or burp maneuver (second attempt). Intubation was considered difficult when a video laryngoscope was required.

Data collection and outcome measures

Age, gender, body mass index, ASA score, and smoking history were determined before surgery, along with the STOP-Bang score. Before preoxygenation (T1), at the end of preoxygenation (T2), during mask ventilation (T3), and at intubation (T4), hemodynamic parameters, ORi and NIRS values were recorded for all patients. PaO_2 values were examined and recorded at T1, T3, and T4. The highest ORi value (maximum ORi) and the time to reach this value (time to reach maximum ORi) were recorded. To examine the relationship between ORi and PaO_2, the difference between T1 and T2 ORi values was recorded as ORi change 1 (ΔORi 1), the difference between T2 and T4 ORi values was recorded as ORi change 2 (ΔORi 2), the difference between T1 and T2 PaO_2 values was recorded as PaO_2 change 1 (ΔPaO_2 1), and the difference between T2 and T4 PaO_2 values was recorded as PaO_2 change 2 (ΔPaO_2 2). Secondary endpoints included the need for stylet use, burp maneuver, video laryngoscope for intubation success, and the grade of mask ventilation.

Sample size calculation

The sample size was determined based on the ORi values at the end of preoxygenation, with a 95% confidence level (1-α), 95% test power (1-β), and $d = 0.826$ effect size, requiring a total minimum of 66 patients.[10] Considering a potential 15% loss in follow-up, 76 patients were included in the study.

Statistical analyses

The data were analyzed using IBM SPSS 22. The normal distribution test was conducted using the Kolmogorov-Smirnov test. Normally distributed data were evaluated using parametric tests, while non-normally distributed data were evaluated using non-parametric tests. The analyses used the Mann-Whitney U, *t*-test, Chi-Square, Friedman, and Spearman correlation analyses. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of participants

Out of the 76 patients assessed for eligibility, 72 were included in the study (Fig. 1). The mean age of the patients included in the study was 44.40 ± 10.98 years (range: 18−65 years). The demographic and clinical characteristics of the two groups are presented in Table 1. There were no significant differences between the groups regarding age, gender, and smoking status. However, Group H had higher numbers of ASA III patients and higher BMI values than Group L, whereas Group L had more ASA I patients.

No significant differences in heart rate and mean arterial pressure were observed between the two groups. However, the SpO_2 values in Group H were significantly lower at T1 ($p = 0.009$). In addition, ORi values were significantly lower in Group H at T3 and T4. It was also determined that both groups had a significant difference in ORi measurements for all four time periods (Table 2).

There were no significant differences in PaO_2 values between the two groups. However, there was a significant difference in the measurements for all periods within both groups (Table 3). The two groups had a statistically significant difference regarding maximum ORi, ORi change during apnea, and ΔPaO_2 1 measurement. Maximum ORi and ΔPaO_2 1 measurements were lower in Group H, while ORi change during apnea duration was greater in Group H (Table 4).

There was no statistically significant difference between the two groups in terms of the Mallampati classification and the Cormack-Lehane classification. However, tonsil size was 25−50% larger in Group H than in Group L ($p = 0.027$). Difficult mask ventilation, BURP maneuver, and stylet use were significantly higher in patients with a high risk of OSA (Table 5).

Values are presented as mean ± standard deviation or number (%). MV: Mask ventilation, VL: Videolaryngoscope.

When examining the correlations between change in PaO_2 and ORi, a weak positive correlation was found between ΔORi 1 and ΔPaO_2 1 ($p = 0.003$, $r = 0.343$), as well as a weak positive correlation between ΔORi 2 and ΔPaO_2 2 ($p = 0.001$, $r = 0.392$).

Discussion

In all patients, regardless of their risk of OSA determined by the STOP-Bang score, ORi values ranged from 0 to 1, and PaO_2 did not fall below 60 mmHg. Preoperative oxygen saturation was lower in the high-risk group, but there was no significant difference in ORi and PaO_2 between the low and high-risk groups. The high-risk group had the lower highest ORi value during preoxygenation, while the ORi and PaO_2 changes tended to increase more in the low-risk group.

Difficult mask ventilation was more frequent in patients with a high STOP-Bang score. The tonsil size was larger in the high-risk group, and the need for stylet use and Burp maneuvers during intubation were higher. There was a weak positive correlation between the change in ORi and PaO_2 before, after preoxygenation, and after intubation.

Early detection of desaturation is crucial for patient safety. Measurement of the oxygen reserve index provides a non-invasive way to monitor real-time oxygenation status in the mildly hyperoxic range ($100\ mmHg < PaO_2 \leq 200\ mmHg$).[7] The oxygen reserve index has been used to detect desaturation in various clinical scenarios, including pediatric intubation and airway surgeries, rapid sequence induction and intubation, and one-lung ventilation.[11-13] In our study, the ORi values of patients ranged from 0 to 1, and there was no decrease in peripheral oxygen saturation. We believe this is due to the low number of high-risk patients with a STOP-Bang score of 6 or higher in the study.

In a previous study comparing SpO_2, ORi, and PaO_2 measurements during general anesthesia induction, ORi showed hypoxia before the decrease in saturation, and ORi and PaO_2 measurements were correlated in the moderately hyperoxic range but weakly correlated in the case of high hyperoxia where PaO_2 exceeds 240 mmHg.[14]

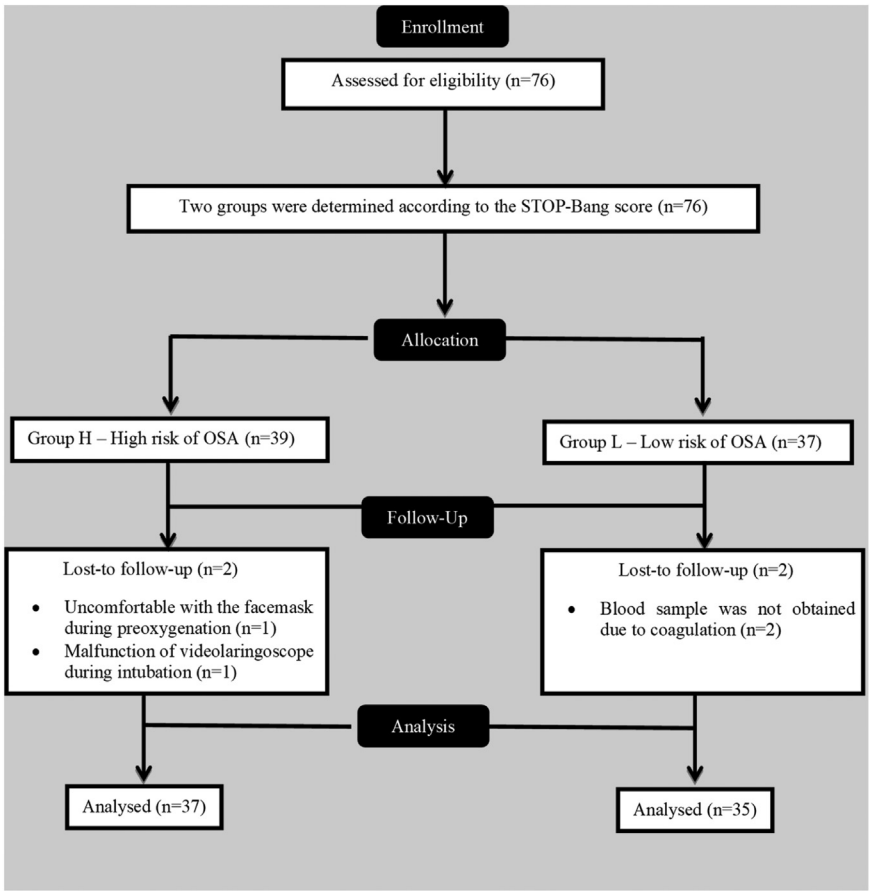


Figure 1 Flowchart of patients' enrolment, allocation, and analysis procedure.

Table 1 Comparison of demographic and clinical characteristics of the groups.

	Group L (n = 35)	Group H (n = 37)	*p*
Gender Female/Male	17/18 (48.6/51.4)	20/17 (54.1/45.9)	0.819
Age, years	41.97 ± 10.77	46.70 ± 10.8	0.068
ASA physical status, I/II/III	8/26/1 (22.9/74.3/2.9)	0/23/14 (0/62.2/37.8)	**<0.001**
Body mass index, $kg.m^{-2}$	29.55 ± 5.93	39.21 ± 5.66	**<0.001**
Smoking status +/-	15 /20 (42.9/57.1)	12 /25 (32.4/67.6)	0.361

Values are presented as mean ± standard deviation or number (%). ASA, American Society of Anesthesiologists.

Table 2 Comparison of ORi values between groups.

	Grup L (n = 35)	Grup H (n = 37)	*p*[a]
T1	0.006 ± 0.02 (0–0.09)	0 (0–0)	0.071
T2	0.79 ± 0.21 (0.33–1)	0.72 ± 0.24 (0.09–1)	0.193
T3	0.56 ± 0.22 (0.15–0.92)	0.42 ± 0.21 (0.05–0.86)	**0.038**
T4	0.52 ± 0.2 (0.13–0.91)	0.38 ± 0.21 (0–0.85)	**0.030**
***p*[b]**	**<0.001**	**<0.001**	

Values are presented as mean ± standard deviation or Minimum–Maximum.
[a] *p*-value, comparison between groups.
[b] *p*-value, compared within the group.
T1, Before preoxygenation; T2, After preoxygenation; T3, End of mask ventilation; T4, After intubation.

This study found a positive, weak correlation between ORi and PaO_2 changes during preoxygenation and after intubation. This may be due to the high degree of hyperoxia achieved after 3 min of preoxygenation with 100% oxygen. Although patients had difficult intubation in both groups, no hypoxemia was observed in blood gases taken after intubation. Further studies with lower FiO_2 or shorter duration preoxygenation methods are needed in

Table 3 Comparison of arterial Partial Pressure of Oxygen (PaO_2) values between groups

	Group L (n = 35)	Group H (n = 37)	p^a
T1	91.49 ± 12.21 (91)	87.97 ± 15.48 (85)	0.102
T2	410.97 ± 72.97 (427)	380.70 ± 81.46 (395)	0.098
T4	330 ± 70.53 (321)	315.41 ± 86.92 (307)	0.333
p^b	**<0.001**	**<0.001**	

Values are presented as mean ± standard deviation.
[a] *p*-value, comparison between groups.
[b] *p*-value, compared within the group.
T1, Before preoxygenation; T2, After preoxygenation; T3, End of mask ventilation; T4, After intubation.

Table 4 Comparison of maximum ORi, time to reach maximum ORi, apnea time, ORi change in apnea time, ΔORi and ΔPaO_2 values between groups.

	Group L (n = 35)	Group H (n = 37)	*p*
Max. ORi	0.86 ± 0.18 (0.94)	0.79 ± 0.21 (0.87)	**0.037**
Time to reach max. ORi	101.26 ± 36.62 (90)	115.57 ± 41.79 (119)	0.159
Apnea time (sec)	34.25 ± 18.70 (29)	38.59 ± 19.84 (32)	0.199
ORi change during apnea	0.04 ± 0.08 (0.02)	0.06 ± 0.11 (0.03)	**0.039**
ΔORİ 1	0.79 ± 0.22 (0.85)	0.72 ± 0.24 (0.79)	0.255
ΔORİ 2	−0.27 ± 0.20 (-0.26)	−0.29 ± 0.23 (-0.23)	0.888
ΔPaO_2 1	319.48 ± 75.56 (333)	292.73 ± 76.65 (297)	**0.048**
ΔPaO_2 2	−80.97 ± 81.78 (-84)	−65.30 ± 82.59 (-57)	0.464

Values are presented as mean ± standard deviation and median.
ΔPaO_2 1, PaO_2 change in T1-T2 time interval; ΔPaO_2 2, PaO_2 change in T2-T4 time interval; ΔORİ 1, ORİ change in T1-T2 time interval; ΔORİ 2, ORİ change in T2-T4 time interval.

Table 5 Comparison of mask ventilation, BURP maneuver and use of stylet and Videolaryngoscope.

	Group L (n = 35)	Group H (n = 37)	p
Easy/Difficult MV	30/5 (85.7/14.3)	23/14 (62.2/37.8)	**0.023**
BURP maneuver +/-	10/25 (28.6/71.4)	20/17 (54.1/45.9)	**0.028**
Use of stylet +/-	8/27 (22.9/77.1)	18/19 (48.6/51.4)	**0.023**
Use of VL +/-	3/32 (8.6/91.4)	5/32 (13.5/86.5)	0.505

Values are presented as mean ± standard deviation or number (%). MV, Mask Ventilation; VL, Videolaryngoscope.

high-risk OSA patients to better understand the relationship between ORi and PaO_2.

Patients with obstructive sleep apnea syndrome are at higher risk for hypoxia and hypercarbia due to factors such as obesity, altered lung mechanics, and airway obstruction during apnea periods.[15] Tsymbal et al.[10] reported that in obese patients, the ORi values at the end of preoxygenation and the beginning of intubation were significantly lower than those of patients with normal BMI, and the tolerable apnea time was also lower in obese patients. Although the tolerable apnea time was not evaluated in this study, ORi values at the end of preoxygenation, mask ventilation, and intubation were significantly lower in the high-risk group for OSA. This may be due to the negative impact of higher BMI on respiratory function in this group.

The relationship between tonsil size and the severity of sleep apnea is well-established in the literature.[16] In a study by Friedman et al,[17] tonsil size was associated with the severity of sleep apnea in 172 cases with suspected sleep apnea, with larger tonsil sizes indicating a higher severity of the disorder. Additionally, studies have reported a significant decrease in the apnea-hypopnea index after tonsillectomy in adults, indicating the potential benefits of surgical intervention in patients with large tonsils and sleep apnea.[18,19] Consistent with these findings, in this study, patients in the high-risk group for OSA had larger tonsil sizes, which may have contributed to increased airway resistance, snoring, apnea, or hypopnea, ultimately leading to a higher STOP-Bang score.

The relationship between sleep apnea and difficult airway was first reported by Hiremath et al.,[20] and it was found that the apnea-hypopnea index was higher in patients with difficult intubation. Most studies examining the relationship between difficult airways and OSA used polysomnography, the gold standard for diagnosing OSA. Instead, the STOP-Bang questionnaire is used to screen patients for OSA, as polysomnography may not be readily available or feasible in certain settings. In a study comparing STOP-Bang scores and polysomnography results in the surgical population, patients with a score of 6 and above were determined to have a high probability of moderate/severe OSA.[21]

A meta-analysis of 72,888 patients reported that patients with OSA had a 3.39-fold higher rate of Difficult Mask Ventilation (DMV) than those without (1.48% vs. 1.11%, respectively). The same study also stated that the risk of difficult intubation increased in OSA patients, and the incidence of this condition increased as the severity of OSA increased (39% mild to moderate and 23% severe OSA).[3] In another study conducted with patients over 45 years of age, the risk of difficult intubation was shown to increase in patients diagnosed with moderate or severe OSA by preoperative polysomnography and with a STOP-Bang score of 3 and above, and DMV was only associated with neck circumference.[22] A study investigating the STOP-Bang questionnaire's role in predicting difficult intubation showed that the frequency of difficult intubation increased in patients with a score of 3 and above.[23] In a single-center study evaluating 307 patients who underwent elective surgery with the STOP-Bang score, the rate of difficult intubation was found to be 28.6% in the high-risk group (> 3 points), while it was not observed in the low-risk group (0–2 points).[24] In our study, the same physician provided the airway of all patients. Although difficult mask ventilation was seen significantly more frequently (37.8%) in high-risk patients, no significant relationship was found with difficult intubation, unlike the literature. The rate of difficult intubation was 13.5% in the high-risk patient group. Although the difference between the two groups regarding the need for a video laryngoscope was insignificant, the use of stylet and the need for Burp maneuver were higher in the high-risk patient group.

Our study has several limitations. First, patients with pulmonary or cardiac comorbidities were excluded, and further studies are necessary to evaluate the efficacy of ORi monitoring in these high-risk patients. Second, the study only used a standard preoxygenation method, and the effect of different preoxygenation methods on patients at risk of OSA was not examined. Third, the data may not be sufficient to estimate the relationship between SpO_2, ORi, and PaO_2 in cases of unexpectedly difficult airways or prolonged apnea duration, as standard difficult airway preparation was applied to each patient. Fourth, the risk of OSA is also present in non-obese patients, but this study was planned without excluding the obesity factor. Finally, the study did not follow up with ORi in the postoperative period, which may have been necessary to monitor patients at risk of hypoxia.

In conclusion, according to the STOP-Bang score, patients at risk of OSA may have a difficult airway, and monitoring ORi in the perioperative period could be useful in managing possible hypoxic conditions in these patients. Although there were no patients with very high stop bang scores in our study, the decrease in ORI during apnea was significantly greater in the high-risk group, so our study provides preliminary evidence that ORi monitoring may be useful in managing perioperative oxygenation in patients at risk for OSA. Furthermore, future studies could explore different preoxygenation methods, the effects of ORi monitoring in patients with pulmonary or cardiac comorbidities, and the long-term outcomes of ORi monitoring in patients at risk for OSA.

Declaration of Competing Interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Ilka D. Alp: Conceptualization, Data curation, Formal analysis, Investigation, Project administration. **Bengü G. Köksal:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Keziban Bollucuoğlu:** Methodology, Resources, Supervision. **Gamze Küçükosman:** Writing – review & editing. **Özcan Pişkin:** Writing – original draft, Writing – review & editing. **Çağdaş Baytar:** Conceptualization, Formal analysis, Methodology. **Rahşan D. Okyay:** Conceptualization, Methodology. **Hilal Ayoğlu:** Supervision.

Funding

This research was supported as a part of the Bülent Ecevit University Scientific Research Project (Project Number: 2021-52053101-03). The sponsoring organization was not involved in the study design, data analysis, or interpretation.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval number

2020-22/16 (The institutional review board of Zonguldak Bülent Ecevit University; meeting date: 18/11/2020).

Clinical trial registration number

NCT05640856 (https://clinicaltrials.gov/ct2/results?cond=&term=+NCT05640856&cntry=&state=&city=&dist=).

References

1. Partinen M, Guilleminault C, Quera-Salva MA, Jamieson A. Obstructive sleep apnea and cephalometric roentgenograms. The role of anatomic upper airway abnormalities in the definition of abnormal breathing during sleep. Chest. 1988;93:1199–205.
2. Wolfe RM, Pomerantz J, Miller DE, Weiss-Coleman R, Solomonides T. Obstructive sleep apnea: preoperative screening and postoperative care. J Am Board Fam Med. 2016;29:263–75.
3. Nagappa M, Wong DT, Cozowicz C, Ramachandran SK, Memtsoudis SG, Chung F. Is obstructive sleep apnea associated with difficult airway? Evidence from a systematic review and meta-analysis of prospective and retrospective cohort studies. PLoS One. 2018;13:e0204904.
4. Chiu HY, Chen PY, Chuang LP, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: A bivariate meta-analysis. Sleep Med Rev. 2017;36:57–70.

5. Christensson E, Franklin KA, Sahlin C, et al. Can STOP-Bang and Pulse Oximetry Detect and Exclude Obstructive Sleep Apnea? Anesth Analg. 2018;127:736—43.
6. Scheeren TWL, Belda FJ, Perel A. The oxygen reserve index (ORI): a new tool to monitor oxygen therapy. J Clin Monit Comput. 2018;32:379—89.
7. Chen ST, Min S. Oxygen reserve index, a new method of monitoring oxygenation status: what do we need to know? Chin Med J (Engl). 2020;133:229—34.
8. Han R, Tremper KK, Kheterpal S, O'Reilly M. Grading scale for mask ventilation. Anesthesiology. 2004;101:267.
9. Brodsky L, Moore L, Stanievich JF. A comparison of tonsillar size and oropharyngeal dimensions in children with obstructive adenotonsillar hypertrophy. Int J Pediatr Otorhinolaryngol. 1987;13:149—56.
10. Tsymbal E, Ayala S, Singh A, Applegate 2nd RL, Fleming NW. Study of early warning for desaturation provided by Oxygen Reserve Index in obese patients. J Clin Monit Comput. 2021;35:749—56.
11. Ishida Y, Okada T, Kobayashi T, Uchino H. ORi™: a new indicator of oxygenation. J Anesth. 2021;35:734—40.
12. Koishi W, Kumagai M, Ogawa S, Hongo S, Suzuki K. Monitoring the Oxygen Reserve Index can contribute to the early detection of deterioration in blood oxygenation during one-lung ventilation. Minerva Anestesiol. 2018;84:1063—9.
13. Yoshida K, Isosu T, Noji Y, et al. Usefulness of oxygen reserve index (ORi™), a new parameter of oxygenation reserve potential, for rapid sequence induction of general anesthesia. J Clin Monit Comput. 2018;32:687—91.
14. Cheng HW, Yeh CY, Chang MY, Ting CK, Chang PL. How early warning with the Oxygen Reserve Index (ORi™) can improve the detection of desaturation during induction of general anesthesia? J Clin Monit Comput. 2022;36:1379—85.
15. Isono S. Obstructive sleep apnea of obese adults: pathophysiology and perioperative airway management. Anesthesiology. 2009;110:908—21.
16. Dahlqvist J, Dahlqvist A, Marklund M, Berggren D, Stenlund H, Franklin KA. Physical findings in the upper airways related to obstructive sleep apnea in men and women. Acta Otolaryngol. 2007;127:623—30.
17. Friedman M, Tanyeri H, La Rosa M, et al. Clinical predictors of obstructive sleep apnea. Laryngoscope. 1999;109:1901—7.
18. Holmlund T, Franklin KA, Levring Jäghagen E, et al. Tonsillectomy in adults with obstructive sleep apnea. Laryngoscope. 2016;126:2859—62.
19. Verse T, Kroker BA, Pirsig W, Brosch S. Tonsillectomy as a treatment of obstructive sleep apnea in adults with tonsillar hypertrophy. Laryngoscope. 2000;110:1556—9.
20. Hiremath AS, Hillman DR, James AL, Noffsinger WJ, Platt PR, Singer SL. Relationship between difficult tracheal intubation and obstructive sleep apnoea. Br J Anaesth. 1998;80:606—11.
21. Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129:198—205.
22. Seet E, Chung F, Wang CY, et al. Association of obstructive sleep apnea with difficult intubation: prospective multicenter observational cohort study. Anesth Analg. 2021;133:196—204.
23. Acar HV, Yarkan Uysal H, Kaya A, Ceyhan A, Dikmen B. Does the STOP-Bang, an obstructive sleep apnea screening tool, predict difficult intubation? Eur Rev Med Pharmacol Sci. 2014;18:1869—74.
24. Ozen V, Ozen N. Obstructive sleep apnea in surgical patients and its relationship with difficult intubation: two years of experience from a single center. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.08.010. Online ahead of print.

Brazilian Journal of Anesthesiology 2024;74(3): 744456



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Decreasing inconsistent alarms notifications: a pragmatic clinical trial in a post-anesthesia care unit

Saullo Queiroz Silveira[a], Rafael Sousa Fava Nersessian[a], Arthur de Campos Vieira Abib[a], Leonardo Barbosa Santos [a,b], Fernando Nardy Bellicieri [a], Karen Kato Botelho[c], Helidea de Oliveira Lima[b], Renata Mazzoni de Queiroz[a], Gabriel Silva dos Anjos[a], Hermann dos Santos Fernandes[d], Glenio B. Mizubuti [e], Joaquim Edson Vieira [f], Leopoldo Muniz da Silva [a,b,*]

[a] *Hospital São Luiz Unidade Itaim, Rede D'Or — Equipe de Anestesia CMA, Departamento de Anestesiologia, São Paulo, SP, Brazil*
[b] *Rede D'Or, Instituto D'Or de Pesquisa e Ensino (IDOR), Rio de Janeiro, RJ, Brazil*
[c] *São Luiz Hospital (ITAIM), Rede D'Or, Departamento de Enfermagem, São Paulo, SP, Brazil*
[d] *University of Toronto, Mount Sinai Hospital, Department of Anesthesiology and Pain Medicine, Toronto, Canada*
[e] *Queen's University, Department of Anesthesiology and Perioperative Medicine, Kingston, Canada*
[f] *Faculdade de Medicina da Universidade de São Paulo (FMUSP), Departamento de Cirurgia, Anestesiologia, São Paulo, SP, Brazil*

Received 12 April 2023; accepted 28 July 2023
Available online 9 August 2023

KEYWORDS
Anesthesia recovery period;
Clinical alarms;
Data management;
Monitoring;
Post-anesthetic care unit

Abstract
Background: Alarms alert healthcare professionals of deviations from normal/physiologic status. However, alarm fatigue may occur when their high pitch and diversity overwhelm clinicians, possibly leading to alarms being disabled, paused, and/or ignored. We aimed to determine whether a staff educational program on customizing alarm settings of bedside monitors may decrease inconsistent alarms in the Post-Anesthesia Care Unit (PACU).
Methods: This is a prospective, analytic, quantitative, pragmatic, open-label, single-arm study. The outcome was evaluated on PACU admission before (P1) and after (P2) the implementation of the educational program. The heart rate, blood pressure, and oxygen saturation alarms were selected for clinical consistency.
Results: A total of 260 patients were included and 344 clinical alarms collected, with 270 (78.4%) before (P1), and 74 (21.6%) after (P2) the intervention. Among the 270 alarms in P1, 45.2% were inconsistent (i.e., false alarms), compared to 9.4% of the 74 in P2. Patients with consistent alarms occurred in 30% in the P1 and 27% in the P2 ($p = 0.08$). Patients with inconsistent alarms occurred in 25.4% in the P1 and in 3.8% in the P2. Ignored consistent alarms were reduced from 21.5% to 2.6% ($p = 0.004$) in the P2 group. The educational program was a protective factor for the inconsistent clinical alarm (OR = 0.11 [95% CI 0.04–0.3]; $p < 0.001$) after adjustments for age, gender, and ASA physical status.

* Corresponding author.
E-mail: leopoldo.muniz@saoluiz.com.br (L.M. da Silva).

https://doi.org/10.1016/j.bjane.2023.07.013
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: Customizing alarm settings on PACU admission proved to be a protective factor against inconsistent alarm notifications of multiparametric monitors.
© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Clinical alarms on multiparameter monitors are important to ensure safety. They aim to alert healthcare professionals to vital sign changes that indicate something is out of the ordinary and direct them to take immediate action.[1] With new technologies, the number of clinical alarms has increased significantly.[2] Many of these alarms, however, have no clinical significance due to factors such as patient characteristics or monitoring errors, often leading to alarm fatigue. This is the phenomenon by which sensory overload leads to desensitization and makes the healthcare professional less likely to respond to alarms that indeed may warn of real risks to the patient.[1,3–5] It is important to note that alarms are specifically designed to cause cognitive distress,[5] thereby drawing the healthcare professional's attention to a potential issue.

Much has been written about this issue in intensive care units,[3,6–7] progressive care units,[8] emergency rooms,[9] and even in pediatrics.[7,10] However, there are limited similar studies on the surgical environment, particularly in the Post-Anesthesia Care Unit (PACU).

Potential causes of alarm fatigue include technical, organizational, and educational factors.[5,11] Therefore, its solution involves actions that impact one or more of these dimensions. Selecting appropriate monitors for each patient (avoiding over-monitoring), judicious selection of alarm limits, and using multimodal alarms can all reduce the number of nuisance alarms.[5]

Customizing alarm limits based on patients' initial vital sign values is a strategy to optimize monitors and more reliably detect real variations from the baseline. Alarm limit customization around patient's baseline values or baseline changes is a strategy to limit alarms to changes that are clinically significant.[12–20] PACU is an environment in which the anesthesiologist can guide the customization of alarms based on preoperative conditions, intraoperative events, and postoperative goals. It is worth noting that at this stage of care, very narrow limits may increase non-clinically significant alarms, as some degree of baseline variation is expected due to the effects of anesthesia and surgical intervention.

We hypothesized that PACU in a general tertiary hospital is a high-risk environment for alarm fatigue, and that customizing alarm limits based on each patient's baseline values by the anesthesiologist could reduce the number of non-clinically significant alarms, increase the rate of clinically significant alarms, and ultimately improve patient safety. The objective of this study was to determine if a staff educational program on customizing alarm settings on bedside monitors decreases inconsistent alarms in the PACU.

Methods

This investigation was approved by the Institutional Research Ethics Committee (Protocol # 5,188,464; CAAE: 54253821.6.0000.0087). This report is in compliance with the CONSORT Extension for Pragmatic Trials Checklist.[21]

This is a prospective, analytic, quantitative, pragmatic, open label, single-arm study, for which the outcome was evaluated on PACU admission before (P1) and after (P2) the implementation of the educational program on customizing alarm settings of bedside monitors. The outcomes of interest were evaluated through direct observation of the multiparametric monitors and patients during 30 consecutive day shifts: 13 in the pre-intervention period (P1), and the remaining 13 in the post-intervention period (P2) (Fig. 1). The educational program was conducted over 4 days between P1 and P2. During each 6-hour shift, two researchers not otherwise involved in patient care, observed 10 patients and were responsible for data collection. Patients were recruited based on convenience, according to the spontaneous demand for admissions and discharges.

Standard care in PACU

Clinical care in the PACU was provided by anesthesiologists, two registered nurses and four nurse technicians. Each anesthesiologist was responsible for his/her patients until PACU discharge. The total number of anesthesiologists in the study was 38. The PACU consisted of 18 bays and a centrally located nursing station. It is noteworthy that the composition of the PACU healthcare team fulfilled the existing legislation and that, at the time of data collection, each professional category was complete. This unit uses the GE Solar 8000i monitoring platform (General Electric Healthcare, Chicago, IL), which allows multilead continuous analysis. Monitoring capabilities at each bedside included a range of physiological parameters, with all patients monitored for Electrocardiogram (ECG) (Heart Rate [HR] and rhythm), Noninvasive Blood Pressure (NIBP), and Oxygen Saturation (SpO_2). Oxygen saturation monitoring was done with a finger probe connected to a specific module. The temperature was measured periodically by a separate thermometer (no temperature alarm system was installed).

Each monitor parameter was programmed with default values for alarm settings common to all monitored beds in the PACU. The default values were based on the monitor manufacturer's suggestions and consensus opinion of expert medical clinicians in the PACU. Default settings take effect each time a patient is discharged, and a new patient is admitted to the bed with that monitor. Bedside alarm settings could be customized by bedside clinicians based on individual patient care situations. When alarm settings

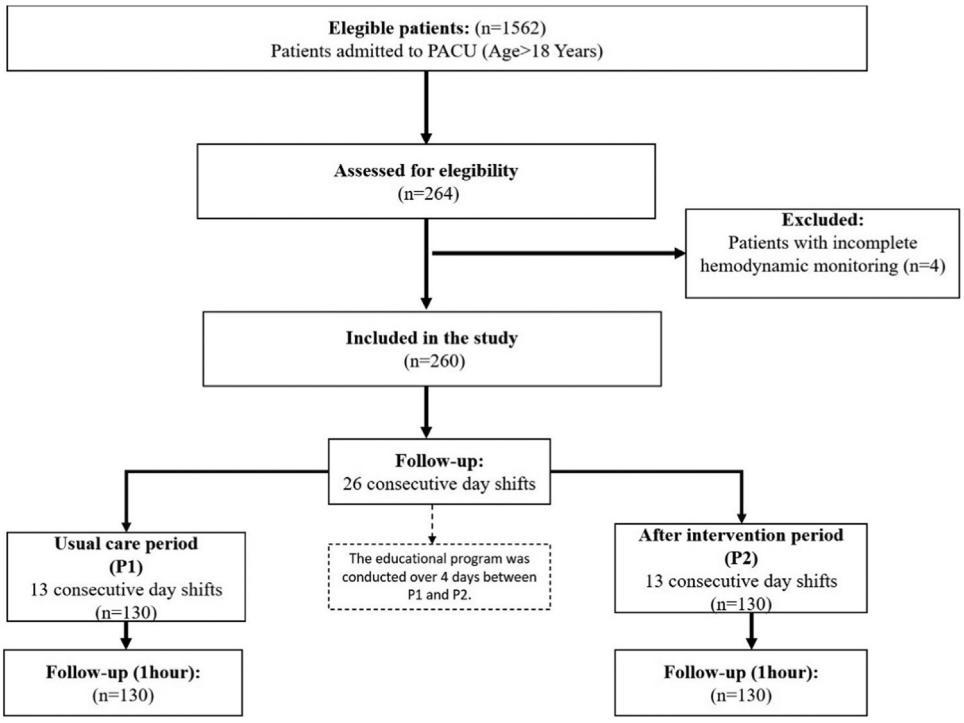


Figure 1 Study flow chart in accordance with the CONSORT Extension for Pragmatic Trials Checklist (www.consort-statement.org).

ranges were exceeded, audible alarms occurred at the bedside. The sound of the alarm was unique and customized to be a continuous double beep alarm.

Study intervention

The P2 intervention had multiple components aimed at achieving behavioral changes to reduce alarm fatigue and inconsistent alarms: 1) A 15-minute session educational program on alarm management designed to review the rationale for minimizing alarms and provide strategies for customizing alarm settings to reduce inconsistencies; 2) Nurses and anesthesiologists were educated on the management of monitor alarms: using appropriate age-specific profiles, customizing parameter thresholds for individual patient needs, and proper electrode placement; 3) Staff reeducation on how to admit, discharge, and readmit a new patient to the monitor to reduce unnecessary alarms.; 4) A summarizing key information for setting alarm limits individualized to each patient according to baseline vital signs and based on current literature data[22,23] on safe values for physiological parameters (Supplementary Table 1) — validated by a group of 24 physicians with expertise and experience in anesthesiology and/or intensive care; 5) Provision of a pocket card summarizing key information for setting alarm limits individualized for each patient; 6) Pocket card attachment to all bedside monitors.

