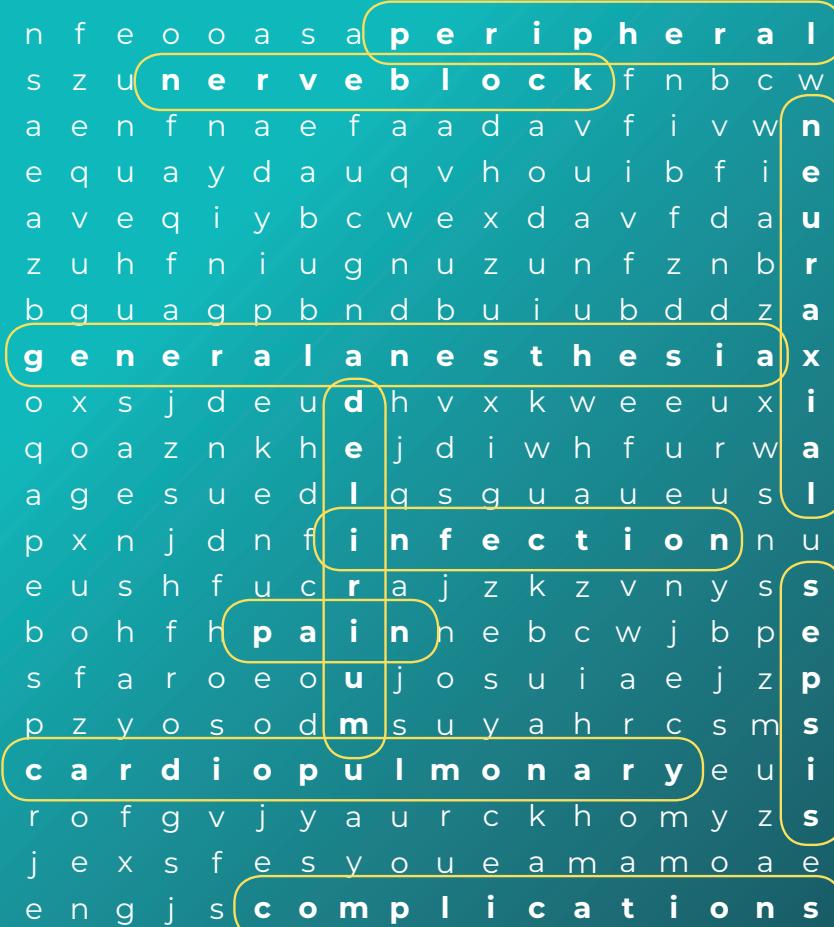




Brazilian Journal of ANESTHESIOLOGY

Revista Brasileira de Anestesiologia



Anesthesia techniques:
impact on postoperative outcomes

III PROVIVE 1% propofol 10 mg/mL

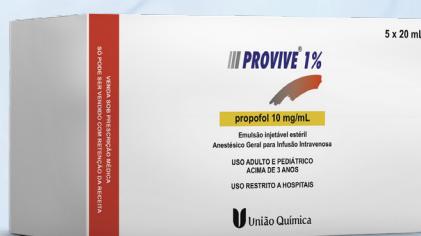
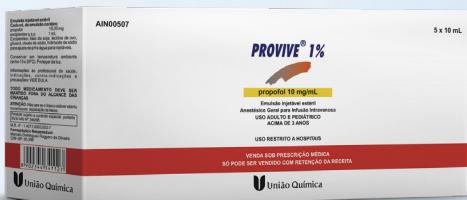


Short-acting sedation with rapid and safe patient recovery



Broad range of packaging content sizes

Appropriate for every kind of procedure



M.S.: 1.04971449

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



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



0800 011 15 59
A dose certa da
INFORMAÇÃO

U União Química
farmacêutica nacional s/a
Hospitalar

Reference: 1. Drug package insert.

Editor-in-Chief

André Prato Schmidt - Hospital de Clínicas da Universidade Federal do Rio Grande do Sul, RS, Brazil

Co-Editor

Norma Sueli Pinheiro Módolo - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, São Paulo, SP, Brazil

Associate Editors

Célio Gomes de Amorim - Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
Cláudia Marquez Simões - Hospital Sírio Libanês, São Paulo, SP, Brazil
Durval Campos Krachtein - Universidade Federal da Bahia, Salvador, BA, Brazil
Eduardo Giroud Joaquim - Universidade Federal de São Paulo, São Paulo, SP, Brazil
Eric Benedet Lineburger - Hospital São José, Criciúma, SC, Brazil
Fábio Papa - University of Toronto, Toronto, ON, Canada
Fátima Carneiro Fernandes - Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Florentino F. 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 A.M. 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
Lara Helena Navarro e Lima - Queen's University, Kingston, ON, Canada
Liana Maria Torres Araújo Azi - Universidade Federal da Bahia, Salvador, BA, Brazil
Lucena Ibiaquim Mendes de Carvalho - Hospital Getúlio Vargas, Teresina, PI, Brazil
Luciana Paula Cadore Stefanini - Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
Luís Vicente Garcia - Faculdade de Medicina da Universidade de São Paulo, Ribeirão Preto, SP, Brazil
Luiz Marcelo Sá Malbouisson - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Marcello Fonseca Salgado-Filho - Universidade Federal Fluminense, Rio de Janeiro, RJ, Brazil
Maria José Carvalho Carmona - Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Paulo do Nascimento Junior - Faculdade de Medicina de Botucatu da Universidade Estadual Paulista, São Paulo, SP, Brazil
Rodrigo Leal Alves - Hospital São Rafael, Salvador, BA, Brazil
Vanessa Henriquez 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

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
Ana Maria Menezes Caetano - Universidade Federal de Pernambuco, Recife, PE, Brazil
Antônio Carlos Aguiar Brandão - Universidade do Vale do Sapucaí, Pouso Alegre, MG, Brazil
Bernd W. Böttiger - University Hospital of Cologne, Klinikum Köln, NW, Germany
Bobbie Jean Switzer - Northwestern Medicine, Chicago, IL, USA
Carlos Galhardo Júnior - Instituto Nacional de Cardiologia (INC/M/S), Rio de Janeiro, RJ, Brasil
Carlos Manuel Correia Rodrigues de Almeida - Hospital CUF Viseu, Viseu, Beira Alta, Portugal
Cádia Sousa Govêa - Universidade de Brasília, Brasília, DF, Brazil
Clarita Bandeira Margarido - Sunnybrook Health Sciences Care, Toronto, ON, Canada
Claudia Regina Fernandes - Universidade Federal do Ceará, Fortaleza, CE, Brazil
Clyde Matawa - The Hospital for Sick Children, Toronto, ON, Canada
Cyril David Mazer - St. Michael's Hospital, Toronto, ON, Canada
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
Domingos Cicarelli - Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo, SP, Brazil
Edmundo Pereira de Souza Neto - Centro Hospitalar de Montaúban, Montaúban, Tarn-et-Garonne, France
Edoardo Quarenghi - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, MI, Italy
Eliane Cristina de Souza Soares - Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
Emery Brown - Massachusetts Institute of Technology, Cambridge, MA, USA
Fabiana A. Penachi Bosco Ferreira - Universidade Federal de Goiás, Goiânia, GO, Brazil
Federico Bilotta - Sapienza Università Di Roma, Roma, RM, Italy
Felipe Chiodini - Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
Fernando Abelha - Hospital de São João, Porto, Portugal
Francisco A. Lobo - Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
Frederic Michard - MiCo, Consulting and Research, Denens, Switzerland
Gastão Duval Neto - Universidade Federal de Pelotas, Pelotas, RS, Brazil
Getúlio Rodrigues de Oliveira Filho - Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
Gildásio de Oliveira Júnior - Albert Medical School, Brown University, Providence, RI, USA
Giovanni Landoni - Vita-Salute San Raffaele University, Milano, LOM, Italy
Gleno 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 - Pierre and Marie Curie University, Paris, France

Jean Louis Teboul - Paris-Sud University, Paris, France

Jean Louis Vincent - Université Libre de Bruxelles, Bruxelles, Belgium

Joana Berger-Estilita - University of Bern, Bern, Switzerland

João Batista Santos Garcia - Universidade Federal do Maranhão, São Luis, MA, Brazil

João Paulo Jordão Pontes - Universidade Federal de Uberlândia, Uberlândia, MG, Brazil

José Carlos Rodrigues Nascimento - Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil

José Otávio Costa Auler Júnior - Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Judymary 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

Ligia Andrade da S. Telles Mathias - Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil

Luciano Gattinoni - University of Göttingen, Göttingen, Germany

Luis Antonio dos Santos Diego - Universidade Federal Fluminense, Niterói, RJ, Brazil

Luiz Fernando dos Reis Falcao - Universidade Federal de São Paulo, São Paulo, SP, Brazil

Luiz Guilherme Villares da Costa - Hospital Israelita Albert Einstein, São Paulo, SP, Brazil

Luiz Marciiano Cangiani - Hospital da Fundação Centro Médico 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 Dismi - Istituto Giannina Gastini, Génova, GE, Italy

Oscar César Pires - Universidade de Taubaté, Taubaté, SP, Brazil

Paolo Pelosi - Università Degli Studi Di Genova, Genoa, LI, Italy

Paulo Alpírio - Universidade Federal Fluminense, Niterói, RJ, Brazil

Pedro Amorim - Centro Hospitalar e Universitário do Porto, Porto, Portugal

Pedro Francisco Brandao - 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

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 Antonio Guimarães Barbosa - Hospital das Clínicas da Faculdade de Medicina da Universidade do São Paulo, São Paulo, SP, Brazil

Ricardo Vieira Carlos - Hospital das Clínicas da Faculdade de Medicina da Universidade do São Paulo, São Paulo, SP, Brazil

Roberto Fumagalli - Università degli studi Milano Bicocca, Milano, MI, Italy

Rodrigo Lima - Queen's University, Toronto, ON, Canada

Rogêne Rodrigues Nunes - Centro de Ensino e Treinamento/SBA (Residência Médica) em Anestesiologia do Hospital Geral de Fortaleza, Fortaleza, CE, Brazil

Ronald Miller - University of California, San Francisco, CA, USA

Sara Lúcia Ferreira Cavalcante - Hospital Geral do Inhôs de Fortaleza, Fortaleza, CE, Brazil

Thais Cancado - Serviço de Anestesiologia de Campo Grande, Campo Grande, MS, Brazil

Thomas Engelhardt - Montreal Children's Hospital, McGill University, Montreal, Canada

Wayniece 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 Vilamil Gonçalves (1965-1979)

Masami Katayama (1980-1988)

Antonio Leite Oliva Filho (1989-1994)

Luiz Marciiano Cangiani (1995-2003)

Judymary 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

Librarian (BJAN): Pedro Saldanha

Librarian (SBA): Teresa Maria Libório

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

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

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

All articles submitted for publication are assessed by two or more members of the Editorial Board or external peer reviewers, assigned at the discretion of the Editor-in-chief or the Associate Editors. Published articles are a property of the Brazilian Society of Anesthesiologists (SBA), and their total or 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 © 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. All rights reserved.

Bryony

sugammadex
sódico 100 mg/mL

Launch

Best option for
NMB reversal¹⁻³

*Neuromuscular blocker

It provides **benefits¹** for the patients during surgical procedures.



Rapid and safe reversal in less than 3 minutes^{1,3}



BRYONY
sugammadex sódico
100 mg/mL
Uso intravenoso
USO ADULTO E PEDIÁTRICO
ACIMA DE 2 ANOS
Solução injetável
Contém: 10 frascos-ampola de 2 mL

VENDA SOB PRESCRIÇÃO MÉDICA

União Química

MS - 1.0497.1478.0012
Informações ao profissional de saúde, indicações, contraindicações e efeitos colaterais: Vide Bula.
TODO PRODUTO DEVE SER MANTIDO FORA DO ALCANCE DAS CRIANÇAS.
CONSERVAR EM TEMPERATURA AMBIENTAL (DE 15 °C A 30 °C) E PROTEGER DA LUZ.
NÃO CONGELAR.
ATENÇÃO: ESTE PRODUTO É SENSÍVEL À LUZ E DEVE SER MANTIDO DEIXADO DA CARA ATÉ ANTES DO USO.
Composição:
Cada mL contém sugammadex sódico.....100,380 mg
*equivalente a 100 mg de sugammadex



M.S - 1.0497.1478

Dosage form:¹

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

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

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

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

If symptoms persist a doctor should be consulted



Please access the complete package insert through QR Code:



0800 011 15 59
The right amount of INFORMATION



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

Material for exclusive distribution to healthcare professionals qualified to prescribe or dispense drug products.

JULHO 2022.

Editorial

- 1 The impact of anesthesia on postoperative outcomes: the effect of regional anesthesia on the incidence of surgical site infections
André P. Schmidt, Clóvis T. Bevilacqua Filho

Original Investigations

- 3 Effect of seasons on delirium in postoperative critically ill patients: a retrospective analysis
Yuwei Qiu, Eva Rivas, Marianne Tanios, Roshni Sreedharan, Guangmei Mao, Ilker Ince, Ahmed Salih, Remie Saab, Jagan Devarajan, Kurt Ruetzler, Alparslan Turan
- 10 Regional analgesia and surgical site infections after colorectal surgery: a retrospective cohort analysis
Gausan Ratna Bajracharya, Wael Ali Sakr Esa, Guangmei Mao, Steve Leung, Barak Cohen, Kamal Maheshwari, Hermann P. Kessler, Emre Gorgun, Daniel I. Sessler, Alparslan Turan
- 16 Implementation of an ERAS program in patients undergoing thoracic surgery at a third-level university hospital: an ambispective cohort study
Soledad Bellas-Cotán, Rubén Casans-Francés, Cristina Ibáñez, Ignacio Muguruza, Luis E. Muñoz-Alameda
- 25 Association between enhanced recovery after surgery protocol compliance and clinical complications: a cohort study
Maria Ana Máximo, Daniel Santos, Afonso Félix-Oliveira, Marta Pereira, Cristina Carmona
- 36 Compliance with Enhanced Recovery After Surgery (ERAS) protocol recommendations for bariatric surgery in an obesity treatment center
Júlia Gonçalves Zandomenico, Fabiana Schuelter Trevisol, Jean Abreu Machado
- 42 Early versus late sphenopalatine ganglion block with ropivacaine in postdural puncture headache: an observational study
Nelson S. Santos, Joana M. Nunes, Maria L. Font, Cristina Carmona, Maria M. Castro
- 46 Minimal fresh gas flow sevoflurane anesthesia and postoperative acute kidney injury in on-pump cardiac surgery: a randomized comparative trial
Eric Benedet Lineburger, Norma Sueli Pinheiro Módolo, Leandro Gobbo Braz, Paulo do Nascimento Junior
- 54 Early mobilization after total hip or knee arthroplasty: a substudy of the POWER.2 study
Javier Ripollés-Melchor, César Aldecoa, Raquel Fernández-García, Marina Varela-Durán, Norma Aracil-Escoda, Daniel García-Rodríguez, Lucia Cabezudo-de-la-Muela, Lucía Hormaechea-Bolado, Beatriz Nacarino-Alcorta, Rolf Hoffmann, Juan V. Lorente, José M. Ramírez-Rodríguez, Ane Abad-Motos, on behalf of The POWER2 Study Investigators Group for the Spanish Perioperative Audit and Research Network (RedGERM-SPARN)

-
- 72 Bilateral versus unilateral erector spinae plane block for postoperative analgesia in laparoscopic cholecystectomy: a randomized controlled study**
Sevim Cesur, Hadi Ufuk Yörükoglu, Can Aksu, Alparslan Kuş

-
- 78 Inkk Trial – Intraoperative ketamine for perioperative pain management following total knee endoprosthetic replacement in oncology: a double-blinded randomized trial**
V. Susan Paulin, Sumitra G Bakshi, Prateek C. Hegde, Akanksha Rathod, Ashish Gulia, Ajeeta M. Kulkarni, Vincent S. Paramanandam

-
- 85 Effect of preoperative anxiety level on postoperative pain, analgesic consumption in patients undergoing laparoscopic sleeve gastrectomy: an observational cohort study**
Yonca Ozvardar Pekcan, Bahattin Tuncali, Varlık Erol

Systematic Reviews

- 91 Impact of topical airway anesthesia on immediate postoperative cough/bucking: a systematic review and meta-analysis**
Thiago Mamoru Sakae, Renato Lucas Passos de Souza, Julio Cesar Mendes Brandão

Case Reports

- 101 Bradycardia in a pediatric population after sugammadex administration: case series**
Erica Viviana Guimarães Carvalho, Sandra Maria Carvalho Caldas, Dinis Fernando Pereira Pinheiro Machado da Costa, Cristina Maria Graça Peixoto Gomes
- 104 Debridement of axillary necrotizing fasciitis under anesthetic blocks of the serratus plane and supraclavicular brachial plexus: a case report**
Leonardo Saraiva Guimarães de Oliveira, Renata de Andrade Chaves
- 108 It's not always postdural puncture headache: a case report and note to the astute anesthesiologist**
Ejaz Khan, Rovnat Babazade, Mohamed Ibrahim, Michelle Simon, Lindsay Juarez, Mandonca Roni, Vadhera Rakesh
- 112 Transient median nerve palsy following ultrasound-guided subscapularis plane block: a case report**
Syahrul Mubarak Danar Sumantri, Anna Surgeon Veterini

Letters to the Editor

- 115 The anesthesiologist thoughts on medical residency in anesthesiology in Brazil**
João S. Castedo, Vanessa Henriques Carvalho
- 117 Factors associated with medical errors in perioperative anesthetic practice: cross-sectional study**
João Marcos do Oliveira Junior, Lauro Ferreira dos Santos Neto, Tiago Braga Duarte, Bruno Mendes Carmona, Luís Vinícius Pires da Costa, Daniela Ferreira Tramontin, Deivid Ramos dos Santos, Lauriana Marques Corrêa
- 120 Burnout risk among anesthesiology residents in Brazil during the second wave of COVID-19: a cross-sectional survey**
Natanael Pietroski dos Santos, Luisa Emanuela Biseo Henriques, Rafael Pivovar De Camargo Rosa, Rebecca Midory Marques Monteiro, Rafael Vicente Sanches Gonçalves, José Carlos Canga, Desiré Carlos Callegari, Esther Alessandra Rocha



EDITORIAL

The impact of anesthesia on postoperative outcomes: the effect of regional anesthesia on the incidence of surgical site infections



Surgical site infections (SSI) are a major contributor to morbidity and mortality in the postoperative care. Current data suggest that SSI are responsible for about 20% of all health-care-associated infections.^{1,2} Importantly, deep surgical site infections are strongly associated with a prolonged hospitalization, significant increase in costs, and poor outcomes, representing a considerable burden for patients and healthcare systems.³

The overall management of SSI comprises prevention, adequate differential diagnosis, and appropriate early treatment as well a rigorous follow-up. Prevention of surgical infection relies on optimization of patient factors and use of a variety of evidence-based pharmacologic and nonpharmacologic measures. Clinical practice guidelines for perioperative antimicrobial prophylaxis are widely available and applied everywhere.⁴ Nevertheless, SSI will continue to impact morbidity and mortality in both hospital and outpatient settings.