Outcomes

For the purposes of this study, HR, NIBP, and SpO_2 alarms were selected as outcomes to be assessed. HR, NIBP and SpO_2 were recorded prior to anesthetic induction (baseline vital signs), upon admission to PACU, and every 15 minutes thereafter until PACU discharge. As per institutional routine, all patients remained in the PACU for a minimum of one hour, during which data collection took place. For those who remained in the PACU for less than 1 hour, data were collected during the first hour upon PACU admission. Patients with incomplete hemodynamic monitoring (any monitor connected to the patient with less than five ECG leads, absence of NIBP cuff or SpO_2 probe) were excluded. Each clinical alarm was classified as consistent or inconsistent, and the professionals' response to the alarm(s) was defined as: (i) Individualized customization; (ii) Pause (disable/mute); (iii) Warrants intervention or consultation for a clinical condition — this event could be considered benign with no further evaluation necessary or alarming, requiring some form of diagnostic or therapeutic intervention; (iv) No action (ignored); or (v) Checking leads and probes.

The alarm classification as inconsistent or consistent was applied prior to clinical evaluation by the attending team and it was not conditioned to their actions. Alarms were deemed inconsistent when they were triggered improperly because there was no individualized parameterization. If the alarm reflected a relevant clinical condition, representing a potential threat to the health status of the patient, or if the parameter was outside of the range (pre-)set for the patient on the bedside monitor, the alarm was considered consistent.

Data collection was done as follows: when hearing the alarm activation, the researcher responsible for data collection specifically identified the sound and visual signals originating from the monitor device, and carefully observed the actions adopted by the attending healthcare team. The number of alarm signal events was reconfirmed through review of existing bedside monitor computer alarm history for each monitored patient on the unit. The alarms were

quantified by the number of automatic activations until some action was taken by the attending team. The duration of each alarm was not recorded. Two types of alarms were not included in this study: (i) Those originating from manipulation of the patient or monitoring system by staff; and (ii) Those occurring until the device or system was properly set immediately after being switched on or reconnected. Two PACU beds were predefined (by the researchers responsible for data collection) at the beginning of each shift to receive patients to be included in the study. Notably, on admission to PACU, the anesthesiologist was unaware that his/her patient's bed would be included in the study.

Statistical analysis

The minimum required sample size was calculated using the online software G*POWER (https://g-power.apponic.com),[24] based on the distribution of the frequency of inconsistent alarms, before and after the parameterization by hemodynamic parameter, with a minimum difference of 30%.[25] For a power of 80%, effect size of 0.3 and a significance level of 5%, using a $\chi 2$ test, 110 participants per period was estimated as needed.

The measure of central tendency and dispersion for the number of alarms was the median and 25–75th percentiles (%), respectively, after analyzing the distribution in the normality curve. Categorical variables are presented as absolute values and percentages. The Mann-Whitney test was used for comparisons between study periods delimited by the interventions. The Pearson Chi-Squared test was employed for categorical variables, and partitioning Chi-Square when value of $p < 0.05$. The analysis of variables related to inconsistent alarms was presented as Odds Ratios (OR) with 95% Confidence Intervals (95% CI) as a measure of the association between P1 and P2, with adjustments for age, sex, and American Society of Anesthesiologists (ASA) physical status. Multivariate logistic regression by the direct method was used for this purpose. A 95% CI and p-value < 0.05 represented statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences 20.0 (SPSS 20.0 Mac, SPSS Inc., Chicago, Illinois, USA). Box plot with jittered data points was performed using R software version 3.4.4 (R Foundation for Statistical Computing, Austria).

Results

A total of 260 patients were included, 50.4% were ASA I, 45.4% ASA II, and 4.2% ASA III. Most of the participants were under the age of 40 years (57.1%) and 55.5% were women. There was no difference between P1 and P2 regarding ASA physical status ($p = 0.55$), age ($p = 0.30$), and gender ($p = 0.79$) (Supplementary Table 2). There was no statistically significant difference between comorbidities between P1 and P2 (Supplementary Fig. 1). A total of 344 clinical alarms were collected: 270 (78.4%) in P1 and 74 (21.6%) in P2. Among the 270 alarms in P1, 45.2% were inconsistent, compared to 9.4% of the 74 in P2. The median of consistent alarms per patient was 2 (1–5.5) in P1 and 2 (1–2) in P2 ($p = 0.05$). The median of inconsistent alarms per patient was 3 (2–4.0) in P1 and 1 (1–2) in P2 ($p = 0.02$)

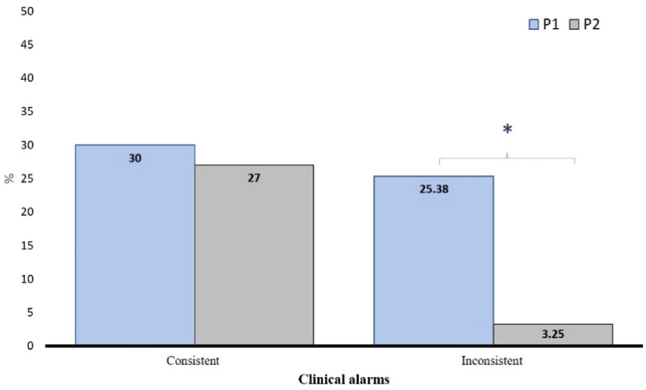


Figure 2 Classification of clinical alarms in the pre-intervention period (P1) and in the post-intervention period (P2). Values expressed in % – Chi-Square test; * $p < 0.05$.

(Supplementary Fig. 2). Consistent alarms occurred in 30% of individuals in the P1 and in 27% in the P2 ($p = 0.08$). On the other hand, inconsistent alarms occurred in 25.4% in the P1 and in 3.8% in the P2 ($p < 0.001$) (Fig. 2). NIBP represented the most alarmed parameter in the P1 and P2 groups (Supplementary Fig. 3). Based on baseline vital signs, individualized parameterization was indicated in P1 for 16.9% and in P2, for 20.8% ($p = 0.42$). In the P1, individualized parameterization was performed in 2.3% and in the P2 in 18.5% ($p = 0.001$) (Table 1). Regarding the clinical consistency of the alarms, there was less inconsistency concerning all parameters in P2. This represents more than 50% reduction in alarms by instituting targeted default monitor alarm limits. In addition to a significant reduction in the total number of clinical alarms that went off, the maintenance in consistent alarms, and decrease in inconsistent alarms, P2 was associated with a protective factor against inconsistent clinical alarms (OR = 0.11 [95% CI 0.04–0.3]; $p < 0.001$) after adjustments for age, gender, and ASA physical status (Fig. 3).

In P1, most inconsistent alarms remained active without any action by care providers (68.5%). In P2, this rate was reduced to 28.5% ($p < 0.001$). Faced with an inconsistent alarm, the two correct actions are individualized customization of the alarm or checking multileads and electrodes. In this scenario, customization occurred in 0% in P1 and 14.3% in P2 ($p < 0.001$), while checking multileads and electrodes was performed in 1.5% in P1 and 28.9% in P2 ($p < 0.001$). For consistent alarms, the expected course of action is clinical intervention or consultation for a clinical condition. In this sample, this action pattern occurred in 19.5% in P1 and 61.6% in P2 ($p < 0.004$) – a significant improvement. Consistent alarms sounding without action reduced from 21.7% to 2.6% ($p = 0.004$) (Fig. 4). No patient required noninvasive mechanical ventilation during the study period. No adverse events occurred in both groups.

Discussion

This study showed reduced bedside alarm inconsistency, lowered sensory overload and less alarm fatigue in the PACU from an educational program on customizing alarm settings to each patient's physiological condition.

Table 1 Need to alarm parameterization by professionals responsible for data collection and rates of individualized parameterization performed by the assistant team in the pre intervention period (P1) and in the post intervention period (P2).

	Period*		*p*-value
Individualized parameterization indicated	P1 % (n)	P2 % (n)	
No	83.08 (108)	79.23 (103)	0.52
Yes	16.92 (22)	20.77 (27)	
Individualized parameterization performed	**P1 % (n)**	**P2 % (n)**	***p*-value**
No	97.69 (127)	81.54 (106)	<0.001
Yes	2.31 (3)	18.46 (24)	

* Values are expressed as relative and absolute frequencies (χ2 test).

Customization of alarm limits is increasingly recognized as an effective solution to reduce inconsistent alarms. This is the first study to analyze an intervention to decrease inconsistent alarm signal events in the PACU. Inconsistent alarms annoy and stress healthcare workers, which may interfere with patient care once the sensory overload from false positive alarms leads to desensitization and makes the health professional more likely to ignore alarms warning of real risks to the patient.[1,3–5] The high rate of inconsistent alarms in the PACU is an issue that impairs the quality of patient care, increases the staff's stress, and the probability of sentinel events. For 2020, the ECRI Institute listed an alarm-related hazard among their Top 10 Health Technology Hazards (ECR). Our intervention, applying a quality-improvement methodology based on an educational program on alarm management, safely reduced the total number of alarms (270 to 74) and reduced the incidence of inconsistent alarm notifications (from 45.2% before, to 9.4% after program implementation). The evidence-driven interventions included high-reliability changes such as implementing alarm logic and changing the alarm notification process. The combination of these interventions enabled sustained improvements in individualized parametrization for 13 shifts in the post-intervention period.

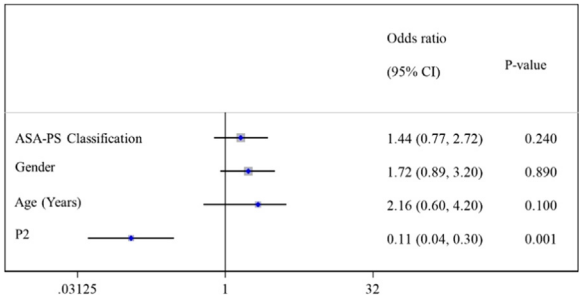


Figure 3 Variables associated with inconsistent alarms (Multivariate logistic regression by the enter method). P2 – post-intervention period.

Although individualizing alarm thresholds might seem trivial, before the intervention there was a significant number of staff members that followed the default thresholds of the monitoring devices and did not adjust the thresholds according to individual patient needs. Our results showed that individualized parameterization was performed in only 2.3% (Table 1). This might be either due to lack of time, will or know-how. According to a previous study, 3—40% of healthcare workers had never used many of the monitoring functions of a monitor.[26]

Alarm fatigue is a significant concern in healthcare settings due to high rates of false positive alarms, poor positive predictive value, and lack of standardization. These issues can lead to desensitization and reduced responsiveness to alarms, which compromise patient safety. While alarms are intended to increase sensitivity and reduce missed events,

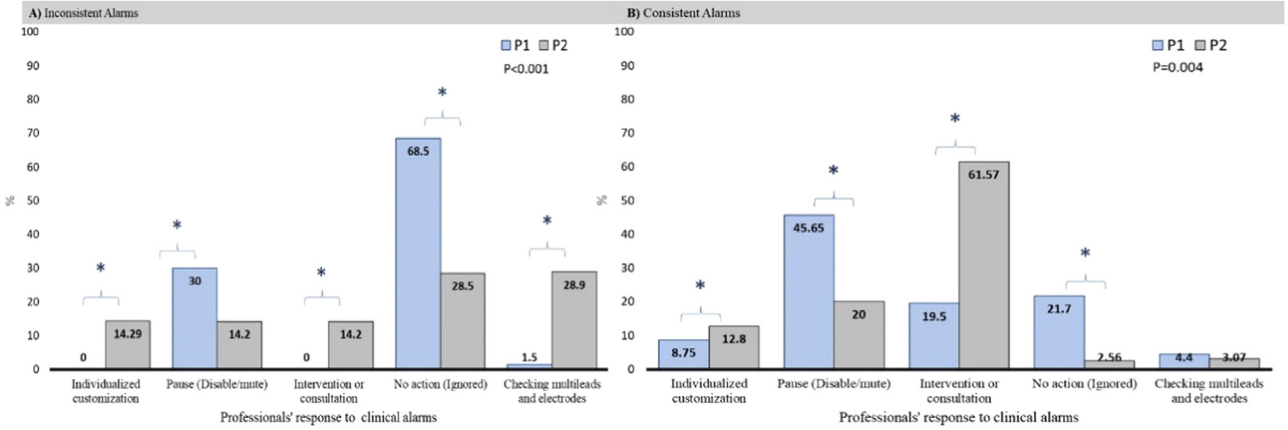


Figure 4 Professionals' response to clinical alarms between the pre-intervention period (P1) and in the post-intervention period (P2). Values expressed in % – Chi-Square test; * Chi-Square test ($p < 0.05$) — partitioning test.

excessive and inconsistent alarms can overwhelm healthcare staff and lead to inattention, distraction, and errors. In fact, there have been reports of alarm fatigue contributing to patient deaths.[12]

Our intervention successfully reduced inconsistent alarms, and also addressed the issue of neglected alarms. Neglected alarms decreased significantly in both the consistent (21.7% to 2.6%; $p < 0.004$) and inconsistent (68.5% to 28.5%; $p < 0.001$) groups after the intervention. After the intervention, the staff was more likely to correctly deal with an inconsistent alarm ($p < 0.001$). There was also an increase in the correct course of action after a consistent alarm ($p < 0.004$) (Fig. 3). Our intervention not only improved patient safety but also reduced alarm fatigue. Similar results have been reported in previous studies conducted in intensive care units.[5,12,27]

The customization of alarm limits studied did not affect the sensitivity of the monitor to detect adverse clinical conditions. The parametrization protocol did not reduce the number of consistent alarms, which is important since inappropriate customization could result in missing critical events. The results from our study indicated that the intervention resulted in no interference on the evaluation of true critical alarms.

The study aimed to develop a monitoring plan that met the patient's target values with joint decision-making of the attending team. A customization table based on baseline vital signs was used to standardize care and reduce individual bias of PACU professionals. How to customize safely is still a challenge in the postoperative period.[28] A recommendation guide on how to customize alarms was used to increase safety and avoid wider alarm limit ranges that could miss a clinically significant change in the patient's HR.[28] Wider alarm limit ranges create the potential for a clinically significant change in the patient's HR to be missed.[29] A recommendation guide on how to customize alarms increased safety in this study and did not reduce consistent alarms.

This study has several limitations. The presence of the research team may have interfered with the response to consistent alarms due to the Hawthorne effect.[30] Secondly, most patients had low complexity, and the findings may not be generalizable to other populations or institutions. Thirdly, patient and family experiences were not measured over the course of this study. Fourthly, the study did not evaluate the effect of the intervention on response time. Finally, as a complex sociotechnical phenomenon there was not a qualitative approach to this phenomenon. Future research should explore other factors, such as night shifts, for instance.

In conclusion, this study demonstrated that a simple staff-based educational program on customizing alarm settings to each patient's physiological condition, rather than using standard alarm values, significantly decreased the most common bedside inconsistent alarms, reduced sensory overload, and consequently alarm fatigue in the PACU, which can be a patient safety risk factor. Our findings, in addition to previous studies, are an important step towards developing alarm management strategies incorporating patient-specific characteristics. We hope that this study encourages further research towards patient-specific effects on monitoring alarms for surgical patients at the PACU.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Support was provided solely from institutional and/or departmental sources.

Disclosure statement

This study did not receive or require any funding sources. The authors have no commercial or non-commercial affiliations representing potential conflicts of interest, nor do they have any associations with consultancies of any type.

Ethics statement

This investigation was approved by the Hospital São Luiz & Rede D'or and Affiliated Teaching Hospitals Research Ethics Committee (Protocol # 5,188,464; CAAE: 54253821.6.0000.0087). Patient consent for publication was not required.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to express our gratitude to all the anesthesiologists of CMA's anesthesia team, especially to Dr. Andre Pla and Dr. José Marcos Silveira, who were the team coordinators. We would also like to extend our appreciation to the nursing staff of the post-anesthesia care unit of São Luiz Hospital (ITAIM).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.07.013.

References

1. Hu X, Sapo M, Nenov V, et al. Predictive combinations of monitor alarms preceding in-hospital code blue events. J Biomed Inform. 2012;45:913–21.
2. Borowski M, Görges M, Fried R, Such O, Wrede C, Imhoff M. Medical device alarms. Biomed Tech (Berl). 2011;56:73–83.
3. Claudio D, Deb S, Diegel E. A Framework to Assess Alarm Fatigue Indicators in Critical Care Staff. Crit Care Explor. 2021;3:e0464.
4. The Joint Commission. National Patient Safety Goals Effective January 2020. Hospital Accreditation Program. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020-hap-npsg-goals-final.pdf. Accessed 12 Feb 2023.
5. Ruskin KJ, Hueske-Kraus D. Alarm fatigue: impacts on patient safety. Curr Opin Anaesthesiol. 2015;28:685–90.

6. Paine CW, Goel VV, Ely E, et al. Systematic review of physiologic monitor alarm characteristics and pragmatic interventions to reduce alarm frequency. J Hosp Med. 2016;11: 136–44.
7. Simpson KR, Lyndon A. False Alarms and overmonitoring: major factors in alarm fatigue among labor nurses. J Nurs Care Qual. 2019;34:66–72.
8. Alsaad AA, Alman CR, Thompson KM, Park SH, Monteau RE, Maniaci MJ. A multidisciplinary approach to reducing alarm fatigue and cost through appropriate use of cardiac telemetry. Postgrad Med J. 2017;93:430–5.
9. Jämsä JO, Uutela KH, Tapper AM, Lehtonen L. Clinical alarms, and alarm fatigue in a University Hospital Emergency Department-A retrospective data analysis. Acta Anaesthesiol Scand. 2021;65:979–85.
10. Sowan AK, Vera AG, Fonseca EI, et al. Nurse competence on physiologic monitors use: Toward eliminating alarm fatigue in intensive care units. Open Med Inform J. 2017;11:1–11.
11. Hravnak M, Pellathy T, Chen L, et al. A call to alarms: Current state and future directions in the battle against alarm fatigue. J Electrocardiol. 2018;51(6S):S44–8.
12. Cvach M. Monitor alarm fatigue: an integrative review. Biomed Instrum Technol. 2012;46:268–77.
13. Honan L, Funk M, Maynard M, Fahs D, Clark JT, David Y. Nurses' perspectives on clinical alarms. Am J Crit Care. 2015;24:387–95.
14. Joshi R, Mortel HV, Feijs L, Andriessen P, Pul CV. The heuristics of nurse responsiveness to critical patient monitor and ventilator alarms in a private room neonatal intensive care unit. PLoS One. 2017;12:e0184567.
15. Wilken M, Hüske-Kraus D, Klausen A, Koch C, Schlauch W, Röhrig R. Alarm fatigue: Causes and effects. Stud Health Technol Inform. 2017;243:107–11.
16. Winters BD, Cvach MM, Bonafide CP, et al. Society for Critical Care Medicine Alarm and Alert Fatigue Task Force. Technological distractions (part 2): a summary of approaches to manage clinical alarms with intent to reduce alarm fatigue. Crit Care Med. 2018;46:130–7.
17. Bonafide CP, Lin R, Zander M, et al. Association between exposure to non-actionable physiologic monitor alarms and response time in a children's hospital. J Hosp Med. 2015;10:345–51.
18. Bonafide CP, Localio AR, Holmes JH, et al. Video analysis of factors associated with response time to physiologic monitor alarms in a children's hospital. JAMA Pediatr. 2017;171:524–31.
19. Mira JJ, Lorenzo S, Carrillo I, et al. Research Group on Second and Third Victims. Lessons learned for reducing the negative impact of adverse events on patients, health professionals and healthcare organizations. Int J Qual Health Care. 2017;29:450–60.
20. American Association of Critical Care Nurses. Managing alarms in acute care across the life span: electrocardiography and pulse oximetry. Crit Care Nurse. 2018;38:el6–20.
21. Zwarenstein M, Treweek S, Gagnier JJ, et al. CONSORT group; Pragmatic Trials in Healthcare (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ. 2008;337:a2390.
22. Graham KC, Cvach M. Monitor alarm fatigue: standardizing use of physiological monitors and decreasing nuisance alarms. Am J Crit Care. 2010;19:28–34.
23. Brantley A, Collins-Brown S, Kirkland J, et al. Clinical Trial of an Educational Program to Decrease Monitor Alarms in a Medical Intensive Care Unit. AACN Adv Crit Care. 2016;27:283–9.
24. Faul F, Erdfelder E, Lang A-G, G*Power Buchner A. 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91.
25. Assis AP, Oliveira FT, Camerini FG, Silva RCLD. Moraes CM. Individualized parameterization of multiparametric monitors alarms in infarcted patients. Rev Bras Enferm. 2019;72:609–16.
26. Sowan AK, Vera AG, Fonseca EI, Reed CC, Tarriela AF, Berndt AE. Nurse competence on physiologic monitors use: Toward eliminating alarm fatigue in intensive care units. Open Med Inform J. 2017;11:1–11.
27. Albert NM, Murray T, Bena JF, et al. Differences in alarm events between disposable and reusable electrocardiography lead wires. Am J Crit Care. 2015;24:67–73.
28. Ruppel H, Funk M, Kennedy HP, Bonafide CP, Wung SF, Whittemore R. Challenges of customizing electrocardiography alarms in intensive care units: A mixed methods study. Heart Lung. 2018;47:502–8.
29. Poncette AS, Wunderlich MM, Spies C, et al. Patient Monitoring Alarms in an Intensive Care Unit: Observational Study with Do-It-Yourself Instructions. J Med Internet Res. 2021;23:e26494.
30. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

CYP2D6 isoenzyme and ABCB1 gene polymorphisms associated with postoperative nausea and vomiting in women undergoing laparoscopic cholecystectomy: a randomized trial

Angela Henrique Silva Ribeiro [a,*], Estêvão Luiz Carvalho Braga [a], Nathalia de Araújo Gouveia Ferreira [b], Beni Olej [a], Nubia Verçosa [b], Leonardo dos Santos Antunes [c], Ismar Lima Cavalcanti [a]

[a] *Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ, Brazil*
[b] *Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[c] *Universidade Federal Fluminense (UFF), Departamento de Formação Específica, Nova Friburgo, RJ, Brazil*

Received 11 September 2022; accepted 13 February 2023
Available online 23 February 2023

KEYWORDS
Antiemetics;
Genetic polymorphism;
Laparoscopic cholecystectomy;
Ondansetron;
Palonosetron;
Postoperative nausea and vomiting

Abstract
Introduction: Postoperative nausea and vomiting is still a common complication. Serotonin receptor antagonists are commonly used in clinical practice for antiemetic prophylaxis. Interindividual variations in drug response, including single nucleotide polymorphisms, are related to pharmacokinetic and pharmacodynamic changes in these drugs and may lead to a poor therapeutic response. This study aimed to evaluate the influence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms on the frequency of postoperative nausea and vomiting with the use of ondansetron or palonosetron.
Methods: A randomized, double-blind clinical trial including 82 women aged 60 years or over undergoing laparoscopic cholecystectomy was conducted. Patients were randomized to receive either ondansetron or palonosetron for postoperative nausea and vomiting prophylaxis. DNA was extracted from saliva. Genetic polymorphisms were analyzed by real-time polymerase chain reaction. The following polymorphisms were analyzed: rs3892097 C/T, rs1128503 A/G, rs16947 A/G, rs1065852 A/G, rs1045642 A/G, rs2032582 C/A, and rs20325821 C/A.
Results: Overall, vomiting, and severe nausea occurred in 22.5% and 57.5% of patients, respectively. In the palonosetron group, patients with the GG genotype (rs16947 A/G) experienced more severe nausea (p = 0.043). In the ondansetron group, patients with the AA genotype (rs16947 A/G) presented mild nausea (p = 0.034), and those with the AA genotype (rs1065852 A/G) experienced more vomiting (p = 0.034).

* Corresponding author.
E-mail: angelahenriqueanest@gmail.com (A.H. Ribeiro).

https://doi.org/10.1016/j.bjane.2023.02.002
0104-0014/© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: A low antiemetic response was observed with ondansetron in the presence of the AA genotype (rs16947 A/G) and the AA genotype (rs1065852 A/G), and a low therapeutic response was found with palonosetron in the presence of the GG genotype (rs16947 A/G) in laparoscopic cholecystectomy.
Register: ClinicalTrials.gov.
© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Postoperative Nausea and Vomiting (PONV) is a frequent postoperative complication despite antiemetic prophylaxis. It affects approximately one third of patients[1] and may be associated with surgical complications. Additionally, PONV causes patient dissatisfaction, is as feared as postoperative pain, delays hospital discharge, and, consequently, increases hospitalization costs.[2,3]

The incidence of PONV in patients undergoing laparoscopic cholecystectomy has been reported to be 50—72% when no prophylactic antiemetic is provided.[4] Variables such as female sex and nonsmoking status are independent predictors of PONV.[5]

In clinical practice, 5-Hydroxytryptamine-3 (5-HT3) receptor antagonists are commonly used to prevent PONV in laparoscopic procedures. However, resistance to prophylaxis remains a problem and may be associated with genetic polymorphisms.[6,7]

Pharmacogenetics is a branch of genetics that deals with the individual response to drugs and drug metabolism.[8-10] Resistance to antiemetic prophylaxis is related to interindividual genetic variation of 5-HT3 receptor polymorphisms.[8-14] Two systematic reviews have observed an association of PONV with genetic polymorphisms.[15,16]

These polymorphisms include alterations in Adenosine triphosphate-Binding Cassette subfamily-B member 1 (*ABCB1*), which encodes P-glycoprotein, a drug transmembrane transporter acting on multiple tissues.[3] A variation in a single base pair in the DNA sequence (single nucleotide polymorphism, SNP) would lead to phenotype differences, which could result in changes in the function and expression of this transporter, affecting drug metabolism and action. CYP2D6, an isoenzyme of cytochrome P450 responsible for the metabolism of 5-HT3 receptor antagonists, also exhibits variations in gene expression that may result in changes in the biotransformation of these drugs, leading to a reduction in their effects.[17] Some of the SNPs in the ABCB1 gene related to different phenotypes of response to 5-HT3 receptor antagonists are C1236T (rs1128503), G2677T (rs2032582), and C3435T (rs1045642).[17]

This study aimed to evaluate the influence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms on the frequency of PONV by comparing the use of 5-HT3 receptor antagonists (palonosetron vs. ondansetron) for PONV prophylaxis in laparoscopic cholecystectomy.

Methods

This is a prospective, randomized, double-blind, single-center clinical trial. The ethical approval for this study was provided by our institution, and the trial is registered at ClinicalTrials.gov. Eighty-two women undergoing laparoscopic cholecystectomy between November 2015 and November 2016 at our institution were consecutively recruited and provided written informed consent. Randomization to one of two groups was performed using GraphPad Prism Quickcalcs (GraphPad Software, Inc., La Toya, CA, USA).

Inclusion and exclusion criteria

Inclusion criteria were female sex, age 60 years or over, American Society of Anesthesiologists (ASA) physical status I, II, or III, being eligible for laparoscopic cholecystectomy under general anesthesia, and an 8- to 10-hour fast. Exclusion criteria were pregnancy, urgent surgery, motion sickness, history of nausea and vomiting in previous surgical procedures, Body Mass Index (BMI) > 35 $kg.m^{-2}$, and lifestyle habits such as smoking and alcoholism.

Sample size

This is a substudy of the original study entitled "Use of palonosetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in women 60 years of age or older undergoing laparoscopic cholecystectomy: a randomized double-blind study".[18] In the original study, sample size was calculated on the basis of the primary outcome (nausea) and using previously published results as a reference.[19] Under the hypothesis of non-inferiority of palonosetron compared with standard ondansetron, a sample size of at least forty patients per treatment group was necessary to detect that 25% of patients in the ondansetron group and 48% in the palonosetron group would have nausea and vomiting, at a significance level of 5%, 80% power, and a maximum acceptable error of 5% equivalence.

Sample collection

Saliva samples were collected for DNA extraction before induction of anesthesia, stored in Falcon tubes, and kept frozen at -20°C. Genomic DNA was extracted from buccal epithelial cells at our clinical research unit. For this extraction process, Falcon tubes were centrifuged to form a pellet of buccal cells. The supernatant was discarded, and 1 mL of proteinase K solution was added. After incubation, undigested proteins were removed with the addition of ammonium acetate, and DNA was then precipitated with isopropyl alcohol. After centrifugation, the supernatant was discarded, the pellet was washed with decanted ethanol, and DNA was resuspended in extraction buffer (10 mM Tris-HCl; 1 mM EDTA, final volume of 50 mL). DNA concentration and

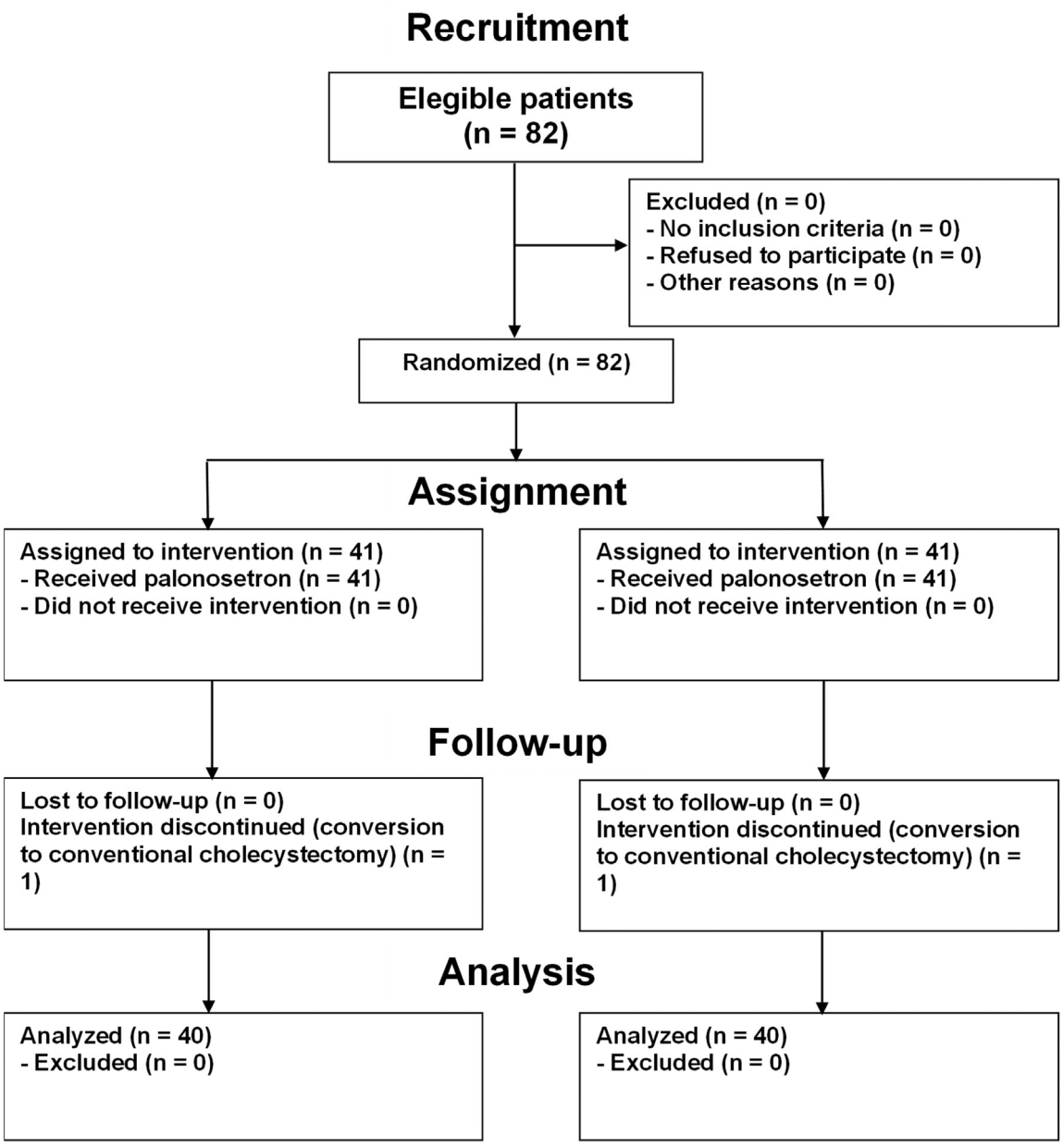


Figure 1 Study flowchart.

purity were determined by a NanoDrop 2000c spectrophotometer (Thermo Scientific™ NanoDrop 2000). DNA concentration was evaluated at 260 nm, and a 260/280 nm ratio was used to estimate DNA purity.[20] Polymerase Chain Reaction (PCR) was quantified in real time in a total volume of 4 μL (4 ng of DNA, 2 μL Taqman PCR master mix, 0.1 SNP; Applied Biosystems probe, Foster City, CA, USA). Amplifications were obtained by thermocycling consisting of an initial denaturation at 95°C for 10 minutes, followed by 40 cycles at 92°C for 15 seconds and 60°C for 1 minute. TaqMan real-time PCR was used for genotyping (Byosistems® 7500 Thermo Fisher Scientific, Foster City, CA, USA). The polymorphisms rs3892097 C/T, rs1128503 A/G, rs16947 A/G, rs1065852 A/G, rs1045642 A/G, rs2032582 C/A, and rs20325821 C/A were selected, evaluated, and tested as expected by Hardy-Weinberg proportions. Applied Biosystems SNP probes and master mix (Foster City, CA, USA) were used. Biological samples were discarded at the end of the study.

Anesthesia

After genetic material was collected, half of the patients randomly received palonosetron 75 mg, and the other half, ondansetron 4 mg. The solutions were prepared by an anesthesiologist not participating in the study and contained ondansetron or palonosetron in 5-mL syringes (0.9% saline was added to dilute the medication and even the volumes). They were then given to the blinded anesthesiologist 1 minute before the induction of Intravenous (IV) anesthesia. General anesthesia with tracheal intubation was performed according to the clinical protocol of the trial. Propofol 1–

2 mg.kg^{-1}, rocuronium 0.6 mg.kg^{-1}, fentanyl 3 μg.kg^{-1}, and lidocaine 1.5 mg.kg^{-1} were used for induction of IV anesthesia. Anesthesia was maintained with remifentanil 0.05 μg.kg^{-1}.min to 0.3 μg.kg^{-1}.min in a continuous IV infusion pump, and sevoflurane 1 to 3 MAC (minimum alveolar concentration) was used for maintenance of hypnosis with inspired concentration adjusted for a Bispectral Index (BIS) between 40–60. Additional IV doses of rocuronium one fourth of the initial dose were also administered as needed for muscle relaxation.

Before the end of surgery, IV parecoxib 40 mg, dipyrone 50 mg.kg^{-1}, and morphine 0.03 mg.kg^{-1} were administered for postoperative analgesia, and the surgical wound was infiltrated with 20 mL of 0.5% ropivacaine. The neuromuscular block was reversed with IV neostigmine 0.04 mg.kg^{-1} and atropine 0.02 mg.kg^{-1}, and the trachea was extubated.

In the ondansetron group, 4 mg every 8 hours was administered postoperatively by the nursing staff. In both groups, at medical discretion, IV metoclopramide 10 mg was used as rescue therapy for PONV. Patients received dipyrone 1g IV every 4 hours and parecoxib 40 mg IV every 12 hours in the first 48 hours after surgery. The patients had oral diet reintroduced 6 hours after surgery.

Postoperative evaluation

All participants received clinical visits by the research team at 2, 6, 24, and 48 hours after the end of laparoscopic surgery, when they were asked about the frequency and intensity of PONV and other adverse effects (headache, vertigo, and/or drowsiness). The primary outcome was a decrease in nausea and vomiting with antiemetic prophylaxis by comparing palonosetron with ondansetron in the presence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms. The secondary outcome was the relationship of CYP2D6 isoenzyme and ABCB1 gene polymorphisms with nausea and vomiting. In this study, nausea was defined as the unpleasant and involuntary sensation of vomiting without expulsion of gastric contents and vomiting as the expulsion of contents of the stomach. The severity of episodes of PONV was measured on a numerical scale ranging from 0 to 10 (0 for no episodes and 10 for the worst possible sensation). A score greater than 5 was considered severe.

A Visual Analog Scale (VAS) was used to measure pain severity. This scale ranges from 0 to 10 (0 refers to no pain and 10 refers to the worst possible pain). Morphine at an IV dose of 0.03 mg.kg^{-1} was indicated in cases of pain $>$ 4 (moderate pain according to the VAS).

The principal investigator did not have access to prescriptions and medical records in the first 48 hours postoperatively because of the use of ondansetron every 8 hours and single use of palonosetron. After this period, the investigator analyzed the medical records and collected data regarding opioids and rescue therapy.

Statistical analysis

Eighty participants completed the study protocol. Numerical variables were described as mean and standard deviation or median and interquartile range. Categorical variables were described as absolute and relative frequencies. To compare numerical variables between groups, the Mann-Whitney test

Table 1 Clinical and surgical characterization of the sample according to study groups.

Variable[a]	Palonosetron (n = 40; 50%)	Ondansetron (n = 40; 50%)	*p*-value
Clinics			
Age (years)	65 (63–70) [66.8]	64 (61.3–70) [66]	0.41
Weight (kg)	66 (60–79.5) [68.6]	70 (60–76.8) [69.1]	0.70
Height (cm)	160 (155–165) [159]	160 (155–169) [162]	0.10
BMI (kg.m^{-2})	26.6 (23.9–29.9) [26.7]	26.3 (23.8–29.1) [26.5]	0.83
ASA			
I	2 (5.0)	7 (17.5)	
II	36 (90.0)	30 (75.0)	0.16
III	2 (5.0)	3 (7.5)	
Comorbidities			
SAH	34 (85.0)	29 (72.5)	0.17
DM2	9 (22.5)	9 (22.5)	1.00
Others	10 (25.0)	7 (17.5)	0.41
Surgery characteristics & drug doses			
Anesthesia duration (min)	115 (86–135) [122]	120 (91–135) [118]	0.70
Surgery duration (min)	89 (60–102) [90.8]	80 (61.8–95) [87.4]	0.92
Pneumoperitoneum duration (min)	50 (35–80) [63.5]	53.5 (41–73.8) [60.7]	0.84
Total dose of fentanyl (μg)	200 (200–240) [211]	205 (200–240) [214]	0.48
Total dose of remifentanil (μg)	334 (179–592) [440]	366 (28–606) [416]	0.89
Total dose of morphine (mg)	2 (2–2) [2.06]	2 (2–2) [2.03]	0.87
Volume of LR administered (mL)	1000 (750–1500) [1103]	1000 (1000–1000) [1084]	0.95

BMI, Body Mass Index; ASA, American Society of Anesthesiologists Physical Status; SAH, Systemic Arterial Hypertension; DM2, Diabetes Mellitus type 2; LR, Lactated Ringer's.
Categorical variables were compared by chi-square or Fisher's exact test, and numerical variables were compared by Mann-Whitney test.
[a] Described by median (25th–75th percentiles) or number of patients (%).

Table 2 Characterization of genotypes.

Variable	Total sample 80 (100%)	n	%
rs 3892097 C/T	55 (68.8 %)		
CC	x	47	85.5
CT		8	14.5
rs 1128503 A/G	49 (61.3 %)		
GG		27	55.1
AG		20	40.8
AA		2	4.1
rs 16947 A/G	60 (75.0 %)		
GG		14	23.3
AG		23	38.3
AA		23	38.3
rs 1065852 A/G	55 (68.8 %)	34	61.8
GG			
AG		18	32.7
AA		3	5.5
rs 1045642 A/G	66 (82.5 %)		
GG		38	57.6
AG		22	33.3
AA		6	9.1
rs 2032582 C/A	60 (75.0 %)		
CC		57	95.0
CA		0	0.0
AA		3	5.0
rs 20325821 C/A	60 (75.0 %)		
CC		29	48.3
CA		20	33.3
AA		11	18.3

Data are presented as number of patients (%).

(to assess the association between polymorphisms and presence of PONV), Pearson's Chi-Square test, or Fisher's exact test were used. In case of polytomous variables, adjusted residual analysis was used to find statistically significant associations. The level of significance was set at 5% ($p \leq 0.05$), and all analyses were performed in SPSS, version 21.0.

Results

This study recruited 82 eligible participants. After randomization, one patient in the palonosetron group (surgery was converted to the conventional technique) and one patient in the ondansetron group (the patient had uncontrollable vomiting that did not stop with rescue therapy) were excluded. Thus, 40 patients were analyzed in each group (Fig. 1).

There were no significant differences between the groups regarding age, physical status classification, and presence of associated diseases. The groups were also homogeneous in terms of surgical variables, such as duration of anesthesia, duration of surgery, duration of pneumoperitoneum, total dose of fentanyl, remifentanil, and morphine, and volume of crystalloid solution administered (Table 1).

There was no increase in opioid consumption in the postoperative period. Morphine was administered postoperatively to two patients (5.0%) in the palonosetron group and to one patient (2.5%) in the ondansetron group ($p = 0.99$).

More than 50% of participants experienced nausea within 48 hours, half of the cases being mild and the other half severe. Also, 22.5% of the participants experienced vomiting. There were no statistically significant differences between groups for nausea within 48 hours ($\chi^2 = 0.46$; $p = 0.497$), mild nausea ($\chi^2 = 0.00$; $p = 1.000$), severe nausea ($\chi^2 = 0.98$; $p = 0.393$), or vomiting ($\chi^2 = 3.51$; $p = 0.061$).

Table 2 shows the characterization of genotypes. SNPs rs1045642 A/G (82.5%), rs16947 A/G (75%), rs2032582 C/A (75%), and rs20325821 C/A (75%) were the most commonly found, respectively. Within rs1045642 A/G, the GG genotype was the most common (57.6%). Within rs16947 A/G, the AG and AA genotypes were the most frequently found (38.3% each). Within rs2032582 C/A and rs20325821 C/A, the CC genotype was the most prevalent (95% and 48.3%, respectively). No statistically significant differences were found between groups in terms of genotypes, as shown in Table 3.

In the palonosetron group, patients with the GG genotype (rs16947 A/G) had a significantly higher presence of severe nausea ($p = 0.043$) compared to patients with the AG and AA genotypes, as shown in Table 4. In the ondansetron group, patients with the AA genotype (rs16947 A/G) had a significantly higher prevalence of mild nausea than patients with the GG and AG genotypes ($p = 0.034$). Moreover, those with

Table 3 Prevalence of genotypes according to study groups.

Variable	Palonosetron	Ondansetron	*p*-value
rs3892097 C/T			1.000[b]
CC	22 (84.6)	25 (86.2)	
CT	4 (15.4)	4 (13.8)	
rs1128503 A/G			0.212[a]
GG	16 (64.0)	11 (45.8)	
AG	9 (36.0)	11 (45.8)	
AA	0 (0.0)	2 (8.3)	
rs16947 A/G			0.216[a]
GG	5 (15.6)	9 (32.1)	
AG	12 (37.5)	11 (39.3)	
AA	15 (46.9)	8 (28.6)	
rs1065852 A/G			0.640[a]
GG	18 (60.0)	16 (64.0)	
AG	11 (36.7)	7 (28.0)	
AA	1 (3.3)	2 (8.0)	
rs1045642 A/G			0.941[a]
GG	19 (55.9)	19 (59.4)	
AG	12 (35.3)	10 (31.3)	
AA	3 (8.8)	3 (9.4)	
rs2032582 C/A			1.000[a]
CC	29 (93.5)	28 (96.6)	
CA	0 (0.0)	0 (0.0)	
AA	2 (6.5)	1 (3.4)	
rs20325821 C/A			0.587[a]
CC	16 (50.0)	13 (46.4)	
CA	9 (28.1)	11 (39.3)	
AA	7 (21.9)	4 (14.3)	

Data are presented as number of patients (%).
[a] Pearson's chi-square test.
[b] Fisher's exact test.

Table 4 Association of polymorphisms with nausea and vomiting in the palonosetron group.

Polymorphism	n	Nausea within 48 hours	Mild nausea	Severe nausea	Vomiting
		n (%)	n (%)	n (%)	n (%)
rs 3892097 C/T					
CC	22	13 (59.1)	6 (27.3)	7 (31.8)	6 (27.3)
CT	4	2 (50.0)	1 (25.0)	1 (25.0)	1 (25.0)
p-value		1.000[b]	1.000[b]	1.000[b]	1.000[b]
rs 1128503 A/G					
GG	16	9 (56.3)	5 (31.3)	4 (25.0)	3 (18.8)
AG	9	6 (66.7)	3 (33.3)	3 (33.3)	2 (22.2)
p-value		0.691[b]	1.000[b]	0.673[b]	1.000[b]
rs 16947 A/G					
GG	5	5 (100)	1 (20.0)	4 (80.0)	3 (60.0)
AG	12	7 (58.3)	5 (41.7)	2 (16.7)	2 (16.7)
AA	15	7 (46.7)	2 (13.3)	5 (33.3)	4 (26.7)
p-value		0.109[a]	0.231[a]	**0.043**[a]	0.191[a]
rs 1065852 A/G					
GG	18	9 (50.0)	3 (16.7)	6 (33.3)	5 (27.8)
AG	11	8 (72.7)	3 (27.3)	5 (45.5)	4 (36.4)
AA	1	1 (100)	1 (100)	0 (0.0)	0 (0.0)
p-value		0.340[a]	0.147[a]	0.597[a]	0.711[a]
rs 1045642 A/G					
GG	19	11 (57.9)	5 (26.3)	6 (31.6)	4 (21.1)
AG	12	7 (58.3)	3 (25.0)	4 (33.3)	4 (33.3)
AA	3	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)
p-value		0.959[a]	0.958[a]	0.994[a]	0.723[a]
rs 2032582 C/A					
CC	29	16 (55.2)	6 (20.7)	10 (34.5)	7 (24.1)
AA	2	2 (100)	2 (100)	0 (0.0)	1 (50.0)
p-value		0.497[b]	0.060[b]	1.000[b]	0.456[b]
rs 20325821 C/A					
CC	16	8 (50.0)	4 (25.0)	4 (25.0)	2 (12.5)
CA	9	6 (66.7)	3 (33.3)	3 (33.3)	5 (55.6)
AA	7	4 (57.1)	1 (14.3)	3 (42.9)	3 (42.9)
p-value		0.721[a]	0.683[a]	0.688[a]	0.063[a]

[a] Pearson's Chi-Square test.
[b] Fisher's exact test; adjusted residual analysis at 5% significance.

the AA genotype (rs1065852 A/G) had a significantly higher presence of vomiting compared to those with the GG genotype ($p = 0.034$), as shown in Table 5.

Discussion

The present study suggests that ABCB1 gene and CYP2D6 isoenzyme polymorphisms have a genetic predisposition that interferes with the response of 5-HT3 receptor antagonists to PONV prophylaxis. In 2017, Song et al.[21] (2017) observed that the ABCB1 2677TT polymorphism was linked to increased nausea and vomiting with the use of palonosetron in spinal surgery. Our results revealed a statistically significant association between the GG genotype (rs16947 A/G) and the presence of severe nausea ($p = 0.043$) in the palonosetron group, which may lead to avoiding to prescribe palonosetron in this setting.

In the ondansetron group, the AA genotype (rs16947 A/G) was associated with mild nausea ($p = 0.034$), while the AA genotype (rs1065852 A/G) was associated with vomiting ($p = 0.034$). The results suggest that an alternative to ondansetron should be considered in the presence of these polymorphisms. Choi et al.[22] (2010) evaluated the use of ondansetron for PONV prophylaxis and showed that 35% of participants had PONV associated with polymorphisms. They found that altered drug pharmacokinetics was related to ABCB1 genotypes. He et al.[23] (2014) reached the same conclusion in a study of patients undergoing cancer treatment. Kim et al.[20] (2015) observed that ondansetron was less effective for PONV prophylaxis in the presence of -100_-102AAG polymorphisms of the 5-HT3B gene.

In the present study, vomiting and severe nausea occurred, respectively, in 22.5% and 28.8% of patients despite antiemetic prophylaxis, consistent with the rates reported by Gan et al.[24] (2006). The prevalence of the rs1045642 A/G polymorphism, found in 82.5% of the sample, did not correlate with increased PONV. The incidence of severe nausea and vomiting could have been higher if higher doses of opioids had been used. The presence of rs16947

Table 5 Association of polymorphisms with nausea and vomiting in the ondansetron group.

Polymorphism	n	Nausea within 48 hours	Mild nausea	Severe nausea	Vomiting
		n (%)	n (%)	n (%)	n (%)
rs 3892097 C/T					
CC	25	13 (52.0)	7 (28.0)	6 (24.0)	3 (12.0)
CT	4	2 (50.0)	0 (0.0)	2 (50.0)	1 (25.0)
p-value		1.000[b]	0.546[b]	0.300[b]	0.467[b]
rs 1128503 A/G					
GG	11	4 (36.4)	3 (27.3)	1 (9.1)	1 (9.1)
AG	11	8 (72.7)	4 (36.4)	4 (36.4)	1 (9.1)
AA	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value		0.078[a]	0.572[a]	0.217[a]	0.906[a]
rs 16947 A/G					
GG	9	5 (55.6)	2 (22.2)[c]	3 (33.3)	1 (11.1)
AG	11	4 (36.4)	1 (9.1)[c]	3 (27.3)	1 (9.1)
AA	8	5 (62.5)	5 (62.5)[c]	0 (0.0)	0 (0.0)
p-value		0.489[a]	**0.034**[a]	0.206[a]	0.640[a]
rs 1065852 A/G					
GG	16	6 (37.5)	5 (31.3)	1 (6.3)	0 (0.0)[c]
AG	7	5 (71.4)	2 (28.6)	3 (42.9)	2 (28.6)[c]
AA	2	1 (50.0)	0 (0.0)	1 (50.0)	1 (50.0)[c]
p-value		0.325[a]	0.650[a]	0.071[a]	**0.034**[a]
rs 1045642 A/G					
GG	19	9 (47.4)	7 (36.8)	2 (10.5)	2 (10.5)
AG	10	7 (70.0)	2 (20.0)	5 (50.0)	1 (10.0)
AA	3	1 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)
p-value		0.393[a]	0.330[a]	0.062[a]	0.518[a]
rs 2032582 C/A					
CC	28	16 (57.1)	10 (35.7)	6 (21.4)	3 (10.7)
AA	1	1 (100)	0 (0.0)	1 (100)	1 (100)
p-value		1.000[b]	1.000[b]	0.241[b]	0.138[b]
rs 20325821 C/A					
CC	13	6 (46.2)	4 (30.8)	2 (15.4)	1 (7.7)
CA	11	6 (54.5)	2 (18.2)	4 (36.4)	2 (18.2)
AA	4	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)
p-value		0.920[a]	0.777[a]	0.497[a]	0.537[a]

[a] Pearson's Chi-Square test.
[b] Fisher's exact test.
[c] Equal letters do not differ by the adjusted residual analysis at 5% significance.

polymorphisms was associated with increased nausea in both groups, thus constituting a risk factor. Stamer et al.[25] (2019) identified the 5-HTTLPR rs4795541 polymorphism as an independent factor for PONV. The Brazilian sample used in this study is extensively diverse, and such diversity may influence the results of pharmacogenomic studies. More than 90 different CYP2D6 alleles have already been described, which makes screening for each drug complex.[26,27]

Although 5-HT3 receptor antagonists are commonly used in clinical practice for PONV prophylaxis in laparoscopic procedures, the incidence of nausea and vomiting remains high,[22] which may be related to genetic polymorphism.[25,28-30] As suggested by Janicki et al.,[30] (2011) understanding the effects of different drugs on polymorphic variants may be helpful in clinical practice.

The current study has several limitations that must be considered. This is a sub study with potential bias and weak potential for non-clinically relevant effects. The sample size was small, and the population was heterogeneous, few polymorphisms were analyzed, and only a single antiemetic prophylaxis was used. Also, only female patients were recruited, and patients with a previous history of nausea and vomiting were excluded. In addition, some degree of subjective error is inevitable in assessing intensity of nausea.

Conclusions

Our results suggest that genetic polymorphisms may influence the outcomes of antiemetic prophylaxis for PONV with 5-HT3 receptor antagonists. This interference may be linked to the SNP GG rs16947 A/G with palonosetron and the SNPs AA rs16947 A/G and AA rs1065852 with ondansetron. Nonetheless, our findings may contribute to the search for the optimal prophylactic approach to PONV, providing more information about the complexity of genetic effects on

PONV treatment. Genetic analysis may be useful for an improved pharmacological approach, and more studies on genotyping are needed.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

Assistance with this article: To Surgery and Anesthesiology Department of Federal Hospital of Bonsucesso (HFB) and the Fluminense Federal University (UFF) support.

Assistance with the study: This study was developed at Federal Hospital of Bonsucesso, Rio de Janeiro, Brazil.

Financial support and sponsorship: This study had no financial support of private, public or with non-profit agencies.

The ethical approval for this study was provided by the Hospital Federal de Bonsucesso (HFB) Ethical Committee (CAAE 48149215.0.0000.5253), Rio de Janeiro, Brazil (Chairperson Prof C. Carvalho) on October 1st 2015.

Trial registration number: NCT02541019 (ClinicalTrials.gov).

References

1. White PF, O'Hara JF, Roberson CR, Wender RH, Candiotti KA, Group P-OS. The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. Anesth Analg. 2008;107(2):452–8.
2. Gan T, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg. 2001;92(2):393–400.
3. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiol Res Pract. 2011;2011:748031.
4. Bala I, Bharti N, Murugesan S, Gupta R. Comparison of palonosetron with palonosetron-dexamethasone combination for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiol. 2014;80(7):779–84.
5. Apfel CC, Roewer N. Risk assessment of postoperative nausea and vomiting. Int Anesthesiol Clin. 2003;41(4):13–32.
6. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118(1):85–113.
7. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350(24):2441–51.
8. Gntech [Internet]. [cited 2022 Feb 5]. Available from: https://gntech.med.br/.
9. Nagele P. Perioperative genomics. Best Pract Res Clin Anaesthesiol. 2011;25(4):549–55.
10. Singh KP, Dhruva AA, Flowers E, Kober KM, Miaskowski C. A review of the literature on the relationships between genetic polymorphisms and chemotherapy-induced nausea and vomiting. Crit Rev Oncol Hematol. 2018;121:51–61.
11. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA. 2001;286(18):2270–9.
12. Borst P, Schinkel AH. P-glycoprotein ABCB1: a major player in drug handling by mammals. J Clin Invest. 2013;123(10):4131–3.
13. Babaoglu MO, Bayar B, Aynacioglu AS, Kerb R, Abali H, Celik I, et al. Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. Clin Pharmacol Ther. 2005;78(6):619–26.
14. Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol. 2006;19(6):606–11.
15. Klenke S, Frey UH. Genetic variability in postoperative nausea and vomiting: A systematic review. Eur J Anaesthesiol. 2020;37(11):959–68.
16. Lopez-Morales P, Flores-Funes D, Sanchez-Migallon EG, Liron-Ruiz RJ, Aguayo-Albasini JL. Genetic factors associated with postoperative nausea and vomiting: a systematic review. J Gastrointest Surg. 2018;22(9):1645–51.
17. Perwitasari DA, Wessels JA, van der Straaten RJ, Baak-Pablo RF, Mustofa M, Hakimi M, et al. Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. Jpn J Clin Oncol. 2011;41(10):1168–76.
18. Carvalho Braga EL, Figueiredo NV, Barrucand L, Cavalcanti IL. Use of palonosetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in women 60 years of age or older undergoing laparoscopic cholecystectomy: A randomised double-blind study. Eur J Anaesthesiol. 2019;36(3):241–2.
19. Laha B, Hazra A, Mallick S. Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial. Indian J Pharmacol. 2013;45(1):24–9.
20. Kim MS, Lee JR, Choi EM, Kim EH, Choi SH. Association of 5-HT3B receptor gene polymorphisms with the efficacy of ondansetron for postoperative nausea and vomiting. Yonsei Med J. 2015;56(5):1415–20.
21. Song JW, Shim JK, Choi SH, Soh S, Jang J, Kwak YL. Comparison of ramosetron and palonosetron for preventing nausea and vomiting after spinal surgery: association with ABCB1 polymorphisms. J Neurosurg Anesthesiol. 2017;29(4):406–14.
22. Choi EM, Lee MG, Lee SH, Choi KW, Choi SH. Association of ABCB1 polymorphisms with the efficacy of ondansetron for postoperative nausea and vomiting. Anaesthesia. 2010;65(10):996–1000.
23. He H, Yin JY, Xu YJ, Li X, Zhang Y, Liu ZG, et al. Association of ABCB1 polymorphisms with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting. Clin Ther. 2014;36(8):1242–52. e2.
24. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg. 2006;102(6):1884–98.
25. Stamer UM, Schmutz M, Wen T, Banz V, Lippuner C, Zhang L, et al. A serotonin transporter polymorphism is associated with postoperative nausea and vomiting: An observational study in two different patient cohorts. Eur J Anaesthesiol. 2019;36(8):566–74.
26. Mitsunaga Y, Kubota T, Ishiguro A, Yamada Y, Sasaki H, Chiba K, et al. Frequent occurrence of CYP2D6*10 duplication allele in a Japanese population. Mutat Res. 2002;505(1-2):83–5.
27. Klenke S, de Vries GJ, Schiefer L, Seyffert N, Bachmann HS, Peters J, et al. CHRM3 rs2165870 polymorphism is independently associated with postoperative nausea and vomiting, but combined prophylaxis is effective. Br J Anaesth. 2018;121(1):58–65.
28. Sim SC, Ingelman-Sundberg M. Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) nomenclature database. Methods Mol Biol. 2013;987:251–9.

29. Braga ELC, Vercosa N, Cavalcanti IL. Comparative study between fosaprepitant and palonosetron in the prophylaxis of postoperative nausea and vomiting in women undergoing laparoscopic cholecystectomy: prospective, randomized and double-blind study. Front Pharmacol. 2022;13:915347.

30. Janicki PK, Vealey R, Liu J, Escajeda J, Postula M, Welker K. Genome-wide Association study using pooled DNA to identify candidate markers mediating susceptibility to postoperative nausea and vomiting. Anesthesiology. 2011;115(1): 54—64.

Brazilian Journal of Anesthesiology 2024;74(3): 744454

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Association of antimicrobial use and incidence of hospital-acquired pneumonia in critically ill trauma patients with pulmonary contusion: an observational study☆

Estevão Bassi [a,b,*], Camila Trevizani Merighi [a], Carlos Issamu Tomizuka [a], Thais Guimarães [c], Fernando da Costa Ferreira Novo [a], Sergio Henrique Bastos Damous [a], Edivaldo Massazo Utiyama [a], Luiz Marcelo Sá Malbouisson [d]

[a] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Departamento de Cirurgia, Disciplina de Cirurgia Geral e Traumatologia, São Paulo, SP, Brazil*
[b] *Hospital Alemão Oswaldo Cruz, Unidade de Tratamento Intensivo, São Paulo, SP, Brazil*
[c] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Comissão de Controle de Infecção Hospitalar, São Paulo, SP, Brazil*
[d] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Divisão de Anestesiologia, São Paulo, SP, Brazil*

Received 1 December 2022; accepted 21 July 2023
Available online 3 August 2023

KEYWORDS
Thoracic injuries;
Lung injury;
Healthcare-associated pneumonia;
Antibacterial agents

Abstract
Background: Pneumonia occurs in about 20% of trauma patients with pulmonary contusions. This study aims to evaluate the association between empirical antibiotic therapy and nosocomial pneumonia in this population.
Methods: Retrospective cohort of adult patients admitted to a trauma-surgical ICU. The Antibiotic Therapy Group (ATG) was defined by intravenous antibiotic use for more than 48 h starting on hospital admission, while the Conservative Group (CG) was determined by antibiotic use no longer than 48 h. Primary outcome was microbiologically documented nosocomial pneumonia within 14 days after hospital admission. Logistic regression was used to estimate the association between group allocation and primary outcome. Exploratory analyses evaluating the association between resistant strains in pneumonia and antibiotic use were performed.
Results: The study included 177 patients with chest trauma and pulmonary contusion on CT scan. ATG were more severely ill than CG, as shown by higher Injury Severity Score, SAPS3, SOFA score, higher rates, and longer duration of mechanical ventilation. In the multivariate analysis, ATG

☆ An earlier version of this work was presented in an abstract form in the ESICM — European society of intensive medicine 31st Annual Congress in Paris (Intensive Care Medicine Experimental 2018 6(Suppl 2):40).

* Corresponding author.
E-mail: estevao.b@hc.fm.usp.br (E. Bassi).

https://doi.org/10.1016/j.bjane.2023.07.011
0104-0014/© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

was associated with a lower incidence of primary outcome (OR = 0.25, 95% CI 0.09—0.64; $p < 0.01$). Similar results were found in the sensitivity analysis with another set of variables. However, each day of antibiotic use was associated with an increased risk of pneumonia by resistant bacteria (OR = 1.18 per day, 95% CI 1.05—1.36; $p < 0.01$).

Conclusions: Empiric antibiotic therapy was independently associated with lower incidence of nosocomial pneumonia in critically ill patients with pulmonary contusion. However, each day of antibiotic use was associated with increased resistant strains in infected patients.

© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The incidence of Ventilator-Associated Pneumonia (VAP) in trauma patients is about 4-fold higher than in ventilated non trauma patients.[1] Pneumonia can occur in 21% of trauma patients with pulmonary contusions.[2] Therefore Hospital-Acquired Pneumonia (HAP) is a concerning complication among trauma patients and there is evidence that nosocomial pneumonia can have long-lasting effects on outcomes in this population. As an example, in patients with Traumatic Brain Injury (TBI), HAP is associated with poor outcomes in severe TBI 5 years after injury.[3]

Mechanisms of pulmonary infection in trauma can differ from those in other clinical situations. Specific risk factors for pneumonia in trauma include rib fractures, pulmonary contusion, and failed prehospital intubation.[4]

Delays in appropriate antibiotic therapy can have deleterious effects on the clinical resolution of nosocomial pneumonia. However, the emergence of drug-resistant bacteria strains, as the result of selective pressure, and serious adverse effects of antimicrobials are a major concern in the widespread use of antibiotics. While there is limited evidence suggesting that prophylactic antibiotics can decrease early-onset HAP in comatose trauma patients,[5] an observational study by Hoth et al suggests that prolonged prophylactic antibiotics can result in a delay in pneumonia diagnosis, an increase in resistant bacteria colonization, and a higher incidence of complications.[6]

The diagnosis of HAP in trauma is challenging, especially in pulmonary contusion patients. In these patients, lung trauma, alveolar hypoxia and blood in alveolar spaces activate inflammatory pathways. Blood in the alveolar space also provides a medium for bacteria growth. Radiologic findings of pulmonary contusions can mimic pneumonia, varying from irregular areas of consolidation to diffuse and extensive homogeneous consolidation.[7]

Signs of Systemic Inflammatory Response Syndrome (SIRS) occur in 91% of critically ill trauma patients in the first week following trauma. However, persistent SIRS is indeed associated with nosocomial infection, and the respiratory tract is the most common source.[8] This brings another challenge to diagnosing HAP in patients with pulmonary contusions since clinical and radiologic signs of infection are unspecific in this situation.

These characteristics make pulmonary contusion patients more prone to prolonged prophylactic or unnecessary antibiotics courses. There is little evidence to investigate the balance between the benefits and harms of early empirical antibiotic therapy in this situation. We sought to investigate if systemic antibiotics given for more than 48 h after Intensive Care Admission are associated with reduced nosocomial pneumonia in trauma patients with pulmonary contusions.

Methods

Study design and population

This is a retrospective cohort study of adult patients admitted to a surgical-trauma Intensive Care Unit (ICU) in a trauma center in São Paulo, Brazil. Between March 2012 and April 2016, we evaluated for inclusion all adult patients (> 18 years old) with thoracic trauma and available chest Computed Tomography (CT). We included in our analysis all patients with pulmonary contusions, which were diagnosed by a trained radiologist based on admission CT scan findings.

The study was approved by the institutional research ethics board (CAPPesq – 63077116600000068 CAAE). Due to the retrospective nature of the study, informed consent was waived by the ethics board.

Exclusion criteria were absence of chest trauma, absence of chest CT scan in the first 48 h after trauma and diagnosis of pneumonia at ICU admission.

All patients who fulfilled the inclusion criteria without any of the exclusion criteria during the period were included in the analysis. No specific calculation of sample size was performed.

Data collection and patient management

All patients with diagnosed pulmonary contusions underwent a chart and chest X-ray review by 2 trained data abstractors. We collected data through the hospital's Electronic Medical Records (EMR) and microbiologic data were individually checked with the hospital's microbiological laboratory.

Antibiotic Therapy Group (ATG) was defined as any systemic antibiotic started at hospital admission and maintained for more than 48 h. The Conservative Group (CG) was defined as any antibiotic use for no greater than 48 h or no antibiotics at all. Antimicrobials used and therapy duration were chosen by the treating physician. Antibiotics for pulmonary contusions and aspiration pneumonitis are not routinely prescribed in this Trauma ICU. The most common reasons for antibiotic prescriptions for more than 48 h were related to trauma severity in other body segments: open fractures, cerebrospinal fluid leakage or peritonitis. The first choice of antibiotic for each indication follows an institutional protocol,

respectively with ceftriaxone plus clindamycin, cefuroxime, or ceftriaxone plus metronidazole.

Microbiological cultures were collected at the treating physician's discretion. Cultures of tracheal aspirate or other samples of the lower respiratory tract were collected only when pulmonary infection was suspected based on these criteria: New or worsening pulmonary infiltrate plus ≥ 2 of the following: body temperature $\geq 38^{\circ}C$ or $\leq 35^{\circ}C$; White Blood Cell count (WBC) > 12000 or < 4000 cells/μL or immature granulocyte at blood sample; purulent sputum; and worsening of pulmonary oxygenation as accessed by a decline in the ratio between the Partial pressure of Oxygen (PaO_2)/Fraction of inspired Oxygen (FiO_2) — the PaO_2/FiO_2 ratio.[9]

Outcomes

The primary outcome was microbiologically documented nosocomial pneumonia in the first 14 days after intensive care admission. Microbiologically documented nosocomial pneumonia was defined using a combination of the clinical and radiological criteria as described above; the registration of diagnosis and treatment specifically for nosocomial pneumonia in chart review; and microbiological confirmation by: positive blood cultures, pleural cultures or lung specimen cultures with bacteria compatible with the site of infection; or quantitative tracheal aspirate or bronchoalveolar lavage cultures of at least 10^6 or 10^5 Colony-Forming Units (CFU) per millilitre, respectively.[9]

For patients not mechanically ventilated, the only respiratory microbiological specimen accepted was bronchoalveolar lavage culture (quantitative tracheal aspirate was not collected in these patients).

Secondary outcomes included nosocomial pneumonia based on the clinical and radiological criteria above but without the need for microbiological confirmation (nosocomial pneumonia with or without microbiological confirmation), duration of mechanical ventilation, ICU length of stay, hospital length of stay and hospital mortality.

Statistical analysis

Continuous variables were expressed as mean and Standard Deviation (SD) or median and Interquartile Range (IQR), depending on data distribution. Discrete variables were expressed as counts and percentages. Differences between groups were compared using Welch's *t*-test, irrespective of the distribution of numeric data, and chi-square or Fisher's Exact test, when appropriate.

A multivariate logistic regression model with the primary outcome as the dependent variable was built to control for potential confounders. Historical confounder definition[10] was used and risk factors for pneumonia complicating pulmonary contusion were independent variables: age, sex, aspiration, duration of mechanical ventilation and tube thoracostomy.[11,12]

A sensitivity analysis for the multivariate logistic regression model, also based on a historical confounder definition, was performed with the variables: Glasgow coma score, sex, heart rate, systolic blood pressure, use of mechanical ventilation and tube thoracostomy. We used the risk factors described by Landeen,[2] except for obesity (data not available in our sample), and the motor component of the Glasgow score (we used the total Glasgow score instead), but we did not use the specific proposed scoring point system by the authors in the present logistic regression. We also included tube thoracostomy as a relevant risk factor for infectious complications in chest trauma patients.[12]

Exploratory subgroup analyses were done to assess the association between the following variables: the duration of antibiotic treatment (days) and the primary outcome; the duration of antibiotic treatment (days) and colonization by antibiotic-resistant bacteria: meticillin-resistant *S. aureus*, *Pseudomonas aeruginosas* or *Acinetobacter baumannii* resistant to quinolones, third generation cephalosporin-resistant *Klebsiella spp.*, *Enterobacter spp.*, *Escherichia coli*, *Streptococcus pneumoniae*, *Proteus spp.* or *Serratia marcescens*; group allocation and pneumonia by drug-resistant bacteria.