In the last few decades, regional anesthesia has gained momentum as an effective strategy to improve perioperative analgesia and potentially changing relevant postoperative outcomes. Previous studies suggested that regional anesthesia might minimize the risk of postoperative SSI and cancer recurrence, subsequently providing the benefits to both short- and long-term outcomes.⁵ There is strong evidence that the avoidance of allogeneic blood transfusion and implementation of an adequate perioperative blood glucose control are all effective measures that reduce postoperative infection rates.⁶ However, significant controversy exists regarding the effects of a high versus a low intraoperative fraction of inspired oxygen (FiO_2) on postoperative SSI in adults undergoing general anesthesia. A recent systematic review has shown that a high FiO_2 did not improve outcomes including surgical site infections, length of stay, or mortality in patients undergoing general anesthesia for non-cardiac surgery.⁷

Previous findings have indicated that regional anesthesia may reduce postoperative infectious complications in several clinical settings. For instance, a recent meta-analysis

has shown that regional anesthesia is associated with a lower incidence of sepsis in vascular patients.⁸ In orthopedic surgery, previous findings based on observational studies have supported the overall beneficial effects of regional anesthesia in decreasing the development of SSI after both knee and hip arthroplasties.⁹ Additionally, a comprehensive systematic review has demonstrated that epidural analgesia reduced the odds of pneumonia after abdominal and thoracic surgery, although this benefit was weak in larger studies.¹⁰ However, further studies were unable to show association of regional analgesia with postoperative infectious complications in abdominal surgeries.^{11,12} In fact, considering all available evidence, clinical data underlying the potential role of regional anesthesia in reducing postoperative infections complications is still controversial and further studies are warranted.

In this issue of the *Brazilian Journal of Anesthesiology*, an interesting, relevant and well-designed retrospective study from the Department of Outcomes Research at Cleveland Clinic provides new insights into the potential effects of regional anesthesia on postoperative infectious complications. In this study, Bajracharya et al.¹³ compared the incidence of a composite of serious infections after colorectal surgery in patients who received postoperative regional analgesia (epidural or transversus abdominis plane blocks) or patient-controlled intravenous analgesia with opioids (IV-PCA). The outcome was defined as a composite of in-hospital serious infections, including intra-abdominal abscess, pelvic abscess, deep or organ-space SSI, clostridium difficile, pneumonia, or sepsis. In their analysis, authors matched 681 regional anesthesia patients to 2862 IV-PCA only patients based on propensity scores derived from potential confounding factors. This study suggests that regional analgesia is not significantly associated with a reduced incidence of postoperative serious infection (odds ratio: 1.14; 95% Confidence Interval 0.87–1.49). Of note, authors observed a weak association of postoperative opioid consumption with serious

infectious complications. Interestingly, considering the use of epidural and systemic opiates, at least in this patient population, regional anesthesia did not reduce the total opioid dose administered to patients perioperatively. Conceivably, future prospective studies could implement more effective opioid-sparing strategies of regional anesthesia, investigating the potential benefits of this approach in the incidence of infections complications after surgery.

It is important to point out that the study design influences the results and hence the quality of the evidence produced. Ideally, determining the risk for each patient or groups of patients should integrate sample selection. The higher the patient's risk the greater the chance for a therapeutic intervention to show positive results (lower Number Needed to Treat). Patients at low or no risk are less likely to develop an outcome and therefore less likely to benefit from the intervention. This issue could have played a role in the negative findings observed by Bajracharia et al.¹³ This is an important consideration to be made in the evaluation of the evidence produced by large observational studies, where additional efforts are needed to identify patients at higher risk of a specific clinical outcome.

Although the number of patients included in the study conducted by Bajracharia et al¹³ is expressive and undoubtedly the results obtained add relevant evidence to the field, a retrospective cohort study brings the inconvenience of multiple biases. It is important that the question raised by the study be evaluated from the perspective of a randomized and controlled trial, where such confounding factors could be minimized. Alternatively, the use of large databases and the technology present in several hospitals can help (albeit retrospectively) in the detection of factors associated with relevant outcomes.¹⁴

In summary, current evidence is still equivocal regarding the effects of anesthesia techniques and SSI. In this context, the study of Bajracharya et al.¹³ reinforces the rationale that regional analgesia techniques should not be selected as a measure to reduce postoperative infections. However, clinical evidence is still growing in this area and new prospective clinical trials, observational studies and systematic reviews are still expected in the near future to further investigate the impact of anesthesia techniques, especially regional anesthesia, on important patient-centered outcomes such as SSI and other postoperative infectious complications.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Mellinghoff SC, Otto C, Cornely OA. Surgical site infections: current management and role of new antibiotics. *Curr Opin Infect Dis.* 2019;32:517–22.
 - Leaper DJ, van Goor H, Reilly J, Petrosillo N, Geiss HK, Torres AJ, Berger A. Surgical site infection - a European perspective of incidence and economic burden. *Int Wound J.* 2004;11:247–73.
 - De Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. *Am J Infect Control.* 2009;37:387–97.
 - Bratzler DW, Dellinger EP, Olsen KM, et al. American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70:195–283.
 - Bugada D, Ghisi D, Mariano ER. Continuous regional anesthesia: a review of perioperative outcome benefits. *Minerva Anestesiol.* 2017;83:1089–100.
 - Kavanagh T, Buggy DJ. Can anaesthetic technique effect postoperative outcome? *Curr Opin Anaesthesiol.* 2012;25:185–98.
 - Høybye M, Lind PC, Holmberg MJ, et al. Fraction of inspired oxygen during general anesthesia for non-cardiac surgery: Systematic review and meta-analysis. *Acta Anaesthesiol Scand.* 2022;66:923–33.
 - Mufarrih SH, et al. A systematic review and meta-analysis of general versus regional anesthesia for lower extremity amputation. *J Vasc Surg.* 2022. <https://doi.org/10.1016/j.jvs.2022.10.005>. Online ahead of print.
 - Zorrilla-Vaca A, Grant MC, Mathur V, Li J, Wu CL. The impact of neuraxial versus general anesthesia on the incidence of postoperative surgical site infections following knee or hip arthroplasty: a meta-analysis. *Reg Anesth Pain Med.* 2016;41:555–63.
 - Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg.* 2008;143:990–9. discussion 1000.
 - Halabi WJ, Jafari MD, Nguyen VQ, et al. A nationwide analysis of the use and outcomes of epidural analgesia in open colorectal surgery. *J Gastrointest Surg.* 2013;17:1130–7.
 - Halabi WJ, Kang CY, Nguyen VQ, et al. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. *JAMA Surg.* 2014;149:130–6.
 - Bajracharya GR, Esa WAS, Mao G, et al. Regional analgesia and surgical site infections after colorectal surgery: a retrospective cohort analysis. *Braz J Anesthesiol.* 2023;73:10–5.
 - Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. *Postgrad Med J.* 2011;87:535–41.
- André P. Schmidt  a,b,c,d,e,f,* Clóvis T. Bevilacqua Filho 
^a Hospital de Clínicas de Porto Alegre (HCPA),
 Serviço de Anestesia e Medicina Perioperatória,
 Porto Alegre, RS, Brazil
^b Universidade Federal do Rio Grande do Sul (UFRGS),
 Instituto de Ciências Básicas da Saúde (ICBS),
 Departamento de Bioquímica, Porto Alegre, RS, Brazil
^c Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Santa Casa de Porto Alegre, Serviço de Anestesia,
 Porto Alegre, RS, Brazil
^d Hospital Nossa Senhora da Conceição,
 Serviço de Anestesia, Porto Alegre, RS, Brazil
^e Universidade Federal do Rio Grande do Sul (UFRGS),
 Faculdade de Medicina, Programa de Pós-graduação em
 Ciências Pneumológicas, Porto Alegre, RS, Brazil
^f Faculdade de Medicina da Universidade de São Paulo
 (FMUSP), Programa de Pós-Graduação em Anestesiologia,
 Ciências Cirúrgicas e Medicina Perioperatória, São Paulo,
 SP, Brazil
- * Corresponding author.
 E-mail: apschmidt@hcpa.edu.br (A.P. Schmidt).



ORIGINAL INVESTIGATION

Effect of seasons on delirium in postoperative critically ill patients: a retrospective analysis



Yuwei Qiu^{a,b,1}, Eva Rivas^{a,c,1}, Marianne Tanios  ^a, Roshni Sreedharan  ^d, Guangmei Mao^{a,e}, Ilker Ince  ^{a,f}, Ahmed Salih^a, Remie Saab  ^a, Jagan Devarajan^g, Kurt Ruetzler^{a,h}, Alparslan Turan  ^{a,h,*}

^a Cleveland Clinic, Anesthesiology Institute, Department of Outcomes Research, Cleveland, USA

^b Shanghai Jiao Tong University, Shanghai Chest Hospital, Department of Anesthesiology, Shanghai, China

^c Universidad de Barcelona, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Department of Anesthesiology, Barcelona, Spain

^d Cleveland Clinic, Anesthesiology Institute, Department of Intensive Care and Resuscitation, Cleveland, USA

^e Cleveland Clinic, Department of Quantitative Health Sciences, Cleveland, USA

^f Altinbas University, School of Medicine, Department of Anesthesiology and Reanimation, Bahcelievler Medical Park Hospital, Istanbul, Turkey

^g Medina Hospital, Cleveland Clinic, Anesthesiology Institute, Department of General Anesthesiology, Medina, USA

^h Cleveland Clinic, Anesthesiology Institute, Department of General Anesthesiology, Cleveland, USA

Received 23 June 2021; accepted 6 February 2022

Available online 17 February 2022

KEYWORDS

Postoperative
delirium;
Seasonal;
Surgical Intensive
care unit

Abstract

Background and objectives: Postoperative delirium is common in critically ill patients and is known to have several predisposing and precipitating factors. Seasonality affects cognitive function which has a more dysfunctional pattern during winter. We, therefore, aimed to test whether seasonal variation is associated with the occurrence of delirium and hospital Length Of Stay (LOS) in critically ill non-cardiac surgical populations.

Methods: We conducted a retrospective analysis of adult patients recovering from non-cardiac surgery at the Cleveland Clinic between March 2013 and March 2018 who stayed in Surgical Intensive Care Unit (SICU) for at least 48 hours and had daily Confusion Assessment Method Intensive Care Unit (CAM-ICU) assessments for delirium. The incidence of delirium and LOS were summarized by season and compared using chi-square test and non-parametric tests, respectively. A logistic regression model was used to assess the association between delirium and LOS with seasons, adjusted for potential confounding variables.

Results: Among 2300 patients admitted to SICU after non-cardiac surgeries, 1267 (55%) had post-operative delirium. The incidence of delirium was 55% in spring, 54% in summer, 55% in fall and 57% in winter, which was not significantly different over the four seasons ($p = 0.69$). The median

* Corresponding author.

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

¹ YQ and ER (Yuwei Qiu, Eva Rivas) contributed equally to this manuscript.

LOS was 12 days (IQR = [8, 19]) overall. There was a significant difference in LOS across the four seasons ($p = 0.018$). LOS during summer was 12% longer (95% CI: 1.04, 1.21; $p = 0.002$) than in winter.

Conclusions: In adult non-cardiac critically ill surgical patients, the incidence of postoperative delirium is not associated with season. Noticeably, LOS was longer in summer than in winter.

© 2022 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Delirium is characterized by acute change in mental status, including inattention and disorganized processing.¹ It is common in hospitalized patients, with a reported incidence of 11% to 43% in the postoperative population,² and affects up to 80% of critically ill patients.³ Postoperative delirium is independently associated with increased postoperative complications, which may lead to longer Intensive Care Unit (ICU) or hospital stay, and higher postoperative mortality.⁴⁻⁶

Postoperative delirium is a multifactorial cognitive dysfunction.⁷⁻⁹ Recently, it has been shown that even among healthy subjects, cognitive function, especially attention and executive processes, may peak in late summer and early fall, and decline in late winter and early spring, with a more dysfunctional pattern during winter.^{10,11} Furthermore, alteration in cognition was robustly associated with seasonal changes.¹¹⁻¹³ Two previous studies showed a seasonal effect on delirium incidence, with higher incidence in autumn-winter compared to summer months.^{14,15} However, these findings are limited to general medical patients, and the seasonal effect on delirium remains poorly understood in critically ill surgical patients.

Seasonal occurrence of cardiovascular, cerebrovascular, or infectious events, as well as seasonal rhythms in psychological state have been previously reported.¹⁶⁻¹⁹ The possible underlying mechanism of this seasonal influence may be related to changes in light-darkness cycle or lower-vitamin D levels in winter. Previous research also showed seasonal variation in hospitalization rate of patients with chronic conditions, namely longer LOS during winter months.²⁰ However, the influence of seasonal changes on LOS in surgical intensive care patients is unclear.

We therefore aimed to evaluate seasonality in the occurrence of delirium in critically ill non-cardiac surgical populations. Specifically, we tested the primary hypothesis that in surgical ICU patients, admission to ICU during the winter is associated with higher incidence of delirium compared to other seasons. Secondarily, we tested the hypothesis that admission to ICU during the winter is associated with longer hospital LOS. Lastly, we tested the seasonal influence on subtypes of delirium as exploratory outcome.

Methods

Subject selection

With local institutional review board approval (IRB #19-271), we conducted a retrospective analysis of adult patients

(18 years or older), who had elective non-cardiac surgery at Cleveland Clinic between March 21, 2013, and March 20, 2018. To limit bias and clarify the immediate postoperative period for critically ill patients, we included patients who were directly admitted to Surgical ICU (SICU) after surgery and remained in SICU for at least 48 hours and up to 5 days, with delirium assessment during the postoperative period. We excluded patients without any Confusion Assessment Method Intensive Care Unit (CAM-ICU) assessment, or with pre-existing encephalopathy, coexisting Alzheimer's disease, dementia, or other cognitive decline preoperatively, or those who had neurosurgical procedures. Patients admitted to SICU more than once were only evaluated for their first admission.

Exposure and outcome

We defined the exposure as the four seasons classified internationally in the Northern Hemisphere as Spring: from March 21st to June 20th; Summer: from June 21st to September 20th; Autumn: from September 21st to December 20th; and Winter: from December 21st to March 20th. On the basis of admission date, all cases were analyzed for seasonal and monthly variation.

Our primary outcome was the incidence of delirium, measured using CAM-ICU^{21,22} during the initial 5 postoperative days, at least once a day by well-trained nurses or physicians. Delirium was defined dichotomically by the presence of at least one positive CAM-ICU assessment accompanied by a Richmond Agitation-Sedation Scale (RASS) of -3 or greater.^{21,22} CAM-ICU assessments in the first 12-hours after surgery were excluded from the analysis as they might represent residual anesthetic effects.

Our secondary outcome was hospital Length Of Stay (LOS). Additionally, we assessed the seasonal influence on subtypes of delirium as exploratory outcome. We classified delirium events into three motoric subtypes: hypoactive (characterized by sedation, motor slowness, lethargy, and withdrawal from interactions), hyperactive (characterized by agitation, aggression, hallucinations, and disorientation), and mixed (fluctuation between hypoactive and hyperactive subtypes) by using CAM-ICU and RASS.^{23,24} Hypoactive delirium was defined as a positive CAM-ICU assessment associated with a daily RASS score of -3 to 0 points. Hyperactive delirium was defined as a positive CAM-ICU assessment associated with a daily RASS score of 1–4 points. Mixed delirium was defined as a positive CAM-ICU assessment associated with a daily RASS score that fluctuates between the hypoactive and hyperactive ranges.

Data collection

Data was retrospectively collected from Cleveland Clinic electronic medical records, the Perioperative Health Documentation System, including intraoperative information from the electronic anesthesia record keeping system, and ICU registry.

Statistical analysis

Primarily, the incidence of delirium was summarized by season and compared using Chi-Square test for overall pattern of seasonal differences. A logistic regression model was used to assess the association between delirium and seasons, adjusted for all the potential confounding variables listed in **Table 1**. The odds ratio of delirium in winter, compared to spring, summer and autumn was reported with a 95% Confidence Interval.

Secondarily, the LOS was summarized by season and compared using non-parametric test due to the non-normal distribution of the data. A linear model was used to assess the association between LOS and seasons, adjusted for the potential confounding variables. LOS was log transformed to meet the assumption of the linear regression model. Ratio of LOS comparing winter to spring, summer and autumn was reported with 95% Confidence Interval.

Additionally, we summarized the subtypes of delirium by seasons using the same method as for the primary outcome, among patients with available RASS assessments.

Moreover, to avoid geographical bias, we conducted a sensitivity analysis including only patients from Ohio.

History of anxiety, depression, psychoses, drug abuse, alcohol abuse, surgery duration, year of surgery, and the latitude of residency address were considered as potential confounders.

Sample size and power

We expected about 3,000 ICU patients eligible for this study from March 21, 2013, and March 20, 2018, based on a preliminary query from the electronic medical records. The incidence of delirium in ICU is about 50%. Thus, we would have 90% power at the 0.05 significance level to detect an odds ratio of 1.40 or higher between two seasons.

SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

In total, 2,300 patients admitted to SICU after non-cardiac surgeries were included in our study. Patient characteristics were summarized in **Table 1**. The average age was 62 (SD = 15) years, 45% females, about 50% of patients had an American Society of Anesthesiologists (ASA) physical status equal or greater than four, and the mean duration of surgery was about 7 hours. Patients' demographic characteristics, surgical variables, and perioperative management were comparable across the four seasons (**Table 1**).

Among the 2300 patients, 1267 (55%) had postoperative delirium. The distribution of eligible patients admitted to

Table 1 Patient characteristics (n = 2300).