Associations are expressed using the Odds Ratio (OR) with 95% Confidence Intervals (95% CI). A *p*-value < 0.05 was considered significant. All statistical analyses were performed using the free R software, version 14.1.[13]

Results

Of the 2040 ICU admissions, 273 patients had chest trauma with available CT scans, of which 172 had pulmonary contusions diagnosed by the radiologist (Fig. 1). A total of 79 patients were included in the conservative group and 98 in the antibiotic therapy group.

Although both groups were balanced regarding age and gender, there were notable differences between groups regarding other variables (Table 1). Patients in the antibiotic therapy group were more severely ill since they had higher admission Injury Severity Score (median 41 vs. 34 in CG), SAPS3 score (54 ± 13 vs. 48 ± 17), SOFA score (median 8 vs. 5), higher rates of mechanical ventilation at ICU admission (63% vs. 88%) and longer mechanical ventilation duration (median 5 vs. 2 days) than the conservative group. Tube thoracostomy insertion did not differ between

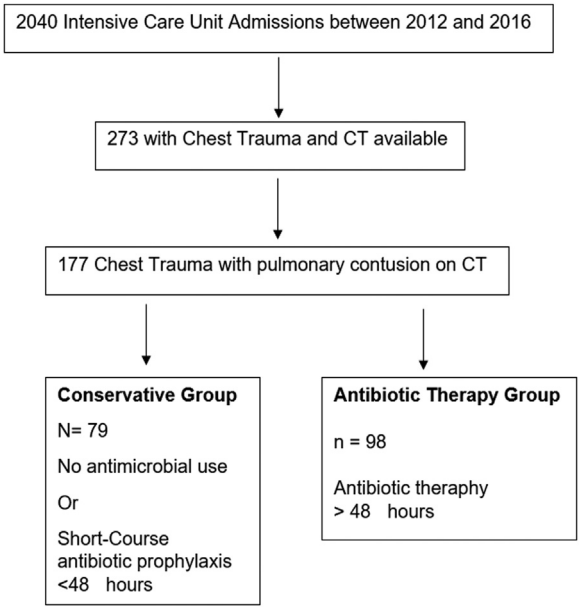


Figure 1 Flowchart.

Table 1 Baseline Variables, antibiotics, and duration of therapy in critically ill trauma patients with CT-confirmed pulmonary contusion admitted to specialized ICU.

	Conservative group	Antibiotic therapy group	*p*-value
N (% of total)	79 (45%)	98 (55%)	
Age (years)	36 ± 16	34 ± 14	0.26
Male sex	67 (84%)	75 (82%)	0.86
At least one comorbidity[a]	2 (3%)	4 (4%)	0.80
Trauma mechanism			0.22
Traffic accident	40 (50%)	34 (37%)	
Trampling	17 (21%)	26 (28%)	
Fall from height	14 (18%)	19 (21%)	
Gunshot wound	3 (4%)	9 (10%)	
Other	6 (8%)	4 (4%)	
Injury Severity Score	34 (28–42)	41 (34–46)	**0.01**
New Injury Severity Score	43 (36–57)	48 (41–57)	0.10
SAPS 3	48 ± 17	54 ± 13	**<0.01**
SOFA	5 (3–9)	8 (5–11)	**<0.01**
Mechanical Ventilation at ICU admission	50 (63%)	81 (88%)	**<0.01**
Tube thoracostomy at ICU admission	32 (40%)	32 (35%)	0,60
Prescribed antibiotics			**<0.01**
Ceftriaxone	5 (6%)	62 (67%)	
Cefuroxime	12 (15%)	16 (17%)	
Cefazolin	12 (15%)	2 (2%)	
Clyndamicin	5 (6%)	62 (67%)	
Others	2 (3%)	7 (8%)	
Duration of antibiotic therapy (days)	0 (0–1)	7 (5–7)	**<0.01**

Data are presented as mean ± standard deviation, median (interquartile range), or N of the group (%) as appropriate. Antibiotic Therapy Group: antibiotic started at hospital admission and maintained for more than 48 h; Conservative Group: antibiotic use for no greater than 48 h or no antibiotics at all; SAPS3, Simplified acute physiology score 3; SOFA, Sequential Organ Failure Assessment score.

[a] Hypertension, diabetes, coronary artery disease, heart failure, chronic pulmonary obstructive disease, chronic kidney disease, HIV, or cancer. A p-value < 0.05 was considered significant.

groups at inclusion or as duration of intervention. Ceftriaxone, cefuroxime, and clindamycin were the most commonly prescribed in both groups, with a median of 7 days (IQR 5–7) in the Antibiotic Therapy Group vs. 0 days (IQR 0–1) in the Conservative Group.

Crude rates of microbiologically documented nosocomial pneumonia did not differ significantly between groups: 25% in CG vs. 20% in ATG (p = 0.50). Rates of nosocomial pneumonia without microbiological documentation were very similar: 26% in CG vs. 21% in ATG (p = 0.59), only one patient in each group had clinical-radiological pneumonia and cultures were negative. Complications of pneumonia, such as bacteremia and empyema did not differ between groups. Although patients in the antibiotic group had higher ICU and in-hospital mortality, this difference was not statistically significant (Table 2).

We could not detect changes in bacteria species profiles between groups. S*taphylococcus aureus, Pseudomonas aeruginosas* and *Acinetobacter baumannii* were the most prevalent pathogens in infected patients in both groups. Nevertheless, the incidence of resistant bacteria to at least one class of antimicrobial was more frequent in the Antibiotic Therapy Group (50 vs. 15%, p = 0.049) (Table 3).

The multivariate analysis models showed that the major risk factor associated with the primary outcome was the duration of mechanical ventilation (OR = 1.37 per day, 95% CI 1.24—1.53; $p < 0.01$). The Antibiotic Therapy Group was associated with a significant reduction in the primary outcome in adjusted analysis (OR = 0.25, 95% CI 0.09—0.64, $p < 0.01$) (Table 4).

Sensitivity analysis with distinct variables showed very similar findings (Table 5). The most important risk factor associated with the primary outcome was the presence of mechanical ventilation at ICU admission (OR = 15.9, 95% CI 2.8–301; $p < 0.01$). Again, the Antibiotic Therapy Group was associated with a significant reduction in nosocomial pneumonia in adjusted analysis (OR = 0.33, 95% CI 0.14—0.79, p = 0.01).

In exploratory analyses, the duration of antibiotic therapy was not associated with nosocomial pneumonia (OR = 0.98 per day, 95% CI 0.88—1.09; p = 0.75); however, it was associated with resistant bacteria in samples of infected patients (OR = 1.18 per day, 95% CI 1.05—1.36; $p < 0.01$), reinforcing the aforementioned association with the Antibiotic Therapy Group (Table 3). In patients with microbiological isolates at the time of diagnosis, the previous use of an effective antibiotic against the bacteria did not decrease ICU length of stay or ICU mortality (OR = 1.2; 95% CI 0.22—6.33; p = 0.83).

Discussion

In our study, we evaluated the relationship between antibiotic therapy in patients with pulmonary contusions and the development of nosocomial pneumonia in the first 14 days

Table 2 Outcome variables of critically ill pulmonary contusion patients.

	Conservative group	Antibiotic therapy group	*p*-value
Primary Outcome: microbiologically documented nosocomial pneumonia[a]	20 (25%)	18 (20%)	0.50
Nosocomial pneumonia with or without microbiological confirmation[a]	21 (26%)	19 (21%)	0.49
Empiema[a]	3 (4%)	2 (2%)	0.87
Bacteremia[a]	4 (5%)	5 (5%)	1.00
Duration of mechanical ventilation (days)[a]	2 (0–7)	5 (3–10)	**0.02**
Duration of tube thoracostomy (days)[a]	0 (0–3)	0 (0–2)	0.65
ICU length of stay	7 (4–14)	12 (6–22)	**0.03**
ICU mortality	13 (16%)	25 (27%)	0.12
Hospital Mortality	14 (18%)	27 (29%)	0.10

Data are presented as mean ± standard deviation, median (interquartile range), or N of group (%) as appropriate.
[a] Within 14 days after ICU admission.
Conservative Group: antibiotic use for no greater than 48 h or no antibiotics at all; Antibiotic Therapy Group: antibiotic started at hospital admission and maintained for more than 48 h. A p-value < 0.05 was considered significant.

after hospital admission. Our data showed that the use of antibiotics for more than 48 h was not associated with a decrease in the incidence of nosocomial pneumonia in the crude analysis, but it was after adjusting for confounders (OR = 0.25, 95% CI 0.09—0.64, Table 4). Sensitivity analysis in a distinct logistic regression model showed very similar results, including the magnitude of effect (OR = 0.33, 95% CI 0.14—0.79, Table 5). However, exposure to antibiotics was associated with resistant strains when pneumonia developed, both when defined as allocation group (Antibiotic Therapy Group with 50% vs. Conservative Group 15%, $p = 0.0049$), and also when exposure was quantified as days of antibiotic use (OR = 1.18 per day of antibiotic use, 95% CI 1.05—1.36; $p < 0.01$).

Pulmonary contusions are both a risk factor for pneumonia and a mimicker of this disease, making it challenging for physicians to differentiate between the two pathologies. Both mechanical and inflammatory injury caused by pulmonary contusions lead to alveolar consolidation and the inflammatory response can lead to systemic inflammatory response syndrome. These characteristics increase the chances of patients receiving antibiotics, even without any confirmed infection.

Insofar, we have chosen CT scan as the diagnostic method for pulmonary contusion due to its increased sensitivity[7] when compared with chest X-rays. Also, we had strict criteria for the diagnosis of nosocomial pneumonia, with obligatory clinical and radiological criteria along with microbiological confirmation. These definitions are important because of the myriad of factors that act as risk factors or confounders in this situation. For instance, signs of SIRS are present in more than 90% of critically ill trauma patients

Table 3 Microbiological outcomes of critically ill pulmonary contusion patients according to the duration of antibiotic therapy.

Patients with pneumonia with bacteria isolated in respiratory or blood samples[a]	Conservative group	Antibiotic therapy group	*p*-value
Diference for all bacteria			0.44
Staphylococcus aureus	6 (30%)	8 (44%)	0.56
Pseudomonas aeruginosas	4 (20%)	5 (28%)	0.85
Acinetobacter baumannii	3 (15%)	6 (33%)	0.34
Klebsiella spp.	2 (10%)	3 (17%)	0.90
Enterobacter spp.	1 (5%)	4 (22%)	0.28
Haemophilus influenzae	3 (15%)	1 (6%)	0.67
Escherichia coli	3 (15%)	0 (0%)	0.27
Coagulase-negative staphylococci	2 (10%)	0 (0%)	0.51
Streptococcus pneumoniae	1 (5%)	1 (6%)	1.00
Proteus spp.	1 (5%)	1 (6%)	1.00
Serratia marcescens	1 (5%)	0 (0%)	1.00
Other (includes normal flora)	5 (25%)	1 (6%)	0.23
Resistant to antimicrobial bacteria[b]	3 (15%)	9 (50%)	**0.049**

Data are presented as N of pneumonia-positive patients in the group (%) as appropriate.
Conservative Group: antibiotic use for no greater than 48 h or no antibiotics at all; Antibiotic Therapy Group: antibiotic started at hospital admission and maintained for more than 48 h.
[a] More than one bacteria may have been isolated from each event of pneumonia, therefore the sum of % is greater than 100%.
[b] Methicillin-resistant S. aureus; *Pseudomonas aeruginosas* or *Acinetobacter baumannii* resistant to quinolones and fourth generation cephalosporins; *Acinetobacter baumannii* resistant to quinolones; third generation cephalosporin-resistant *Klebsiella spp.*, *Enterobacter spp.*, *Escherichia coli*, *Streptococcus pneumoniae*, *Proteus spp.* or *Serratia marcescens*.

Table 4 Multivariate analysis: association of antibiotic strategy and primary outcome.

	Odds Ratio	95% CI	*p*-value
Duration of mechanical ventilation, per day	1.37	1.24–1.53	<0.01
Antibiotic Therapy Group (vs. Conservative Group)	0.25	0.09–0.64	<0.01
Duration of chest thoracostomy, per day	0.94	0.85–1.03	0.23
Bronchoaspiration	0.41	0.07–1.69	0.26
Age, per year	0.99	0.95–1.02	0.38
Male Sex	1.15	0.37–3.91	0.82

Variables were selected among those available as known risk factors for pneumonia in severely injured patients with thoracic trauma, as described by Wutzler et al.[11] in addition to tube thoracostomy.[12]
Conservative Group: antibiotic use for no greater than 48 h or no antibiotics at all; Antibiotic Therapy Group: antibiotic started at hospital admission and maintained for more than 48 h.
Variance Inflation Factor varied between 1.00 and 1.36 for all variables, indicating no significant multicollinearity.

Table 5 Sensitivity analysis: multivariate analysis based on the risk factors described by Landenn et al.[2] with the addition of chest tube thoracostomy.[12] Association of antibiotic strategy and primary outcome.

	Odds Ratio	95% CI	*p*-value
Heart Rate at admission, per bpm (Highest)	0.97	0.95–0.99	<0.01
Mechanical Ventilation at ICU admission	15.9	2.8–301.9	0.01
Antibiotic Therapy Group (vs. Conservative Group)	0.33	0.14–0.79	0.01
Glasgow Coma Score at admission	0.94	0.84–1.04	0.22
Systolic Arterial Pressure at admission, per mmHg (lowest)	1.01	0.99–1.03	0.36
Duration of chest thoracostomy, per day	0.98	0.89–1.07	0.67
Age, per year	0.99	0.98–1.02	0.85

Variables were selected among those available as known risk factors for pneumonia in pulmonary contusion patients, as adapted from[2] with the addition of chest tube thoracostomy.[12]
Conservative Group: antibiotic use for no greater than 48 h or no antibiotics at all; Antibiotic Therapy Group: antibiotic started at hospital admission and maintained for more than 48 h.
Variance Inflation Factor varied between 1.00 and 1.14 for all variables, indicating no significant multicollinearity.

during the first week of ICU.[8] Also, the incidence of nosocomial pneumonia, especially VAP is higher in trauma patients than in other populations.[1] This association between VAP and trauma was highlighted in our study by the fact that only two patients in our study population had non-VAP nosocomial pneumonia. The strict criteria guaranteed that the incidence of nosocomial pneumonia in our study was similar to that reported by other authors.[2,14]

Two different sets of historical confounder variables[10] were used to mitigate differences between groups in adjusted analysis. In both main and sensitivity analysis we chose to include tube thoracostomy as a potential confounder, given its relevant role as a risk factor for pulmonary infection in trauma patients.[12]

The baseline characteristics were different between groups, and the Antibiotic Therapy Group had more severely ill patients, as suggested by higher ISS, SAPS3, SOFA, mechanical ventilation duration and ICU length of stay. The crude incidence of pneumonia was very similar between the groups. Nevertheless, due to imbalances between baseline variables, the Antibiotic Therapy Group was expected to have a higher incidence of nosocomial pneumonia. Therefore, after adjusting for confounders, this group was associated with a decreased incidence of microbiologically confirmed pneumonia.

The present findings of protective effects of antibiotics on preventing pulmonary infections in chest trauma are in line with previous studies in patients with thoracostomy,[12] while the present work focuses on pulmonary contusion.

Despite this protective association for nosocomial pneumonia incidence, antibiotic use for more than 48 hours was associated with infection by resistant bacteria both when categorized as a group (Antibiotic Therapy Group) and when quantified as days of antibiotic use. This suggests that even short periods of antibiotic exposure might affect patients' flora and lead to an increase in multi-drug resistance infection. These findings are in general agreement with other published works, showing increases in colonization and infection by resistant bacteria associated with previous antimicrobial use.[15-17]

We speculate that antibiotic therapy could be associated with reduced nosocomial pneumonia by susceptible bacteria, while the remaining episodes of infection are probably caused by a resistant pathogen.

As a quality of our study, definitions of exposures and outcomes were clear and rigorous. Sensitivity analysis showed the same results of the primary analysis, so intern validity seems strong.

Our study has several limitations. The observational nature of our data led to unbalances between groups, which were accounted for in our analysis method. Markedly, patients in the antibiotic group had more severe trauma evaluated by the ISS, more organ dysfunctions evaluated by the SOFA score, and more frequent and longer duration of mechanical ventilation. Despite the use of multivariate logistic regression,

possibly additional imbalances between groups still played a role in our findings. But all these factors could be associated with worse outcomes and higher pneumonia occurrence, therefore the direction of our findings would probably not change, since the protective association was found in more severely ill patients (Antibiotic Therapy Group).

On the other hand, the use of antibiotics in this group could have artificially decreased the primary outcome of our study: microbiologically documented nosocomial pneumonia. In patients with prior antibiotic treatment, quantitative bacterial respiratory samples have lower sensitivity in the diagnosis of nosocomial pneumonia (36—50%), when compared to patients without prior antimicrobial use (sensitivity as high as 80%).[18] In our sample, however, we could not find differences between the proportion of patients with positive cultures, and just one patient in each group fulfilled the clinical and radiological definition, but had no microbiological confirmation. So, it is not probable that the decreased accuracy of cultures with prior antibiotic exposure had any impact on our results.

Due to the high incidence of pneumonia and associated lesions (open fractures, peritonitis, cerebrospinal fluid leakage etc.), critically ill trauma patients often receive empiric antibiotics for several days, even when samples from the respiratory tract are sterile.[19] Our study suggests that this may be associated with lower pneumonia incidence, however, it may also lead to significant collateral effects, especially colonization and infection by drug-resistant bacteria.[6] Since colonization for drug-resistant bacteria can last for months,[20] a randomized powered trial in trauma patients with a high risk of nosocomial pneumonia with patient-centred outcomes and extended follow-up is necessary to assess the real benefit of this approach.

In conclusion, empiric antibiotic therapy lasting for more than 48h in critically ill patients with pulmonary contusion was associated with a lower incidence of nosocomial pneumonia. Nevertheless, it was associated with resistant strains in the respiratory samples of infected patients. A randomized trial of a short course of antibiotic therapy with patient-centred outcomes on thoracic trauma and risk factors for developing nosocomial pneumonia is warranted, to confirm these findings and assess the true benefit of this approach.

Conflicts of interest

The authors declare no conflicts of interest

CRediT authorship contribution statement

Estevão Bassi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing — original draft, Writing — review & editing. **Camila Trevizani Merighi:** Conceptualization, Data curation, Investigation, Methodology, Writing — review & editing. **Carlos Issamu Tomizuka:** Conceptualization, Data curation, Investigation, Methodology, Writing — review & editing. **Thais Guimarães:** Conceptualization, Investigation, Methodology, Writing — original draft, Writing — review & editing. **Fernando da Costa Ferreira Novo:** Conceptualization, Methodology, Supervision, Writing — original draft, Writing — review & editing. **Sergio Henrique Bastos Damous:** Supervision, Validation, Writing — review & editing. **Edivaldo Massazo Utiyama:** Project administration, Supervision, Validation, Writing — review & editing. **Luiz Marcelo Sá Malbouisson:** Conceptualization, Methodology, Project administration, Supervision, Writing — review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.07.011.

References

1. Cook A, Norwwod S, Berne J. Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically Ill patients. J Trauma. 2010;69(5):1083—91.
2. Landeen C, Smith HL. Examination of pneumonia risks and risk levels in trauma patients with pulmonary contusion. J Trauma Nurs. 2014;21:41—9.
3. Kesinger MR, Kumar RG, Wagner AK, et al. Hospital-acquired pneumonia is an independent predictor of poor global outcome in severe traumatic brain injury up to 5 years after discharge. J Trauma Acute Care Surg. 2015;78:396—402.
4. Mangram AJ, Sohn J, Zhou N, et al. Trauma-associated pneumonia: time to redefine ventilator-associated pneumonia in trauma patients. Am J Surg. 2015;210:1056—62.
5. Poole D, Chieregato A, Langer M, et al. Systematic review of the literature and evidence-based recommendations for antibiotic prophylaxis in trauma: results from an Italian Consensus of Experts. PLoS ONE. 2014;9:e113676.
6. Hoth JJ, Franklin GA, Stassen NA, Girard SM, Rodriguez RJ, Rodriguez JL. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. J Trauma. 2003;55:249—54.
7. Rendeki S, Molnár TF. Pulmonary contusion. J Thorac Dis. 2019;11:S141—51.
8. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma. 2006;61:310—7.
9. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61—111.
10. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies. guidance for authors from editors of respiratory, sleep, and critical care journals. Ann Am Thorac Soc. 2019;16:22—8.
11. Wutzler S, Bläsius FM, Störmann P, et al. Pneumonia in severely injured patients with thoracic trauma: results of a retrospective observational multi-centre study. Scand J Trauma Resusc Emerg Med. 2019;27:31.
12. Ayoub F, Quirke M, Frith D. Use of prophylactic antibiotic in preventing complications for blunt and penetrating chest trauma requiring chest drain insertion: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2019;4:e000246.
13. R Core Team. R: The R Project for Statistical Computing [Internet]. https://www.R-project.org/. 2022. Available from: http://www.R-project.org.
14. Tejada Artigas A, Bello Dronda S, Chacón Vallés E, et al. Risk factors for nosocomial pneumonia in critically ill trauma patients. Crit Care Med. 2001;29:304—9.

15. Salomão MC, Guimarães T, Duailibi DF, et al. Carbapenem-resistant Enterobacteriaceae in patients admitted to the emergency department: prevalence, risk factors, and acquisition rate. J Hosp Infect. 2017;97:241—6.
16. Skjøt-Arkil H, Mogensen CB, Lassen AT, et al. Carrier prevalence and risk factors for colonisation of multiresistant bacteria in Danish emergency departments: a cross-sectional survey. BMJ Open. 2019;9:e029000.
17. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of Subsequent Sepsis Within 90 Days After a Hospital Stay by Type of Antibiotic Exposure. Clin Infect Dis. 2017;66:1004—12.
18. Chastre J, Trouillet J, Combes A, Luyt C. Diagnostic techniques and procedures for establishing the microbial etiology of ventilator-associated pneumonia for clinical trials: the pros for quantitative cultures. Clin Infect Dis. 2010;51:S88—92.
19. Loftus TJ, Brakenridge SC, Moore FA, et al. Intubated trauma patients receiving prolonged antibiotics for pneumonia despite negative cultures: predictors and outcomes. Surg Infect (Larchmt). 2016;17:766—72.
20. Haverkate MR, Weiner S, Lolans K, et al. Duration of colonization with klebsiella pneumoniae carbapenemase-producing bacteria at long-term acute care hospitals in Chicago, Illinois. Open Forum Infect Dis. 2016;3:ofw178.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Impact of withholding early antibiotic therapy in nonseptic surgical patients with suspected nosocomial infection: a retrospective cohort analysis

Estevão Bassi [a,b,*], Bruno Martins Tomazini [a,c], Bárbara Vieira Carneiro [a], Amanda Rodrigues de Oliveira Siqueira [d], Sara Rodrigues de Oliveira Siqueira [d], Thais Guimarães [e], Fernando da Costa Ferreira Novo [a], Edivaldo Massazo Utiyama [a], Paolo Pelosi [f,g], Luiz Marcelo Sá Malbouisson [h]

[a] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Departamento de Cirurgia, Disciplina de Cirurgia Geral e Traumatologia, São Paulo, SP, Brazil*
[b] *Hospital Alemão Oswaldo Cruz, Unidade de Tratamento Intensivo, São Paulo, SP, Brazil*
[c] *Hospital Sírio-Libanês, Instituto de Ensino e Pesquisa, São Paulo, SP, Brazil*
[d] *Irmandade da Santa Casa de Misericórdia, Departamento de Medicina Interna e Cardiologia, São Paulo, SP, Brazil*
[e] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Departamento de Controle de Infecção, São Paulo, SP, Brazil*
[f] *University of Genoa, Department of Surgical Sciences and Integrated Diagnostics, Genoa, Italy*
[g] *San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Anaesthesia and Intensive Care, Genoa, Italy*
[h] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Divisão de Anestesiologia, São Paulo, SP, Brazil*

Received 20 August 2022; accepted 14 March 2023
Available online 23 March 2023

KEYWORDS
Antimicrobial stewardship;
Critical care;
Prescription drug overuse;
Sepsis;
Septic shock

Abstract

Background: Systemic inflammatory responses mimicking infectious complications are often present in surgical patients.

Methods: The objective was to assess the association between withholding early antimicrobial therapy while investigating alternative diagnoses and worse outcomes in nonseptic patients with suspected nosocomial infection in a retrospective cohort of critically ill surgical patients. The initiation of antibiotic therapy within 24 h of the suspicion of infection was defined as the Early Empirical Antibiotic strategy (EEA) group and the initiation after 24 h of suspicion or not prescribed was defined as the Conservative Antibiotic strategy (CA) group. Primary outcome was composite: death, sepsis, or septic shock within 14 days. Main exclusion criteria were sepsis or an evident source of infection at inclusion.

Abbreviations: 95% CI, 95% Confidence Interval; CA, Conservative Group; DAG, Direct Acyclic Graphic; EEA, Early Empirical Antibiotic Group; EMR, Electronic Medical Records; ICU, Intensive Care Unit; IQR, Interquartile Range; SAPS-3, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; VIF, Variance Inflation Factor; WBC, White Blood Cell.

* Corresponding author.
E-mail: estevao.b@hc.fm.usp.br (E. Bassi).

https://doi.org/10.1016/j.bjane.2023.03.003
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Results: Three hundred and forty patients were eligible for inclusion (74% trauma patients). Age, sex, reason for hospital admission, SAPS3 score, SOFA score, and use of vasopressors or mechanical ventilation were not different between the groups. Within 14 days of inclusion, 100% (130/130) of EEA patients received antibiotics compared to 57% (120/210) of CA patients. After adjusting for confounding variables, there was no association between primary outcome and the groups. In a post hoc subgroup analysis including only patients with *a posteriori* confirmed infection (by microbiological cultures), delay in initiation of adequate antimicrobial therapy was independently associated with the primary outcome (Odds Ratio = 1.19 per day of delay; 95% CI 1.05—1.37).
Conclusions: Withholding early empiric antibiotic therapy was not associated with progression of organ dysfunction within 14 days in nonseptic surgical patients with suspected nosocomial infection without an obvious source.
© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Early antimicrobial drugs are the cornerstone of treatment of bacterial infections.[1] In patients with sepsis or septic shock, delays in antibiotic therapy are strongly associated with worse outcomes.[2-5] The Surviving Sepsis Campaign Guidelines advocate "immediate" empirical antimicrobial therapy, ideally within 1h of recognition, in patients with a high likelihood of sepsis or septic shock.[6]

On the other hand, the evidence for early empirical antimicrobial therapy is not strong in stable surgical patients with suspected infections.[7] The causal inference for this strict time-dependent benefit in this situation lacks robust causal association.[8] Early empiric antibiotic treatment is often prescribed to these patients, even in the absence of a clear infectious source, driven by the belief that antibiotics could prevent stable patients from deteriorating or by fear of litigation.[9] Antibiotic overuse is associated with an increase in the rate of systemic adverse effects,[10] and colonization and infection by multidrug resistant microorganisms.[11-14] Millions of deaths are estimated to be caused by or associated with multidrug-resistant bacteria.[12] Critically ill surgical patients admitted to the Intensive Care Unit (ICU) commonly have a persistent inflammatory response that mimics nosocomial infection,[15,16] which influences clinical reasoning and may contribute to the excessive use of antibiotics.

Our study aimed to evaluate the impact of withholding early empirical antibiotics during diagnostic workup on clinical outcomes in nonseptic surgical patients with suspected nosocomial infections.

Methods

We retrospectively evaluated a cohort of adult patients admitted to an emergency surgical Intensive cCare Unit (ICU) in a tertiary university hospital in São Paulo, Brazil between 2012 and 2016. The analysis plan, study design, and definition of the groups and outcomes were defined before data extraction and mining from the Electronic Medical Record (EMR) database. The study was approved by the institutional research ethics board (CAPPesq — CAAE 44661615.7.0000.0068). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics board. This article was written based on the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the reporting of cohort studies (Supplemental Fig. 1).[17]

The inclusion criteria were as follows: stable postsurgical or trauma (irrespective of the mechanism or site or surgery) patients who were admitted to the ICU, who were older than 14 years, and who had a suspected nosocomial infection during ICU stay. Suspected nosocomial infection was defined when microbiological cultures were drawn after 48 hours of hospital admission due to a suspicion of infection, as documented in the EMRs. Stable patients were those with no significant increase in their Sequential Organ Failure Assessment (SOFA) score (< 2 points) within the previous 24 hours.[18] Surveillance cultures (rectal, nasal, and axillary swabs) were excluded. The exclusion criteria were as follows: a) Rapid progression of organ dysfunctions with an increase in the SOFA score that is > 1 (sepsis) or hyperlactatemia, hypotension and vasopressor use (septic shock) according to the Sepsis 3.0 definitions[19] within 24 hours of inclusion; b) Hemodynamic deterioration within the first 24 hours of the suspected infection defined as an increase > 0.1 mcg.kg^{-1}.min^{-1} in the norepinephrine dosage; c) An obvious infectious source identified in the EMR (e.g., antibiotics initiated for pneumonia, urinary tract infection, meningitis); d) An ICU length of stay less than 48 hours after inclusion; e) Missing data on the primary outcome; f) Patients in palliative care; and g) Predicted death within 48 hours of inclusion. Vasopressor use was not an exclusion criterion *per se* if the patient did not meet the sepsis, septic shock, or hemodynamic deterioration definitions. All patients who fulfilled the inclusion criteria without any of the exclusion criteria during the period were included in the analysis. Time zero was defined as the moment in which the first microbiological cultures were drawn led to suspicion for the presence of a nosocomial infection.

Data collection and patient management

We divided the study population into two groups: 1) The Early Empirical Antibiotic strategy (EEA) group, in which the patients received antibiotic therapy within 24 hours of the clinical suspicion of infection, and 2) The Conservative Antibiotic strategy (CA) group, in which the patients received antibiotics 24 hours or later after the clinical suspicion of infection or did not receive antibiotics within 14 days of

inclusion. The physiological and laboratory variables up to 24 hours after inclusion were considered the baseline values and included the following variables: the use of mechanical ventilation or vasopressors, highest and lowest heart rate, highest and lowest body temperature, serum lactate, white blood cell count, and C-reactive protein levels. When more than one measure of these variables were available, the most abnormal value within this time window was chosen. Respiratory rate was not available in all patients and was not used in this study. Sustained tachycardia was defined when the lowest heart rate in the first 24 h of inclusion was ≥ 90 bpm. Blood cultures were drawn if there was any suspicion of infection. Respiratory, urinary, or cerebral spine fluid samples were collected when infection was suspected. Presumed infection was defined when a specific source of infection (e.g., lung, abdomen, central nervous system, etc.) was diagnosed more than 24 hours after inclusion and within 14 days according to the EMR. Confirmed infection was defined by the isolation of a pathogenic microorganism from the presumed source during the study period. Infection was defined when positive microbiological data were used to guide antibiotic treatment; otherwise, it was considered colonization. Whether antibiotic treatment was indicated, the timing of the initiation of antibiotics and the choice of the specific drug were defined at the discretion of the attending physician. Time to adequate antibiotic treatment was defined as the time from inclusion in the study up to the first day when an active antibiotic against the isolated microorganism was administered, according to the susceptibility on the antibiogram.

Outcomes

The primary outcome was defined *a priori* as a composite outcome including death, hypotension, hyperlactatemia and vasopressor use (septic shock) or worsening of organ dysfunction (an increase > 1 in the SOFA score — sepsis) within 14 days of inclusion, according to the Sepsis 3.0 definitions.[19] The secondary outcomes were ICU and hospital length of stay, and in-hospital mortality. Follow-up was performed until the end of hospitalization.

The timeline with the time points of the study is presented in Supplemental Figure 2.

Statistical analysis

All patients admitted to the ICU during the period were evaluated for inclusion in the study. Continuous variables were expressed as the mean and Standard Deviation (SD) or the median and Interquartile Range (IQR), according to data distribution. Discrete variables were reported as counts and percentages. Differences between the groups were compared using Welch's *t*-test, irrespective of the distribution of the numeric data,[20] or chi-square when appropriate. Confounding variables were evaluated using a Direct Acyclic Graphic (DAG), as shown in Figure 1.[21-23]

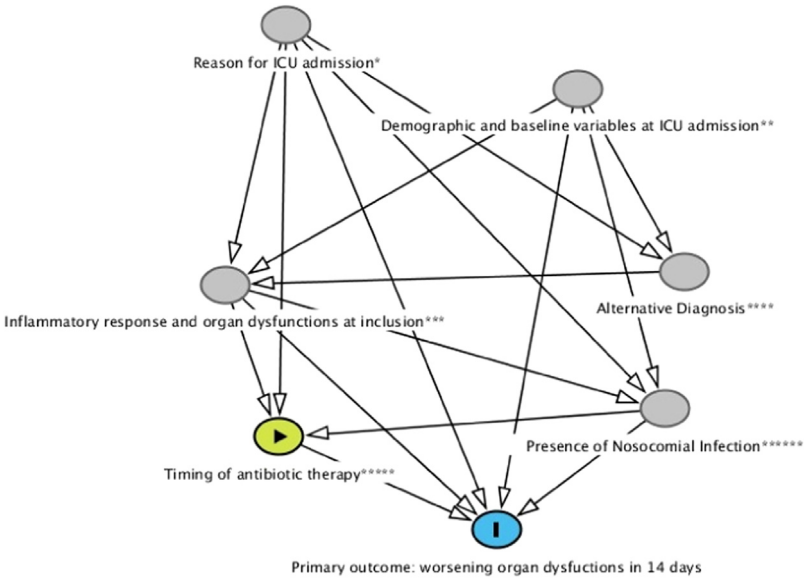


Figure 1 Direct acyclic graph for causal inference. The direction of the arrows indicates potential causality. The inference tested was between variables "Timing of antibiotic therapy" (independent variable) and "Primary outcome: worsening organ dysfunctions in 14 days" (dependent variable). Variables included in the model were the following: *Reason for Intensive Care Unit admission: trauma or surgery. ** Sex, age, comorbidities, Simplified acute physiology score-3. *** Inflammatory Response: dysregulation of body temperature (hypothermia or hyperthermia), white blood cell count alteration (leucocytosis or leukopenia) and sustained tachycardia (heart rate above 90 bpm in 24 h); Organ Dysfunctions: defined as the SOFA (Sequential Organ Failure Assessment) score. **** Alternative Diagnostics to nosocomial infection: such as inflammatory response to trauma or surgery, intracranial hypertension, thromboembolic events, heart failure etc. ***** Timing of Antibiotic: defined as the group (CA or EEA). ****** Nosocomial Infection: presumed or confirmed infection, according to different analyses that were performed. Data were imputed at http://www.dagitty.net/dags.html.[20-22]. Minimal adjustment sets for estimating the total effect of "Timing of antibiotic therapy" on "Primary Outcome" were: Reason for Intensive Care Unit admission*, Inflammatory response and organ dysfunctions at inclusion***, Presence of Nosocomial Infection******

Following the guidance of the DAG, a multivariate analysis was performed. The potential confounding variables in the association between time point of starting antibiotics and the primary outcome were dysregulation of body temperature (hypothermia or hyperthermia), white blood cell count alteration (leukocytosis or leukopenia), sustained tachycardia (heart rate above 90 bpm in 24 h), baseline SOFA score and diagnosis of a presumed nosocomial infection within the 14 days after inclusion. A sensitivity analysis was performed using univariate logistic regression to assess the variables potentially associated with the primary outcome. Clinically relevant variables with a *p*-value of less than 0.2 were included in a stepwise backward logistic regression model. A post hoc subgroup analysis including only the patients with confirmed infection was also performed. In this case, the variable "Timing to antibiotic therapy" had two components: group (CA or EEA) and time to adequate antibiotic treatment, as described above. Multicollinearity was evaluated through the variance inflation factor. VIF > 5 was considered to have significant multicollinearity.[24] Associations were expressed using the Odds Ratio (OR) with 95% Confidence Intervals (CIs). A *p*-value < 0.05 was considered significant. Statistical analyses were performed using R free source software.[25]

Results

Of the 2007 ICU admissions, 751 patients had suspected nosocomial infections and were screened. As shown in Figure 2, 340 patients were included in the cohort. The most common reasons for exclusion were sepsis (221 patients), septic shock (81 patients) or an obvious infectious source (51 patients) at inclusion. The group allocation was as follows: 210 patients to the CA group and 130 to the EEA group. The median ICU length of stay before study inclusion was 5 days in the CA group and 6 days in the EEA group ($p = 0.8$).

In Table 1, patients' characteristics at ICU admission and time of infection suspicion (inclusion) are shown. The groups had a similar mean age (44±18 years in both). Male sex was predominant in both groups. Seventy-four percent of the ICU admissions were due to trauma, and most of the trauma patients had a traumatic brain injury. The mean SAPS 3 score (55±14 vs. 56±12), median SOFA (5, IQR 3–7 vs. 5, IQ 4–7), rate of mechanical ventilation (119/210, 57% vs. 82/130, 63%) and vasopressor use (43/210, 21% vs. 28/130, 22%) were similar in the CA and EEA groups, respectively. Body temperature was also similar in both groups: the highest body temperature was 37.8 ± 0.7°C vs. 37.8 ± 0.8°C, and the lowest body temperature was 35.6 ± 0.8°C vs. 35.6 ±

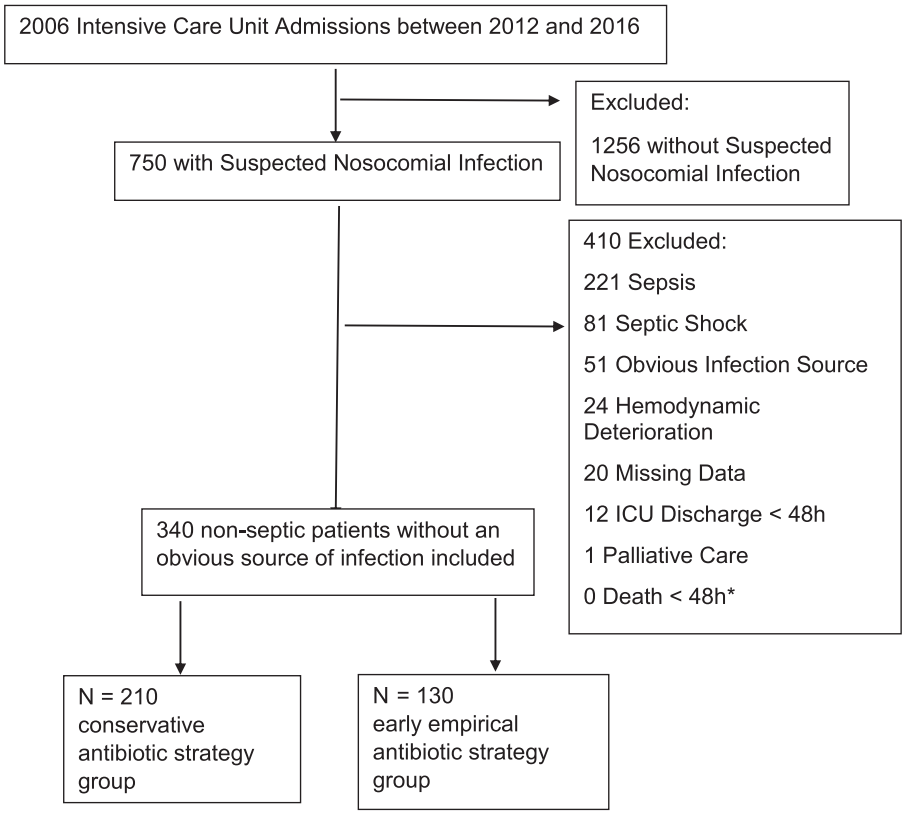


Figure 2 Flowchart. Flow diagram for the study population and number of patients analysed for suspected nosocomial infection, according to the STROBE statement.[25] Patients were selected to constitute the study population based on suspected infection after 48h of Intensive Care Unit admission. STROBE, Strengthening for Reporting of Observational Studies in Epidemiology. Conservative antibiotic strategy group: patients received antibiotics after 24 hours or later from the initial clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion. early empirical antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection. *Without other exclusion criteria.

Table 1 Baseline patients' characteristics at Intensive Care Unit admission and at infection suspicion (study inclusion).

	CA group	EAA group	*p*-value
N (% of total)	210 (62%)	130 (38%)	
Age (years)	44±18	44±18	0.81
Male, n (%)	166 (79%)	91 (70%)	0.08
Reason for Hospital Admission, n (%)			
Trauma	155 (74%)	97 (75%)	0.94
Brain Trauma Injury	109 (52%)	75 (58%)	0.35
Surgery[a]	55 (26%)	32 (26%)	0.38
Neurosurgery	31 (57%)	15 (47%)	
Abdominal	15 (27%)	15 (47%)	
Vascular	6 (11%)	1 (3%)	
Other	3 (6%)	1 (3%)	
Number of Comorbidities, n (%)	0 (0–1)	0 (0–0)	0.45
Arterial Hypertension	49 (23%)	24 (19%)	
Alcohol Abuse	28 (13%)	16 (12%)	
Diabetes Mellitus	19 (9%)	10 (8%)	
SAPS-3	55±14	56±12	0.48
Baseline at infection suspicion			
Previous Length of Stay at ICU (days)	5 (3–10)	6 (3–10)	0.80
SOFA score	5 (3–7)	5 (4–7)	0.18
On antibiotics, n (%):	108 (51%)	61 (47%)	0.49
Ceftriaxone ou Cefuroxime, n (%)	68 (32%)	43 (33%)	0.99
Clindamycin, n (%)	43 (21%)	30 (23%)	0.67
Other antibiotics, n (%)	41 (20%)	19 (15%)	0.31
On vasopressors, n (%)	43 (21%)	28 (22%)	0.92
Lactate (mmoL.L^{-1})	1.8-2.8 (2.2)	1.8-3.2 (2.4)	**<0.01**
On Mechanical Ventilation, n (%)	119 (57%)	82 (63%)	0.29
Highest Heart Rate (bpm)	113±20	119±21	**<0.01**
Highest Body Temperature (°C)	37.8±0.7°C	37.8±0.8°C	0.80
Lowest Body Temperature (°C)	35.6±0.8°C	35.6±0.9°C	0.62
White Blood Cell count (per μL)	12625 (10095–16282)	15870 (10960–20140)	**<0.01**
C-Reactive Protein (mg.L^{-1})	16 (10–24)	22 (11–30)	**<0.01**

Data are presented as mean ± standard deviation, median (interquartile range), or N of group (%) as appropriate.
CA, Conservative Antibiotic sStrategy group – patients received antibiotics after 24 hours or later from the clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion; EEA, Early Empirical Antibiotic strategy group – patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection. ICU, Intensive Care Unit; LOS, Length Of Stay; SAPS-3, Simplified Acute Physiology Score-3; SOFA, Sequential Organ Failure Assessment score.
Values within 24 hours on the day of infection suspicion.
[a] Value of p for differences in types of surgery in the groups.
** Hypertension, diabetes, alcohol abuse, coronary artery disease, heart failure, chronic pulmonary obstructive disease, chronic kidney disease, HIV, or cancer.

0.9°C in the CA and EEA groups, respectively. Other markers of inflammation, such as heart rate, white blood cell count, and C-reactive protein, were slightly but significantly higher in the EEA group than in the CA group (Table 1).

In both groups, patients with neurologic and respiratory organ dysfunction were prevalent at baseline (Supplemental Fig. 3).

The composite primary outcome of death, sepsis or septic shock within 14 days after inclusion occurred in 40% of the patients in the CA group and 56% of the patients in the EEA group, $p < 0.01$. There was no difference in the incidence of 14 day death or septic shock between the groups. Length of stay in the ICU or hospital and hospital mortality were not significantly different between the groups (Table 2). The main organs that had worsening dysfunction within the first 14 days after study inclusion were cardiovascular and renal (Supplemental Fig. 3).

During the 14 days of observation, 57% of the patients in the CA group had received antibiotics (vs. 100% of the patients in the EEA group). The patients in the EEA group had more suspected lung (50% vs. 24%) and abdominal infections (9% vs. 3). The EEA group had a higher *a posteriori* proportion of patients with presumed (88% vs. 53%) and microbiologically confirmed infections (70% vs. 45%) ($p < 0.01$). The median time to adequate antibiotic treatment was 3 days (IQR 2−5 days) in the CA group vs. 1 day (IQR 0−3 days) in the EEA group ($p < 0.01$) (Supplemental Table 1).

The multivariate analysis, which was adjusting with confounding variables according to the DAG model, showed that EEA was no longer associated with the primary outcome (OR = 1.27; 95% CI 0.77−2.08) (Table 3). A sensitivity analysis was performed using stepwise backward logistic regression based on the univariate analysis (Supplemental Table 2) and yielded similar results (Supplemental Table 3).

Table 2 Primary and secondary outcomes.

	CA group	EAA group	Odds Ratio (95% CI)	*p*-value
Primary Outcome[a]	85 (40%)	73 (56%)	1.88 (1.21–2.93)	**<0.01**
Sepsis[a]	76 (36%)	67 (52%)	1.88 (1.20–2.92)	**<0.01**
Septic Shock[a]	28 (13%)	21 (16%)	1.25 (0.68–2.31)	0.58
Mortality[a]	24 (11%)	20 (15%)	1.41 (0.74–2.67)	0.37
Cause of death[b]				0.56
Infection associated	9 (4%)	11 (8%)		
Intracranial Hypertension/Brain death	9 (4%)	6 (5%)		
Other causes	6 (3%)	3 (2%)		
Length of ICU stay (days)	18 (13–29)	24 (14–37)	–	0.27
Length of hospital stay (days)	36 (21–76)	44 (24–68)	–	0.40
In-hospital mortality	68 (32%)	54 (42%)	1.48 (0.94–2.33)	0.11

Data are presented as median (interquartile range) or n (%) as appropriate.
CA, Conservative Antibiotic strategy group – patients received antibiotics after 24 hours or later from the clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion; EEA Early Empirical Antibiotic strategy group – patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection; ICU, Intensive Care Unit.
The Primary Outcome, Mortality in 14 days, Septic Shock in 14 days, Sepsis in 14 days, and In-hospital mortality were evaluated with Chi-Square.
ICU length of stay and hospital length of stay were evaluated with Welch's *t*-test.
[a] In the timeframe of 14 days, as defined in the primary outcome.
[b] According to Electronic Medical Record analysis.

A subgroup analysis including only patients with confirmed infection (by cultures) also did not detect an association between the groups (CA or EEA) and the primary outcome. However, delays in initiating appropriate antibiotic therapy in these patients were associated with worse outcomes, irrespective of the group (Table 4), with an Odds Ratio of 1.19 per day of delay with 95% CI 1.05—1.37 (p-value < 0.01).

Discussion

In this study, withholding early empirical antibiotics during diagnostic workup in nonseptic surgical patients with suspected nosocomial infections was not associated with death, worsening of organ dysfunction, or shock. In critically ill patients, signs indicating the presence of infection are nonspecific and may occur in many noninfectious conditions, particularly in trauma and surgical patients,[16,26] making a definitive diagnosis harder to achieve. In this setting, antibiotics are often prescribed, even to nonseptic patients who do not have an identifiable infectious source.

However, the adverse effects of antimicrobials are significant[10,27] and, in noninfected patients, may not be counterbalanced by the benefits. The present findings suggest that widespread administration of early empiric antimicrobials to a heterogeneous group of nonseptic surgical patients with and without a true infection (diagnosed posteriorly) does not translate into an overall clinical benefit. Efforts should be made to establish a diagnosis as soon as possible. In the meantime, antimicrobial therapy should be promptly administered to septic or deteriorating patients. Additionally, stable patients with a high likelihood of infection with a probable source who have been diagnosed based

Table 3 Multivariate Analysis Association of early empiric antibiotic strategy and primary outcome.[a]

	Odds ratio	95% CI	*p*-value
Presumed infection[b]	2.57	1.48–4.56	**<0.01**
Sustained tachycardia[c]	1.74	1.02–2.98	**0.04**
Reason for admission: surgical (non-trauma)	1.69	1.00–2.88	0.05
Abnormal WBC count[d]	1.39	0.82–2.37	0.22
SOFA at inclusion (per point)	1.04	0.97–1.12	0.29
Early Empirical Antibiotic strategy (EEA) group	1.27	0.77–2.08	0.35
Hyperthermia or Hypothermia[e]	1.01	0.62–1.65	0.96

OFA, Sequential Organ Failure Assessment; WBC, White Blood Cell; EEA, Early Empirical Antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection.
Variance Inflation Factor varied between 1.03 and 1.25 for all variables, indicating no significant multicollinearity.
[a] Variables were selected from the Direct Acyclic Graphic depicted in Figure 1.
[b] Probable infection site diagnosed according to Electronic Medical Records within 14 days (as opposed to a source of infection none or unknown), confirmed or not by cultures
[c] Lowest Heart Rate > 90 bpm within 24 hours of inclusion.
[d] WBC count > 12000 cells.mm^{-2} or WBC count < 4000 cells.mm^{-2}.
[e] Body Temperature > 38°C and/or < 36°C.

Table 4 Multivariate Analysis Association of timing of antibiotic therapy and primary outcome[a]. Post-hoc subgroup analysis in patients with confirmed infection by microbiological cultures.

	Odds ratio	95% CI	*p*-value
Time until adequate antibiotic therapy (per day)[b]	1.19	1.05–1.37	**<0.01**
Reason for admission: Surgical (non-trauma)	2.11	1.01–4.53	0.05
Sustained Tachycardia[c]	2.07	0.95–4.70	0.07
Early Empirical Antibiotic strategy (EEA) group	1.82	0.91–3.71	0.09
Abnormal WBC count[d]	1.67	0.82–3.47	0.16
Hyperthermia or Hypothermia[e]	0.73	0.37–1.43	0.36
SOFA at inclusion (per point)	1.02	0.92–1.13	0.74

Post-hoc analyses including only patients with confirmed infection (by cultures).
WBC, White Blood Cell; EEA, Early Empirical Antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection.
Variance Inflation Factor varied between 1.04 and 1.28 for all variables, indicating no significant multicollinearity.
[a] Variables were selected from the Direct Acyclic Graphic depicted in Figure 1.
[b] As defined in Methods.
[c] Lowest Heart Rate > 90 bpm within 24 hours of inclusion.
[d] WBC count > 12000 cells.mm^{-2} or WBC count < 4000 cells.mm^{-2}.
[e] Body Temperature > 38°C and/or < 36°C.

on clinical, radiologic and laboratory criteria should not have therapy withheld, since nonseptic patients who have a confirmed infection *a posteriori* also have a time-dependent benefit from therapy according to our data and others.[3,28]

Similar to our findings, in a multicentric, open-label, randomized trial, Alam et al did not find better outcomes of early antimicrobial therapy in 2672 prehospital patients with suspicion of infection and with various degrees of severity.[29] A before and after observational cohort study in critically ill surgical patients also did not observe an association of better outcomes when using a strategy of early antibiotic therapy in patients with suspected nosocomial infections without septic shock before the results of the microbiologic exams were available.[7] However, even when an infection is present, early administration of antibiotics may not be the main factor associated with better outcomes in critically ill nonseptic patients.[11,30-32]

An apparent paradox merits further discussion in our study. Delays in initiating appropriate therapy were associated with worse outcomes in the subgroup of patients with confirmed infections. The patients in the early empiric antibiotic group were prescribed adequate therapy faster in cases of confirmed infection (median 1 day vs. 4 days in CA, Table 1 Supplement); however, this was not sufficient to translate into better outcomes for the group. Two possible explanations are provided below.

First, despite our best efforts to adjust for confounding factors in the multivariate analysis, the patients included in the EEA group may have been more severely ill than the patients in the CA group as perceived by the attending physician but were not captured by the registered standard clinical data. In addition to the multivariate analysis, a paired analysis of the SOFA score and the associated subcomponents, as shown in Supplemental Figure 3, functioned as an additional way to adjust for the baseline organ dysfunction severity. This analysis also did not detect a benefit for early antibiotic therapy regarding any organ dysfunction or total SOFA.

Second, the uncertainty of the diagnosis of infection in stable patients is very common in nosocomial settings.[33] Large observational studies showed an association between the timing of antibiotic therapy administration and worse outcomes in septic patients in a time-dependent fashion.[2-4] Nevertheless, nonseptic surgical patients and patients with suspected infections (not confirmed posteriorly) are often excluded from most of the studies. The benefit of earlier appropriate therapy obtained in some patients may not be valid for a heterogeneous group including infected and non-infected patients, simulating real-life situation scenarios when a confirmed infection is only granted *a posteriori*.

We opted to perform a multivariate analysis based on a direct acyclic graphic model to control for the confounders as the primary analysis. This kind of analysis takes into account clinically relevant variables that can be inappropriately removed from the model due to insufficient power related to a small sample size and avoids the impact of collider variables.[21-23] Furthermore, direct acyclic graphic models bring transparency to the proposed causal inference. We also performed a sensitivity multivariate analysis based on a more traditional stepwise backward regression model with data derived from the univariate analysis. The variables included in the sensitivity analysis were different from those used in the primary analysis, but both these analyses yielded similar results. Therefore, we can hypothesize that our results are consistent and have internal validity.

Our study has limitations. It was a single-center observational trial, and confounders such as selection and information biases might have influenced the results. There was no standardization in the criteria for the initiation of antibiotic therapy, with the attending physician being responsible for the decision. This might explain the higher number of culture-confirmed infections in the EEA group. Although there was no difference between the groups in the markers of severity of disease, we cannot underestimate the importance of the clinical impression of the treating physician, who takes into account numerous known and intangible factors in the process of decision-making. Finally, since 74% of our cohort was trauma patients and the mean age was 44 years, our results are valid only for a strict number of critically ill patients.

Conclusions

In critically ill nonseptic surgical patients with a suspected nosocomial infection without an obvious source, withholding early empiric antibiotic therapy was not associated with the progression of organ dysfunction in 14 days. In the subanalysis including only confirmed infection patients, delays in the administration of active therapy against the isolated pathogens were associated with worse outcomes. Our results only apply to a strict number of critically ill surgical patients.

Conflicts of interest

The authors declare no have conflicts of interest.

No specific funding has been received for this work. Data were generated as part of the routine work of the Trauma Intensive Care Unit in HCFMUSP.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.03.003.

References

1. Hutchings M, Truman A, Wilkinson B. Antibiotics: past, present and future. Curr Opin Microbiol. 2019;51:72–80.
2. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
3. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017;196:856–63.
4. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–44.
5. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med. 2017;45:623–9.
6. Evans L, Rhodes A, Alhazzani W, et al. Executive summary: surviving sepsis campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49:1974–82.
7. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: A quasi-experimental, before and after observational cohort study. Lancet Infect Dis. 2012;12:774–80.
8. Rothman K, Greenland S, Poole C, Lash T. Causalidade e inferência causal. In: Rothman K, Greenland S, Lash T, eds. Epidemiologia Moderna, 3rd ed., Porto Alegre: Artmed; 2011:15–45.
9. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care - Reasons for caution. N Engl J Med. 2014;370:1673–6.
10. Arulkumaran N, Routledge M, Schlebusch S, Lipman J, Conway Morris A. Antimicrobial-associated harm in critical care: a narrative review. Intensive Care Med. 2020;46:225–35.
11. Hranjec T, Sawyer RG. Conservative initiation of antimicrobial treatment in ICU patients with suspected ICU-Acquired infection: More haste less speed. Curr Opin Crit Care. 2013;19:461–4.
12. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629–55.
13. Almagor J, Temkin E, Benenson I, Fallach N, Carmeli Y. The impact of antibiotic use on transmission of resistant bacteria in hospitals: Insights from an agent-based model. PLoS One. 2018;13:e0197111.
14. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018;11:1645–58.
15. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma. 2006;61:310–6.
16. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: Effect of intensive care unit resuscitation. Arch Surg. 1999;134:81–7.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
18. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10.
19. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801–10.
20. Rasch D, Kubinger KD, Moder K. The two-sample t test: Pre-testing its assumptions does not pay off. Stat Pap. 2011;52:219–31.
21. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: The R package "dagitty. Int J Epidemiol. 2016;45:1887–94.
22. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies, 16. Ann Am Thorac Soc; 2019. p. 22–8.
23. Brumback BA. Causal Directed Acyclic Graphs. Fundam Causal Inference with R. 2021;327:81–98.
24. P. Vatcheva K, Lee M. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiol Open Access. 2016;06:1–20.
25. Core R Team. A Language and Environment for Statistical Computing [Internet]. Vol. 2, R Foundation for Statistical Computing. 2019. p. https://www.R–project.org. Available from: http://www.r-project.org.
26. Miller PR, Munn DD, Meredith JW, Chang MC. Systemic inflammatory response syndrome in the trauma intensive care unit: Who is infected? J Trauma. 1999;47:1004–8.
27. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017;177:1308–15.
28. Zasowski EJ, Bassetti M, Blasi F, et al. A Systematic Review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections. Chest. 2020;158:929–38.
29. Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med. 2018;6:40–50.
30. Abe T, Kushimoto S, Tokuda Y, et al. Implementation of earlier antibiotic administration in patients with severe sepsis and septic shock in Japan: A descriptive analysis of a prospective observational study. Crit Care. 2019;23:360.
31. Singer M. Antibiotics for sepsis: Does each hour really count, or is it incestuous amplification? Am J Respir Crit Care Med. 2017;196:800–2.
32. Abe T, Tokuda Y, Shiraishi A, et al. In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission. Crit Care. 2019;23:202.
33. Klein Klouwenberg PMC, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: A cohort study. Crit Care. 2015;19:319.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Comparison of terbutaline and atosiban as tocolytic agents in intrauterine repair of myelomeningocele: a retrospective cohort study

Shirley Andrade Santos[a,b], Fernando Souza Nani[b], Elaine Imaeda de Moura[b], Diogo Lima de Carvalho[b], Guilherme Jorge Mattos Miguel[b], Cristiane Maria Federicci Haddad[b], Joaquim Edson Vieira[b], Victor Bunduki[c], Mário Henrique Burlacchini de Carvalho[c], Rossana Pulcineli Vieira Francisco[c], Daniel Dante Cardeal[d], Hermann dos Santos Fernandes[a,b,*]

[a] *University of Toronto, Mount Sinai Hospital, Department of Anesthesia and Pain Management, Toronto, Canada*
[b] *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Departamento de Anestesiologia, São Paulo, SP, Brazil*
[c] *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Departamento de Obstetrícia e Ginecologia, São Paulo, SP, Brazil*
[d] *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Departamento de Neurologia, São Paulo, SP, Brazil*

Received 30 June 2023; accepted 4 March 2024
Available online 22 March 2024

KEYWORDS
Atosiban;
Perinatology;
Myelomeningocele;
Terbutaline;
Tocolysis

Abstract
Background: Myelomeningocele (MMC) is a neural tube defect disease. Antenatal repair of fetal MMC is an alternative to postnatal repair. Many agents can be used as tocolytics during the in utero fetal repair such as β2-agonists and oxytocin receptor antagonists, with possible maternal and fetal repercussions. This study aims to compare maternal arterial blood gas analysis between terbutaline or atosiban, as tocolytic agents, during intrauterine MMC repair.
Methods: Retrospective cohort study. Patients were divided into two groups depending on the main tocolytic agent used during intrauterine MMC repair: atosiban (16) or terbutaline (9). Maternal arterial blood gas samples were analyzed on three moments: post induction (baseline, before the start of tocolysis), before extubation, and two hours after the end of the surgery.
Results: Twenty-five patients were included and assessed. Before extubation, the terbutaline group showed lower arterial pH (7.347 ± 0.05 vs. 7.396 ± 0.02 for atosiban, $p = 0.006$) and higher arterial lactate (28.33 ± 12.76 mg.dL^{-1} vs. 13.06 ± 6.35 mg.dL^{-1}, for atosiban, $p = 0.001$) levels.
Conclusions: Patients who received terbutaline had more acidosis and higher levels of lactate, compared to those who received atosiban, during intrauterine fetal MMC repair.
© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author
E-mail: hermannfernandes@alumni.usp.br (H. dos Santos Fernandes).

https://doi.org/10.1016/j.bjane.2024.844495
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Myelomeningocele (MMC) is a neural tube defect disease, and this malformation affects approximately 3.4 pregnancies per 10,000 in the USA.[1] The surgical repair can be performed with an antenatal intrauterine approach or on the first days after childbirth. Intrauterine surgery reduces the exposure of fetal neural tissues to the intrauterine environment, which potentially can decrease the incidence and the intensity of neurological deficits.[2] In 2011, the MOMS trial (Management of Myelomeningocele Study) showed better neurological outcomes for children undergoing an antenatal repair compared to postnatal treatment. However, the study also showed an increased risk of premature labor and maternal hemorrhage during delivery.[3]

One of the most important perioperative goals in intrauterine MMC repair is the avoidance of uterine contractions and placental abruption. Uterine relaxation can be achieved by using tocolytic agents. Many agents can be used such as magnesium sulfate, calcium channel blockers (nifedipine), non-steroidal anti-inflammatory drugs (indomethacin), β2-agonists (terbutaline) and oxytocin receptor antagonists (atosiban),[4] and the choice is based on subjective criteria like institutional protocols, availability, costs and physicians' preference.

Terbutaline is a β2-agonist widely used as a tocolytic drug for preterm labor[5] and is associated with tachycardia, arrythmias, hyperglycemia, hypokalemia, and hypocalcemia.[6] Lactic acidosis and hyperlactatemia have also been associated with β2-agonists even in the absence of hypoperfusion or shock.[7] Atosiban is an oxytocin and vasopressin receptor antagonist as effective as β2-agonists,[8] with a higher uterine specificity and less systemic side effects.[9] Despite the higher cost, UK's Royal College of Obstetricians and Gynaecologists (RCOG) recommends oxytocin antagonists as one of the first choices for preterm labor management.[10] There are some studies comparing betamimetics and atosiban for preterm labor, but there is no study comparing them for in utero MMC repair. We hypothesized that terbutaline is associated with more side effects than atosiban, especially lactic acidosis and hyperlactatemia.

The primary objective of this study was to evaluate maternal arterial blood gas differences between terbutaline or atosiban use as the main tocolytic agent during intrauterine MMC repair.

Methods

This was a retrospective cohort study. Patients submitted to intrauterine fetal MMC surgical repair in a low-income country tertiary care obstetrics center (Obstetric Clinic of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo), from November of 2017 to January of 2020, were included. The study was approved by the Ethics in Research Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAAE: 03681918.2.0000.0068, n° 3.077.257, December 12, 2018; Chairperson Dr. Alfredo Jose Mansur) and is registered at ClinicalTrials.gov (NCT04468568).

Patients were candidates and underwent the surgical procedure when they fulfilled the following criteria: single pregnancy of fetus with MMC, older than 18 years of age, normal karyotype fetuses, with gestational age between 19 and 26 weeks and with American Society of Anesthesiologists (ASA) physical status equal to II. The patients who were submitted to an open intrauterine fetal MMC surgical repair under the institutional standard perioperative management and had arterial blood gas analysis done for the three aimed timepoints were included in the study. Patients who had undergone the fetal MMC repair surgery but did not receive the perioperative institutional standard of care or did not have arterial blood gas analysis done for all three aimed timepoints were not included. The exclusion criteria were patient's decision to withdraw from the study or who would not wish to participate and, therefore, would not sign the consent form. This was a retrospective cohort study (patients were included after their exposure to a factor, and the outcome happened after the exposure, however the data collection was performed retrospectively). The patients were contacted and asked about their agreement to participate in the study when they returned to the hospital to deliver their babies (weeks after the intrauterine fetal MMC repair surgery), or when they should be returning for the delivery (by phone, in case of fetal demise). Consent was obtained, authorizing the research team to gather the data from patient`s charts and data base.

Patients were organized into two groups, depending on which tocolytic agent was used as first line during the surgical procedure: Terbutaline Group (Terbutaline: 2.5 mg in 500 mL of normal saline, as intravenous [IV] infusion, at a rate of 150 mcg.h^{-1} for 24 hours) or Atosiban Group (atosiban: IV loading dose of 6.75 mg and IV maintenance of 300 mcg.min^{-1} for the first 3 hours, followed by an IV infusion of 100 mcg.min^{-1} for 21 hours). The tocolytic agent was initiated 15–30 minutes before starting the surgical incision.

The standardized perioperative management for all open fetal MMC repair surgeries was performed according to institutional protocol and based on previous studies.[11] With the exception of the main tocolytic agent, all perioperative care was the same for all patients, with no modifications. Terbutaline or atosiban were part of the protocol, and the choice for one of them was based on availability on the day of the procedure.

Patients were previously consulted for a pre-anesthesia assessment by an anesthesiologist, in the ward. The anesthetic technique was a combination of general anesthesia and epidural anesthesia. Initially, patients were monitored with standard noninvasive monitors (ECG, pulse oximetry and noninvasive blood pressure). Two large bore peripheral IV catheters were inserted (14–18G) under local anesthesia, followed by administration of IV metoclopramide 10 mg and ranitidine 50 mg for aspiration prophylaxis. A thoracic epidural catheter (T11–T12, T12–L1 or L1–L2 level) was placed under mild sedation (fentanyl 50–100 mcg), in the sitting position, followed by epidural injection of fentanyl 100 mcg. Patients were laid on supine position with left uterine displacement with a wedge and had Bispectral Index (BIS) and the neuromuscular block monitor installed. They were preoxygenated for 5–7 minutes, induced with IV fentanyl 4–6

mcg.kg^{-1}, lidocaine 1.5 mg.kg^{-1}, propofol 1−2 mg.kg^{-1} and rocuronium 1.2 mg.kg^{-1} and intubated in a rapid sequence intubation (RSI) with endotracheal tube size 6.5−7.0. The target for $EtCO_2$ was in a range of 28−30 mmHg and FiO_2 > 50%. Monitorization was completed with esophageal temperature probe, bladder catheter and invasive blood pressure monitoring through a radial artery catheter. Fifteen to thirty minutes before the skin incision, patients received antibiotic prophylaxis with cefazolin 2g IV and the first line tocolytic was initiated (terbutaline or atosiban). General anesthesia was maintained with sevoflurane at 1 MAC and increased to 2−3 MAC for tocolysis supplementation when the procedure started. Bolus of IV nitroglycerine (100 mcg) was given in case of insufficient tocolysis.

Fetal monitoring was performed by the obstetrics team through echocardiography and fetal heart rate vigilance. Fetal anesthesia was supplemented by intramuscular (IM) injection of fentanyl 10−20 mcg.kg^{-1} and pancuronium 0.1 −0.3 mg.kg^{-1} (fetal weight based), if needed, although this was not required for any of the cases.

Maternal systolic blood pressure was maintained at the patient's baseline levels, avoiding decreases of more than 10% of the baseline for systolic blood pressure. Metaraminol was used as vasopressor in a continuous infusion (2.5−10 mg.h^{-1}) or intermittent bolus (200 mcg) regimen.[12,13] A restrictive fluid management strategy was adopted to avoid postoperative pulmonary edema, aiming a total perioperative fluid intake of 500−2000 mL. Normothermia (36°−37.5°C) was aimed during the entire procedure.

Once the myelomeningocele repair was finished and the uterus was closed, a loading dose of IV magnesium sulfate (5g in 20 minutes) was given, and sevoflurane was decreased to 1 MAC. Magnesium sulfate was maintained for 5 hours in an infusion of 1 g.h^{-1}. Neuromuscular block was reversed with sugammadex, patients received dipyrone 2 g IV, ondansetron 4 mg IV and an epidural dose of morphine 2 mg, for postoperative analgesia. At the Postanesthesia Care Unit (PACU), tocolysis was switched to oral nifedipine 80 mg daily and vaginal progesterone 400 mg daily for long term tocolysis, until the delivery.