	Spring (n = 570)	Summer (n = 574)	Fall (n = 609)	Winter (n = 547)
Age, years	62±15	62±14	61±15	62±14
Sex, female%	257 (45)	257 (45)	284 (47)	245 (45)
Charlson comorbidity index	3 [1,6]	3 [1,5]	3 [1,5]	3 [2,6]
ASA status, %				
I	20 (4)	16 (3)	15 (2)	17 (3)
II	249 (44)	238 (41)	274 (45)	251 (46)
III	290 (51)	307 (53)	314 (52)	268 (49)
IV	11 (2)	13 (2)	6 (1)	11 (2)
Disease history of				
Anxiety, %	79 (14)	94 (16)	103 (17)	99 (18)
Psychoses, %	30 (5)	25 (4)	33 (5)	22 (4)
Depression, %	101 (18)	116 (20)	97 (16)	93 (17)
Drug abuse, %	19 (3)	16 (3)	18 (3)	15 (3)
Alcohol abuse, %	35 (6)	37 (6)	40 (7)	21 (4)
Use of Benzos, %	94 (16)	88 (15)	94 (15)	75 (14)
Emergency surgery, %	154 (27)	163 (28)	163 (27)	161 (29)
Type of anesthesia				
General only	523 (92)	531 (93)	548 (90)	483 (88)
Other	47 (8)	43 (7)	61 (10)	65 (12)
Intraoperative information				
Surgery duration, h	6.7±4.0	7.1±5.4	7.1±4.2	7.0±4.0
Estimated blood loss, mL	350 [100–1500]	400 [100–1500]	500 [100–2000]	400 [100–1500]
Total blood given, mL	362 [0–1323]	335 [0–1387]	389 [0–1513]	345 [0–1208]
Total fluid, L	4.5 [2.5–6.8]	4.5 [2.4–7.2]	4.4 [2.5–7.0]	4.4 [2.5–7.0]
Use of urine catheter	10 (2)	6 (1)	20 (3)	11 (2)
APACHE 2 score	61 (24)	62 (25)	60 (25)	60 (23)

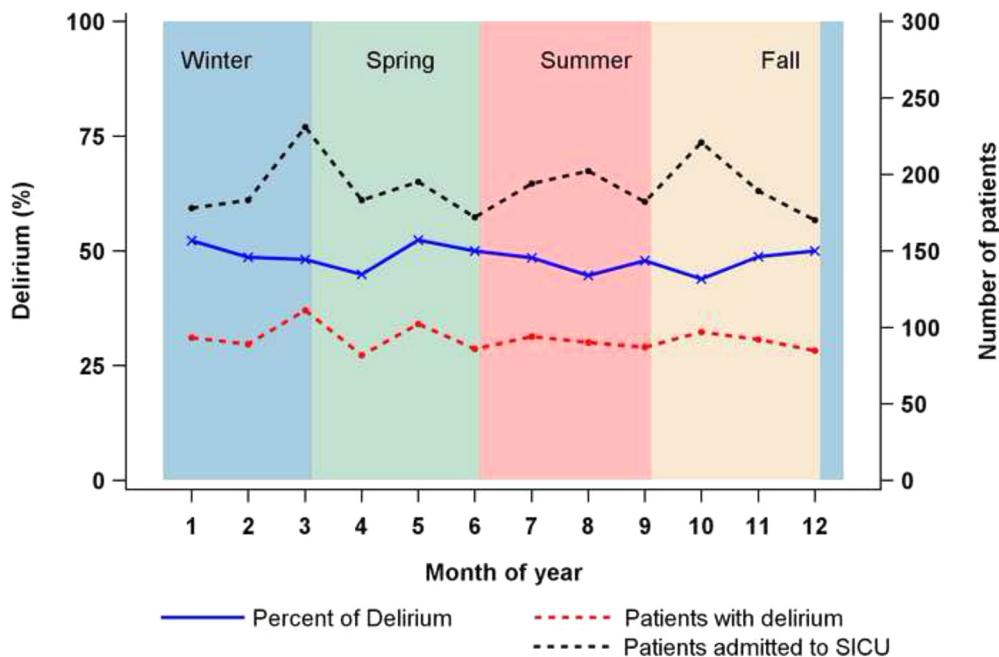


Figure 1 Dash lines show the total number of patients admitted to SICU (black color) and with delirium (red color). Continuous blue line represents the incidence (percentage) of patients with delirium. There are no differences of delirium among seasons (four different colors) nor months (x axis).

ICU and the number of patients who had delirium by month are presented in **Figure 1**.

According to the seasonal distribution, the incidence of delirium was 55% in spring, 54% in summer, 55% in fall and 57% in winter, which was not significantly different over the four seasons (Chi-Square $p = 0.69$). After adjusting for potential confounding variables, seasonal variation was still not associated with the odds of delirium (joint test $p = 0.81$). The odds ratio of delirium in spring, summer and fall compared to winter are presented in **Table 2**. The median length of delirium was 24 hours (IQR = [10, 76]) overall and it was not significantly different across the four seasons (Kruskal-Wallis $p = 0.50$).

To eliminate the geographic bias, we conducted a sensitivity analysis by including only patients from Ohio

($n = 1877$), and the result was consistent with the main analyses ($p = 0.39$). Furthermore, we identified the subtypes of delirium among 1104 patients with available RASS assessment and listed the incidence of each subtype in **Table 3**. The subtypes of delirium were not significantly different across the four seasons (Fisher exact test $p = 0.059$).

The overall median LOS was 12 days (IQR = [8, 19]). We found a marginally significant difference in LOS across the four seasons without adjustment (Kruskal-Wallis $p = 0.024$) and after adjusting for potential confounders ($p = 0.018$). The LOS during summer was 1 day longer (95% CI: 1.04, 1.21; $p = 0.002$) than in winter, adjusted for confounders (**Table 2**, **Fig. 2**).

Table 2 Adjusted difference in delirium and length of hospital stay by seasons ($n = 2300$).

	Summary	Estimated difference	<i>p</i>
Delirium incidence		Odds Ratio (95% CI)	
Winter	310 (57%)	ref	
Spring	313 (55%)	1.00 (0.79–1.28)	0.65
Summer	309 (54%)	0.97 (0.76–1.24)	0.96
Fall	335 (55%)	0.91 (0.71–1.15)	0.34
Delirium duration		Ratio of geometric means (95% CI)	
Winter	24 [8, 72]	ref	
Spring	28 [10, 78]	0.94 (0.77–1.15)	0.56
Summer	24 [12, 84]	0.95 (0.77–1.16)	0.61
Fall	24 [12, 60]	0.84 (0.68–1.03)	0.09
Length of hospital stay		Ratio of geometric means (95% CI)	
Winter	11 [8, 18]	ref	
Spring	12 [9, 18]	1.09 (1.02–1.18)	0.018
Summer	12 [9, 20]	1.12 (1.04–1.21)	0.002
Fall	11 [8, 19]	1.08 (1.01–1.16)	0.036

Table 3 Subtypes of delirium by seasons (n = 1104).

Subtypes	Spring (n = 278)	Summer (n = 274)	Fall (n = 282)	Winter (n = 270)
Hyperactive	121 (43%)	110 (40%)	106 (38%)	114 (42%)
Hypoactive	2 (1%)	8 (3%)	3 (1%)	0 (0%)
Mixed	155 (56%)	156 (57%)	173 (61%)	156 (58%)

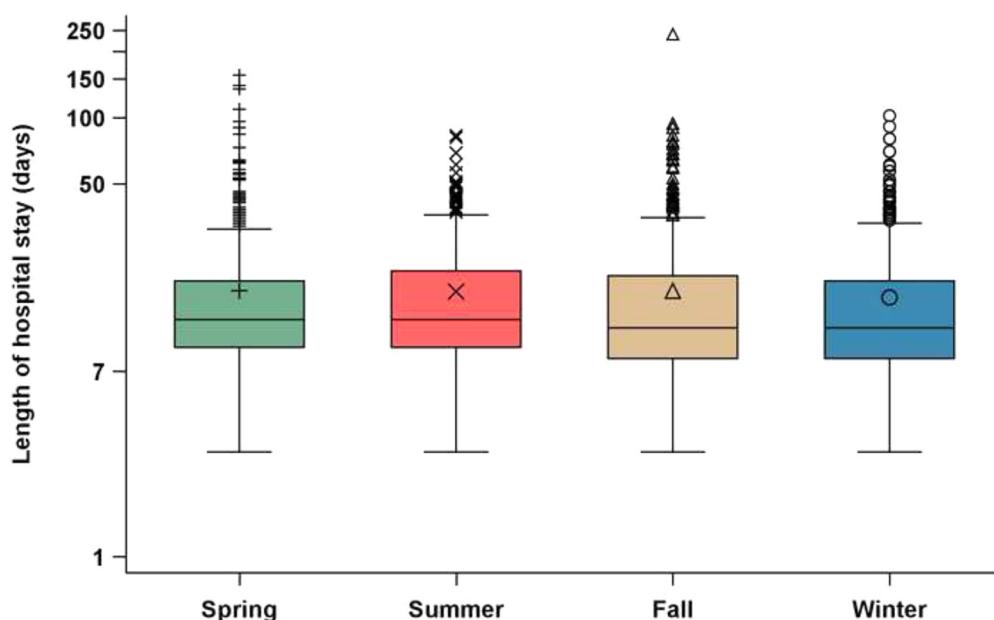
Discussion

In the current study, more than half of patients had postoperative delirium during their postoperative stay in the SICU. In contrast to our expectation, the incidence of postoperative delirium in critically ill patients was not significantly different across the four seasons. Even after adjusting for potential confounding variables and geographical location, seasonal variation was not associated with delirium incidence in this surgical population. Noticeably, hospital LOS was about one day longer in summer than in winter.

We found that the incidence of delirium in SICU is over 50%, which is consistent with previous studies.³ Critically ill surgical patients are at increased risk of delirium owing to the severity of illness, tissue damage associated with the surgical procedure, acute metabolic changes, advanced age, and comorbidities. Nevertheless, SICU-acquired delirium did not differ across the seasons. These results contrast with previous studies^{14,15,17,18} that showed a higher incidence of delirium during autumn and winter months. These inconsistencies may be explained by differences in study populations as previous studies were restricted to elderly¹⁸ and ICU¹⁷ medical patients with higher incidence in winter.^{14,15} Most of our patients had elective surgery. We did not find significant differences in admission rates to SICU along the year. Furthermore, patients' demographics and comorbidities were comparable over the four seasons. Gallegiani et al.¹⁴ investigated all admissions to medical intensive care units and found significant variability in cerebral

atherosclerosis or generalized ischemic disease over the year.¹⁴ However, they used discharge International Classification of Diseases and Related Health Problems (ICD-9) codes for delirium diagnosis rather than daily clinical assessments. ICD-9 coding was shown to have good specificity, but low sensitivity.²⁵ One of the main explanations of the seasonal effect on cognitive function is the association with sunlight exposure. Simons et al.²⁶ assessed whether the amount of sunlight exposure before medical ICU admission was associated with delirium during ICU stay. They assessed delirium incidence with CAM-ICU twice a day during ICU stay, and similarly to our results, they did not find a relationship between pre-admission sunlight exposure and the development of ICU-acquired delirium.²⁶

We found a significant difference in LOS across the four seasons, with LOS during the summer about 1 day longer than in the winter. This increment in summer morbidity has been previously reported and might partly be related to the beginning of a new academic year and therefore trainee inexperience.²⁷ The American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) data over a 3-year period showed worsen surgical morbidity and mortality in July, which contrasts with previously reported literature. In the general non-surgical populations, there is an increase in all-cause mortality during winter months. The underlying explanations may include seasonal variation in blood pressure, lipid levels, changes in activity of the coagulation cascade, and/or seasonal variation in the prevalence of viral or bacterial pneumonia.²⁷ Nevertheless, these

**Figure 2** Boxplot of length of stay in days over the four seasons.

factors do not seem to account for postsurgical morbidity.²⁷ In this setting, trainee inexperience and nurse staffing ratios, as well as the increased incidence of surgical site infections during the summer months, are the main potential factors affecting outcome.²⁸

Strengths and limitations

We selected the widely accepted CAM-ICU tool to diagnose postoperative delirium. This screening tool remains the most feasible test to detect delirium for well-trained nurses or physicians on site. To eliminate the residual effects of anesthetics, we excluded delirium assessments during the initial 12 postoperative hours, and we assessed delirium at least once daily. Moreover, we had robust power to detect seasonal changes in delirium after confounder adjustment, based on our sample size.

Our study has several limitations. The retrospective design is subject to unobserved confounding. Therefore, some bias may still exist even though we adjusted for many demographics and perioperative variables. Our study critically ill population did not include cardiothoracic surgery, vascular surgery, and pediatric patients. Thus, our result cannot be generalized to the entire surgical population. Eighteen of our 30 SICU beds are exposed to sunlight. However, it was not possible to assess delirium incidence according to sunlight exposure because patients often switch to other SICU beds during admission. Similarly, we were unable to adjust for opioid and sedative administration which may lead to delirium. Finally, we only considered overall delirium incidence as well as the type of delirium, but not the severity of delirium. Therefore, our results may be conservative.

Summary

We did not find an association between seasonal variation and occurrence of delirium in critically ill surgical patients. However, we found an association between seasonal variation and hospital length of stay.

Funding

This study was supported by internal funding of the Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA. None of the authors has a personal financial interest in this research.

Authorship

YQ, ER: study design, data collection, data interpretation, and manuscript writing; MA, RS, AS, RS, JD, II: data collection and manuscript review; GM: data analysis and interpretation; KR: data interpretation and manuscript writing; and AT: study design, data interpretation, and manuscript writing.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Delaney A HN, Litton E. Preventing delirium in the intensive care unit. *JAMA*. 2018;319:659–60.
- Bryson GL, Wyand A. Evidence-based clinical update: General anesthesia and the risk of delirium and postoperative cognitive dysfunction. *Can J Anesth*. 2006;53:669–77.
- Devlin JW, Brummel NE, Al-Qadheeb NS. Optimising the recognition of delirium in the intensive care unit. *Best Pract Res Clin Anaesthesiol*. 2012;26:385–93.
- Slooter AJC, Van De Luer RR, Zaal IJ. Handbook of clinical neurology. 2017;141:449–66.
- Salluh JIF, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2015;350:h2538.
- Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg*. 2011;112:1202–11.
- Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271:134–9.
- Densky J, Eskander A, Kang S, et al. Risk factors associated with postoperative delirium in patients undergoing head and neck free flap reconstructionpostoperative delirium in patients undergoing head and neck free flap reconstructionpostoperative delirium in patients undergoing head and neck free flap reconstruction. *JAMA Otolaryngology Head Neck Surg*. 2019;145:216–21.
- Moshed RA, Young JS, Safaei M, et al. Delirium risk factors and associated outcomes in a neurosurgical cohort: a case-control study. *World Neurosurg*. 2019;126:e930–6.
- Meyer C, Muto V, Jaspar M, et al. Seasonality in human cognitive brain responses. *Proc Natl Acad Sci U S A*. 2016;113:3066–71.
- Lim ASP, Gaiteri C, Yu L, et al. Seasonal plasticity of cognition and related biological measures in adults with and without Alzheimer disease: Analysis of multiple cohorts. *PLoS Med*. 2018;15:e1002647.
- Lyall LM, Wyse CA, Celis-Morales CA, et al. Seasonality of depressive symptoms in women but not in men: A cross-sectional study in the UK Biobank cohort. *J Affect Disord*. 2018;229:296–305.
- Wynchank DS, Bijlenga D, Lamers F, et al. ADHD, circadian rhythms and seasonality. *J Psychiatr Res*. 2016;81:87–94.
- Gallerani M, Manfredini R. Seasonal variation in the occurrence of delirium in patients admitted to medical units of a general hospital in Italy. *Acta Neuropsychiatrica*. 2013;25:179–83.
- Balan S, Leibovitz A, Freedman L, et al. Seasonal variation in the incidence of delirium among the patients of a geriatric hospital. *Arch Gerontol Geriatr*. 2001;33:287–93.
- Quraishi SA, Litonjua AA, Elias KM, et al. Association between pre-hospital vitamin D status and hospital-acquired new-onset delirium. *Br J Nutr*. 2015;113:1753–60.
- Abraha I, Trotta F, Rimland JM, et al. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP Series. *PLoS One*. 2015;10:e0123090.
- Hanazawa T, Asayama K, Watabe D, et al. Association between amplitude of seasonal variation in self-measured home blood pressure and cardiovascular outcomes: HOMED-BP (Hypertension Objective Treatment Based on Measurement By Electrical Devices of Blood Pressure) Study. *J Am Heart Assoc*. 2018;7:e008509.
- Abbasi J. Is There a Seasonal Influence on Cognition and Demenia? *JAMA*. 2018;320:1848–9.

20. Argha A, Savkin A, Liaw S-T, Celler BG. Effect of seasonal variation on clinical outcome in patients with chronic conditions: analysis of the Commonwealth Scientific and Industrial Research Organization (CSIRO) National Telehealth Trial. *JMIR Med Inform.* 2018;6:e16.
21. Jones RN, Cizginer S, Pavlech L, et al. Assessment of instruments for measurement of delirium severity: a systematic review assessment of instruments for measurement of delirium severity assessment of instruments for measurement of delirium severity. *JAMA Internal Medicine.* 2019;179:231–9.
22. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA.* 2001;286:2703–10.
23. Krewulak KD, Stelfox HT, Leigh JP, Ely EW, Fiest KM. Incidence and prevalence of delirium subtypes in an adult icu: a systematic review and meta-Analysis*. *Crit Care Med.* 2018;46:2029–35.
24. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc.* 2006;54:479–84.
25. Romano PS CB, Schembri ME, Rainwater JA. Can administrative data be used to compare postoperative complication rates across hospitals? *Med Care.* 2002;40:856–67.
26. Simons KS, Workum JD, Slooter AJC, van den Boogaard M, van der Hoeven JG, Pickkers P. Effect of preadmission sunlight exposure on intensive care unit–acquired delirium: A multicenter study. *J Crit Care.* 2014;29:283–6.
27. Englesbe MJ PS, Magee JC, Gauger P, et al. Seasonal variation in surgical outcomes as measured by the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP). *Ann Surg.* 2007;246:456–62.
28. Malik AT JN, Scharschmidt TJ, Mayerson JL, Khan SN. Factors associated with post-operative sepsis following surgery for spinal tumors: An analysis of the ACS-NSQIP database. *Clin Neurol Neurosurg.* 2018;172:1–7.



ORIGINAL INVESTIGATION

Regional analgesia and surgical site infections after colorectal surgery: a retrospective cohort analysis



Gausan Ratna Bajracharya ^{a,b}, Wael Ali Sakr Esa ^{a,b}, Guangmei Mao ^{a,c}, Steve Leung ^{a,d}, Barak Cohen ^{a,e}, Kamal Maheshwari ^{a,b}, Hermann P. Kessler ^f, Emre Gorgun ^f, Daniel I. Sessler ^a, Alparslan Turan ^{a,b,*}

^a Cleveland Clinic, Anesthesiology Institute, Department of Outcomes Research, Cleveland, USA

^b Cleveland Clinic, Anesthesiology Institute, Departments of General Anesthesia, Cleveland, USA

^c Cleveland Clinic, Departments of Quantitative Health Science, Cleveland, USA

^d Metro Health, Department of Radiology, Cleveland, USA

^e Tel-Aviv University, Sackler Faculty of Medicine, Tel-Aviv Medical Center, Division of Anesthesia, Critical Care, and Pain Management, Tel-Aviv, Israel

^f Cleveland Clinic, Department of Colorectal Surgery, Cleveland, USA

Received 8 October 2021; accepted 15 June 2022

Available online 5 July 2022

KEYWORDS

Regional analgesia;
Analgesia, patient-controlled;
Colorectal surgery;
Opiate alkaloids;
Surgical wound infection;
Sepsis

Abstract

Background: The effect of regional analgesia on perioperative infectious complications remains unknown. We therefore tested the hypothesis that a composite of serious infections after colorectal surgery is less common in patients with regional analgesia than in those given Intravenous Patient-Controlled Analgesia (IV-PCA) with opiates.

Methods: Patients undergoing elective colorectal surgery lasting one hour or more under general anesthesia at the Cleveland Clinic Main Campus between 2009 and 2015 were included in this retrospective analysis. Exposures were defined as regional postoperative analgesia with epidurals or Transversus Abdominis Plane blocks (TAP); or IV-PCA with opiates only. The outcome was defined as a composite of in-hospital serious infections, including intraabdominal abscess, pelvic abscess, deep or organ-space Surgical Site Infection (SSI), clostridium difficile, pneumonia, or sepsis. Logistic regression model adjusted for the imbalanced potential confounding factors among the subset of matched surgeries was used to report the odds ratios along with 95% confidence limits. The significance criterion was $p < 0.05$.

Results: A total of 7811 patients met inclusion and exclusion criteria of which we successfully matched 681 regional anesthesia patients to 2862 IV-PCA only patients based on propensity scores derived from potential confounding factors. There were 82 (12%) in-hospital postoperative serious infections in the regional analgesia group vs. 285 (10%) in IV-PCA patients. Regional analgesia was not significantly associated with serious infection (odds ratio: 1.14; 95%

* Corresponding author.

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

Confidence Interval 0.87–1.49; *p*-value = 0.339) after adjusting for surgical duration and volume of intraoperative crystalloids.

Conclusion: Regional analgesia should not be selected as postoperative analgesic technique to reduce infections.

© 2022 Published by Elsevier Editora Ltda. 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

Serious infections are a major source of morbidity and increased healthcare costs, especially deep surgical site infections, intra-abdominal and pelvic abscesses, pulmonary infections, and sepsis. These infections are common after colorectal surgery.^{1–5} In 2017, more than one-third of deep or organ space infections in patients undergoing surgeries in acute care hospitals occurred after colorectal surgery.⁶

Low tissue perfusion is an important risk factor for post-surgical infections. Regional blocks have been shown to improve tissue perfusion by enhancing peripheral blood flow,^{7–11} thereby enhancing delivery of essential nutrients to healing wounds and deprived tissues. Increased tissue perfusion with epidural anesthesia even extended beyond the dermatomal levels of the block.¹² Additionally, regional blocks have shown to reduce inflammation as well as plasma norepinephrine levels which may influence wound repair by affecting microcirculation.^{13–17} Regional blocks could also indirectly reduce infections by sparing opioids which appear to promote infections in both surgical and non-surgical patients.^{18–23} There is conflicting evidence regarding protective effects of regional analgesia on infectious complications. A meta-analysis of fifty-eight trials²⁴ showed that epidural analgesia reduced the odds of pneumonia after abdominal and thoracic surgery. However, this association was weak in patients using intravenous patient-controlled analgesia and in larger studies. Further studies^{25–27} were unable to show association of regional analgesia with post-operative infectious complications like pneumonia, sepsis, and wound complications in abdominal surgeries.

We therefore tested the primary hypothesis that a composite of serious infections after colorectal surgery is less common in patients who received post-operative regional analgesia compared to patient-controlled intravenous analgesia with opioids. Secondarily, we tested the hypothesis that the overall postoperative opioid consumption during the initial 72 postoperative hours is associated with a composite of serious infections.

Methods

Use of de-identified registry data with waived consent was approved by the Cleveland Clinic Institutional Review Board, Cleveland, Ohio. Our retrospective cohort study included patients who had elective open or laparoscopic colorectal surgery lasting longer than one hour with general anesthesia at the Cleveland Clinic Main Campus between 2009 and 2015.

We excluded patients with pre-existing infections, a history of chronic pain conditions, or who were on long-term

opioid therapy. We also excluded patients with missing data regarding exposure and confounding factors.

Postoperative analgesic technique

We compared patients who received regional analgesia, including epidurals or Transversus Abdominis Plane (TAP) blocks (regional analgesia group), to the patients who received only Intravenous Patient-Controlled Analgesia (IV-PCA group). Epidural catheters were inserted preoperatively, but infusions were initiated postoperatively, typically in the postanesthesia care unit (PACU). Epidural solutions typically contained a mixture of local anesthetics and opioids, usually bupivacaine 0.1% and fentanyl 2 µg·mL^{−1}. TAP blocks were performed with injection of long-acting local anesthetics, either as a single injection or by continuous infusion. Patients who received regional analgesia, but then had IV-PCA started within 4 hours after surgery and lasting at least 4 hours were assumed to have had failed blocks and were included into the IV-PCA group. Exposure analysis was restricted to the initial 72 postoperative hours.

Outcomes

Data were obtained from the Cleveland Clinic Perioperative Health Documentation System, EPIC electronic medical records, and the Colorectal Registry. Serious infections were defined as at least one of the following postoperative complications: intra-abdominal abscess, pelvic abscess, deep or organ-space Surgical Site Infection (SSI), clostridium difficile, pneumonia, or sepsis within 30 days after surgery.

Statistical analysis

To account for potential confounding due to systematic differences between study groups, we matched each patient with regional analgesia to five patients with IV-PCA-only on baseline demographic, morphometric, and the pre-surgical and intraoperative variables listed in Table 1. For analysis purposes, types of surgeries derived from Current Procedural Terminology (CPT) codes were collapsed into four main categories: 1) Colostomy or colorectal resection; 2) Ileostomy, small bowel resection and other enterostomy; 3) Lysis of adhesions; and 4) Other procedures.

Matching was implemented on the basis of the propensity score (i.e., the estimated probability of regional analgesia, as a function of the potential confounding variables) using a greedy distance-based matching algorithm. Propensity score was estimated with a multivariable logistic regression. We required an exact match on surgical category and propensity scores within 0.2 standard deviations of the propensity score logits. Balance between the two study groups on baseline and

Table 1 Patient characteristics.

Factor	Before Matching			After Matching		
	Regional (n = 684)	PCA (n = 7127)	ASD	Regional (n = 681)	PCA (n = 2862)	ASD
Age (years)	51 ± 16	53 ± 17	0.15	51 ± 16	51 ± 17	-0.00
Female (%)	354 (52)	3609 (51)	0.02	353 (52)	1479 (52)	0.00
BMI ($\text{kg} \cdot \text{m}^{-2}$)	27 ± 6.4	27 ± 6.3	0.04	27 ± 6.4	27 ± 6.7	0.01
Charlson Score	1.6 ± 2.2	1.6 ± 2.2	0.01	1.6 ± 2.2	1.5 ± 2.2	0.03
ASA (%)			0.24			0.06
I	2 (0.3)	83 (1)		2 (0.3)	19 (0.7)	
II	231 (34)	3133 (44)		230 (34)	1036 (36)	
III	401 (59)	3564 (50)		399 (59)	1610 (56)	
IV-V	50 (7)	347 (5)		50 (7)	197 (7)	
Preoperative medication						
Steroid (%)	201 (29)	2024 (28)	0.02	201 (30)	875 (31)	0.02
Immunosuppressive drug (%)	21 (3)	236 (3)	0.01	21 (3)	89 (3)	0.00
Comorbidities						
Diabetes w/o chronic complications (%)	75 (11)	865 (12)	0.04	75 (11)	309 (11)	0.01
Peripheral vascular disease (%)	42 (6)	382 (5)	0.03	42 (6)	180 (6)	0.01
Coagulopathy (%)	67 (10)	447 (6)	0.13	65 (10)	250 (9)	0.03
Obesity (%)	146 (21)	1204 (17)	0.11	145 (21)	565 (20)	0.04
Other neurological disorders (%)	37 (5)	296 (4)	0.06	37 (5)	131 (5)	0.04
Metastatic cancer (%)	64 (9)	586 (8)	0.04	63 (9)	235 (8)	0.04
Congestive heart failure (%)	20 (3)	250 (4)	0.03	20 (3)	89 (3)	0.01
Valvular disease (%)	26 (4)	281 (4)	0.01	26 (4)	112 (4)	0.00
Hypertension (%)	235 (34)	2680 (38)	0.07	235 (35)	958 (33)	0.02
Renal failure (%)	31 (5)	319 (4)	0.00	31 (5)	131 (5)	0.00
Liver disease (%)	19 (3)	178 (2)	0.02	19 (3)	80 (3)	0.00
Solid tumor w/out metastasis (%)	111 (16)	1577 (22)	0.15	111 (16)	469 (16)	0.00
Deficiency anemias (%)	167 (24)	1409 (20)	0.11	167 (25)	671 (23)	0.03
Drug abuse (%)	23 (3)	91 (1)	0.14	23 (3)	63 (2)	0.07
Psychosis (%)	43 (6)	262 (4)	0.12	42 (6)	151 (5)	0.04
Depression (%)	164 (24)	1095 (15)	0.22	164 (24)	628 (22)	0.05
Surgery duration (minute)	281 (203,376)	237 (173,310)	0.38	281 (203,374)	255 (180,343)	0.21
Laparoscopic surgery (%)	47 (7)	2611 (37)	0.77	47 (7)	238 (8)	0.05
Surgery types (%)			0.35			0.07
Colostomy or colorectal resection	339 (50)	4719 (66)		338 (50)	1516 (53)	
Ileostomy, small bowel resection and other enterostomy	120 (18)	704 (10)		118 (17)	458 (16)	
Lysis of adhesions	33 (5)	247 (3)		33 (5)	133 (5)	
Other procedures	192 (28)	1457 (20)		192 (28)	755 (26)	
Intraoperative information						
Opioids amount – iv morphine equivalent mg	28 (20,38)	30 (22,38)	0.06	28 (20,38)	30 (22,38)	0.05
Acetaminophen use (%)	16 (2)	143 (2)	0.02	16 (2)	63 (2)	0.01
Hypotension (%)	235 (34)	2506 (35)	0.02	235 (35)	980 (34)	0.01
Estimated blood loss (mL)	200 (75,400)	110 (50,275)	0.30	200 (75,400)	200 (50,350)	0.10
Crystalloids (L)	3.2 (2.0,4.3)	2.8 (2.0,3.7)	0.30	3.2 (2.3,4.20)	3.0 (2.0,4.00)	0.16
Colloids (mL)	0 (0.750)	0 (0.500)	0.18	0 (0.750)	0 (0.500)	0.06
Transfusion	105 (15)	611 (9)	0.21	103 (15)	363 (13)	0.07

Summary statistics are presented as means ± standard deviations, medians (Q1, Q3), or n (%) as appropriate. PCA, Patient Controlled Analgesia; ASD, Absolute Standardized Difference; ASA, American Society of Anesthesiologists physical status; Absolute standardized difference defined as the absolute difference between groups divided by the pooled standard deviation. Variables with an ASD > 0.10 are defined as imbalanced between groups.

intraoperative potential confounding variables was assessed before and after matching using Absolute Standardized Differences (ASDs), defined by the absolute difference between means, mean rankings, or proportions divided by a combined estimate of standard deviation. We considered an ASD > 0.1 after matching as indicative of potential residual confounding and subsequently adjusted for such factors directly in the primary analysis comparing the groups on outcomes.

To assess the adjusted association between postoperative analgesic technique (regional analgesia vs. IV-PCA only) and the composite outcome of serious infections, we used a logistic regression model adjusted for the imbalanced potential confounding factors, if any, among the subset of matched surgeries. The odds ratios (odds of having serious infection with regional analgesia over with IV-PCA-only approach) along with 95% confidence limits were reported. Secondarily, we assessed the association between overall postoperative opioid consumption during the initial 72 postoperative hours and the composite of serious infections in a multivariable logistic regression model.

The significance criterion was $p < 0.05$ for primary and secondary outcomes. All statistical tests were two-tailed.

Power considerations

We planned to retrieve records from approximately 10,000 patients in the colorectal registry. The infection rate for major colorectal surgery at the Cleveland Clinic is about 15%. A 20% reduction in infections would most certainly be clinically important. Assuming 20% of patients received regional anesthesia, we anticipated having approximately 9000 matched patients in total (1500 with regional analgesia and 7500 with IV-PCA only). With a type I error rate of 5%, we would have 80% power to detect an odds ratio of 0.8 (or smaller) for collapsed composite infectious complications comparing the regional analgesia group and PCA-only group.

In fact, there were fewer patients than expected who had regional analgesia. A post-hoc power estimation showed that we had 80% power to detect an Odds Ratio of 0.7 (or smaller) for postoperative serious infection in 681 patients in the regional analgesia group, and 2682 matched only patients in the IV-PCA group.

Results

We identified 7811 patients who met inclusion and exclusion criteria (Fig. 1), including 684 (9%) who had regional anesthesia and 7127 (91%) who had IV-PCA. In the regional anesthesia group, 125 patients had TAP blocks, 552 patients had epidural, and 7 patients had both. Seventy-nine patients who had failed epidurals, 134 patients who had failed TAP blocks, and one who failed both epidural and TAP blocks were considered to be in the IV-PCA group. We successfully matched 681 regional anesthesia patients to 2862 IV-PCA patients based on propensity scores derived from all potential confounding factors listed in Table 1. The balance of confounding variables among matched patients was much better than before matching, but surgery duration and intraoperative volume of crystalloids administered still had ASD > 0.1 (Table 1).

Within the matched groups of patients, there were 82 (12%) in-hospital serious postoperative infections in the

regional anesthesia group vs. 285 (10%) in the IV-PCA group. Regional analgesia was not significantly associated with serious infection (OR = 1.14; 95% CI 0.87–1.49; $p = 0.339$), after adjusting for surgical duration and volume of intraoperative crystalloids (Table 2).

We further compared opioid consumption within the matched pairs of patients. The median total amount of postoperative morphine equivalent consumption during the initial 72 postoperative hours was 169 mg ([Q1, Q3] = [97, 313]) in patients given regional analgesia vs. 202 mg ([Q1, Q3] = [109, 342]) in the PCA group (p -value = 0.005). After excluding postoperative epidural opioids, the median total amount of opioid consumption in 72 hours was 79 (25, 230) mg IV morphine equivalents in the regional analgesia group and 198 (107, 340) mg in the PCA group. Opioid consumption was therefore significantly lower in the regional analgesia group than the PCA group (p -value < 0.001).

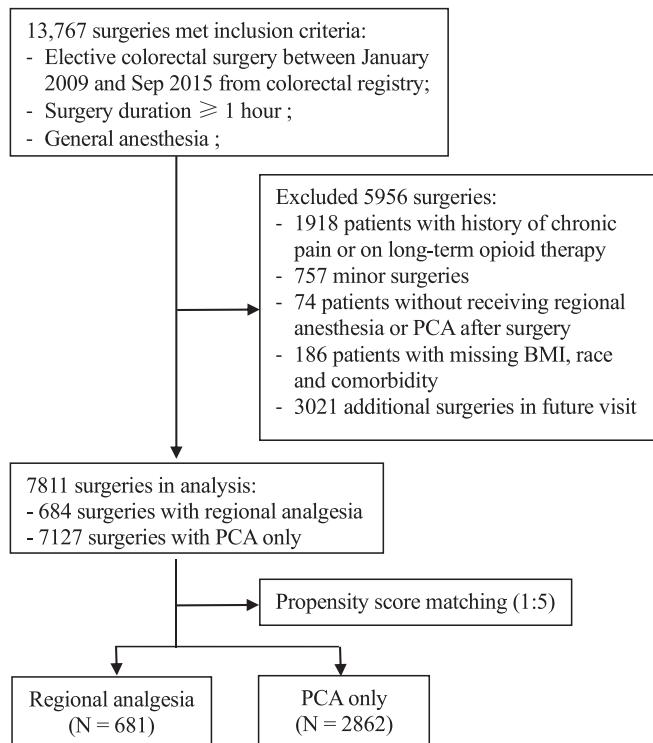
Among all eligible patients, including both PCA and regional analgesia, increase in postoperative opioid consumption was significantly associated with higher odds of serious infection. The estimated odds ratio related with a 50-mg increase in morphine equivalent opioid consumption was 1.03 (97.5% CI 1.01, 1.05; $p = 0.002$), adjusted for all confounding variables listed in Table 1.

Discussion

We did not observe an association between postoperative regional analgesia and a composite of serious infectious complications compared to patient-controlled analgesia with opioids. Our findings extend previous work by Park et al.²⁵ who studied the effect of epidural analgesia on perioperative outcomes in a randomized trial of 1021 patients having intra-abdominal surgery. There was no difference in the incidence of pneumonia and sepsis in patients given general anesthesia and postoperative analgesia with parenteral opioids compared with epidural analgesia. Recent analyses of the Healthcare Cost and Utilization Project Nationwide Inpatient Sample evaluated associations between epidural analgesia and postoperative outcomes in patients who had open²⁶ and laparoscopic²⁷ colorectal surgery. These retrospective studies were unable to identify associations between epidural analgesia and postoperative pneumonia, anastomotic leak, or wound complications.

We observed a weak association of postoperative opioid consumption with serious infectious complications which might not be clinically important. A 50-mg increase in intravenous morphine equivalents was associated with 3% increase in the odds of serious infectious complications, roughly equivalent to a quarter percent increase in the absolute difference of incidence. Patients given postoperative regional analgesia used similar amounts of total opioids when including epidural opiates, i.e., despite reducing the use of IV and PO opioids, the use of regional analgesia did not significantly reduce total opioid use.

The CPT coding for procedures used for our analysis limited our ability to further classify and match procedures based upon their complexity. Regional analgesia is most likely to be offered to patients having larger and more complex surgery who will presumably have more pain. These patients are also most likely to develop infections. Although our analysis was

**Figure 1** Study flow diagram.

adjusted for duration of surgeries, there could be other attributes of surgical complexity which remained unadjusted, resulting in unobserved confounding which might have diminished putative benefit from regional analgesia. Our analysis included surgeries conducted in our hospital across 6 years during which collateral changes in infection prevention protocols, surgical teams, perioperative pain management strategies, as well as changing trends of utilization of regional analgesia as primary postoperative pain management modalities have been apparent. These, in addition to other unknown confounders, may have affected the results of our analysis.

In conclusion, our analysis demonstrated that the use of regional analgesic techniques was not associated with lower risk of postoperative serious infections, compared with

patient-controlled analgesia with opioids. However, opioid consumption after colorectal surgery was associated with a small increase in the odds of serious infection. Hence, regional analgesia should not be selected as postoperative analgesic technique to reduce infections.

Glossary of terms

IV-PCA, Intravenous Patient Controlled Analgesia; TAP, Transversus Abdominis Plane; PACU, Post Anesthesia Care Unit; SSI, Surgical Site Infections; ASD, Absolute Standardized Differences; Q1, First Quartile; Q3, Third Quartile; CI, Confidence Interval; CPT, Current Procedural Terminologies.

Table 2 Association between regional analgesia vs. PCA only and postoperative serious infection after colorectal surgery.

Outcome	Incidence – n (%)		Odds ratio (95% CI) ^a (Regional vs. PCA)	p-value ^b
	Regional (n = 681)	PCA only (n = 2862)		
Serious infection	82 (12.0)	285 (10.0)	1.14 (0.87, 1.49)	0.339
Abscess – Intra-abdominal	21 (3.1)	72 (2.5)		
Abscess – Pelvic	28 (4.1)	104 (3.6)		
Clostridium Difficile	5 (0.7)	29 (1.0)		
Pneumonia	10 (1.5)	29 (1.0)		
Pneumonia (Aspiration)	2 (0.3)	6 (0.2)		
Sepsis	16 (2.3)	70 (2.4)		
SSI – deep (Facia)	2 (0.3)	6 (0.2)		
SSI – organ space	40 (5.9)	139 (4.9)		

^a Odds Ratio was estimated from matched cohort using logistic regression, adjusted for surgery duration and total volume of intraoperative Crystalloid fluid.

^b Significant criterion was p-value < 0.05. Correspondingly, 95% Confidence Interval (95% CI) was presented with Odds Ratio.

PCA, Patient Controlled Analgesia; CI, Confidence Interval; SSI, Surgical site infection.