Three arterial blood gas samples were routinely collected, as part of the standard of care protocol: after induction and intubation, before starting the tocolytic agent infusion (baseline); at the end of the surgical procedure (before extubation); and at PACU discharge, (typically 2 hours after surgery is finished). Samples were sent immediately, in standard proper syringes, to the laboratory for processing and results (ABL800, Radiometer).

All patients had their medical records assessed for demographic characteristics (age, Body Mass Index − BMI, gestational age), primary outcomes (pH and lactate measures) and secondary outcomes (pCO_2, bicarbonate and Base Excess [BE] levels, total fluid intake, estimated blood loss and vasopressor consumption as surrogate variables for intraoperative hemodynamic instability and poor peripheral tissue perfusion). The patients were also analyzed for their delivery related outcomes: preterm labor and premature rupture of membranes incidence, gestational age, newborn weight, newborn umbilical artery pH, newborn Apgar scores.

The variables were tested for normality (Kolmogorov-Smirnov Test of Normality). Data were expressed as mean ± Standard Deviation (SD) (for normally distributed variables), median (minimum − maximum) (for not normally distributed variables), and as percentages (for categorical variables) and a *p*-value lower than 0.05 was considered significant. Study data were collected and managed using REDCap (Research Eletronic Data Capture)[12] and were analyzed using the Mann-Whitney *U* (for non-parametric continuous variables), Student's *t* (for parametric continuous variables), and Chi-Square test for categorical variables. SPSS Statistics software was used for statistical analysis.

Results

Twenty-five patients were included in the study: 16 in the Atosiban Group and 9 in the Terbutaline Group (Fig. 1).

Baseline maternal demographic data are shown in Table 1 and had no difference between groups.

Maternal arterial blood gas analysis results are shown in Table 2. Baseline values were similar between both groups. The Terbutaline group had lower pH and Base Excess (BE) values at the end of the surgery, and also lower bicarbonate and BE levels at PACU discharge, with higher levels of lactate at the end of the surgery and at PACU discharge.

Table 3 shows that the estimated blood loss, total fluid intake and amount of vasopressor used were similar between the groups.

Table 4 shows the outcomes for the moment of delivery (preterm labor and premature rupture of membranes incidence, gestational age, newborn weight, newborn umbilical artery pH, newborn Apgar scores). One patient from the Terbutaline group was excluded from this analysis, due to the fact that the fetus had a demise during the intrauterine surgery. The groups presented no differences for delivery related outcomes.

Discussion

The aim of this study was to compare maternal arterial blood gas features between two tocolytic agents, during intrauterine fetal MMC surgical repair. Terbutaline is widely used as a tocolytic agent in preterm labor,[5] however it is a unspecific drug for uterine muscle receptors. Hence, it is postulated that the use of terbutaline could be associated with systemic maternal effects such as acidosis and increased arterial lactate levels. The mechanism is not completely clear, but can be due to stimulation of β-adrenergic receptors leading to a variety of metabolic effects such as increased adenylate cyclase activity, lipolysis, free fatty acids and increased glycogenolysis and gluconeogenesis.[7] Atosiban is a selective oxytocin receptor antagonist and seems to have less systemic effects.

Atosiban has less cardiovascular effects when compared to β2-agonist agents.[8,14] A large multicentric randomized trial with 742 patients compared atosiban and β2-agonist agents for preterm labor. Authors found equivalent clinical effectiveness with fewer side effects in the Atosiban Group. They evaluated maternal side effects such as cardiovascular issues, hypotension, nausea, hyperglycemia, and hypokalemia, as well as fetal outcomes. However, they did not study maternal arterial blood gas changes.[8] In our study, in a fetal surgery situation, findings for lower pH values and higher

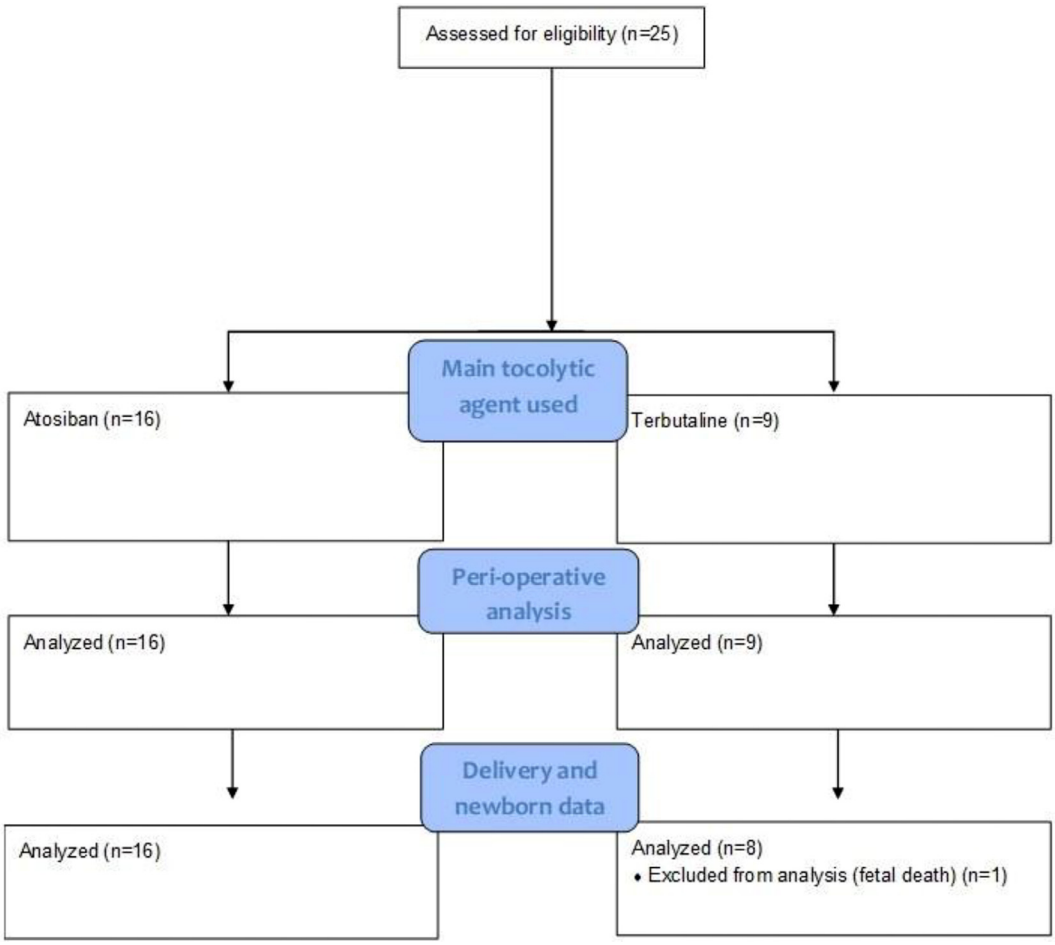


Figure 1 Flow diagram.

lactate levels in maternal arterial blood samples at the end of the surgery, for the patients who received terbutaline, were significant. There was a significant decrease in pH at the end of the surgery, as well as in bicarbonate, BE and pCO_2 values before discharge at the PACU, which can indicate metabolic acidosis and a compensatory respiratory response. Lactate levels were significantly higher after the procedure. Estimated blood loss, fluid intake and amount of vasopressor (surrogate outcomes for tissue hypoperfusion) were also compared between the groups and showed no difference. Manrique et al., in a retrospective cohort using atosiban for tocolysis for spina bifida repair with fetoscopy surgery, found no changes in maternal blood gases even after CO_2 insufflation.[15] Based on their results, the blood gas differences found in our study might have been due to a non-specific activation of adrenergic receptors by terbutaline.[16]

Some degree of adrenergic stimulation can be found in neonates of mothers who received β2-agonist agents.[14] However, a systematic review with the most used drugs for acute tocolysis did not show differences in efficacy to inhibit uterine contractions. On the other hand, they also found no differences for neonatal outcomes, which the authors attributed to small sample sizes and heterogeneity of included studies.[17] In our results, delivery and neonatal outcomes were statistically similar between groups. However, one critical event of fetal death during the immediate

Table 1 Maternal baseline demographic data.

	Groups		
Variables	Atosiban (n = 16)	Terbutaline (n = 9)	*p*
Maternal age (years)	29.06 ± 6.83	27.11 ± 5.58	0.473
Weight (kg)	69.31 ± 12.89	76.11 ± 10.79	0.194
Height (cm)	158.81 ± 6.59	163.89 ± 5.44	0.062
BMI ($kg.m^{-2}$)	27.30 ± 3.99	28.36 ± 4.09	0.529
Gestational age (weeks)	24.37 ± 1.08	24.44 ± 1.67	0.900
Surgery length (minutes)	244.37 ± 41.46	247.77 ± 41.46	0.845

Student's *t*-test. Data is shown as Mean ± SD.

Table 2 Maternal arterial blood gas analysis.

Variables	Groups		p[a]
	Atosiban (n = 16)	Terbutaline (n = 9)	
pH			
Baseline	7.395 ± 0.03	7.371 ± 0.04	0.110
Before extubation	7.396 ± 0.02	7.347 ± 0.05	**0.003**
PACU	7.382 ± 0.03	7.352 ± 0.04	**0.029**
pCO_2 (mmHg)			
Baseline	33.73 ± 1.83	35.73 ± 2.78	0.051
Before extubation	33.03 ± 2.51	35.33 ± 5.70	0.194
PACU	33.92 ± 3.10	29.20 ± 4.99	**0.015**
Bicarbonate ($mEq.L^{-1}$)			
Baseline	20.30 ± 0.93	20.22 ± 1.12	0.899
Before extubation	19.87 ± 1.29	18.84 ± 2.32	0.165
PACU	19.72 ± 1.12	15.87 ± 3.03	**0.0001**
Base excess			
Baseline	−3.40 ± 1.15	−3.87 ± 1.76	0.426
Before extubation	−3.73 ± 1.28	−5.66 ± 2.40	**0.014**
PACU	−4.14 ± 1.04	−8.12 ± 3.37	**0.0002**
Lactate ($mg.dL^{-1}$)			
Baseline	12.66 ± 3.57	17.55 ± 9.72	0.098
Before extubation	13.06 ± 6.35	28.33 ± 12.76	**0.0004**
PACU	13.73 ± 4.96	44.66 ± 18.9	**< 0.00001**

[a] Student *t*-test.
Data is shown as Mean ± SD.

postoperative period was described with one of the patients who received terbutaline. Despite this event not representing statistical significance for our results, a fetal demise is clinically relevant[3] and further studies are required to elucidate if β2-agonist agents can be directly related to unfavorable neonatal events.

Other tocolytic agents are available for use and their indication is based on maternal side effects, fetal effects, safety, costs, and approval by regulatory agencies. Atosiban use is not allowed by regulatory agencies in North America. β2-agonists and nifedipine are considered safe for the fetus but have maternal side effects.[14] There is no intravenous presentation for nifedipine in some countries which limits its intraoperative use. Magnesium sulfate, an alternative agent, is associated with tachyarrhythmias, drug interactions, pulmonary edema, and prolonged neuromuscular block. A prospective cohort study with 30 fetal procedures has shown more complications related to magnesium compared to atosiban and the authors suggest using atosiban as the drug of choice for open fetal surgeries.[18] Indomethacin is associated with constriction of the ductus arteriosus and there is evidence of that effect on fetuses during the intraoperative period among mothers who received preoperative indomethacin.[19] However, Novoa y Novoa et al., in a systematic review, concluded that information about the best regimen for tocolysis for open repair of myelomeningocele is still insufficient given the heterogeneity, lack of consistent design and multiple confounders of the studies.[20]

The current study has considerable limitations. It is a non-randomized study, and the anesthesia care provider was not blinded to the tocolytic agent used. There were no criteria for the choice of tocolytic agents, other than availability: when atosiban was available at the hospital pharmacy, it was used. When it was not available due to its high cost, terbutaline was used. This was the consequence of the irregular funding conditions for the hospital (a public institution). The retrospective nature of this study can justify some caveats about its results. Given the surgical procedure has its perioperative management strictly standardized by an institutional protocol, and the review of the medical records demonstrated that no deviations of the protocol were made, it is fair to assume that the only difference between the groups was the tocolytic agent used. The small number of

Table 3 Fluid and hemodynamic management.

	Groups		*p*[a]
	Atosiban (n = 16)	Terbutaline (n = 9)	
Crystalloids (mL)	1321.87 ± 536	1655.55 ± 655	0.181
Estimated blood loss (mL)	987.5 ± 471.2	755.4 ± 462.8	0.246
Metaraminol consumption (mg)	21.58 ± 6.26	19.17 ± 9.12	0.441

[a] Student *t*-test.
Data is shown as Mean ± SD.

Table 4 Delivery and newborn data.

	Groups		*p*
	Atosiban (n = 16)	Terbutaline (n = 8)	
Newborn weight (g)	2207.50 ± 735.92	2102.37 ± 637.36	0.739[a]
Newborn umbilical artery pH	7.222 ± 0.03	7.244 ± 0.07	0.477[a]
Gestational age (weeks)	33.9 ± 4.3	33.2 ± 2.63	0.722[a]
Apgar score on 1st minute	8 (4 − 9)	8 (8 − 9)	0.101[b]
Apgar score on 5th minute	9 (6 − 10)	9 (4 − 10)	0.631[b]
Apgar score on 10th minute	9.14 ± 0.86	8.75 ± 1.03	0.350[a]
Preterm labor	10 (62.50%)	6 (75.00%)	0.540[c]
Premature rupture of membranes	5 (31.25%)	4 (50.00%)	0.371[c]

[a] Student's *t*-test.
[b] Mann-Whitney test.
[c] Chi-square test.
Data is shown as Mean ± SD, Median (minimum − maximum) or n (%).

patients is also a considerable limitation. However, fetal MMC intrauterine repair is not a frequent performed procedure. Its sporadic nature creates difficulty to achieve more cases for a much larger study. A retrospective cohort carried out in Spain enrolled 29 patients between 2011 and 2016, seven for open surgery and 22 for fetoscopy surgery.[15] Even with the small sample size, a difference on the outcomes was observed.

The first case of antenatal intrauterine open surgery for fetal myelomeningocele was performed at our hospital in 2015[21] and atosiban use was limited due to its high cost. After the execution of this study and the critical event that happened in one of the cases, the institutional protocol for the in utero MMC repair surgery was revised. As atosiban had shown a safer profile, terbutaline was excluded from the standard of care for this specific procedure.

Conclusions

In conclusion, patients undergoing antenatal intrauterine fetal MMC repair surgery who received terbutaline as the main tocolytic agent had higher levels of arterial lactate and lower levels of arterial pH at the end of the procedure when compared to patients who received atosiban, with no differences for delivery and neonatal outcomes. The lactic acidosis founded seemed to be partially compensated by a respiratory alkalosis shown by a pCO_2 decrease. The literature is heterogeneous about tocolytics and outcomes for fetal surgery and their use is often based on the experience and previous knowledge from preterm labor tocolysis, and this study, even with a small sample size and its limitations, can be a starting point for more studies. Larger randomized clinical trials comparing the perioperative maternal and fetal impacts of terbutaline, atosiban and other tocolytic agents in fetal surgeries are necessary to have more evidence about safety and efficacy of each drug.

What is known

Fetal Myelomeningocele (MMC) antenatal repair is a potentially preferable alternative when compared to postnatal repair.

One of the most important perioperative goals in intrauterine MMC repair is the avoidance of uterine contractions and placental abruption, by using tocolytic agents.

What is new

This study compares maternal arterial blood gas analysis between terbutaline and atosiban when they are used as tocolytic agents during intrauterine myelomeningocele surgical repair.

Patients who received terbutaline had more acidosis and higher levels of arterial lactate during in uterus fetal MMC surgical repair.

Conflicts of competing interest

The authors declare no conflicts of interest.

Funding

The authors have no sources of funding to declare for this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844495.

References

1. Boulet SL, Yang Q, Mai C, et al. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008;82:527–32.
2. Fichter MA, Dornseifer U, Henke J, et al. Fetal spina bifida repair-current trends and prospects of intrauterine neurosurgery. Fetal Diagn Ther. 2008;23:271–86.
3. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364:993–1004.

4. Devoto JC, Alcalde JL, Otayza F, Sepulveda W. Anesthesia for myelomeningocele surgery in fetus. Childs Nerv Syst. 2017;33:1169–75.
5. Lam F, Gill P. beta-Agonist tocolytic therapy. Obstet Gynecol Clin North Am. 2005;32:457–84.
6. Cotton DB, Strassner HT, Lipson LG, Goldstein DA. The effects of terbutaline on acid base, serum electrolytes, and glucose homeostasis during the management of preterm labor. Am J Obstet Gynecol. 1981;141:617–24.
7. Claret PG, Bobbia X, Boutin C, Rougier M, de la Coussaye JE. Lactic acidosis as a complication of beta-adrenergic aerosols. Am J Emerg Med. 2012;30:1319.. e5-6.
8. Worldwide Atosiban versus Beta-agonists Study G. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. The Worldwide Atosiban versus Beta-agonists Study Group. BJOG. 2001;108:133–42.
9. de Heus R, Mulder EJ, Derks JB, Visser GH. Acute tocolysis for uterine activity reduction in term labor: a review. Obstet Gynecol Surv. 2008;63:405.. 383-8quiz.
10. Preterm Labour and Birth. National Institute for Health and Care Excellence: Clinical Guidelines. London. 2015.
11. Ferschl M, Ball R, Lee H, Rollins MD. Anesthesia for in utero repair of myelomeningocele. Anesthesiology. 2013;118:1211–23.
12. Fitzgerald JP, Fedoruk KA, Jadin SM, Carvalho B, Halpern SH. Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials. Anaesthesia. 2020;75:109–21.
13. Singh PM, Singh NP, Reschke M, Ngan Kee WD, Palanisamy A, Monks DT. Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes. Br J Anaesth. 2020;124:e95–e107.
14. Lamont RF, Jorgensen JS. Safety and Efficacy of Tocolytics for the Treatment of Spontaneous Preterm Labour. Curr Pharm Des. 2019;25:577–92.
15. Manrique S, Maiz N, Garcia I, et al. Maternal anaesthesia in open and fetoscopic surgery of foetal open spinal neural tube defects: A retrospective cohort study. Eur J Anaesthesiol. 2019;36:175–84.
16. Chan J, Cabrol D, Ingemarsson I, Marsal K, Moutquin JM, Fisk NM. Pragmatic comparison of beta2-agonist side effects within the Worldwide Atosiban versus Beta Agonists study. Eur J Obstet Gynecol Reprod Biol. 2006;128:135–41.
17. Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ. Acute tocolysis for uterine tachysystole or suspected fetal distress. Cochrane Database Syst Rev. 2018;7:CD009770.
18. Ochsenbein-Kolble N, Krahenmann F, Husler M, et al. Tocolysis for in utero Surgery: Atosiban Performs Distinctly Better than Magnesium Sulfate. Fetal Diagn Ther. 2018;44:59–64.
19. Howley LW, Chatterjee D, Patel SS, et al. Indomethacin Dosing and Constriction of the Ductus Arteriosus During Open Fetal Surgery for Myelomeningocele Repair. Fetal Diagn Ther. 2019;45:339–44.
20. Novoa YNV, Shazly S, Araujo Junior E, Tonni G, Ruano R. Tocolysis for open prenatal repair of myelomeningocele: systematic review. J Matern Fetal Neonatal Med. 2020;33:1786–91.
21. da Rocha LSN, Bunduki V, de Amorim Filho AG, et al. Open fetal myelomeningocele repair at a university hospital: surgery and pregnancy outcomes. Arch Gynecol Obstet. 2021;304:1443–54.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

The effect of low dose intra-articular S(+) ketamine on osteoarthritis in rats: an experimental study

Eugênio dos Santos Neto [a], **Pedro Paulo de Alcantara Pedro** [b], **Maria do Socorro de Sousa Cartágenes** [c,d,e], **José Osvaldo Barbosa Neto** [d,e,*], **João Batista Santos Garcia** [d,f]

[a] *Universidade de Brasília, Brasília, DF, Brazil*
[b] *Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[c] *Universidade Federal do Maranhão, Departamento de Ciências Fisiológicas*
[d] *Universidade Federal do Maranhão, Laboratório Experimental para Estudo da Dor, São Luiz, MA, Brazil*
[e] *Faculdade de Medicina da Universidade Ceuma, São Luiz, MA, Brazil*
[f] *Universidade Federal do Maranhão, Departamento de Anestesiologia, Dor e Paliativos, São Luiz, MA, Brazil*

Received 21 March 2023; accepted 4 March 2024
Available online 9 April 2024

KEYWORDS
Osteoarthritis;
S(+)-Ketamine;
Synovial Membrane;
Animal models;
Synovitis

Abstract
Background: This study aimed to investigate the analgesic impact of S(+)-ketamine on pain behavior and synovial inflammation in an osteoarthritis (OA) model.
Methods: Animals were grouped as follows: OA-Saline (n = 24) and OA-Ketamine (n = 24), OA induced via intra-articular sodium monoiodoacetate (MIA); a Non-OA group (n = 24) served as the control. On the 7th day post OA induction, animals received either saline or S(+)-ketamine (0.5 mg.kg^{-1}). Behavioral and histopathological assessments were conducted up to day 28.
Results: S(+)-ketamine reduced allodynia from day 7 to 28 and hyperalgesia from day 10 to 28. It notably alleviated weight distribution deficits from day 10 until the end of the study. Significant walking improvement was observed on day 14 in S(+)-ketamine-treated rats. Starting on day 14, OA groups showed grip force decline, which was countered by S(+)-ketamine on day 21. However, S(+)-ketamine did not diminish synovial inflammation.
Conclusion: Low Intra-articular (IA) doses of S(+)-ketamine reduced MIA-induced OA pain but did not reverse synovial histopathological changes.
IRB approval number: 23115 012030/2009-05.
© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author
E-mail: jose.barbosa@ceuma.br (J.O. Neto).

https://doi.org/10.1016/j.bjane.2024.844502
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The mechanisms underlying the origin of joint pain in Osteoarthritis (OA) remain poorly understood. Articular cartilage and the meniscus are structures devoid of nerves and, therefore, cannot directly serve as sources of painful sensations. However, alterations in these structures and even in the synovial fluid could indirectly contribute to the pathophysiology of pain in OA. Fragments of cartilage containing nociceptor sensitization in these areas are likely to contribute to the initiation and persistence of pain.[1] Furthermore, distinct elements such as collagen, proteoglycans, crystals, proteolytic enzymes, or cytokines released into the synovial fluid could potentially trigger a synovial inflammatory response associated with pain. Afferent nerve fibers are present in various parts of the joint, including the joint capsule, synovium, periosteum, subchondral bone, ligaments, and tendons.[2]

Evidence from pharmacological, electrophysiological, and behavioral research indicates that glutamate receptors play a pivotal role in pain pathways. Modulation of these receptors has been implicated in various types of pain, including central and peripheral neuropathic pain as well as joint inflammatory pain. Elevated levels of glutamate have been detected in the synovial fluid of OA patients.[3,4] Additionally, glutamate's involvement as a modifier of OA has been observed, leading to increased receptor expression in cells such as osteoblasts, osteoclasts, and chondrocytes, revealing a significant role in bone and cartilage remodeling.[3]

The principal excitatory effect of glutamate within the nervous system occurs via N-Methyl-D-Aspartate receptors (NMDA), which have been identified as key contributors to central sensitization and the chronicity of pain. Animal studies have demonstrated the presence of NMDA receptors (NMDAr) in both myelinated and non-myelinated axons within somatic peripheral tissues.[4]

In a study that examined the role of glutamate signaling in chondrocytes, it was noted that these cells might express a distinctive NMDA receptor (NMDAr) with unique attributes. This receptor could potentially be involved in the inflammatory process linked to cartilage degradation, thus emerging as a promising pharmacological target in the context of OA.[5]

Effective pain management has become a therapeutic challenge in the context of osteoarthritis (OA), leading to investigations into various intra-articular (IA) drug interventions aimed at enhancing analgesia.[6] Among these interventions, racemic ketamine has been tested in various experimental OA models, indicating its potential not only in alleviating joint pain but also in mitigating inflammatory mediators and reversing histopathological changes.[7,8] The drug's primary mechanism of action, NMDAr antagonism, is widely recognized. However, its broader impacts on chronic pain management are equally significant, including the modulation of voltage-gated Na+ and K+ channels, antagonism of serotonin, norepinephrine, and dopamine reuptake, and suppression of pro-inflammatory cytokines.[9,10] Notably, S (+)-ketamine exhibits an analgesic potency four times greater than that of R(-)-ketamine due to its higher affinity for NMDAr, allowing for the use of smaller doses with minimized adverse effects.[11]

The primary objective of this study was to evaluate the analgesic effect of a low dose of S(+)-ketamine on pain behavior and the extent of synovial membrane inflammation in an experimental rat model of osteoarthritis (OA).

Methods

For the experimental phase, male Wistar strain Rattus norvegicus rats weighing approximately 230—280 g were used. The animals were acclimated and housed under controlled conditions of humidity (45—65%) and temperature (23±2 °C), with a 12-hour light/dark cycle and unrestricted access to food and water. A week before the experimental protocol began, the animals underwent daily adaptation to devices and behavioral tests.

The experiments were conducted in accordance with the guidelines of the Brazilian College of Animal Experimentation and were approved by the Research Ethics Committee of the Universidade Federal do Maranhão under protocol number 23115 012030/2009-05.

Model of osteoarthritis induced by sodium monoiodoacetate

The animals were anesthetized with sodium thiopental (40 mg.kg^{-1} intraperitoneally), followed by trichotomy of the right hind paw. Local antisepsis was performed using a 10% iodine polyvinylpyrrolidone solution. Osteoarthritis (OA) was induced in the right knee by a single intra-articular injection of 2 mg of sodium monoiodoacetate (MIA) dissolved in a maximum of 50 μL of solution. The MIA solution was administered through the patellar ligament into the intra-articular space of the right knee using a 26G needle. The left knee received an equivalent volume of saline as a contralateral control specific to the animal.[12,13]

Experimental design

In this study, 72 Wistar rats were divided into three groups. The OA-Saline Group (n = 24) and the OA-Ketamine Group (n = 24) were subjected to MIA-induced osteoarthritis. The Non-OA Group (n = 24) did not undergo osteoarthritis induction. Behavioral assessments were conducted prior to osteoarthritis induction and on the fifth day following MIA induction. On the 7th day after osteoarthritis induction, the groups received an intra-articular injection (IA) of S (+)-ketamine (0.5 mg.kg^{-1}) or 0.9% saline, with a maximum volume of 50 μL. Behavioral assessments were conducted six hours after the injection of the study solution and subsequently on days 10, 14, 18, 21, 24, and 28 after osteoarthritis induction. On days 7, 14, 21, and 28, six animals from each group were anesthetized and euthanized to harvest the synovial membrane for histopathological analysis (Fig. 1).

The main outcome was pain reduction in the ketamine group, as indicated by behavioral assessment. The secondary outcome was the effect of ketamine treatment on synovial inflammation.

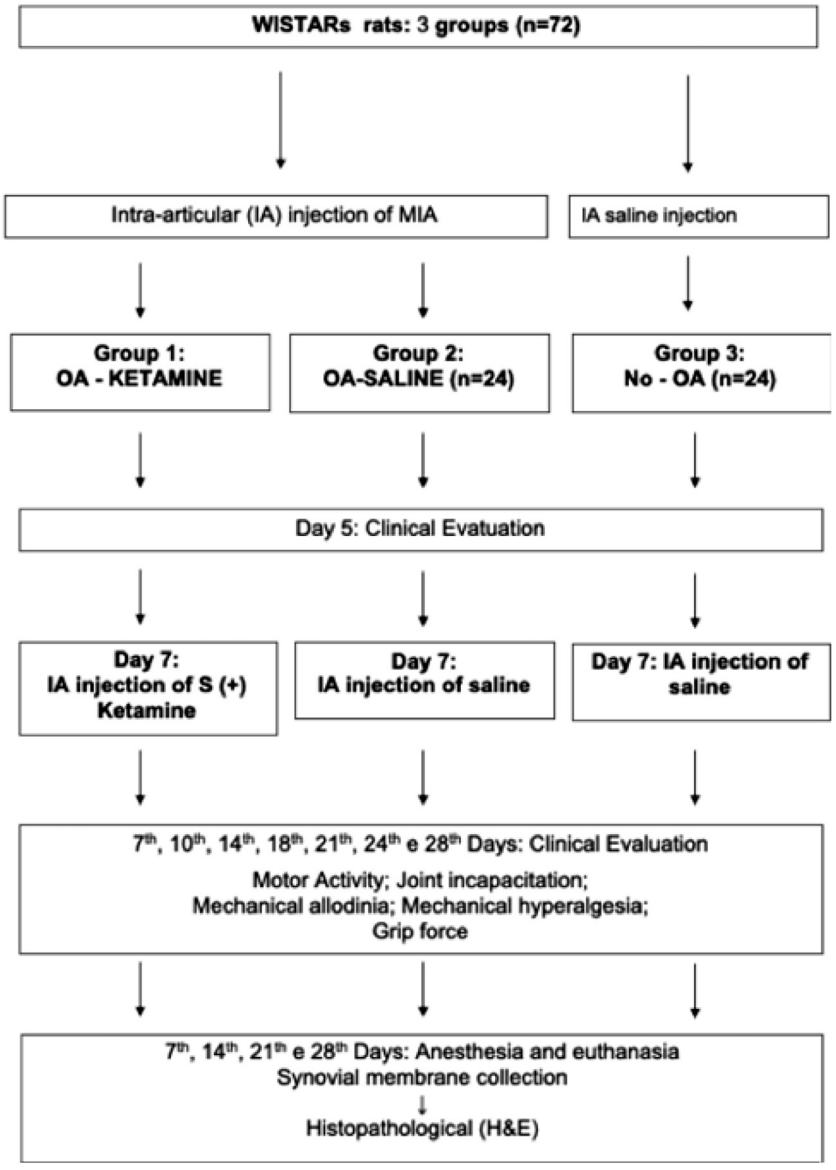


Figure 1 Study flowchart.

Behavioral assessment

Motor activity assessment/RotaRod test

The RotaRod (Model IITC Life Science, California, USA) comprises a rotating bar with adjustable speed, measured in revolutions per minute (rpm), featuring a 2.5 cm diameter and 60 cm length. Positioned 40 cm above small platforms, the rotating bar automatically stops the digital timer when animals fall off. The bar is divided into five 20 cm sections, where individual animals are placed during testing.[14]

Animals were positioned on the RotaRod, set at a speed of 16 rpm, for a duration of 300 seconds. Assessment of the affected limb's utilization was conducted through forced walking, and the utilization of the paw was rated using a numerical scale spanning from 5 to 1, where: 5 – corresponds to the limb's normal use; 4 – slight lameness; 3 – severe lameness; 2 – sporadic non-use of the affected paw; and 1 – complete non-use of the affected paw.[14]

Disability test/Hind leg weight distribution (weight bearing test)

Changes in weight distribution between the right (OA+) and left (OA) hind legs were indicative of discomfort due to MIA-induced OA. A disability test apparatus (Model IITC Life Science, California, USA) with a sensor linked to a small platform was used to gauge the animal's weight distribution on its hind legs.[14,15]

The animals were positioned within an angled glass chamber, ensuring that each hind leg rested on distinct platforms. The weight exerted on each hind leg (measured in grams) was assessed over a span of five seconds. The ultimate measurement of weight distribution was determined by calculating the average of three measurements.[14,15]

Mechanical allodynia assessment (Von Frey test)

Mechanical allodynia was evaluated using a digital algesimeter (Model Insight, São Paulo, Brazil) equipped with a

pressure transducer connected to a digital force counter measured in grams (g). The device is calibrated to record a maximum force of 150 g, maintaining precision within 0.1 g for forces up to 80 g. The contact between the pressure transducer and the animals' paws was established using a disposable polypropylene tip with a diameter of 0.5 mm, specially designed for this purpose.[14,16]

The animals were acclimated for 15 minutes before the experiment in an acrylic box (12 × 20 × 17 cm) with a floor made of a 5 mm^2 mesh network composed of non-malleable wire that was 1 mm thick. Mirrors were positioned 25 cm below the experimental boxes to enhance visibility of the animals' plantar region. The test involved applying increasing pressure to the central area of the rat's paw until the animal exhibited a "flinch" response to the stimulated paw. The stimuli were repeated up to six times on both the ipsilateral and contralateral paws until the animal demonstrated three similar responses with a clear "flinch" after paw removal.[14,16]

The Paw Withdrawal Threshold (PWT) was determined as the percentage of force required to induce active suspension in the affected ipsilateral paw.[14,16]

Mechanical hyperalgesia (Randall Selitto test)

Mechanical hyperalgesia was evaluated by assessing the paw withdrawal threshold in response to a mechanical stimulus delivered through a pressure algesimeter (Model IITC Life Science, California, United States), following the methodology previously outlined by Randall and Selitto.[17] A wedge-shaped apparatus (with an area of 1.75 mm^2) was placed on the dorsal surface of the hind limbs, applying incremental linear pressure until the animal exhibited a response characterized by paw withdrawal. Three measurements were taken on both the ipsilateral and contralateral paws. A predefined cutoff threshold of 250 g was implemented to prevent potential tissue damage.[1,13,18]

The Paw Withdrawal Threshold (PWT) was measured in grams and defined as the force percentage required to induce removal of the affected ipsilateral paw.[1,13,18]

Grip force test

The assessment of hind leg grip force was conducted by recording the maximum force applied during gripping using a stress measurement system (IITC Life Science model, California, USA). During the test, each rat was gently restrained to allow its hind legs to grasp a wire mesh (10 × 12 cm^2) connected to a strain gauge. The rats were positioned in a manner ensuring that their front legs did not touch the strain gauge.