Funding statement

Supported by internal funds.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Kirkland KB, Briggs JP, Trivette SL, et al. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol*. 1999;20:725–30.
2. Zerey M, Paton BL, Lincourt AE, et al. The burden of Clostridium difficile in surgical patients in the United States. *Surg Infect*. 2007;8:557–66.
3. Brown E, Talbot GH, Axelrod P, et al. Risk factors for Clostridium difficile toxin-associated diarrhea. *Infect Control Hosp Epidemiol*. 1990;11:283–90.
4. Lundein SJ, Otterson MF, Binion DG, et al. Clostridium difficile enteritis: an early postoperative complication in inflammatory bowel disease patients after colectomy. *J Gastrointest Surg*. 2007;11:138–42.
5. Lawson EH, Hall BL, Ko CY. Risk factors for superficial vs deep/organ-space surgical site infections: implications for quality improvement initiatives. *JAMA Surg*. 2013;148:849–58.
6. Healthcare-associated infections (HAIS) [Internet]. Centers for disease control and prevention. centers for disease control and prevention; 2021 [cited 2022Jun7]. Available from: <https://www.cdc.gov/hai>
7. Davis FM, Laurenson VG, Gillespie WJ, et al. Leg blood flow during total hip replacement under spinal or general anaesthesia. *Anaesth Intensive Care*. 1989;17:136–43.
8. Foate JA, Horton H, Davis FM. Lower limb blood flow during transurethral resection of the prostate under spinal or general anaesthesia. *Anaesth Intensive Care*. 1985;13:383–6.
9. Perhoniemi V, Linko K. Hemodynamics of the legs and clinical symptoms following regional blocks for transurethral surgery. *Eur Urol*. 1986;12:244–8.
10. Poikolainen E, Hendolin H. Effects of lumbar epidural analgesia and general anaesthesia on flow velocity in the femoral vein and postoperative deep vein thrombosis. *Acta Chir Scand*. 1983;149:361–4.
11. Modig J, Malmberg P, Karlstrom G. Effect of epidural versus general anaesthesia on calf blood flow. *Acta Chir Scand*. 1980;24:305–9.
12. Treschan TA, Taguchi A, Ali SZ, et al. The effects of epidural and general anesthesia on tissue oxygenation. *Anesth Analg*. 2003;96:1553–7.
13. Bagry H, de la Cuadra Fontaine JC, Asenjo JF, et al. Effect of a continuous peripheral nerve block on the inflammatory response in knee arthroplasty. *Reg Anesth Pain Med*. 2008;33:17–23.
14. Martin F, Martinez V, Mazoit JX, et al. Antiinflammatory effect of peripheral nerve blocks after knee surgery. *Anesthesiology*. 2008;109:484–90.
15. Breslow MJ, Parker SD, Frank SM, et al. Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. *Anesthesiology*. 1993;79:1202–9.
16. Yokoyama M, Itano Y, Katayama H, et al. The effects of continuous epidural anesthesia and analgesia on stress response and immune function in patients undergoing radical esophagectomy. *Anesth Analg*. 2005;101:1521–7.
17. Jensen J, Jonsson K, Hunt T, et al. Epinephrine lowers subcutaneous wound oxygen tension. *Current Surg*. 1985;42:472–4.
18. Horn SD, Wright HL, Couperus JJ, et al. Association between patient-controlled analgesia pump use and postoperative surgical site infection in intestinal surgery patients. *Surg Infect (Larchmt)*. 2002;3:109–18.
19. Munch T, Christiansen CF, Pedersen L, et al. Impact of preadmission opioid treatment on 1-year mortality following nonsurgical intensive care. *Crit Care Med*. 2018;46:860–8.
20. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc*. 2011;59:1899–907.
21. Schwacha MG, McGwin Jr G, Hutchinson CB, et al. The contribution of opiate analgesics to the development of infectious complications in burn patients. *Am J Surg*. 2006;192:82–6.
22. Wiese AD, Griffin MR, Stein CM, et al. Opioid analgesics and the risk of serious infections among patients with rheumatoid arthritis: a self-controlled case series study. *Arthritis Rheumatol*. 2016;68:323–31.
23. Wiese AD, Griffin MR, Schaffner W, et al. Opioid analgesic use and risk for invasive pneumococcal diseases: a nested case-control study. *Annals Inter Med*. 2018;168:396–404.
24. Pöpping DM, Elia N, Marret E, et al. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg*. 2008;143:990–9.
25. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Annals Surg*. 2001;234:560.
26. Halabi WJ, Jafari MD, Nguyen VQ, et al. A nationwide analysis of the use and outcomes of epidural analgesia in open colorectal surgery. *J Gastrointest Surg*. 2013;17:1130–7.
27. Halabi WJ, Kang CY, Nguyen VQ, et al. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. *JAMA Surg*. 2014;149:130–6.



ORIGINAL INVESTIGATION

Implementation of an ERAS program in patients undergoing thoracic surgery at a third-level university hospital: an ambispective cohort study



Soledad Bellas-Cotán ^{a,*}, Rubén Casans-Francés ^b, Cristina Ibáñez ^a, Ignacio Muguruza ^c, Luis E. Muñoz-Alamedá ^a

^a Hospital Universitario Fundación Jiménez Díaz, Department of Anaesthesiology, Madrid, Spain

^b Hospital Universitario Infanta Elena, Department of Anaesthesiology, Valdemoro, Madrid, Spain

^c Hospital Universitario Fundación Jiménez Díaz, Department of Thoracic Surgery, Madrid, Spain

Received 5 August 2020; accepted 14 April 2021

Available online 27 April 2021

KEYWORDS

Fast-track rehabilitation;
Enhanced recovery after surgery;
VATS

Abstract

Objective: To analyze the effects of an ERAS program on complication rates, readmission, and length of stay in patients undergoing pulmonary resection in a tertiary university hospital.

Methods: Ambispective cohort study with a prospective arm of 50 patients undergoing thoracic surgery within an ERAS program (ERAS group) versus a retrospective arm of 50 patients undergoing surgery before the protocol was implemented (Standard group). The primary outcome was the number of patients with 30-day surgical complications. Secondary outcomes included ERAS adherence, non-surgical complications, mortality, readmission, reintervention rate, pain, and hospital length of stay. We performed a multivariate logistic analysis to study the correlation between outcomes and ERAS adherence.

Results: In the univariate analysis, we found no difference between the two groups in terms of surgical complications (Standard 18 [36%] vs. ERAS 12 [24%], $p=0.19$). In the ERAS group, only the readmission rate was significantly lower (Standard 15 [30%] vs. ERAS 6 [12%], $p=0.03$). In the multivariate analysis, ERAS adherence was the only factor associated with a reduction in surgical complications ($OR [95\% CI]=0.02 [0.00, 0.59]$, $p=0.03$) and length of stay ($HR [95\% CI]=18.5 [4.39, 78.4]$, $p<0.001$).

Conclusions: The ERAS program significantly reduced the readmission rate at our hospital. Adherence to the ERAS protocol reduced surgical complications and length of stay.

© 2021 Published by Elsevier Editora Ltda. 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/>).

* Corresponding author.

E-mail: soledad.bellas@quironsalud.es (S. Bellas-Cotán).

Introduction

Lung cancer is the leading cause of cancer death worldwide, representing 20.55% and 14% of cancer deaths in Spain¹ and the United States,² respectively. Pulmonary resection is currently the treatment of choice for lung cancer.³ However, this procedure is associated with significant complications in almost 50% of cases and can delay patient recovery and increase hospitalization costs.⁴

Professor Henrik Kehlet first described ERAS programs at the end of the last century.⁵ He believed that applying specific, evidence-based measures during the perioperative period could decrease the stress produced by surgical aggression.⁶ Thus, in recent years, ERAS programs have proven effective in reducing surgical complications, length of stay, and hospital costs.^{7–9}

Specific ERAS approaches have recently been described for thoracic surgery.^{10–12} Nevertheless, there is still insufficient evidence to support ERAS programs for pulmonary resection surgery, particularly in terms of the clinical outcomes associated with minimally invasive procedures.

We hypothesized that the ERAS program in patients undergoing pulmonary resection in a tertiary university hospital would reduce complications, readmissions, and length of stay.

Methods

Study design and participants

This study analyzes the implementation of an ERAS in the thoracic surgery service of a third level hospital (Hospital Fundación Jiménez Díaz, Madrid, Spain). To this end, we designed an ambispective cohort study, with a prospective arm of patients undergoing lobectomy within an ERAS program (ERAS group) versus a retrospective arm of patients undergoing surgery before the protocol was implemented (Standard group). The study was approved by the hospital's research ethics committee before the start of patient recruitment in January 2018 (Reference: E0071-18_FJD; ClinicalTrials.gov Identifier: NCT04579601). The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.¹³

After obtaining informed consent, we included patients consecutively after implementation of the ERAS program, except for those who refused to take part or were under 18 years of age. We also asked for informed consent from patients included in the retrospective cohort. We calculated the sample size on the assumption that the ERAS program would result in a 25% reduction in the absolute risk of presenting surgical complications in our center. As our surgical complication rate in 2016 was 40%, a type-I error of 5%, and a power of 80% would require 47 patients per arm.

Procedures

We recruited 50 patients during 2018 and 2019 and compared them with data from the last 50 patients in 2016, the year for which data on the surgical complication rate were avail-

able. We followed up patients for 30 days after surgery using hospital and primary care medical records. We collected demographic and comorbidity data from all patients, which were used to calculate the Charlson's comorbidity index.¹⁴

Our center's ERAS program includes different strategies for the preoperative, intraoperative, and postoperative periods. During the preoperative period, the patients and their families received comprehensive multidisciplinary information about the protocol, the steps to be taken during each day of hospitalization, and the expected discharge date. Patients were taught a series of pulmonary expansion exercises to be performed until surgery by a team specialized in treating lung diseases. Smoking cessation interventions and nutritional screening were also performed at this stage.

Patients underwent Video-Assisted Thoracoscopic Surgery (VATS) whenever possible, placing a chest tube for drainage at the end of the surgery. All subjects received antibiotics and antithrombotic prophylaxis. None of the patients in either group fasted for more than 2 hours before surgery. We performed general anesthesia combined with regional techniques for pain control, avoiding benzodiazepines and opioids. The anesthesiologist was free to choose between thoracic epidural analgesia, intercostal block, and erector spinae block. If a thoracic epidural catheter was placed, it was left in for postoperative patient-controlled analgesia. We also used a hot air system to warm patients during surgery to maintain normothermia. In both groups, no more than $2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ fluids were administered. Extubation was performed as soon as possible after the end of the surgery, and we encouraged early removal of the urinary catheter.

After extubation, patients started oral intake, respiratory physiotherapy exercises, and early ambulation. Patients were discharged when they were free of complications, without severe pain, and the urinary catheter or chest tube had been removed.

Outcomes

The primary outcome was the number of patients with 30-day surgical complications. We defined air leakage, bleeding, infection, and reintervention as surgical complications, classifying all other complications as "non-surgical complications" or "other complications". Secondary outcomes included ERAS adherence, non-surgical complications, mortality, readmission, reintervention rate, pain (defined as any level of pain level that prevented early ambulation), and hospital length of stay. ERAS adherence was evaluated on the basis of seven items: VATS approach, regional analgesia, oral intake within 6 hours, urinary catheter removal within 24 hours, ambulation within 24 hours, respiratory physiotherapy within 24 hours, and chest tube removal within 48 hours.

Statistical analysis

We analyzed outcomes depending on whether the patient belonged to the ERAS program or the retrospective standard cohort. We describe discrete and continuous variables as number and percentage and median (Interquartile Range

Table 1 Patient demographics and comorbidity. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance is set at $p < 0.05$.

Variable	Standard (n=50)	ERAS (n=50)	<i>p</i>
Age (y), median (IQR)	64.5 (53.5–70)	64 (57–70.8)	0.82
Weight (kg), median (IQR)	70 (63–80)	73 (61–82.8)	0.77
Height (cm), median (IQR)	160 (160–163)	165 (158–171.5)	0.04*
BMI, median (IQR)	27.5 (24.7–29.9)	25.3 (22.7–29.4)	0.16
Men, n (%)	31 (62.0)	25 (50.0)	0.23
ASA class, n (%)			0.25
I	2 (4.0)	2 (4.0)	
II	21 (42.0)	30 (60.0)	
III	23 (46.0)	17 (34.0)	
IV	4 (8.0)	1 (2.0)	
ASA class > 2	26 (52.0)	15 (30.0)	0.03*
Hypertension, n (%)	29 (58.0)	17 (34.0)	0.02*
Cardiac Arrest, n (%)	5 (10.0)	7 (14.0)	0.54
Chronic Heart Failure, n (%)	2 (4.0)	0 (0.0)	0.49
Vascular Disease, n (%)	0 (0.0)	0 (0.0)	1
Stroke, n (%)	1 (2.0)	1 (2.0)	1
Diabetes, n (%)	7 (14.0)		1
Dementia, n (%)	0 (0.0)	0 (0.0)	1
Chronic Kidney Disease, n (%)	3 (6.0)	0 (0.0)	0.24
COPD, n (%)	12 (24.0)	4 (8.0)	0.03*
AIDS, n (%)	0 (0.0)	1 (2.0)	1
Metastasis, n (%)	0 (0.0)	1 (2.0)	1
Charlson Comorbidity Index, median (IQR)	2 (1–3)	2 (1–3)	0.9

* $p < 0.05$.

[IQR]), and differences were analyzed using the Pearson test or the Wilcoxon rank-sum tests. We performed a multivariate logistic analysis of adherence to ERAS items in both cohorts in order to determine the correlation between complication rates, readmission, or pain and ERAS adherence, clinical and demographic data, showing the results in forest plots as odds ratio with 95% Confidence Interval. Similarly, we used Cox regression for the multivariate analysis of length of stay, showing the results as hazard ratio with 95% Confidence Interval. To avoid errors due to multiple comparisons, we calculated the respective *q*-value for each *p*-value to keep the false discovery rate below 5%.¹⁵ We considered comparisons in which *p*-value and *q*-value were below 0.05 as being statistically significant.

Results

No patients refused to take part in the study. Patient demographics and comorbidities are shown in Table 1. The cohorts were not totally homogeneous: a higher number of patients in the Standard cohort versus the ERAS cohort presented hypertension (26 [52%] vs. 15 [30%], $p = 0.03$) and chronic obstructive pulmonary disease (12 [24%] vs. 4 [8%], $p = 0.02$), respectively. Although the number of patients with ASA class > 2 was higher in the standard group versus the ERAS group (26 [52%] vs. 15 [30%]), we found no difference between the cohorts in terms of the Charlson's comorbidity index. We included these three items, along with age and sex, in the subsequent multivariate analyses.

Data on ERAS adherence and compliance for each of the protocol items are shown in Table 2. Adherence to items in the ERAS protocol was significantly higher in the ERAS vs. the Standard cohort (median: Standard 0.29 [0.14–0.43] vs. ERAS 0.71 [0.57–0.82], $p < 0.001$). The VATS approach was more common in the ERAS group (29 [58%] vs. 11 [22%], $p < 0.001$), and more patients in the ERAS group ambulated on the first postoperative day [40 (80%) vs. 0 (0%), $p < 0.001$], but no difference was found in the use of regional analgesia. Time to oral intake and removal of the urethral catheter were also lower in the ERAS group; median (h): Standard 24 (24–24) vs. ERAS 6 (6–7.5), and Standard 48 (24–48) vs. ERAS 19 (6–24), respectively.

The primary and secondary outcomes are shown in Table 3. We found no difference between the two groups in terms of surgical complications (Standard 18 [36%] vs. ERAS 12 [24%], $p = 0.19$), non-surgical complications (Standard 21 [42%] vs. ERAS 12 [24%], $p = 0.06$) or length of stay (median [days]: Standard 4 [3–6] vs. ERAS 4 [3–5], $p = 0.19$); only the readmission rate was significantly lower in the ERAS group (Standard 15 [30%] vs. ERAS 6 [12%], $p = 0.03$). No deaths were recorded in the ERAS group compared to two deaths in the retrospective cohort.

The results of the multivariate analyses are shown in Figures 1, 2 and 3. ERAS adherence was the only factor associated with a reduction in surgical complications (OR [95% CI] = 0.02 [0.00, 0.59], $p = 0.03$) (Fig. 1A), and post-operative pain (OR [95% CI] = 0.01 [0.00, 0.28], $p = 0.01$) (Fig. 2A). It was also associated with a lower readmission rate (OR [95% CI] = 0.01 [0.00, 0.24], $p = 0.007$) (Fig. 2B) and

Table 2 ERAS adherence. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance was set at $p < 0.05$.

Variable	Standard (n = 50)	ERAS (n = 50)	<i>P</i>
ERAS Adherence, median (IQR)	0.29 (0.14–0.43)	0.71 (0.57–0.82)	< 0.001*
Antithrombotic prophylaxis, n (%)	50 (100.0)	50 (100.0)	1
Nutritional screening, n (%)	50 (100.0)	50 (100.0)	1
Avoid fasting, n (%)	50 (100.0)	50 (100.0)	1
Surgical approach, n (%)			< 0.001*
Thoracotomy	37 (74.0)	16 (32.0)	
VATS	11 (22.0)	29 (58.0)	
Reconverted	2 (4.0)	4 (8.0)	
Robotic	0 (0.0)	1 (2.0)	
Regional analgesia, n (%)	42 (84.0)	42 (84.0)	1
Analgesia type, n (%)			0.01*
Intravenous	7 (14.0)	8 (16.0)	
Thoracic epidural	34 (68.0)	26 (52.0)	
Intercostal block	9 (18.0)	7 (14.0)	
Erector spinae block	0 (0.0)	9 (18.0)	
Regional analgesia administration, n (%)			0.69
No regional analgesia	7 (14.0)	8 (16.0)	
Bolus	9 (18.0)	12 (24.0)	
Catheter	34 (68.0)	30 (60.0)	
Mobilization on POD-0, n (%)	0 (0.0)	40 (80.0)	< 0.001*
Time to oral Intake (h), median (IQR)	24 (24–24)	6 (6–7.5)	< 0.001*
Time to respiratory physiotherapy (h), median (IQR)	25 (24–24)	26 (24–24)	0.33
Time to chest drain removal (h), median (IQR)	72 (48–96)	48 (48–72)	0.18
Time to urethral catheter removal (h), median (IQR)	48 (24–48)	19 (6–24)	< 0.001*

* $p < 0.05$.**Table 3** Results of main and secondary outcomes. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance was set at $p < 0.05$.

Variable	Standard (n = 50)	ERAS (n = 50)	<i>P</i>
Surgical complications, n (%)	18 (36.0)	12 (24.0)	0.19
Other complications, n (%)	21 (42.0)	12 (24.0)	0.06
Mortality, n (%)	2 (4.0)	0 (0.0)	0.49
Reintervention, n (%)	2 (4.0)	0 (0.0)	0.49
Readmission, n (%)	15 (30.0)	6 (12.0)	0.03*
ICU readmission, n (%)	0 (0.0)	0 (0.0)	1
Pain, n (%)	16 (32.0)	10 (20.0)	0.17
Death, n (%)	2 (4.0)	0 (0.0)	0.49
Length of stay (d), median (IQR)	4 (3–6)	4 (3–5)	0.39

* $p < 0.05$.

an increased likelihood of early discharge from the hospital (HR [95% CI] = 18.5 [4.39, 78.4], $p < 0.001$) (Fig. 3). Thoracic epidural analgesia was the only factor that showed an association with lower rates of non-surgical complications (OR [95% CI] = 0.09 [0.01, 0.49], $p = 0.008$) (Fig. 1B). It was also associated with lower rates of postoperative pain (OR [95% CI] = 0.16 [0.03, 0.86], $p = 0.03$) (Fig. 2A) and increased likelihood of discharge from the hospital (HR [95% CI] = 3.14 [1.39, 7.07], $p = 0.006$) (Fig. 3). Intercostal blockade also increased this likelihood (HR [95% CI] = 7.55 [2.94, 19.3], $p < 0.001$) (Fig. 3).

No significant *p*-value was rejected after calculating the *q*-value within the multiple comparability study.

Discussion

Our study has shown that adherence to the ERAS protocol is one of the essential factors in reducing complications in patients undergoing pulmonary resection. An increase in the adherence rate was associated with a reduction in the number of complications and the length of stay. In other words, although the small marginal gains caused by each of the items in isolation have little effect on the results, it is the combination of all the measures applied that is responsible for the improvement. These findings are consistent with those of Madani et al.,¹⁰ who observed that compliance with

Complications (multivariate logistic regression)

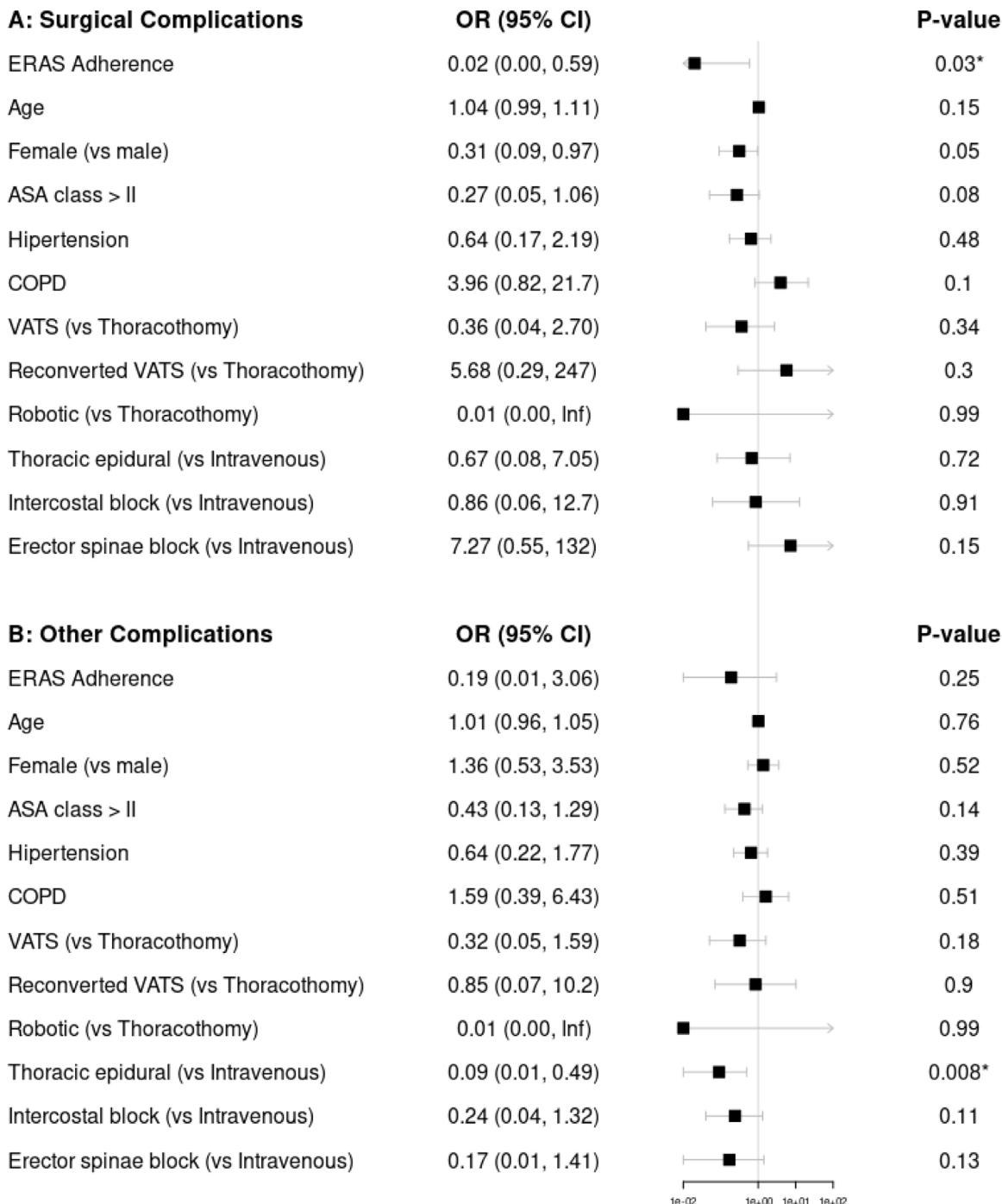


Figure 1 Forest plot of multivariate logistic analysis of the influence of patient comorbidity and ERAS on complications. A, Surgical complications. B, Non-surgical complications. Results are shown as odds ratio with a 95% Confidence Interval. A value of less than 1, left of the y-axis, implies risk reduction. We accept $p < 0.05$ as significant.

the full ERAS program is probably the most critical factor, more than individually applied elements.

However, it is also important to note that it is one thing to include a patient in an ERAS program, and another to have the patient comply with all the program items. Resistance to change, especially in the initial stages of the program,

can make it hard for patients to complete the program.¹⁶ Added to this is the lack of multidisciplinarity often found among clinicians and the difficulties involved in overcoming patient passivity. In these cases, ERAS programs can appear to be ineffective. In Spain, this was clearly shown by the POWER study,¹⁷ a prospective multi-center study of

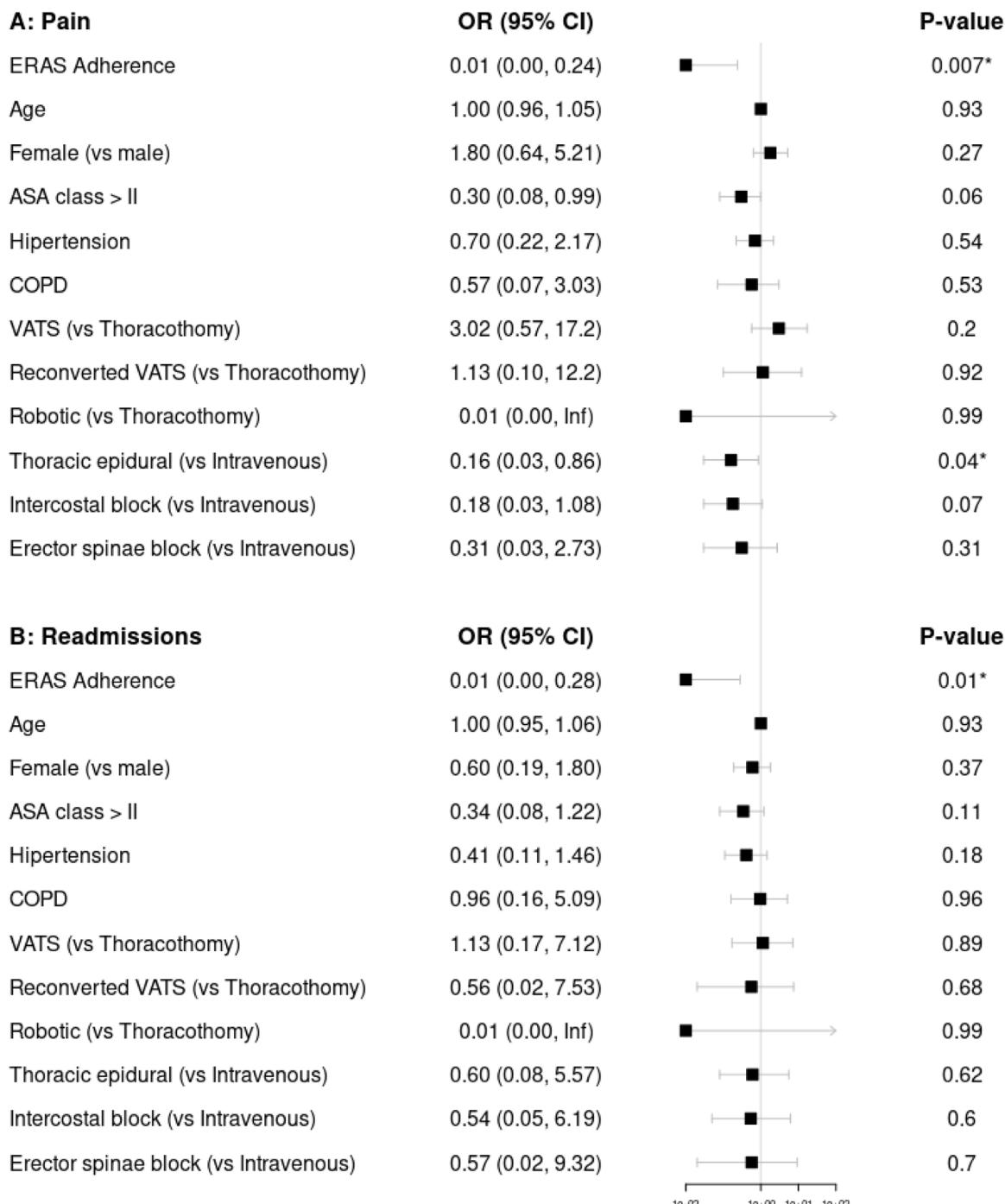
Other outcomes (multivariate logistic regression)

Figure 2 Forest plot of multivariate logistic analysis of the influence of patient comorbidity and ERAS on other outcomes. A, Pain. B, Readmission. Results are shown as odds ratio with a 95% Confidence Interval. A value of less than 1, left of the y-axis, implies risk reduction. We accept $p < 0.05$ as significant.

80 hospitals and more than 2000 patients. Hospitals were asked to state whether they used ERAS programs on their patients, and then independently collected ERAS compliance data. The results showed that although moderate or severe complications did not differ between non-ERAS and ERAS groups, differences were observed when the patients

were divided into adherence quartiles. In our study, we observed a similar trend in respect of length of stay, insofar as we did not find differences between groups, but a very high adjusted hazard ratio was observed when compliance with the protocol increased.

Length of Stay (Hazard Ratio, Cox's regression)

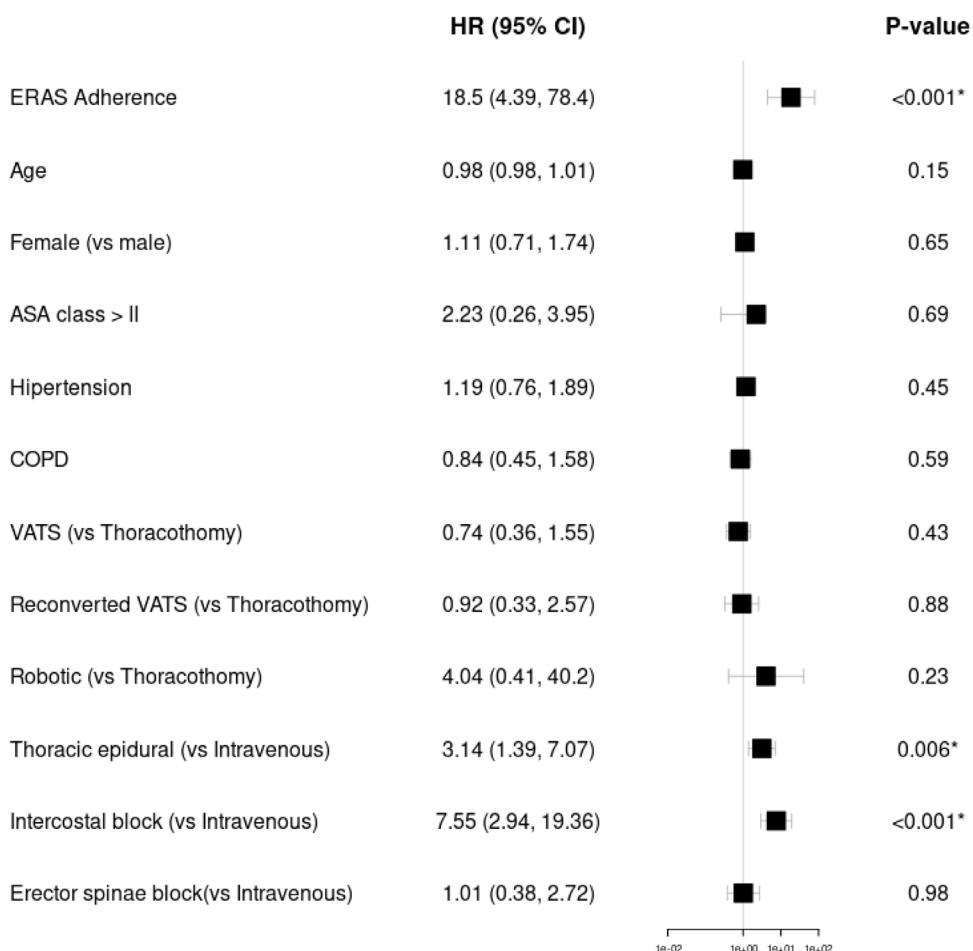


Figure 3 Forest plot of Cox regression of the influence of patient comorbidity and ERAS on length of stay. Results are shown as hazard ratio with a 95% Confidence Interval. A value of more than 1, right of the y-axis, implies an increased probability of early hospital discharge. We accept $p < 0.05$ as significant.

One of the critical points of the ERAS program is that it facilitates standardization in perioperative patient care. This standardization, as several studies have shown, tends to translate into improved outcomes. Cerfolio et al.¹⁸ implemented an ERAS program for pulmonary resections with an approach focused on patient education, epidural analgesia, standardized and early withdrawal of urethral catheters and chest drains, and early ambulation. These interventions enabled early discharge without negatively affecting morbidity or mortality. Another example is the randomized controlled clinical trial conducted by Muehling et al.,¹⁹ who observed how a protocol based on avoidance of extended fasting, administration of regional analgesia, early oral intake, and early ambulation resulted in a significant reduction in pulmonary complications.

The sum of the marginal effects of each individual factor is responsible for the benefit of ERAS programs. However, this does not mean that all items are equally important – some have a greater effect than others. It is as yet unclear whether adherence to the program or the weight of specific items is responsible for the improvement in thoracic

surgery. However, experience in colorectal surgery indicates that both approaches may be correct.²⁰

We found that only regional analgesia improved outcomes, and this effect was only found in multivariate analyses. This factor has a substantial impact on other protocol items influenced by pain, such as immobility. Immobility after thoracic surgery is not uncommon due to factors such as pain, nausea, or the presence of a chest tube.²¹ Early mobilization is a critical factor in reducing complications in ERAS programs,²² but we did not observe this to have an effect on our study outcomes. Another influential factor is the early removal of chest tubes. Although our analysis did not show this to have any impact, the literature indicates that the earlier the withdrawal, the better the results.^{23,24}

We also found that VATS did not affect our results. Minimally invasive surgery seems to be an independent predictor of favorable outcomes after colorectal cancer surgery in ERAS programs.²⁵ The use of VATS for pulmonary resection surgery has gradually increased following the publication of new data showing that it is effective, and can potentially improve outcomes.^{26,27}

Many clinicians fear that implementing an ERAS program for pulmonary resection surgery will increase the number of readmissions, a factor that is associated with reduced survival in both the short and long term.²⁸ An increase in readmissions has not been observed after implementing ERAS programs for pulmonary resection.¹⁰ In our study, the readmission rate was 12%, and it was the only outcome that improved due to inclusion in the ERAS program, a finding consistent with other published studies.²⁸ We found no relationship between improved functionality and certain items of the ERAS protocol. We believe that this was due to the main limitation of our study, i.e., our over-optimism about the theoretical effect of the ERAS protocol on the complication rate. The estimated 25% absolute risk reduction resulted in a reduction in the theoretical sample size and decreased power. A more conservative value would have increased the power of the study.

In conclusion, the ERAS program significantly reduced the readmission rate at our hospital. Likewise, adherence to the ERAS protocol helped reduce the number of surgical complications and length of stay.

Level of authorship

Studio design: SBC, IM, LEMA. Studio execution: SBC, CI. Statistical analysis: RCF. First draft: SBC, RCF, Final Draft: SBC, RCF, LEMA.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.04.014>.

References

1. Sociedad Española de Oncología Médica -SEOM-. Las cifras del cáncer en España, 2020. https://seom.org/seomcms/images/stories/recursos/Cifras_del_cancer_2020.pdf [accessed 5 August 2020].
2. American Cancer Society. Cancer Facts & Statistics. <http://cancerstatisticscenter.cancer.org/> [accessed 5 August 2020].
3. Royal College of Physicians. Lung cancer clinical outcomes publication 2018 (for surgical operations performed in 2016). London: RCP; 2018.
4. Chen FF, Zhang D, Wang YL, et al. Video-assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage I non-small cell lung cancer: a meta-analysis. Eur J Surg Oncol. 2013;39:957–63.
5. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78:606–17.
6. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248:189–98.
7. Nicholson A, Lowe MC, Parker J, et al. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg. 2014;101:172–88.
8. Lee L, Mata J, Ghitulescu GA, et al. Cost-effectiveness of enhanced recovery versus conventional perioperative management for colorectal surgery. Ann Surg. 2015;262:1026–33.
9. Paton F, Chambers D, Wilson P, et al. Effectiveness and implementation of enhanced recovery after surgery programmes: a rapid evidence synthesis. BMJ Open. 2014;4: e005015.
10. Madani A, Fiore JF, Wang Y, et al. An enhanced recovery pathway reduces duration of stay and complications after open pulmonary lobectomy. Surgery. 2015;158:899–908, discussion 908–910.
11. Giménez-Milà M, Klein AA, Martínez G. Design and implementation of an enhanced recovery program in thoracic surgery. J Thorac Dis. 2016;8:S37–45.
12. Scariati M, Solli P, Bedetti B. Enhanced recovery pathway for thoracic surgery in the UK. J Thorac Dis. 2016;8:S78–83.
13. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495–9.
14. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
15. Storey JD. A direct approach to false discovery rates. J R Statistical Soc B (Statistical Methodol). 2002;64:479–98.
16. Casans Francés R, Ripollés Melchor J, Abad-Gurumeta A, et al. The role of the anaesthesiologist in enhanced recovery programs. Rev Esp Anestesiol Reanim. 2016;63:273–88.
17. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, et al. Association between use of enhanced recovery after surgery protocol and postoperative complications in colorectal surgery: the postoperative outcomes within enhanced recovery after surgery protocol (POWER) Study. JAMA Surg. 2019;154:725–36.
18. Cerfolio RJ, Pickens A, Bass C, et al. Fast-tracking pulmonary resections. J Thorac Cardiovasc Surg. 2001;122:318–24.
19. Muehling BM, Halter GL, Schelzig H, et al. Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway. Eur J Cardiothorac Surg. 2008;34:174–80.
20. Gustafsson UO, Hausel J, Thorell A, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011;146:571–7.
21. Agostoni PJ, Naidu B, Rajesh P, et al. Potentially modifiable factors contribute to limitation in physical activity following thoracotomy and lung resection: a prospective observational study. J Cardiothorac Surg. 2014;9:128.
22. Das Neves Pereira JC, Bagan P, Coimbra Israel AP, et al. Fast-track rehabilitation for lung cancer lobectomy: a five-year experience. Eur J Cardiothorac Surg. 2009;36: 383–91.
23. Bjerregaard LS, Jensen K, Petersen RH, et al. Early chest tube removal after video-assisted thoracic surgery lobectomy with serous fluid production up to 500 ml/day. Eur J Cardiothorac Surg. 2014;45:241–6.
24. Cerfolio RJ, Bryant AS. Results of a prospective algorithm to remove chest tubes after pulmonary resection with high output. J Thorac Cardiovasc Surg. 2008;135:269–73.
25. ERAS Compliance Group. The Impact of enhanced recovery protocol compliance on elective colorectal cancer resection: results from an international registry. Ann Surg. 2015;261:1153–9.
26. Bendixen M, Jørgensen OD, Kronborg C, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 2016;17:836–44.