The evaluator then applied a rostro-caudal movement until the hind leg of the animal lost contact with the mesh. Three measurements were taken, and the results were averaged. Each rat underwent the test twice, with a 2- to 3-minute interval, to obtain the grip force values in their raw form (CFmax).[19,20]

Histopathological analysis

After administering anesthesia with sodium thiopental (40 $mg.kg^{-1}$) and euthanizing the animals, the synovial membranes were extracted and fixed in 10% buffered formaldehyde. Subsequently, they were immersed in a 5% formic acid solution for 72 hours. The samples underwent dehydration through a series of ethanol solutions and were embedded in paraffin, followed by creating 4 μm thick sections, which were later stained with hematoxylin-eosin. Inflammation was identified by the expansion of the synovial membrane due to fluid edema of a protein and fibrin nature, along with the infiltration of macrophages, neutrophils, plasmocytes, and lymphocytes.

A grading system was employed to evaluate the extent of synovial inflammation, with the following grades: Grade 0 indicating no inflammation; Grade 1 for minimal inflammation; Grade 2 for mild inflammation; Grade 3 for moderate inflammation; and Grade 4 for marked inflammation.[15,21] All samples were assessed blindly by the same pathologist.

Statistical analysis

The results of behavioral tests were analyzed using One-way ANOVA, followed by the Tukey test. Intra-group comparisons at different time points during the experiment were conducted with the Friedman test. The Kruskal-Walli's test was applied to compare the results related to synovial inflammation, followed by the Dunn post-hoc test for multiple comparisons. A significance level of $p < 0.05$ was used to determine statistical significance, and data analysis was performed using GraphPad Instat® software (GraphPad Software, San Diego, CA).

Results

Effect of S(+)-ketamine on forced ambulation

Five days after MIA injection, the rats exhibited a decrease in RotaRod test scores, with a significant reduction in the OA-Ketamine and OA-Saline groups. Following the administration of S (+)-ketamine (0.5 $mg.kg^{-1}$), the animals demonstrated an improvement in forced walking, which showed statistical significance on the 14th day post OA induction. By the 18th day, all groups exhibited similar performance on the RotaRod test (Fig. 2).

Effect of S(+)-ketamine on weight distribution on hind legs

Following the MIA injection, the animals began exhibiting sings of joint discomfort, resulting in a predominant weight distribution on the healthy paw. S(+)-ketamine significantly alleviated the impairment in weight distribution from the 10th day of OA induction until the conclusion of the experiment, which spanned approximately three weeks. Starting from the 14th day, no notable distinction was observed between the OA-Ketamine group and the Non-OA group (Fig. 2).

Effect of S(+)-ketamine on mechanical alodinia

The animals developed mechanical allodynia after OA induction, as demonstrated by the Von Frey test. Treatment with S(+)-ketamine (0.5 $mg.kg^{-1}$-IA) reduced the intensity of allodynia from the 7th to the 28th day, when the difference between the OA-Ketamine and OA-Saline groups remained

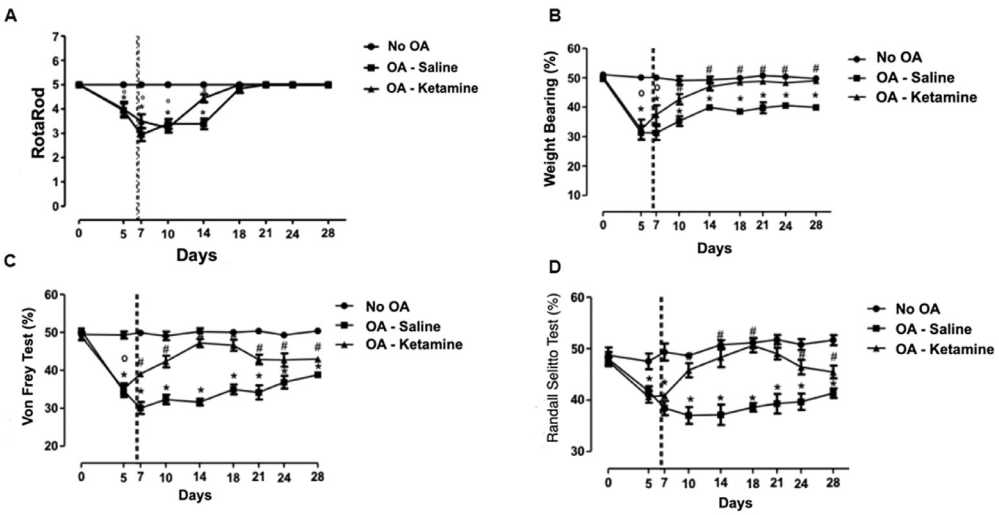


Figure 2 Results concerning the impact of S(+)ketamine in the experimental tests conducted within this study. (A) Forced Ambulation. (B) Hind Leg Weight Distribution. (C) Paw Withdrawal (Mechanical Allodynia). (D) Paw Withdrawal (Mechanical Hyperalgesia). Vertical symbols and lines denote the mean and standard error of means. The vertical dashed line signifies the beginning of treatment. * Significant difference between the OA-Saline group and the Non-OA group. ° Significant difference between the OA-Ketamine group and the Non-OA group. # Significant difference between the OA-Ketamine group and the OA-Saline group. Statistical significance: $p < 0.05$.

significant. On the 14th and 18th days, there was no significant difference between the OA Ketamine and Non-OA groups (Fig. 2).

Effect of S(+)-ketamine on mechanical hyperalgesia

The animals also exhibited the development of mechanical hyperalgesia after MIA injection, as indicated by the decrease in the paw withdrawal threshold during the Randall Selitto test. Treatment with S(+)-ketamine mitigated hyperalgesia from the 10th to the 28th day, in comparison to the OA-Saline group. From the 14th to the 24th day, the S (+)-ketamine group demonstrated complete reversal of hyperalgesia, producing results akin to those of the Non-OA group (Fig. 2).

Effect of S(+)-ketamine on grip force

Following MIA injection, the grip force of the animals decreased after the 14th day of induction. Treatment with S (+)-ketamine led to an increase in grip force from the 21st day to the 28th day, exhibiting a statistically significant difference when compared to the Saline group. On the 21st and 28th days, there were no significant differences between the OA-Ketamine and Non-OA groups (Fig. 3).

Effect of S(+)-ketamine on synovial membrane inflammation

The injection of MIA induced histopathological changes in the synovial membrane. Throughout the experiment, a significant difference was observed between the Saline-treated group and the group without osteoarthritis; however, this difference was not observed between the OA-Ketamine group and the group treated with OA-saline. Additionally, there were no significant differences within each group at different time points during the experiment. It is important to note that the group treated with ketamine did not exhibit any histopathological damage (Table 1). The maximum degree of inflammation was characterized by the expansion of the synovial membrane and the infiltration of inflammatory cells such as macrophages, neutrophils, and lymphocytes, as depicted in Figure 4H. Figure 4D displays an intact and healthy section of the synovial membrane, while Figure 4L represents a graded degree of inflammation with a score of 3 (Fig. 4).

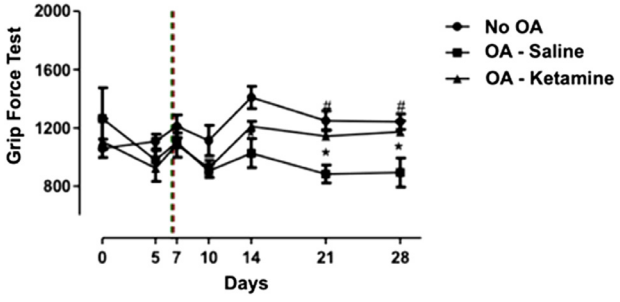


Figure 3 Grip force assessment in rats treated with S(+)-ketamine (n = 6). The data is presented as the nociceptive paw withdrawal threshold in percentage. Vertical symbols and lines indicate the mean and standard error of the means. ANOVA – Tukey's test was performed ($p < 0.05$). The vertical dashed line signifies the beginning of treatment. *Significant difference between the OA-Saline group and the Non-OA group. °Significant difference between the OA-Ketamine group and the Non-OA group. #Significant difference between the OA-Ketamine group and the OA-Saline group.

Table 1 Grading of synovial membrane inflammation (Mean ± standard deviation).

Groups	T			
	Day 7	Day 14	Day 21	Day 28
Non-OA (n = 6)	1.33 ± 1.3	0.16 ± 0.40	0.83 ± 0.75	0.16 ± 0.40
OA-Saline (n = 6)	3.00 ± 0.89[a]	2.66 ± 0.81[a]	3.16 ± 0.75[a]	2.83 ± 1.16[a]
OA-K (n = 6)	3.16 ± 0.40[a]	2.33 ± 0.51[a]	2.16 ± 0.75	1.83 ± 0.98

[a] $p < 0.05$ in comparison to NO-OA (Kruskal-Wallis Test and post-hoc test Dunn).
OA, Osteoarthritis; K, Ketamine.

Discussion

In this study, we employed an experimental model of MIA-induced osteoarthritis. The choice for MIA was based on its established capacity to induce specific changes that closely resemble those found in OA, such as subchondral bone sclerosis, osteophyte formation, cartilage damage, and alterations in biomarkers like glycosaminoglycans and metalloproteinases.[12,20,22] The articular condition that developed in the animals after induction resulted in a reduction in forced walking scores, with the animals displaying signs of joint discomfort, in line with previous findings by other researchers.[7,14,23] Rats treated with S(+)-ketamine showed improved gait as early as the second week of the

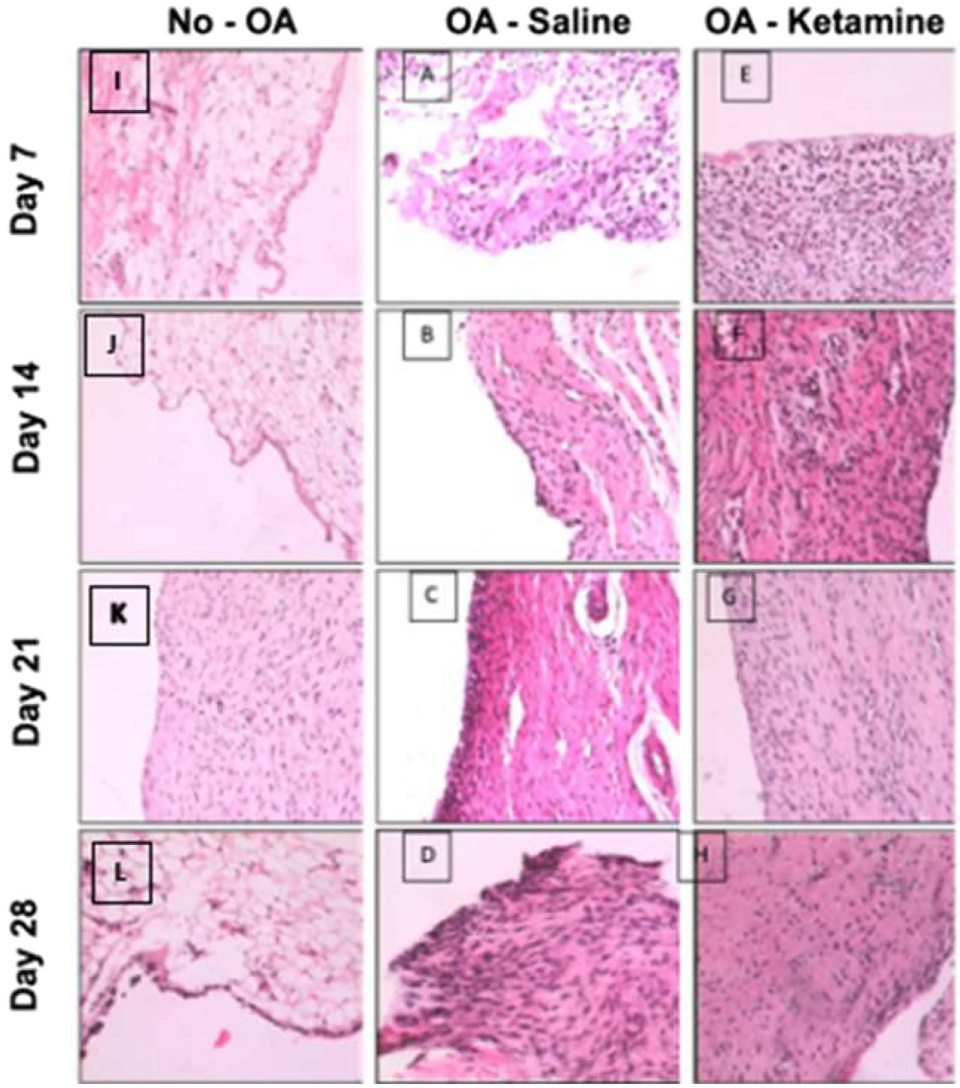


Figure 4 Photomicrograph of the synovial membrane in an experimental model of MIA-induced osteoarthritis. OA-Saline Group (A to D), OA-Ketamine Group (E to H), and NON-OA Group (I to L) stained with hematoxylin and eosin. Notable changes in D show synovial cell proliferation, subsynovial tissue growth, and inflammatory cell infiltration, classified as Grade 4. Grade 0 inflammation score is observed in L, while a Grade 3 inflammation score is seen in C. Magnification: 100 ×.

experiment. Regarding joint discomfort, S(+)-ketamine ameliorated the weight distribution deficit, and by the 14th day, no significant difference was observed between the OA-Ketamine and Non-OA groups.

Moreover, in terms of behavioral assessment, this study demonstrated that MIA injection induced both allodynia and mechanical hyperalgesia. Treatment with S(+)-ketamine effectively reduced the intensity of both allodynia and hyperalgesia until the end of the experiment. MIA injection was observed to decline grip force OR MIA injection led to a decline in grip force from the second week until the conclusion of the study in the saline-treated group, indicating a potential decrease in muscle strength. This finding aligns with those reported in other studies.[19,24] Conversely, S(+)-ketamine resulted in an increase in grip force, possibly attributed to pain relief and subsequent enhanced usage of the affected paw.

The significant differences observed between the groups treated with S(+)-ketamine and saline in behavioral tests can be attributed to NMDAr antagonism. These agents have demonstrated potential in blocking or preventing hypersensitivity states.[2,25] NMDAr antagonists have already proven effective in reducing chronic pain and preventing hyperalgesic phenomena. For instance, a study using MgSO4, known as an NMDAr blocker, in an animal model of OA observed effects on disease progression, including reduced chondrocyte apoptosis and decreased nociception. This study also investigated the behavior of the NR1 receptor, a subtype of NMDAr, on chondrocyte membranes, revealing a decrease in receptor expression, indicating potential prevention of articular cartilage damage.[20] Another study examining NMDAr expression in normal human chondrocytes affected by OA concluded that NR1, NR2A, and NR2B receptors were present in OA-affected human chondrocytes, with NR2B absent in normal chondrocytes. Furthermore, this study demonstrated the blocking of these receptors by NMDAr antagonists.[17]

S(+)-ketamine exhibits a high affinity for NMDAr with NR1/NR2A and NR1/NR2B subunit composition.[26] Its greater affinity (fourfold) for the receptor results in superior analgesic potency. Studies in rats and mice have demonstrated that S(+)-ketamine possesses approximately threefold greater analgesic potency than its isomer and twice the potency of the racemic mixture.[11,27] In our study, we opted for a low dose of S(+)-ketamine (0.5 $mg.kg^{-1}$), in contrast to the doses used in a similar study (12 and 24 $mg.kg^{-1}$) involving a racemic mixture.[7] Despite the differences in dosing between the two studies, behavioral assessment data indicated a reduction in hyperalgesia and mechanical allodynia, as well as an improved gait pattern, suggesting effective pain control. These findings support the idea that low doses of intra-articular (IA) S(+)-ketamine could provide analgesic benefits.

In another study, intraperitoneal administration of S(+)-ketamine was employed to evaluate its antiallodynic effect in conjunction with ketamine and electroacupuncture in a neuropathic pain model. The authors concluded that ketamine injection reduced mechanical allodynia, except at low doses (1 $mg.kg^{-1}$).[28] In our experiment, using a lower dose (0.5 $mg.kg^{-1}$) and an alternative route of administration, the drug effectively alleviated painful behavior within 6 hours of injection.

Our study also included a histopathological analysis to assess synovial membrane inflammation at different time points. However, we found no significant difference between the S(+)-ketamine and saline-treated groups at any time, which contrasts with the findings of two other studies — one conducted in mice[7] and another in rabbits.[8] These studies differed from ours in using racemic mixtures and higher doses of ketamine. Both studies demonstrated dose-dependent effects of ketamine in reversing histopathological changes associated with OA. In the mouse study, which utilized an MIA-induced OA model, histopathological findings were reversed only with a 24 $mg.kg^{-1}$ dose of racemic ketamine — 48 times higher than the dosage in our study.[7] The rabbit study employed a different OA induction model involving immobilization with plaster bandages, resulting in fewer inflammatory cells, and reduced pathological changes with increasing ketamine dosage.[8] These results suggest that higher doses of S(+)-ketamine may have an impact on histopathological findings related to OA.

One of the limitations of this study is the absence of a direct investigation into the mechanisms underlying the observed improvements in behavioral test responses. Therefore, future studies should consider conducting synovial lavage and collecting articular cartilage samples to measure cytokine levels (both anti-inflammatory and pro-inflammatory), nitric oxide levels, receptor expression, and other relevant factors.

Conclusions

In summary, low doses of IA S(+)-ketamine effectively alleviated painful behavior in rats following MIA-induced OA, as evidenced by improvements in behavioral assessments. However, it is important to note that the reversal of histopathological changes in the synovial membrane of the studied joint was not achieved.

Data access

The study data is available upon request to the corresponding author. For inquiries or to request access to the data, please contact corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used CHAT GTP in order to translate and for language improvement. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare no conflicts of interest.

References

1. Ahmed AS, Li J, Erlandsson-Harris H, Stark A, Bakalkin G, Ahmed M. Suppression of pain and joint destruction by inhibition of the proteasome system in experimental osteoarthritis. Pain. 2012;153:18–26.

2. Lorenz H, Richter W. Osteoarthritis: cellular and molecular changes in degenerating cartilage. Prog Histochem Cytochem. 2006;40:135—63.
3. Miller KE, Hoffman EM, Sutharshan M, Schechter R. Glutamate pharmacology and metabolism in peripheral primary afferents: physiological and pathophysiological mechanisms. Pharmacol Ther. 2011;130:283—309.
4. Medeiros P, Negrini-Ferrari SE, Palazzo E, Maione S, Ferreira SH, de Freitas RL, et al. N-methyl-D-aspartate Receptors in the Prelimbic Cortex are Critical for the Maintenance of Neuropathic Pain. Neurochem Res. 2019;44:2068—80.
5. Matta C, Juhász T, Fodor J, Hajdú T, Katona É, Szűcs-Somogyi C, et al. N-methyl-D-aspartate (NMDA) receptor expression and function is required for early chondrogenesis. Cell Commun Signal. 2019;17:166.
6. Richards MM, Maxwell JS, Weng L, Angelos MG, Golzarian J. Intra-articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. The Physician and sportsmedicine. 2016;44:101—8.
7. Shetty YC, Patil AE, Jalgaonkar SV, Rege NN, Salgaonkar S, Teltumbde PA, et al. Intra-articular injections of ketamine and 25% dextrose improve clinical and pathological outcomes in the monosodium iodoacetate model of osteoarthritis. Journal of basic and clinical physiology and pharmacology. 2017;28:543—53.
8. Lu W, Wang L, Wo C, Yao J. Ketamine attenuates osteoarthritis of the knee via modulation of inflammatory responses in a rabbit model. Molecular medicine reports. 2016;13:5013—20.
9. Hocking G, Cousins MJ. Ketamine in Chronic Pain Management: An Evidence-Based Review. Anesth Analg. 2003;97:1730—9.
10. Lange M, Bröking K, van Aken H, Hucklenbruch C, Bone HG, Westphal M. Role of ketamine in sepsis and systemic inflammatory response syndrome. Anaesthesist. 2006;55:883—91.
11. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clin Pharmacokinet. 2016;55:1059—77.
12. Combe R, Bramwell S, Field MJ. The monosodium iodoacetate model of osteoarthritis: A model of chronic nociceptive pain in rats? Neurosci Lett. 2004;370:236—40.
13. Fernihough J, Gentry C, Malcangio M, et al. Pain related behaviour in two models of osteoarthritis in the rat knee. Pain. 2004;112:83—93.
14. Kalff KMM, El Mouedden M, van Egmond J, et al. Pre-treatment with capsaicin in a rat osteoarthritis model reduces the symptoms of pain and bone damage induced by monosodium iodoacetate. Eur J Pharmacol. 2010;641:108—13.
15. Bove SE, Calcaterra SL, Brooker RM, et al. Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis. Osteoarthritis Cartilage. 2003;11:821—30.
16. Vivancos GG, Verri WA, Cunha TM, et al. An electronic pressure-meter nociception paw test for rats. Braz J Med Biol Res. 2004;37:391—9.
17. Ramage L, Martel MA, Hardingham GE, Salter DM. NMDA receptor expression and activity in osteoarthritic human articular chondrocytes. Osteoarthritis Cartilage. 2008;16:1576—84.
18. Knights CB, Gentry C, Bevan S. Partial medial meniscectomy produces osteoarthritis pain-related behaviour in female C57BL/6 mice. Pain. 2012;153:281—92.
19. Chandran P, Pai M, Blomme EA, Hsieh GC, Decker MW, Honore P. Pharmacological modulation of movement-evoked pain in a rat model of osteoarthritis. Eur J Pharmacol. 2009;613:39—45.
20. Lee CH, Wen ZH, Chang YC, et al. Intra-articular magnesium sulfate (MgSO4) reduces experimental osteoarthritis and nociception: association with attenuation of N-methyl-d-aspartate (NMDA) receptor subunit 1 phosphorylation and apoptosis in rat chondrocytes. Osteoarthritis Cartilage. 2009;17:1485—93.
21. Gerwin N, Bendele AM, Glasson S, Carlson CS. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the rat. Osteoarthritis Cartilage. 2010;18(Suppl 3):S24—34.
22. Guzman RE, Evans MG, Bove S, Morenko B, Kilgore K. Mono-Iodoacetate-Induced Histologic Changes in Subchondral Bone and Articular Cartilage of Rat Femorotibial Joints: AN Animal Model of Osteoarthritis. Toxicol Pathol. 2003;31:619—24.
23. Pomonis JD, Boulet JM, Gottshall SL, et al. Development and pharmacological characterization of a rat model of osteoarthritis pain. Pain. 2005;114:339—46.
24. Lee Y, Pai M, Brederson JD, et al. Monosodium iodoacetate-induced joint pain is associated with increased phosphorylation of mitogen activated protein kinases in the rat spinal cord. Mol Pain. 2011;7:39.
25. Boettger MK, Weber K, Gajda M, Bräuer R, Schaible HG. Spinally applied ketamine or morphine attenuate peripheral inflammation and hyperalgesia in acute and chronic phases of experimental arthritis. Brain Behav Immun. 2010;24:474—85.
26. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res. 2012;65:411—29.
27. Trimmel H, Helbok R, Staudinger T, Jaksch W, Messerer B, Schöchl H, et al. S(+)-ketamine : Current trends in emergency and intensive care medicine. Wiener klinische Wochenschrift. 2018;130:356—66.
28. Huang C, Li HT, Shi YS, Han JS, Wan Y. Ketamine potentiates the effect of electroacupuncture on mechanical allodynia in a rat model of neuropathic pain. Neurosci Lett. 2004;368:327—31.

Brazilian Journal of Anesthesiology 2024;74(3): 744446



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Does dexmedetomidine reduce the risk of acute kidney injury after cardiac surgery? A meta-analysis of randomized controlled trials



Chunxiao Zhao [a,1,*], **Shuo Liu** [b,1], **Huiquan Zhang** [a], **Mengqi Gao** [a]

[a] *Capital Medical University, Beijing Shijitan Hospital, Department of Intensive Care Unit, Beijing, China*
[b] *Capital Medical University, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, Department of Pharmacy, Beijing, China*

Received 12 January 2023; accepted 3 July 2023
Available online 14 July 2023

KEYWORDS
Acute kidney injury;
Cardiac surgery;
Dexmedetomidine;
Meta-analysis

Abstract
Background: Acute Kidney Injury (AKI) is a common complication after cardiac surgery and has been associated with poor outcomes. Dexmedetomidine (DEX) has been shown to confer direct renoprotection based on some animal and clinical studies, but data from other trials came to the opposite conclusion following cardiac surgery. This meta-analysis was conducted to evaluate the effects of perioperative DEX administration on the occurrence of AKI and the outcomes after cardiac surgery.
Methods: We searched databases including EMBASE, PubMed, and Cochrane CENTRAL for Randomized Controlled Trials (RCTs) focused on DEX for AKI in adult patients after cardiac surgery. The primary outcome was incidence of AKI. Secondary outcomes were Mechanical Ventilation (MV) duration, Intensive Care Unit (ICU) Length Of Stay (LOS), hospital LOS and mortality.
Results: Fifteen trials enrolling 2907 study patients were collected in the meta-analyses. Compared with controls, DEX reduced the incidence of postoperative AKI (Odds Ratio [OR = 0.66]; 95% Confidence Interval [95% CI 0.48—0.91]; $p = 0.01$), and there was no significant difference between groups in postoperative mortality (OR = 0.63; 95% CI 0.32—1.26; $p = 0.19$), MV duration (Weighted Mean Difference [WMD = -0.44]; 95% CI -1.50—0.63; $p = 0.42$), ICU LOS (WMD = -1.19; 95% CI -2.89—0.51; $p = 0.17$), and hospital LOS (WMD = -0.31; 95% CI -0.76—0.15; $p = 0.19$).
Conclusions: Perioperative DEX reduced the incidence of postoperative AKI in adult patients undergoing cardiac surgery. No significant decrease existed in mortality, MV duration, ICU LOS and hospital LOS owing to DEX administration.
© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

* Corresponding author.
E-mail: 15830171446@163.com (C. Zhao).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bjane.2023.07.003
0104-0014/© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Acute Kidney Injury (AKI) is a recognized complication following cardiac surgery with a reported incidence between 5% and 42%.[1] Postoperative AKI results in poor outcomes, prolonged hospital Length of Stay (LOS), increased hospital costs and mortality.[2] The mechanism of AKI after cardiac surgery is tightly associated with the hemodynamic instability and sympathetic activity during Cardiopulmonary Bypass (CPB).[3-5] Although numerous trials attempted to identify strategies to prevent AKI, the incidence is still around 40% and no definite strategy exists yet.[6-10]

Dexmedetomidine (DEX) is a highly selective α2 adrenoreceptor agonist and has been widely used for sedation during cardiac surgery. DEX differs from other sedatives by the properties of anti-inflammatory and sympatholytics.[11,12] These properties offer a hypothesis that DEX might reduce the incidence of postoperative AKI. Preclinical studies indicated the renoprotective effect of DEX in various animal models.[13-15] Several single-center Randomized Controlled Trials (RCTs) have also addressed this question and the results are controversial.[16-19] Previous meta-analyses had evaluated the effect of DEX in cardiac surgery and showed a reduced risk of postoperative AKI.[20-22] However, the studies were limited by high heterogeneity and relatively small sample size. Moreover, some strengthened studies focused on this issue were published in recent years.[23,24] Therefore, we conducted this meta-analysis to assess if DEX is associated with a protective effect of AKI after cardiac surgery.

Methods

Search strategy and study criteria

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[25] and three electronic databases including MEDLINE (through PubMed), Embase (through OVID) and Cochrane Library were searched to identify relevant studies. The search strategy for PubMed was performed using the keywords “dexmedetomidine”, “cardiac surgery”, “heart surgery”, “kidney”, and “renal”. Various combinations of key words and different search strategies were developed for another two databases. The search encompassed the period between January 1997 and November 2022. All eligible studies met the following conditions: 1) Randomized controlled trials only, and as an original article, 2) Studies published in English, 3) Adult patients undergoing cardiac surgery with or without cardiopulmonary bypass, including coronary artery bypass graft or cardiac valve replacement or coronary artery bypass graft combined with cardiac valve replacement; 4) Intervention: DEX; 5) Comparison: placebo or control (other therapy); 6) Outcome measure: the incidence of postoperative AKI. Exclusion criteria were as follows: retrospective study, observational study, conference abstracts, expert opinion, review articles, case reports, abstracts, editorials, and letters to the editor, animal studies, studies involving pediatric population, and studies lacking clinical outcome data, and failure to contact the authors. Furthermore, the references of relevant studies were also assessed.

Literature review and data extraction

The literature review and data extraction were independently completed by 2 investigators. In the case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion to reach consensus. Quality assessment was completed using the Cochrane risk of bias tool: randomization, allocation concealment, blinding, withdrawals and dropouts, and intention-to-treat analysis. Data extraction included characteristics of included studies and patients.

Postoperative outcomes

The primary end point was incidence of AKI defined based on three definitions, consisting of KDIGO (Kidney Disease: Improving Global Outcome), RIFLE (Risk, Injury, Failure, Loss of kidney function, and End−stage kidney disease), AKIN (Acute Kidney Injury Network) and undergoing RRT (Renal Replacement Therapy) for new onset of AKI after cardiac surgery. Secondary outcomes included mortality, Mechanical Ventilation (MV) duration, ICU LOS, and hospital LOS.

Statistical analysis

For dichotomous outcomes (reported with incidence), we calculated the Odds Ratio (OR) with 95% Confidence Interval (95% CI). For continuous outcomes (reported as mean $\pm$ standard deviation, median and interquartile range, or median and range), we calculated mean differences for each study according to the statistical method of Hozo et al.[26] and used weights to pool the estimate (Weighted Mean Difference – WMD) with 95% CI. Random-effect models were used to analyze the data in light of the heterogeneity. Heterogeneity was assessed with Inconsistency statistic (I^2). Publication bias was assessed by Begg’s test, Egger’s test and Macaskill test. Meta-regression and subgroup analysis were conducted to explore the potential sources of significant heterogeneity. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates: $p < 0.05$ (2 sided) was considered to be statistically significant for hypothesis testing. All statistical analyses were performed in REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 15.0; StataCorp LP).

Results

Study characteristics

Figure 1 shows the flow chart for the study screening and selection process in this meta-analysis. Fifteen trials with sixteen groups of data ultimately met our criteria.[16-19,23,24,27-35] Two studies were for coronary artery bypass grafting, nine were for combined cardiac surgery, two for valve replacement surgery, and two for aortic vascular surgery. Nine trials used placebo as control, whereas four used propofol, one used morphine or remifentanil. DEX was continuously infused at a rate of approximately 0.2 to

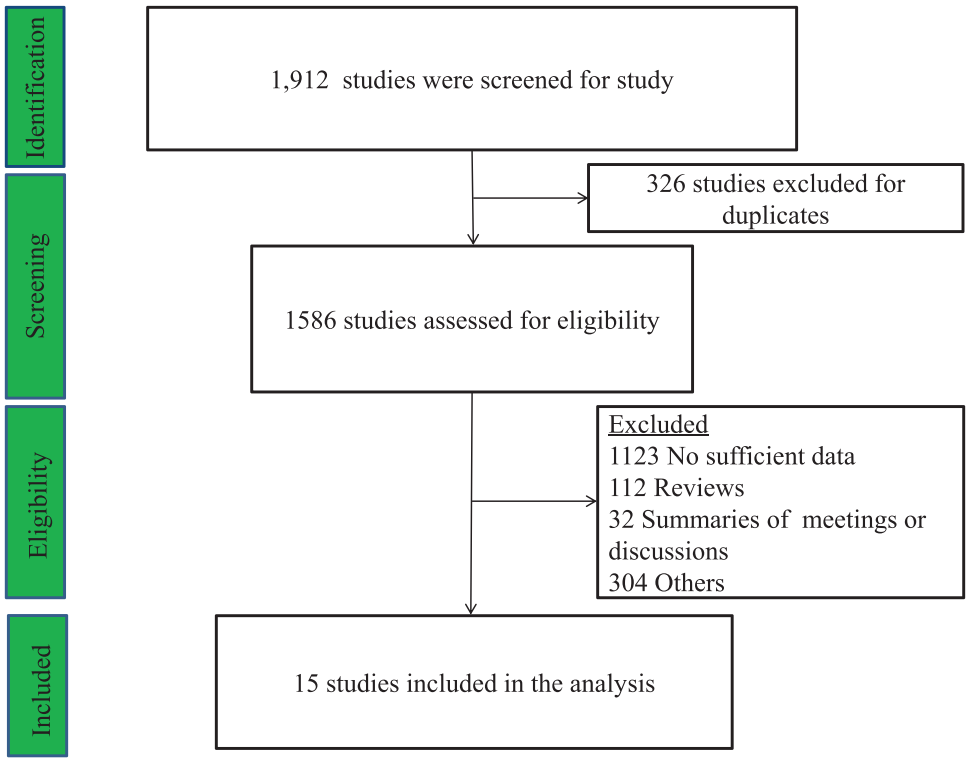


Figure 1 Flow diagram of studies included into meta-analyses.

0.8 mcg.kg^{-1}.h^{-1} for 24 hours after a loading dose (0.4–1 mcg.kg^{-1}) in six studies or infused at a rate of approximately 0.04 to 1.5 mcg.kg^{-1}.h^{-1} without a loading dose in nine. DEX was used intraoperatively in eleven studies and postoperatively in four.

For primary outcomes, AKI incidence was reported in fifteen trials, including two showing the number of patients needed for dialysis owing to the new onset of AKI after cardiac surgery; For second endpoint, mortality, in seven; mechanical ventilation duration, in twelve; ICU LOS, in thirteen; and hospital LOS, in ten.

Study design and patient characteristics are summarized in Tables 1 and 2. The quality assessment is listed in Figure 2 and Table 3.

Effect of DEX on incidence of AKI, and mortality

The outcome of AKI was reported in 2907 study participants, and the overall incidence was 7.95% (DEX group, 6.52%; control group, 9.37%). The postoperative incidence of AKI was significantly reduced by DEX (fifteen studies; OR = 0.66; 95% CI 0.48–0.91; p = 0.01; I^2 = 6%); (Fig. 3). There was no evidence of publication bias (Begg's test p = 0.96; Egger's test p = 0.55).