27. Falcoz PE, Puyraveau M, Thomas PA, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg*. 2016;49:602–9.
28. Puri V, Patel AP, Crabtree TD, et al. Unexpected readmission after lung cancer surgery: a benign event? *J Thorac Cardiovasc Surg*. 2015;150:1496–504, 1505.e1-1505; discussion 1504-1505.



ORIGINAL INVESTIGATION

Association between enhanced recovery after surgery protocol compliance and clinical complications: a cohort study

Maria Ana Máximo ^{ID a,*}, Daniel Santos ^a, Afonso Félix-Oliveira ^{b,c}, Marta Pereira ^d, Cristina Carmona ^a



^a Hospital Prof. Doutor Fernando Fonseca, E.P.E., Anesthesiology Department, Lisbon, Portugal

^b Centro Hospitalar Lisboa Ocidental, E.P.E., Hospital de Santa Cruz, Cardiology Department, Lisbon, Portugal

^c Centro Académico de Medicina de Lisboa, Universidade de Lisboa, Faculdade de Medicina, Instituto de Farmacologia e Neurociências, Lisbon, Portugal

^d Champalimaud Centre for the Unknown - Champalimaud Clinical Centre Lisbon, Anesthesiology Department, Lisbon, Portugal

Received 6 June 2020; accepted 8 August 2021

Available online 7 October 2021

KEYWORDS

Anesthesiology;
Colorectal surgery;
Compliance;
Enhanced recovery
after surgery;
Perioperative care

Abstract

Background: Enhanced Recovery After Surgery (ERAS) protocol is composed by evidence-based interventions that aim to improve recovery through a reduction in surgical stress response. Although ERAS protocols have been introduced across the globe, exhaustive implementation is not as common. We aimed to study the ERAS protocol compliance in colorectal surgery, assessing the relationship between compliance and postoperative complications.

Methods: A single-center cohort study was conducted. All consecutive patients admitted to elective colorectal surgery were included. We assessed study endpoints according to ERAS protocol perioperative compliance score above 75%. Our primary endpoint was a composite of postoperative events, which includes in-hospital postoperative complications and need for reoperation after 30 days and need for readmission after discharge. Secondary endpoints were surgery-to-discharge time, postoperative use of only non-opioid adjuvants and the individual components of the primary endpoint.

Results: A total of 224 colorectal patients were included. The primary endpoint occurred in 59.2% ($n = 58$) of non-compliant patients comparing to 34.1% ($n = 43$) in compliant patients. In univariate analysis, compliance to ERAS protocol had an inferior risk for the primary endpoint ($p < 0.001$). In a logistic regression model, compliance was independently associated with a reduced risk for the primary endpoint with a odds-ratio of 0.42 (95% CI 0.23–0.75, $p = 0.004$).

* Corresponding author.

E-mail: maximosilva.ana@gmail.com (M.A. Máximo).

Conclusion: Compliance with the ERAS protocol is associated with less complications, a reduced surgery-to-discharge time and use of only non-opioid adjuvants in the postoperative period. More studies are needed to target the most appropriate compliance goal.
 © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Enhanced Recovery After Surgery (ERAS) guidelines for colorectal surgery were published for the first time in 2005.¹ Since then, they have been in continuous development and the most recent guidelines were published in 2018.² ERAS protocol is composed by evidence-based interventions that aim to improve recovery through a reduction in surgical stress response.³ Ultimately, they may reduce complications, length of stay and time to return to work, thus improving patient satisfaction.⁴ ERAS protocols have been implemented in Europe,^{5,6} America,³ Asia,⁷ and Oceania,⁸ and in several surgical areas (colorectal, vascular, thoracic, urologic, spine, neurosurgery, orthopedic, liver, pancreatic, and cardiac surgery).⁹ In Brazil, first data has been published in 2019, and it included colorectal surgery¹⁰ and liver surgery,¹¹ both with feasible and beneficial results. Although ERAS protocols have been implemented across the globe, exhaustive implementation is not as common.^{3,12,13} The main limiting factor for wider acceptance is that it requires a challenge on adopted local protocols and a multidisciplinary collaboration including the Colorectal Surgical and Anesthesiology teams, the Physical Medicine and Rehabilitation Unit, ward nurses, and a nutrition network support.¹⁴ Anesthesiologists play a pivotal role in the implementation of such protocols, since preoperative assessment and preparation, perioperative fluid management, and perioperative pain relief constitute part of the core of the ERAS program.⁹

The main focus of research has been on the implementation and the limiting factors of the adoption of the program.^{5,14} The impact of each intervention on patient outcomes remains uncertain,¹² and there is still a lack of standardization methods to ascertain outcomes. This uncertainty contributes to partial protocol implementation in some centers.⁸ In fact, there have been studies evaluating the inclusion in ERAS protocols while others assessed the actual compliance with ERAS items. This distinction is important, as mean compliance rate among patients included in ERAS protocols varies between 60% and 80% in some published cohorts.¹³

In our view, actual compliance rather than mere inclusion in ERAS protocols should be assessed and correlated with outcomes in order to successfully implement these protocols in clinical practice. We aimed to study the impact of high compliance perioperative ERAS protocol in in-hospital complications reinterventions, rehospitalizations and time to discharge.

Methods

Setting

Our hospital has an overall 700 bed capacity, and manages 200 colorectal surgical patients per year.

Our center was certified as an ERAS Center for colorectal surgery by ERAS society in October 2018. The ERAS group is in charge of program implementation and auditing. Our institution ERAS protocol is summarized in Table 1.

Study hypothesis

The compliance with ERAS protocols is variable among patients submitted to elective colorectal surgery. We aimed to assess the hypothesis that high compliance with ERAS protocols is associated with decreased incidence of in-hospital complications, reinterventions, rehospitalizations, and time to discharge.

Study design, institutional review board approval

We performed a single-center cohort study of all consecutive patients admitted to elective colorectal surgery in the defined study periods.

The study includes data on two separate time periods (Fig. 1). Between March and September 2017, which was previous to ERAS training, data was registered retrospectively; Between June 2018 and December 2019, data was registered prospectively. In between these periods, patients admitted during a transition phase between pre- and post-ERAS protocols, while training was performed, were not included in the study.

Patients admitted pre-ERAS were managed according to local approved protocols at the time of surgery. Patients admitted post-ERAS were managed according to ERAS protocol policies and compliance with every single item was actively encouraged. Between these two periods, ERAS training and accreditation was taking place and patients operated in the meantime were not included in the analysis.

This study was done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines¹⁵ as well as the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) checklist.⁴ Revised Standards for the Quality Improvement Reporting Excellence (SQUIRE 2.0)¹⁶

Table 1 Overview of local ERAS protocol.

Our institution ERAS protocol (according to the Guidelines for Perioperative Care in Elective Colonic and Rectal Surgery: ERAS Society Recommendations)(2)

1. Preadmission education (4-5 weeks before surgery, at least one week before surgery)

- Meeting with Anesthesiologist, ERAS nurse specialist, Nutritionist, Stoma counseling, and Physiatrist;
- Booklet describing the protocol.

2. Preoperative screening

- Nutritional deficiency: Malnutrition Universal Screening Tool – MUST and the Scored Patient-Generated Subjective Global Assessment (PG-SGA);
- Prescription of a diet;
- Tobacco and ethanol: referred preoperatively for counseling.

3. Prehabilitation

- Physical exercises according to Physiatrist.

4. Fasting and carbohydrate loading guidelines

- Normal diet until midnight and hydration encouraged;
- One carbohydrate drink (200 mL) until 21 h and half until 23 h the day before surgery;
- Half carbohydrate drink (100 mL) until 2 h before surgery;
- Fasting is according to international guidelines.

5. Bowel preparation

- Colonic surgery: administration of laxative therapy only;
- Rectal surgery: bowel preparation with a 2-L electrolytic solution the day before surgery.

6. Thromboembolic prophylaxis

- Prophylactic-dose enoxaparin subcutaneously 12 h before surgery and regular administration at the same schedule (starting 6 h after surgery);
- Use of compression socks since the day of surgery until discharge day.

7. Antibiotic prophylaxis

- Cefoxitin 2 g and metronidazole 1 g, 60–30 min before surgical incision;
- Intraoperatively, cefoxitin 1 g is administered every 2 h and metronidazole 500 mg every 6 h.

8. Preemptive analgesia

- We usually do not administer preemptive analgesia.

9. Anti-emetic prophylaxis

- According to Apfel score;
- All patients are administered at least one anti-emetic; common agents are dexamethasone and ondansetron.

10. Standard Anesthetic protocol – general principles

- Avoiding pre-medication and long-acting opioids;
- Monitoring neuromuscular block;
- Use of cerebral monitoring for depth of anesthesia.

11. Intraoperative fluid management strategy

- Restrictive fluid approach with "zero balance";
- Hypotension is preferably approached according to etiology. If patient is not hypovolemic, vasopressors are preferred;
- If high risk patient, or expected relevant blood loss, goal-directed therapy is encouraged.

12. Patient warming strategy

- The warming measures start at the induction room;
- Forced air heating and intravenous fluids warming;
- Esophageal temperature monitorization to $T \geq 36.1^{\circ}\text{C}$.

13. Surgical access

- Preferably minimal invasive approaches.

14. Plan for intraoperative opioid minimization

- Open surgery: thoracic epidural (colonic surgery – T7/T9 level; rectum surgery – T10/T11 level);
- Laparoscopic surgery: Other locoregional techniques can be useful (in our institution, a transverse abdominis plane (TAP) block is the most frequent option).

15. Drain and line management

- No routine wound drains;
- Nasogastric tube is removed in the operating room;
- Foley catheter: If colonic surgery, removal at day 1 postoperative; if rectal surgery, its removal is decided individually.

16. Postoperative fluids

- Balanced solutions until 24 h post-surgery at $1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

17. Postoperative analgesia

- Visual Analogue Scale (VAS) punctuation < 4;

Table 1 (Continued)

Our institution ERAS protocol (according to the Guidelines for Perioperative Care in Elective Colonic and Rectal Surgery: ERAS Society Recommendations)(2)

- Open surgery: epidural analgesia. The catheter is removed by postoperative day 2, if colonic surgery, and by postoperative day 4, if rectal surgery;
 - Open surgery and laparoscopic surgery: non-opioid adjuvants (paracetamol and metamizol) during first 48 h at 6 h-intervals; after which NSAIDs or COX-2 inhibitors can be added. Tramadol can also be administered, if needed;
 - In the first 24 h, analgesics are administered intravenously.
- 18. Early mobilization strategy**
- Ambulation to chair at day 0 postoperative, for 2 h;
 - At day 1 postoperative, the patient starts to walk in hallways (3 times during the day, minimum 2 h).
- 19. Postoperative diet and bowel regimen management**
- Gut motility stimulation with Bisacodyl 5 mg.
 - On the day of surgery: liquid diet, 2–4 h after surgery. Goal: 600 mL and 300 Kcal; End of first day: low-residue diet.
- 20. Criteria for discharge**
- Postoperative autonomy guaranteed;
 - Pain well controlled on oral medication (VAS < 4);
 - Gastrointestinal transit recovered.
- 21. Tracking of post-discharge outcomes**
- Follow-up at 48 h and at 30-days;
 - Phone call by the ERAS team nurse.

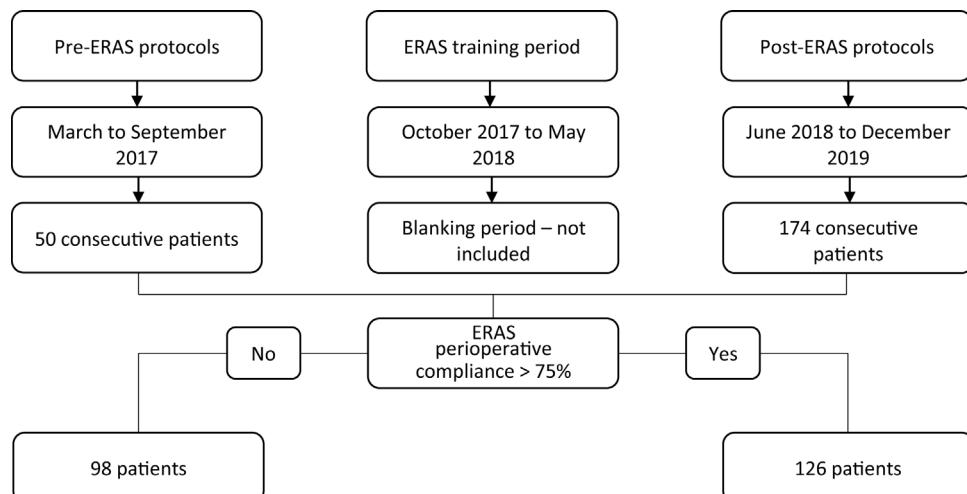


Figure 1 Time frame and patients included flowchart.

checklist was also considered and relevant topics were included. The ethics and investigation committee gave its approval on the 14th April 2020 (protocol number 33/2020). Informed consent for the study was dismissed regarding the rigorous confidentiality provided by the ERAS database. Patients did not receive any financial compensation.

Enhanced recovery auditing

Data was registered by the same ERAS team nurse in the auditing official ERAS tool – ERAS Interactive Audit Tool System® (EIAS). Individual compliance elements and outcomes were reviewed by the ERAS surgical and anesthesiology team.

Perioperative compliance score

We assessed study endpoints according to ERAS protocol perioperative compliance. Therefore, we divided our population in two groups according to a score threshold of 75% (Fig. 1).^{17,18}

Perioperative compliance score was calculated based in the EIAS compliance score in the pre-admission, pre-operative and intraoperative period. The postoperative period was excluded from perioperative compliance score, since compliance with these recommendations is dependent on postoperative complications, which are a part of our defined primary endpoint. Therefore, from the 32 compliance variables only 19 entered the perioperative compliance score.

Endpoints

The primary endpoint was a composite of postoperative events, which includes in-hospital postoperative complications at 30 days (medical and surgical complications described in Supplement 1 and part of ERAS outcomes assessment form), need for reoperation at 30 days and need for readmission after discharge. The secondary endpoints were surgery-to-discharge time, postoperative use of only non-opioid adjuvants and the individual components of the primary endpoint.

The ERAS team nurse was responsible for assessing the primary outcomes. The ERAS team nurse was not blinded for study period, i.e., pre- or post-ERAS implementation, but was unaware of the perioperative compliance score which was the main focus of our analysis. The ERAS team received specific training regarding outcomes assessment for accurate auditing of the program.

Statistical analysis

Categorical variables are presented as absolute numbers and frequencies and are compared using the Pearson χ^2 or Fisher exact test. Continuous variables are presented as mean +/- standard deviation (SD) or median with 25th and 75th percentiles for normal and non-normal distribution, respectively. Normality was tested using the Kolmogorov-Smirnov test.

The H_0 for our study is that occurrence of the primary and secondary endpoints would be similar between high and low compliance with ERAS protocols. The alternative hypothesis, as stated above, would be for decreased incidence of the primary and secondary outcomes in patients with high compliance to ERAS protocols, irrespective of the study period. A two-sided α level of 0.05 was assumed to be statistically significant. The observational and exploratory nature of the study, as well as the variability of previously reported data on the effects of ERAS compliance, did not allow for sample size calculations.

For normally distributed variables, the Student's t -test was used for comparison between groups. For non-normal distributed variables, the non-parametric Mann-Whitney or Kruskal-Wallis tests were chosen.

Regression models for multivariate analysis of the primary endpoint and individual components of the secondary endpoints included variables that were clinically relevant for the study endpoints and had a statistically significant association with the primary endpoint in univariate analysis. Therefore, compliance $\geq 75\%$, age, gender, ASA physical status, laparoscopic surgery, hemicolectomy (left or right), anterior rectum resection, and preoperative chemotherapy or any radiotherapy to operating field were included in the multivariate models.

Logistic regression was used for binary endpoints, using the enter method with fixed effects, whereas surgery-to-discharge time was analyzed through Cox-regression and Kaplan-Meier of time vs. the proportion of discharged patients. Statistical analysis was performed using SPSS software® (SPSS 23, IBM).

Results

A total of 224 patients were included in the study: 50 consecutive patients operated previously to ERAS protocol implementation and 174 consecutive patients operated after ERAS protocol implementation. All colorectal elective patients were eligible to be introduced in EIAs and, therefore, analyzed. All included patients were divided according to ERAS protocol perioperative compliance score threshold of 75% in two groups: perioperative compliance score $< 75\%$ (98 patients) and perioperative compliance score $\geq 75\%$ (126 patients), as clarified in [Figure 1](#).

Baseline characteristics

The clinical and demographic characteristics of patients with high and low perioperative compliance are shown in [Table 2](#). Previous abdominal surgery was more frequent in non-compliant patients – 49% ($n = 48$) vs. 32.5% ($n = 41$), $p = 0.013$ – while hemicolectomy was more common in compliant patients – 33.7% ($n = 33$) vs. 48.4% ($n = 61$), $p = 0.027$. Analyzing compliance to individual measures, it is interesting to note that compliance with smoking, iron replacement treatment, preoperative oral bowel preparation, PONV prophylaxis compliance, resection-site drainage compliance, and nerve blocks or local anesthetic compliance were not significantly different between non-compliant and compliant patients. On the contrary, pre-admission education, nutritional support, and epidural compliance, among others, were significantly different between groups ([Table 2](#)).

The effect of compliance on the primary endpoint of postoperative events

Our primary endpoint was a composite of postoperative events including in-hospital postoperative complications, need for reoperation at 30-days and need for readmission after discharge.

The primary endpoint occurred in 59.2% ($n = 58$) of non-compliant patients comparing to 34.1% ($n = 43$) in compliant patients ([Table 3](#)). In univariate analysis, compliance to ERAS protocol had an inferior risk for the primary endpoint ($p < 0.001$). The same finding is observed when comparing high vs. low compliance only in patients treated after ERAS implementation ($p < 0.001$).

In univariate analysis of co-variates ([Table 4](#)), male sex ($p = 0.005$), ASA III or IV classification ($p = 0.034$), preoperative chemotherapy, or any radiotherapy to operating field ($p = 0.015$) and anterior rectum resection ($p = 0.05$) were associated with increased risk for the primary endpoint. In contrast, hemicolectomy ($p = 0.023$) and laparoscopic surgery ($p < 0.001$) were associated with decreased risk for the primary endpoint. Other relevant clinical variables, such as previous abdominal surgery, were not associated with different rates of the primary outcome and therefore were not included in the multivariate models described below. These results are summarized in [Table 4](#), which describes the variables that were associated with the occurrence of the primary endpoint in univariate analysis, as well as the results of multivariate analysis using logistic regression.

Table 2 Baseline patient characteristics according to perioperative compliance $\geq 75\%$.