Subgroup analyses revealed similar trends to those of postoperative AKI outcome based on different characteristics such as age (≥ 62.5 vs. < 62.5 years), male proportion (≥ 62% vs. < 62%), diabetes proportion (≥ 25% vs. < 25%), hypertension proportion (≥ 25% vs. < 25%), previous Myocardial Infarction (MI) proportion (≥ 15% vs. < 15%), Left Ventricular Ejection Fraction (LVEF) (≥ 60% vs. < 60%), Cardiopulmonary Bypass (CPB) duration (≥ 100 vs. < 100 min), β-blocker (≥ 50% vs. < 50%), Statin (≥ 65% vs. < 65%), loading dose (use or not), type of control (placebo vs. others), administration timing (pre/intraoperative vs. postoperative) and surgery type (combined surgery vs. others) (Supplementary Table 1).

Meta-regression analyses performed for the potential sources of significant heterogeneity are listed in Supplementary Table 2, and there were no significant differences for postoperative AKI in all the subgroups.

Sensitivity analyses excluding each included study at a time revealed that all the studies were consistent with the direction and size of the overall AKI-reducing effect of DEX (p < 0.05 for all) except Cho.

The outcome mortality was reported in 1883 study participants, and the overall incidence was 1.86% (DEX group, 1.38%; control group, 2.34%). There was no significant difference between DEX and the risk of mortality (Seven studies; OR = 0.63; 95% CI 0.32–1.26; p = 0.19; I^2 = 0%); (Supplementary Figure 1).

Effect of DEX on MV duration, ICU LOS, and hospital LOS

Postoperative MV duration was reported in twelve studies, and no statistically significant reduction by DEX was found (eleven studies; WMD = -0.44; 95% CI -1.50–0.63; p = 0.42; I^2 = 73%); (Supplementary Fig. 2). There was no significant difference in ICU LOS (thirteen studies; WMD = -1.19; 95% CI -2.89–0.51; p = 0.17; I^2=74%); (Supplementary Fig. 3), as well as in hospital LOS (ten studies; WMD = -0.31; 95% CI -0.76–0.15; p = 0.19; I^2 = 76%); (Supplementary Fig. 4).

Table 1 Summarized study design of included randomized trials.

Study	Country	Surgery	Dexmedetomidine dose	Control	Time and duration of intervention or control	N° of patients	Clinical end point	AKI definition	Follow-up
Balkanay 2015I	Turkey	On-PUMP CABG	0.04 $\mu g.kg^{-1}.h^{-1}$ – 0.05 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start preCPB and last for 24h	31 vs. 28	AKI; MV duration; ICU stay; Hospital stay	RIFLE	In hospital
Balkanay 2015II	Turkey	On-PUMP CABG	0.04 $\mu g.kg^{-1}.h^{-1}$ -0.05 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start preCPB and last for 24h	29 vs. 28	AKI; MV duration; ICU stay; Hospital stay	RIFLE	In hospital
Valery 2020	Russia	Combined	0.4 $\mu g.kg^{-1}.h^{-1}$ – 0.7 $\mu g.kg^{-1}.h^{-1}$	Placebo	Started in the surgical theater and continued in the intensive care unit	84 vs. 85	AKI; Mortality; MV duration; ICU stay; Hospital stay	NA	In hospital
Cho 2015	Korea	Combined	0.04 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start immediately after anesthetic induction and last for 24h	100 vs. 100	AKI; Mortality; ICU stay;	AKIN	In hospital
Tang 2020	China	Valve surgery	1 $\mu g.kg^{-1}$ 0.3 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start before induction and last for 15 min	38 vs. 37	AKI; MV duration; ICU stay; Hospital stay	KDIGO	In hospital
DjaianiG 2016	Canada	Combined	0.4 $\mu g.kg^{-1}$ 0.2–0.7 $\mu g.kg^{-1}.h^{-1}$	Propofol	Start postsurgery and last for 24h	91 vs. 92	AKI; Mortality; MV duration; ICU stay; Hospital stay	NA	In hospital
Alparslan 2020	USA	Combined	0.1 $\mu g.kg^{-1}.h^{-1}$– 0.4 $\mu g.kg^{-1}.h^{-1}$	Placebo	Started before the surgical incision and last for 24h	398 vs. 396	AF; Stroke; Mortality; ICU stay; Hospital stay	AKIN	90 days after surgery
Li 2017	China	Combined	0.1 $\mu g.kg^{-1}.h^{-1}$ – 0.6 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start preCPB and last until the end of MV	142 vs. 143	AKI; MV duration; ICU stay	KDIGO	30 days after surgery
Liu 2016	China	Combined	< 1.5 $\mu g.kg^{-1}.h^{-1}$	Propofol	Start after surgery and last until the end of MV	44 vs. 44	AKI; Mortality; MV duration; ICU stay; Hospital stay	AKIN	In hospital
Zhai 2017	China	Valve surgery	0.6 $\mu g.kg^{-1}$ 0.2 $\mu g.kg^{-1}.h^{-1}$	Placebo	before anesthesia and last until the end of operation	36 vs. 36	AKI; MV duration	RIFLE	In hospital
Park 2014	Korea	Combined	0.5 ug.kg^{-1} 0.2–0.8 $\mu g.kg^{-1}.h^{-1}$	Remifentanil	Start after surgery and last until extubation	67 vs. 75	AKI; MV duration; ICU stay; Hospital stay	Cr > 100%abovebaseline or new dialysis need	In hospital
Zi 2020	China	Off-PUMP CABG	0.2–1 $\mu g.kg^{-1}.h^{-1}$	Propofol	Start from analepsia until the end of ICU	62 vs. 61	AF; MV duration; ICU stay	NA	In hospital
Shehabi 2009	Australia	Combined	0.1–0.7 $\mu g.kg^{-1}.mL^{-1}$	Morphine	Start within 1h of adminssin to CICU until the removal of chest drains	152 vs. 147	AKI; Mortality; MV duration; ICU stay; Hospital stay	NA	12 days after surgery
Seongsu 2021	Korea	Thoracic aortic surgery	0.4 $mg.mL^{-1}$	Placebo	After the induction until 12h after ACC-off	26 vs. 25	AF; Stroke; MV duration; ICU stay; Hospital stay	NA	In hospital
Shi 2019	China	Combined	0.4–0.6 $\mu g.kg^{-1}.h^{-1}$	Propofol	NA	84 vs. 80	AF; MV duration; ICU stay; Hospital stay	NA	In hospital
Soliman 2016	Egypt	Aortic vascular surgery	1 $\mu g.kg^{-1}$ 0.3 $\mu g.kg^{-1}.h^{-1}$	Placebo	Start 15 min before induction maintained to the end of surgery	75 vs. 75	AKI; Mortality;	Cr > 115 $\mu mol.L^{-1}$	In hospital

AKI, Acute Kidney Injury; CABG, Coronary Artery Bypass Graft; CPB, Cardiopulmonary Bypass; ICU, Intensive Care Unit; CICU, Cardiac Intensive Care Unit, MV, Mechanical Ventilation; NA, Not Available; Cr, Creatinine. RIFLE, Risk-Injury-Failure-Loss-End-stage renal disease; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes.

Table 2 Summarized patient characteristics of the included randomized trials.

Study	Age	Male (%)	DM (%)	HP (%)	PreMI (%)	LVEF (%)	CPB duration (min)	Anesthetics	Baseline serum creatinine	β-blocker (%)	Statins (%)
Balkanay 2015I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Balkanay 2015II	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Valery 2020	62.5	72.2	43.8	79.3	27.8	55.4	121.5	Sevoflurane	NA	63.9	NA
Cho 2015	63	48	19.5	45.5	NA	61.5	131	Sevoflurane	33	NA	63
Tang 2020	55.0	61.3	NA	NA	NA	57.9	71.0	Sevoflurane	NA	NA	NA
DjaianiG 2016	72.55	75.4	21.9	75.4	16.4	NA	98.99	Isoflurane	53	68.85	72.55
Alparslan 2020	62.5	69.6	20.8	67.1	10.8	60	NA	NA	NA	49.1	55
Li 2017	67.18	69.1	32.3	63.2	9.8	NA	102.99	Sevoflurane	69.73	48.42	67.18
Liu 2016	54.75	39.8	12.5	29.5	NA	65	71.15	Sevoflurane	NA	NA	54.75
Zhai 2017	46	45.8	NA	NA	NA	49	72.5	NA	NA	NA	NA
Park 2014	53.81	55.6	9.15	27.5	NA	61.87	166.75	Sevoflurane	NA	NA	53.81
Zi 2020	65.4	67.5	46.3	64.2	16.3	56.5	NA	NA	NA	NA	
Shehabi 2009	71.25	75.3	29.5	80.1	36.6	NA	98.98	Sevoflurane	NA	NA	71.25
Seongsu 2021	61.5	54.9	11.8	68.6	13.7	63	NA	NA		23.5	NA
Shi 2019	74.5	72.6	NA	NA	NA	NA	112.9	NA		54.3	79.9
Soliman 2016	58.1	50	30.7	48.7	8.6	52.9	NA	NA	36.67	NA	58.1

Note: Values are given as means unless otherwise specified.
DM, Diabetes Mellitus; HP, Hypertension; PreMI, Previous Myocardial Infarction; LVEF, Left Ventricular Ejection Fraction; CPB, Cardiopulmonary Bypass; NA, Not Available.

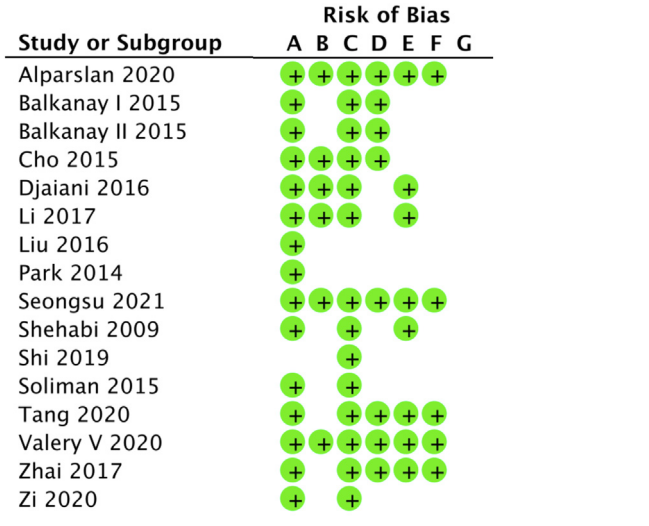


Figure 2 Quality assessment of studies included into meta-analyses.

Discussion

In this meta-analysis of fifteen RCTs involving 2907 adult patients undergoing cardiac surgery, we found that perioperative DEX was associated with a decrease in postoperative AKI. However, postoperative parameters including MV duration, ICU, hospital LOS and mortality did not seem to present a significant reduction as a result of the DEX.

AKI is common after cardiac surgery and small increases in postoperative serum creatinine levels have been reported to be related with worse outcome, even when renal function returns to normal ultimately.[36,37] The reason that cardiac surgery can cause AKI is always accompanied by renal Ischemia-Reperfusion Injury (I/RI), elevated sympathetic activity, and hemodynamic instability. For this reason, pharmacologic or other prophylaxis which have these properties may reduce AKI after cardiac surgery and this is an important research area to clinicians.[38-40]

DEX has been widely used in anesthesia procedures and has shown organ protection by stabilizing the sympathetic system, exerting anti-inflammatory effects, and attenuating Ischemia/Reperfusion (I/R) injury in vivo and vitro studies.[41-45] There is a hypothesis that the incidence of AKI may be reduced owing to the use of DEX in cardiac surgery.[46,47] Several studies have compared the efficacy of DEX at enhancing urine output and at decreasing the concentration of blood urea nitrogen and creatinine after surgery,[19,48,49] and other randomized controlled trials have reported a lower rate of kidney injury.[17,50,51] No general consensus was reached on the effect of DEX for AKI.[52-54] A few meta-analyses have been conducted to address this issue. However, a meta-analysis performed by Peng,[20] which included nine

Table 3 Summarized quality assessment of included randomized trials.

Study	Random sequencegeneration	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Attrition bias	Selective reporting
Balkanay 2015I	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear
Balkanay 2015II	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear
Valery 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cho 2015	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Tang 2020	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Djaiani G 2016	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Alparslan 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2017	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Liu 2016	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear personnel
Zhai 2017	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Park 2014	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear
Zi 2020	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear
Shehabi 2009	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear
Seongsu 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shi 2019	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Soliman 2016	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear

RCTs with a total of 1308 patients, showed low heterogeneity (I^2 = 30%). Another meta-analysis by Liu[21] including ten RCTs with a total of 1575 patients showed only eight groups of data from seven studies on the main outcome. Our study with an almost two times larger sample size collected some high-quality research published in recent years and provided a more convincing conclusion.

Based on our literature review, positive reno-protective effects were reported in two studies. Moreover, in our data analysis, the combined results with a random-effects model revealed lower AKI incidence in patients with DEX, and the pooled OR succeeded to reach statistical significance. However, this benefit did not translate into the second outcomes, such as MV duration, ICU LOS, hospital LOS and mortality. A possible explanation is that our meta-analysis with a relatively small sample size may account for such differences. Another is that heterogeneity for the MV duration, ICU and hospital LOS is almost over 50%. In fact, there are trends toward lower MV duration, ICU LOS, hospital LOS and mortality. Further randomized studies with large sample sizes are encouraged to verify the current findings.

Our analysis has several limitations. Firstly, many factors could influence AKI after cardiac surgery, such as age, degree of hypertension, and drugs used for treating

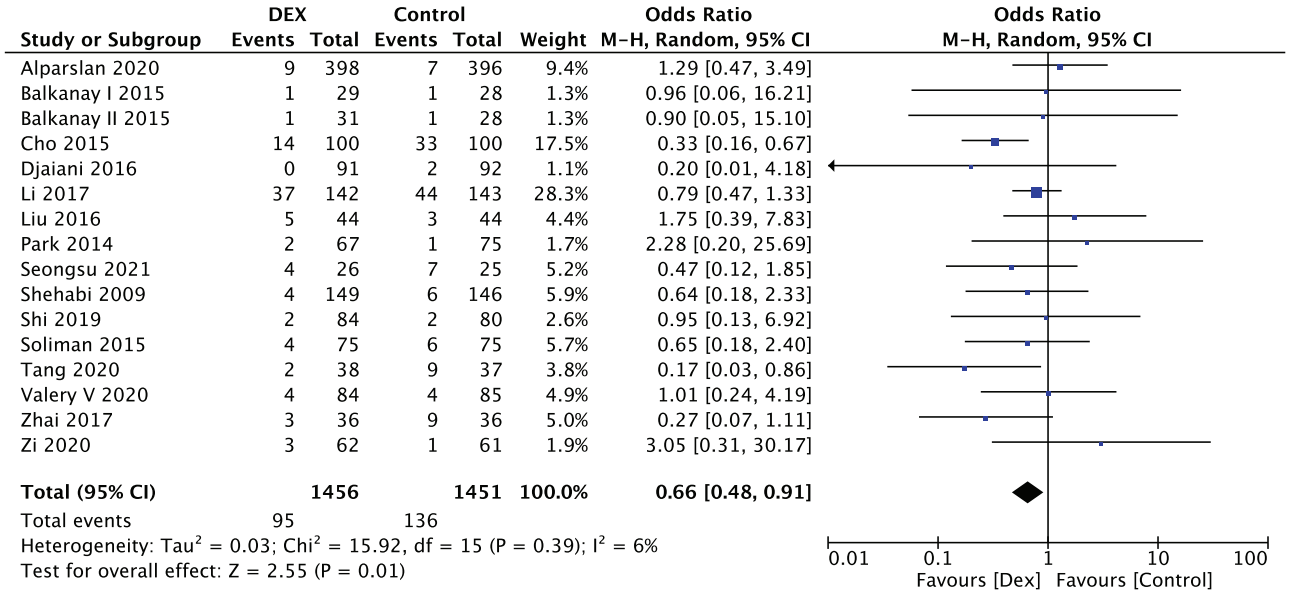


Figure 3 DEX reduced the incidence of AKI.

hypertension and diabetes mellitus. We were unable to access individual patient data, so the influences of confounding factors may be underestimated. Secondly, we only included English language trials and published studies, which may lead to publication bias. Thirdly, many design differences among these studies made it difficult to reduce clinical heterogeneity. Subgroup analyses and meta-regression were performed for the potential sources of heterogeneity. Finally, based on the included data, there are four different definitions of AKI, including RIFLE, AKIN, KDIGO, and need for RRT. Six studies did not mention the definition of AKI. According to previous studies,[55,56] the incidence of AKI can vary greatly according to the definition used, and our study might draw a misleading conclusion. Given only three or less studies were included, a subgroup analysis based on AKI definition was not performed.

Conclusion

In summary, our meta-analysis indicated that perioperative DEX use reduced postoperative AKI in patients receiving cardiac surgery. However, DEX use is not associated with MV duration, ICU LOS, hospital LOS and mortality. Future, much larger trials are needed to verify the current findings.

Data availability statement

The data used to support the findings of this study are included within the supplementary information file.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical statement

Since this was a meta-analysis, ethical approval was not required under the arrangements of the Institutional Review Board in our hospital.

Declaration of Competing 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.2023.07.003.

References

1. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13:697–711.
2. Ortega-Loubon C, Fernández-Molina M, Carrascal-Hinojal Y, et al. Cardiac surgery-associated acute kidney injury. Ann Card Anaesth. 2016;19:687–98.
3. Guan C, Li C, Xu L, et al. Risk factors of cardiac surgery-associated acute kidney injury: development and validation of a perioperative predictive nomogram. J Nephrol. 2019;32:937–45.
4. Ranucci M, Ambrogi F, Pistuddi V. Cardiac surgery associated acute kidney injury and the role of cardiopulmonary bypass technique. J Thorac Cardiovasc Surg. 2019;157:301.
5. Liu D, Liu B, Liang Z, et al. Acute Kidney Injury following Cardiopulmonary Bypass: A Challenging Picture. Oxid Med Cell Longev. 2021;2021:8873581.
6. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017;43:1551–61.
7. Küllmar M, Zarbock A, Engelman DT, et al. Prevention of acute kidney injury. Crit Care Clin. 2020;36:691–704.
8. Couturier C, Maillard N, Mariat C, et al. Prevention of cardiac surgery-associated acute kidney injury by risk stratification using (TIMP-2)*(IGFBP7). Biomark Med. 2021;15:1201–10.
9. Presta P, Bolignano D, Coppolino G, et al. Antecedent ACE-inhibition, inflammatory response, and cardiac surgery associated acute kidney injury. Rev Cardiovasc Med. 2021;22:207–13.
10. Li S, Fu S, Xiao Y, et al. Recent Perioperative Pharmacological Prevention of Acute Kidney Injury after Cardiac Surgery: A Narrative Review. Am J Cardiovasc Drugs. 2017;17:17–25.
11. Weerink MAS, Struys M, Hannivoort LN, et al. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet. 2017;56:893–913.
12. Gallego-Ligorit L, Vives M, Vallés-Torres J, et al. Use of Dexmedetomidine in Cardiothoracic and Vascular Anesthesia. J Cardiothorac Vasc Anesth. 2018;32:1426–38.
13. Zhao Y, Feng X, Li B, et al. Dexmedetomidine Protects Against Lipopolysaccharide-Induced Acute Kidney Injury by Enhancing Autophagy Through Inhibition of the PI3K/AKT/mTOR Pathway. Front Pharmacol. 2020;11:128.
14. Feng X, Guan W, Zhao Y, et al. Dexmedetomidine ameliorates lipopolysaccharide-induced acute kidney injury in rats by inhibiting inflammation and oxidative stress via the GSK-3β/Nrf2 signaling pathway. J Cell Physiol. 2019;234:18994–9009.
15. Wang Z, Wu J, Hu Z, et al. Dexmedetomidine Alleviates Lipopolysaccharide-Induced Acute Kidney Injury by Inhibiting p75NTR-Mediated Oxidative Stress and Apoptosis. Oxid Med Cell Longev. 2020;2020:5454210.
16. Tang C, Hu Y, Gao J, et al. Dexmedetomidine pretreatment attenuates myocardial ischemia reperfusion induced acute kidney injury and endoplasmic reticulum stress in human and rat. Life Sci. 2020;257:118004.
17. Cho JS, Shim JK, Soh S, et al. Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery. Kidney Int. 2016;89:693–700.
18. Balkanay OO, Goksedef D, Omeroglu SN, et al. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. Interact Cardiovasc Thorac Surg. 2015;20:209–14.
19. Zhai M, Kang F, Han M, et al. The effect of dexmedetomidine on renal function in patients undergoing cardiac valve replacement under cardiopulmonary bypass: A double-blind randomized controlled trial. J Clin Anesth. 2017;40:33–8.

20. Peng K, Li D, Applegate 2nd RL, et al. Effect of dexmedetomidine on cardiac surgery-associated acute kidney injury: a meta-analysis with trial sequential analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2020;34:603—13.
21. Liu Y, Sheng B, Wang S, et al. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2018;18:7.
22. Chen X, Huang T, Cao X, et al. Comparative efficacy of drugs for preventing acute kidney injury after cardiac surgery: a network meta-analysis. Am J Cardiovasc Drugs. 2018;18:49—58.
23. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet. 2020;396:177—85.
24. Subramaniam B, Shankar P, Shaefi S, et al. Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: The DEXACET Randomized Clinical Trial. Jama. 2019;321:686—96.
25. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
27. Djaiani G, Silverton N, Fedorko L, et al. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial. Anesthesiology. 2016;124:362—8.
28. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. PLoS One. 2017;12:e0170757.
29. Liu X, Zhang K, Wang W, et al. Dexmedetomidine sedation reduces atrial fibrillation after cardiac surgery compared to propofol: a randomized controlled trial. Crit Care. 2016;20:298.
30. Park JB, Bang SH, Chee HK, et al. Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. Korean J Thorac Cardiovasc Surg. 2014;47:249—54.
31. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine-based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology. 2009;111:1075—84.
32. Shi C, Jin J, Qiao L, et al. Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: a double-blinded, multi-center, randomized study. Clin Interv Aging. 2019;14:571—5.
33. Soliman R, Zohry G. The myocardial protective effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery. Ann Card Anaesth. 2016;19:606—13.
34. Zi J, Fan Y, Dong C, et al. Anxiety Administrated by dexmedetomidine to prevent new-onset of postoperative atrial fibrillation in patients undergoing off-pump coronary artery bypass graft. Int Heart J. 2020;61:263—72.
35. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative dexmedetomidine supplement decreases delirium incidence after adult cardiac surgery: a randomized, double-blind, controlled study. J Cardiothorac Vasc Anesth. 2021;35:449—57.
36. Lau G, Wald R, Sladen R, et al. Acute kidney injury in cardiac surgery and cardiac intensive care. Semin Cardiothorac Vasc Anesth. 2015;19:270—87.
37. Lassnigg A, Schmid ER, Hiesmayr M, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med. 2008;36:1129—37.
38. Brown JR, Shore-Lesserson L, Fox AA, et al. The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury. J Extra Corpor Technol. 2022;54:267—90.
39. Yu Y, Li C, Zhu S, et al. Diagnosis, pathophysiology, and preventive strategies for cardiac surgery-associated acute kidney injury: a narrative review. Eur J Med Res. 2023;28:45.
40. Peng K, McIlroy DR, Bollen BA, et al. Society of Cardiovascular Anesthesiologists Clinical Practice Update for Management of Acute Kidney Injury Associated with Cardiac Surgery. Anesth Analg. 2022;135:744—56.
41. Ueki M, Kawasaki T, Habe K, et al. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia. 2014;69:693—700.
42. Bao N, Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. Mediators Inflamm. 2020;2020:6136105.
43. Singh D, Jagannath S, Priye S, et al. The comparison of dexmedetomidine, esmolol, and combination of dexmedetomidine with esmolol for attenuation of sympathomimetic response to laryngoscopy and intubation in patients undergoing coronary artery bypass grafting. Ann Card Anaesth. 2019;22:353—7.
44. Liu X, Rabin PL, Yuan Y, et al. Effects of anesthetic and sedative agents on sympathetic nerve activity. Heart Rhythm. 2019;16:1875—82. 2019/06/30. DOI: 10.1016.
45. Yang SJ, Fan CN, Wang MJ, et al. Effects of dexmedetomidine on renal microcirculation in ischemia/reperfusion-induced acute kidney injury in rats. Sci Rep. 2021;11:2026.
46. Honore PM, De Bels D, Preseau T, Spapen HD. Dexmedetomidine: the first new kid on the block for preventing cardiac surgery-associated acute kidney injury? Crit Care. 2018;22:151.
47. Li S, Fu S, Xiao Y, Xu G. Recent Perioperative Pharmacological Prevention of Acute Kidney Injury after Cardiac Surgery: A Narrative Review [published correction appears in Am J Cardiovasc Drugs. 2018 Feb 26] Am J Cardiovasc Drugs. 2017;17:17—25.
48. Wu S, Yao H, Cheng N, Guo N, Chen J, Ge M, Cai J. Determining whether dexmedetomidine provides a reno-protective effect in patients receiving laparoscopic radical prostatectomy: a pilot study. Int Urol Nephrol. 2019;51:1553—61.
49. Wu F, Duan H, Xie Y. Preventive effects of dexmedetomidine on renal dysfunction and hemodynamic stability in malignant obstructive jaundice patients during peri-operative period. Med Sci Monit. 2019;25:6782—7.
50. Soh S, Shim JK, Song JW, Bae JC, Kwak YL. Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. Br J Anaesth. 2020. https://doi.org/10.1016/j.bja.2019.12.036. Online ahead of print.
51. Bayram A, Ulgey A, Baykan A, Narin N, Narin F, Esmaoglu A, Boyaci A. The effects of dexmedetomidine on early stage renal functions in pediatric patients undergoing cardiac angiography using non-ionic contrast media: a double-blind, randomized clinical trial. Paediatr Anaesth. 2014;24:426—32.
52. Ostermann M, Kunst G, Baker E, Weerapolchai K, Lumlertgul N. Cardiac Surgery Associated AKI Prevention Strategies and Medical Treatment for CSA-AKI. J Clin Med. 2021;10:5285.
53. Massoth C, Zarbock A, Meersch M. Acute Kidney Injury in Cardiac Surgery. Crit Care Clin. 2021;37:267—78.
54. Küllmar M, Zarbock A, Engelman DT, Chatterjee S, Wagner NM. Prevention of acute kidney injury. Crit Care Clin. 2020;36:691—704.
55. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol. 2014;9:12—20.
56. Koeze J, Keus F, Dieperink W, van der Horst IC, Zijlstra JG, van Meurs M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. BMC Nephrol. 2017;18:70.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



LETTER TO THE EDITOR

The impact of early feeding on optimizing gastrointestinal recovery after cesarean section: a non-randomized, open-label, clinical trial

Dear Editor,

Gastrointestinal disorders, such as nausea, vomiting, distension, and dry mouth have negative impacts such as pain, difficulties in nutrition, and increased susceptibility to infections.

In this non-randomized open-label clinical trial conducted at the Unimed Maceió Hospital from May to October 2022, 132 postpartum women were included in the study with n = 66 in the control group (following the standard early feeding protocol of the obstetrics service) and n = 66 in the intervention group (receiving an industrialized liquid preparation within 1 hour after surgery).

The trial included parturient aged between 18 and 45 years who underwent cesarean section under spinal anesthesia using an aseptic technique. Exclusion criteria encompassed patients with twin pregnancies, emergency procedures and comorbidities related to pregnancy.

All study participants were visited at 24 and 48 hours after the anesthetic procedure. During these visits, they were asked about various gastrointestinal aspects, including the presence of nausea/vomiting (considered as the primary outcome), elimination of flatus within 24 hours, occurrence of bowel movements within 48 hours, and the sensation of dry mouth (considered as secondary outcomes).

This clinical trial was registered in ReBEC (Registro Brasileiro de Ensaios Clínicos), number RBR-78gvj3g, and was approved by the Ethics and Research Committee with Human Beings — Brazil Platform of the Federal University of Alagoas, CAAE 55504221.1.0000.5013, number: 5,389,994.

The mean age of participants was 30.1±3.9 years and the mean gestational age was 38.6±1.6 weeks. Most participants had completed higher education (n = 93; 70.5%), whilst the rest had completed high school (n = 39; 29.5%). The average duration of preoperative fasting among the participants was 9.2±3.3 hours, with no significant difference between the intervention and control groups. The patients in the control group had an average fasting duration of 14.7±3.7 hours (including preoperative and postoperative fasting), following the standard hospital feeding protocol. On the other hand, the participants in the intervention group had an average fasting duration of 10.38±3.7 hours, and this difference was statistically significant ($p < 0.001$). After performing logistic binary regression adjusted for age and gestational age (Table 1), the results revealed a significant impact of early feeding on the recovery of puerperal women.

The analysis showed a lower presence of nausea and vomiting (OR = 27.1; 95% CI 3.4—215.4; $p = 0.002$), a higher occurrence of flatulence rate in 24 hours (OR = 0.8; 95% CI 0.3—0.2; $p < 0.001$) and evacuation in 48 hours (OR = 0.1; 95% CI 0.05—0.3; $p < 0.001$), as well as a reduced incidence of dry mouth sensation (OR = 24.4; 95% CI 5.4—109.7; $p < 0.01$). These findings demonstrate the beneficial effects of early feeding on gastrointestinal symptoms and highlight its potential for enhancing postoperative recovery in puerperal women.

The participants in the intervention group reported no discomfort related to the administered supplement. All participants who agreed to take part in the study successfully completed the assessment.

The restoration of postoperative gastrointestinal function, a topic extensively discussed in studies such as Saad et al.[1] and a recent meta-analysis by Li et al.[2] consistently highlights the favorable effects of early feeding in facilitating the recovery of puerperal women. These findings collectively highlight the protective role of early feeding in the postoperative period and its alignment with both national and international guidelines advocating for abbreviated fasting approaches.

Cesarean section introduces a substantial volume of blood and amniotic fluid into the peritoneal cavity, requiring abdominal cavity cleaning, which can trigger intestinal disorders,[2] and consequently pain, abdominal distension, and difficulties in initiating adequate breastfeeding.[3] Previous research has demonstrated that early feeding post-cesarean section, by mitigating nausea and vomiting and promoting more frequent bowel movements, plays a vital role in the recovery of patients.[4]

In our study, the provision of early feeding significantly improved gastrointestinal signs and symptoms among puerperal women, contributing to a more effective and expedited recovery. It is worth noting that maintaining metabolic health in the body relies on the delicate balance between caloric intake and utilization, encompassing processes such as nutrient absorption, metabolism, transportation, and

https://doi.org/10.1016/j.bjane.2023.11.002
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1 Association between gastrointestinal signs and symptoms and early pre-elective cesarean feeding in puerperal women.

Gastrointestinal signs and symptoms	OR	95% CI	*p*-value[a]
Nausea and vomiting	27,125	3,416– 215,365	0.002
Flatulence rate in 24 h	0.790	0.300 – 0.209	< 0.001
Evacuation in 48 h	0.130	0.053 – 0.315	< 0.001
Dry mouth sensation	24,421	5,438 – 109,669	< 0.001

[a] Binary logistic regression, adjusted to age and gestational age.

storage. Surgical procedures often lead to physiological disruptions, which can involve autonomic system impairment (particularly the parasympathetic division), inflammatory processes, and potential interactions with drugs and opioids, especially in a surgery that involves extensive manipulation in the intestinal region.[5]

Despite the limitations present in this study, such as its non-randomized and non-double-blind nature and being conducted in a single private center where participants have a high level of education, our study's findings have significant implications for pregnant women and puerperal patients. The results we have obtained are of considerable importance, offering valuable insights into the care of pregnant women. Specifically, our research underscores the critical role of early feeding in the context of spinal anesthesia with opioids during cesarean sections.

These findings are anticipated to drive improvements in maternal care. By emphasizing the importance of early feeding, our research can potentially influence the development of protocols within maternity services. This emphasis on early feeding not only optimizes the recovery process but also enhances the overall well-being of this demographic. The outcomes of our study thus serve as a fundamental cornerstone in the ongoing endeavor to enhance the care and experience of pregnant women and puerperal patients.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Support

Programa de Pós-Graduação em Ciências Médicas (PPGCM)/ UFAL and Hospital UNIMED de Maceió

References

1. Saad AF, Saoud F, Diken ZM, et al. Early versus Late Feeding after Cesarean Delivery: A Randomized Controlled Trial. Am J Perinatol. 2016;33:415–9.
2. Li H, Chen Y, Hu Z, et al. Effectiveness of acupuncture for the recovery of gastrointestinal function of patients with gastric cancer in the postoperative period: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100:e23950.
3. Mousavi Vahed SH, Afiat M, Dadgar S. Peppermint drop effect on ileus following cesarean section. J Family Med Prim Care. 2022;11:1435–42.
4. Tan PC, Alzergany MM, Adlan AS, Noor Azmi MA, SZ Omar. Immediate compared with on-demand maternal full feeding after planned caesarean delivery: a randomised trial. BJOG. 2017;124:123–31.
5. Luzny J, Valihrachova S, Novak J, Zapletal T, Donek E, Arogunmati O. Ileus states – conditions connecting psychiatrists and surgeons? Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2010;154:261–4.

Graziela Cyntia Silva Santos [a], Glaucevane da Silva Guedes [b], Alane Cabral Menezes de Oliveira [a,c], Fabiana Andrea Moura [a,c,*]

[a] *Universidade Federal de Alagoas (UFAL), Programa de Pós-Graduação em Ciências Médicas (PPGCM), Maceió, AL, Brazil*
[b] *Universidade Federal de Alagoas (UFAL), Faculdade de Nutrição (FANUT), Maceió, AL, Brazil*
[c] *Universidade Federal de Alagoas (UFAL), Programa de Pós-Graduação em Nutrição (PPGNUT), Maceió, AL, Brazil*

[*] Corresponding author.
E-mail: fabiana.moura@fanut.ufal.br (F.A. Moura).
Received 11 July 2023; accepted 7 November 2023
Available online 14 November 2023

BJAN

Brazilian Journal of Anesthesiology

Contact us

editor.bjan@sbahq.org www.bjan-sba.org +55 21 979 770 024