Characteristic	Non-compliant (n = 98)	Compliance \geq 75% (n = 126)	p-value
Patient characteristics			
Age, median (IQR), years	68 (58–78.25)	70 (61–76.25)	0.533
Male sex (%)	57 (58.2)	71 (56.3)	0.785
BMI, mean (SD)	25.6 (4.7)	26.5 (4.5)	0.167
ASA classification (%)	–	–	–
I or II	66 (67.3)	94 (74.6)	0.233
III or IV	32 (32.7)	32 (25.4)	
Diabetes mellitus (%)	24 (24.5)	27 (21.4)	0.588
Severe heart disease (%)	15 (15.3)	13 (10.3)	0.263
Severe pulmonary disease (%)	5 (5.1)	15 (11.9)	0.077
WHO performance score pre-operative (%)	–	–	–
0	62 (63.3)	80 (63.5)	0.072
1	35 (35.7)	36 (28.5)	
2	1 (1)	9 (7.1)	
4	0	1 (0.8)	
Recent immunosuppressive treatment (%)	6 (6.1)	2 (1.6)	0.142
Preoperative chemotherapy or any radiotherapy to operating field (%)	20 (20.4)	20 (15.9)	0.379
Previous surgery to same abdominal region (%)	48 (49)	41 (32.5)	0.013
Surgical procedure (%)	–	–	–
Anterior rectum resection	39 (39.8)	43 (34.1)	0.382
Hemicolectomy (left or right)	33 (33.7)	61 (48.4)	0.027
Surgical major procedure (%)	91 (92.9)	115 (91.3)	0.665
Laparoscopic surgery (%)	36 (36.7)	76 (60.3)	< 0.001
Adherence to ERAS protocol recommendations			
Pre-admission education compliance (%)	39/98 (39.8)	102/126 (81)	< 0.001
Preoperative nutritional status assessment compliance (%)	55/87 (63.2)	123/126 (97.6)	< 0.001
Preoperative nutritional treatment compliance (%)	52/86 (60.5)	123/126 (97.6)	< 0.001
Alcohol usage compliance (%)	91/98 (92.9)	125/126 (99.2)	0.023
Smoking compliance (%)	89/98 (90.8)	122/126 (96.8)	0.056
Patient screened for anemia preop compliance (%)	21/21 (100)	106/106 (100)	–
Iron replacement treatment given compliance (%)	21/21 (100)	104/106 (98.1)	1.00
Carbohydrates preload compliance (%)	45/98 (45.9)	126/126 (100)	< 0.001
Preoperative oral bowel preparation (%)	71/92 (77.2)	107/126 (84.9)	0.144
Sedative compliance (%)	82/93 (88.2)	126/126 (100)	< 0.001
Antibiotic prophylaxis compliance (%)	89/98 (90.8)	126/126 (100)	< 0.001
Antithrombotic prophylaxis compliance (%)	58/95 (61.1)	124/126 (98.4)	< 0.001
PONV prophylaxis compliance (%)	96/96 (100)	125/126 (99.2)	1.00
Resection-site drainage compliance (%)	48/98 (49)	76/126 (60.3)	0.090
Systemic opioids given compliance (%)	57/98 (58.2)	124/126 (98.4)	< 0.001
Epidural/spinal compliance (%)	58/98 (59.2)	108/126 (85.7)	< 0.001
Nerve blocks or LA compliance (%)	7/90 (7.8)	20/126 (15.9)	0.076
Forced air heating compliance (%)	56/98 (57.1)	124/126 (98.4)	< 0.001
Nasogastric tube used postoperatively compliance (%)	53/98 (54.1)	120/126 (95.2)	< 0.001

Bold values indicates that p value is assumed to be statistically significant.

In order to assess the independent effect of compliance status on the primary endpoint, we performed a logistic regression model including the variables associated with the primary endpoint in univariate analysis (Table 4). In this model, compliance was independently associated with a reduced odds of the primary endpoint with an odds-ratio of 0.42 (95% CI 0.23–0.75, $p = 0.004$). Moreover, laparoscopic surgery was also independently associated with a reduced odd, having an odds-ratio of 0.46 (95% CI 0.25–0.84, $p = 0.012$) whereas male sex was associated with increased odds with an odds-ratio of 1.85 (95% CI 1.02–3.37, $p = 0.044$).

The analysis of secondary endpoints

The individual components of the primary endpoint were assessed as a secondary endpoint. Regarding postoperative complications, high compliance was independently associated with reduced risk of in-hospital complications with a odds-ratio of 0.45 (95% CI 0.25–0.81, $p = 0.008$) – 52.6% ($n = 51$) in non-compliant vs. 30.2% ($n = 38$) in compliant patients. Infectious complications and postoperative paralytic ileus were the most frequent complications (Supplement 1).

Table 3 Assessment of postoperative outcomes according to perioperative compliance.

Outcome	Non-compliant (n = 98)	Compliance \geq 75% (n = 126)	p-value	Univariate Analysis		Multivariate Analysis ^a	
						OR 95% CI	p-value
Composite postoperative event (complications + reoperations + readmissions) (%)	58/98 (59.2)	43/126 (34.1)	< 0.001			0.42 (0.23–0.75)	0.004
In-hospital postoperative complications (%)	51/97 (52.6)	38/126 (30.2)	0.001			0.45 (0.25–0.81)	0.008
Reoperations at 30 days (%)	11/98 (11.2)	10/126 (7.9)	0.402			0.66 (0.26–1.71)	0.394
Readmissions (%)	9/98 (9.2)	6/126 (4.8)	0.189			0.51 (0.16–1.58)	0.241
Analgesic adjuvants only (paracetamol, NSAIDs) (%)	69/98 (70.4)	111/126 (88.1)	0.001			3.36 (1.62–6.95)	0.001
30-day survival (%)	93/96 (96.9)	123/123 (100)	-			-	-
Surgery-to-discharge time, mean (SEM)	13.4 (1.8)	7.71 (0.7)	0.002			< 0.001	

Bold values indicates that p value is assumed to be statistically significant.

^a Adjusted for: Laparoscopic surgery, Preoperative chemotherapy or any radiotherapy to operating field, Hemicolectomy (left or right), Anterior rectum resection, age, gender, ASA physical status, compliance \geq 75%.

The rate of reoperation was not different between non-compliant and compliant patients although the number of events was low in both groups. Similarly, the rate of readmissions was not different between groups (**Table 3**).

The rate of use of only non-opioid adjuvants was also a secondary endpoint in our study. In fact, compliance was independently associated with reduced opioid prescription having a odds-ratio of OR 3.36, 95% CI 1.62–6.95 (**Table 3**).

Surgery-to-discharge time was included as a secondary endpoint and analyzed using a multivariate model. We performed a Cox regression adjusting for sex, ASA physical status, preoperative chemotherapy or any radiotherapy to operating field, anterior rectum resection, hemicolectomy (left or right), and laparoscopic surgery. In our model, perioperative compliance was independently associated with inferior surgery-to-discharge time. In fact, mean surgery-to-discharge time was 13.4 ± 1.8 in non-compliant patients and 7.71 ± 0.7 in compliant patients ($p < 0.001$) (**Fig. 2**).

Discussion

Our study analyzed the effects of high perioperative compliance with ERAS protocols on short-term surgical outcomes. We have found that a compliance score $\geq 75\%$ was independently associated with decreased risk of the composite endpoint of in-hospital complications, reoperations and readmissions. Furthermore, surgery-to-discharge time was

also reduced with protocol compliance independently of other covariates.

The study data was collected in order to audit the implementation of the ERAS program at our center. There were 224 consecutive patients included that were admitted to elective colorectal surgery in two different time periods – one before implementation of the ERAS program and other after ERAS protocols had been fully implemented. In our analysis, we compared patients with high compliance to the perioperative ERAS protocols, defined as compliance $\geq 75\%$,¹⁹ with patients with low compliance. Our study hypothesis was that higher compliance to protocols would be associated with improved results in what should be regarded as a hypothesis generator study. Below, we discuss the potential advantages and main limitations of our study in light of the published literature on this topic.

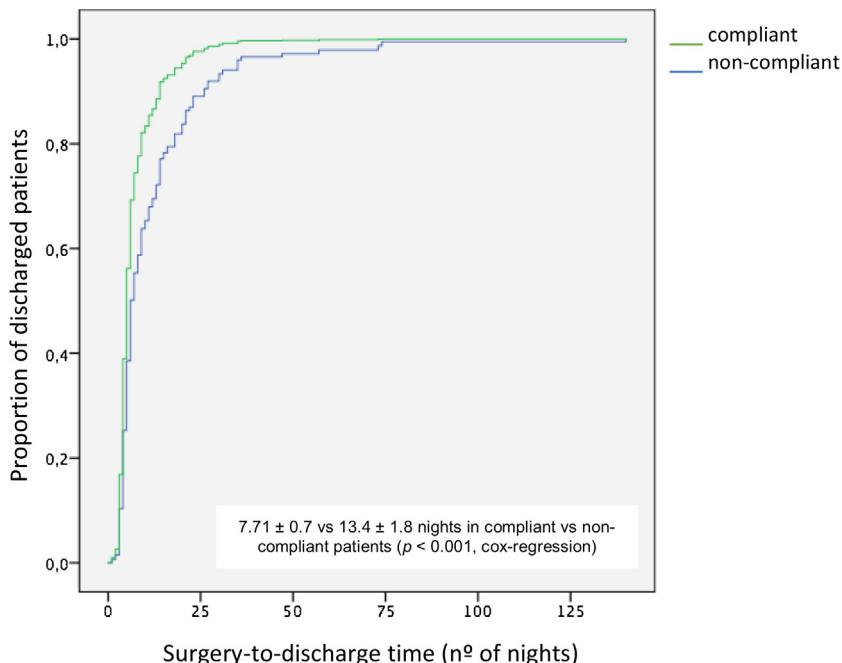
The ERAS guidelines were first published in 2005, but adoption of protocol principles has been slow in many countries and hospitals. There are huge barriers to protocol implementation like strong individualized surgeon and anesthesiologist-based preferences, complex systems of care, financial settlements and focus in traditional endpoints of mortality.²⁰ The published papers on ERAS protocols have focused most often on comparing patients included in the protocol vs. those managed with local guidelines. This comparison has been done independently of compliance. However, ERAS protocol is a perioperative assembly of elements, and benefits come from its whole application. The role of each separated element is hard to

Table 4 Multivariate analysis of the primary endpoint – composite of postoperative events.

Parameter	Total (n)	No composite postoperative event (n = 123)	Composite postoperative event (n = 101)	Univariate Analysis p-value	Multivariate analysis ^a	
					OR 95% CI	p-value
Perioperative compliance $\geq 75\%$ (%)	126	83 (65.9)	43 (34.1)	< 0.001	0.42 (0.23–0.75)	0.004
Age, median (IQR), years	70 (61–76.25)	69 (60–76)	70 (60.5–78.5)	0.401	1 (0.98–1.02)	0.974
Male sex (%)	128	60 (46.9)	68 (53.1)	0.005	1.85 (1.02–3.37)	0.044
ASA classification (%)	-	-	-	-	-	-
I or II	160	95 (59.4)	65 (40.6)	0.034	1.47 (0.74–2.9)	0.273
III or IV	64	28 (43.8)	36 (56.3)	-	-	-
Preoperative chemotherapy or any radiotherapy to operating field (%)	40	15 (37.5)	25 (62.5)	0.015	1.81 (0.8–4.2)	0.156
Surgical procedure (%)	-	-	-	-	-	-
Anterior rectum resection	82	38 (46.3)	44 (53.7)	0.05	1.33 (0.59–2.97)	0.494
Hemicolectomy (left or right)	94	60 (63.8)	34 (36.2)	0.023	0.97 (0.43–2.2)	0.949
Laparoscopic surgery (%)	112	77 (68.8)	35 (31.3)	< 0.001	0.46 (0.25–0.84)	0.012

Bold values indicates that p value is assumed to be statistically significant.

^a Adjusted for: Laparoscopic surgery, Preoperative chemotherapy or any radiotherapy to operating field, Hemicolectomy (left or right), Anterior rectum resection, age, gender, ASA physical status, compliance $\geq 75\%$.

**Figure 2** Adjusted length of stay according to compliance $\geq 75\%$.

define and probably not enough on its own to change outcomes. In order to increase ERAS protocol adherence, it is very important to demonstrate a beneficial effect of ERAS compliance on surgical outcomes. Furthermore, since in-hospital mortality for elective surgery is currently a rare event we should focus on alternative endpoints related to improved patient care.

When analyzing the impact of ERAS programs implementation, a shift towards compliance evaluation would further allow the assessment of individual elements and guide future versions of the protocol. However, there are some barriers to assess compliance. Overall compliance, as it is calculated by the EIIS, looks at protocol adherence and includes postoperative aspects (e.g., mobilization or energy intake). Postoperative events can also be regarded as outcomes. Therefore, it would be of outmost interest if the EIIS would be modified in order to exclude every variable that can be simultaneously an outcome and a protocol adherence parameter to properly evaluate compliance role in the perioperative period.

In order to avoid this limitation, several observational studies have tried to calculate their own compliance scores based on the analysis of individual elements. Authors have selected the variables of interest for their particular study and compliance thresholds have also been selected in a case-by-case manner.^{17,21,22} This scenario imposes several limitations to the comparison across surgical programs and makes it virtually impossible to conduct metanalysis of the effects of compliance on surgical outcomes.

In our work, the mean between pre-admission, preoperative and intraoperative compliance, as it is reported by the EIIS, was calculated in order to define the score of perioperative compliance. The 75% compliance threshold was defined in line with previously published data. Arrick et al. 2019¹⁹ has also used the 75% threshold; however, in literature, other thresholds can be found.²¹ A group of non-compliant patients, that comprise all the patients operated before ERAS implementation and the 27.6% ($n = 48$) of non-compliant patients operated after the implementation of the ERAS protocol was created.

The comparison between high vs. low compliance patients has several advantages. Firstly, the focus is on ERAS compliance rather a comparison between pre- or post-ERAS implementation outcomes where other treatment variables might also have changed. Secondly, given the observational nature of the study, the investigators were aware of the changes brought by ERAS implementation. However, since the research team were unaware of the compliance status when recording the outcomes, this helped to minimize bias in the evaluation of study results. Thirdly, by analyzing the effects of ERAS on surgical outcomes, we can estimate the event rates of each treatment group and contribute with our data for a sample size calculation used in a future trial.

A topic that deserves detailed discussion is the choice of outcomes for the assessment of ERAS protocols. Outcome measures should reflect the personal, social, and economic consequences of adverse events after major abdominal surgery. Our primary endpoint – composite postoperative event – includes the main incidents after major abdominal surgery. Compliant patients had an inferior risk of postoperative events independently of covariates. Furthermore, compliant patients had a shorter surgery-to-discharge

time and less frequent postoperative systemic opioid analgesia also independently of other risk factors. Off note, laparoscopic surgery was also independently associated with decreased risk of the postoperative primary endpoint whereas male sex was associated with increased risk.

Our results are in line with studies in different surgical fields that have shown that higher compliance with the protocol can improve surgical outcomes by allowing decreased morbidity and shortening the length of stay.^{13,17,21,23} Pisarka et al.,¹³ in a prospective cohort study, showed that full implementation of the ERAS protocol significantly improves short term outcomes. Patients with higher compliance had less postoperative morbidity rate and a shorter median length of stay. Gianotti et al.,¹⁷ in a report of observational data described association between an ERAS compliance > 70% and a reduced risk of complications. Zaouter et al., in a cardiac surgery population, suggested that the preoperative and intraoperative elements of the study's ERAS protocol offered appropriate conditions to start early mobilization, early feeding and early physiotherapy compared with the standard protocol.¹⁸ Together with these results, our conclusions reinforce that adherence to perioperative protocol guidelines improves postoperative outcomes.

Regarding pain management, we were able to demonstrate that the use of opioids was less frequent in our compliant patients' cohort. Pain control is a fundamental component of patient care. It is directly related to patient quality of life inside hospital and after discharge. Multimodal analgesia to minimize opioid consumption is of utmost importance in colorectal surgery to reduce postoperative ileus.² Regional analgesia with epidural analgesia for colorectal surgery is recommended in ERAS Society guidelines.² Lumbar supplementary analgesia and spinal adjunct to general anesthesia (the latter mainly in case of laparoscopic surgery) has been more recently added to guidelines and protocols and its use is still on growing. Spinal analgesia is considered simpler to administer and manage compared to epidural analgesia.²⁴ In Kjolhede et al.,²⁴ a randomized trial, spinal analgesia was given to patients submitted to midline laparotomy for gynecological malignancy under ERAS protocol routines. They have reported shorter length of stay in the spinal analgesia group, similar quality of life parameters and similar overall assessment of pain between both groups. This opioid-sparing approach in combination with early hospital discharge contributes to improving patient care.

The pathophysiological mechanisms behind the impact of ERAS protocols on surgical endpoints are varied. The catabolic effect⁹ associated with surgical procedures is believed to be detrimental to patients, and probably the main factor leading to postoperative morbidity. The ERAS protocols address these metabolic changes by minimizing stress response through controlling preoperative fasting and optimization of pre-operative status, by controlling intraoperative anesthetic and surgical factors associated with the stress response, by performing multimodality pain management and enhancing early postoperative rehabilitation.²⁵ This may justify the importance of a thorough implementation and compliance to the protocol.

Limitations

We acknowledge the limitations of our work in several domains. We have performed an observational study and therefore confounding factors cannot be eliminated from our analysis. We adopted a composite endpoint and individual components may not have the same importance to patients and magnitude of effect across components.²⁶ The research team was not blinded to the ERAS program implementation, although it was unaware of the compliance status of each patient when assessing the study outcomes. Moreover, neither the compliance threshold that we used nor the perioperative score are completely established in the literature, although we expect to have contributed to improvements in this regard. Our sample size is relatively small, it is a single center study, and the included patients were treated during a 3-years period which introduces heterogeneity. However, by focusing our analysis on compliance irrespective of the time of surgery with minimized the potential bias of comparing cohorts treated in a different time period.

Despite the acknowledged limitations, we believe that our study has merits in auditing our program and in generating the hypothesis that ERAS compliance might be of benefit to our patients. We firmly believe that only a randomized clinical trial will fully assess the effects of ERAS implementation. We hope that the data from our study can be used to prepare a clinical trial on this matter.

Conclusions

In our study, higher compliance to perioperative ERAS protocols is associated with less postoperative complications and a reduced surgery-to-discharge time. Given the observational nature of the data, the current study should be regarded as a hypothesis generator and the results confirmed in a randomized control trial. We recommend that a standardized definition of compliance thresholds and outcomes should be implemented in future ERAS programs to foster research on this important topic.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.08.018>.

References

1. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24:466–77.
2. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. *World J Surg*. 2019;43:659–95.
3. Wijk L, Udumyan R, Pache B, et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. *Am J Obstet Gynecol*. 2019;221:237.e1–11.
4. Elias KM, Stone AB, McGinigle K, et al. The Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) Checklist: A Joint Statement by the ERAS® and ERAS® USA Societies. *World J Surg*. 2019;43:1–8.
5. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, et al. Association between Use of Enhanced Recovery after Surgery Protocol and Postoperative Complications in Colorectal Surgery: The Postoperative Outcomes Within Enhanced Recovery after Surgery Protocol (POWER) Study. *JAMA Surg*. 2019;154:725–36.
6. Ripollés-Melchor J, Fuenmayor-Varela ML de, Criado Camargo S, et al. Enhanced recovery after surgery protocol versus conventional perioperative care in colorectal surgery. A single center cohort study. *Brazilian J Anesthesiol*. 2018;68:358–68.
7. Li J, Li H, Xv ZK, et al. Enhanced recovery care versus traditional care following laminoplasty: A retrospective case-cohort study. *Medicine (Baltimore)*. 2018;97:e13195.
8. Tan NLT, Hunt JL, Gwini SM. Does implementation of an enhanced recovery after surgery program for hip replacement improve quality of recovery in an Australian private hospital: A quality improvement study. *BMC Anesthesiol*. 2018;18:1–10.
9. Moningi S, Patki A, Padhy N, et al. Enhanced recovery after surgery: An anesthesiologist's perspective Srilata Moningi, Abhiruchi Patki, Narmada Padhy, and Gopinath Ramachandran Department. *J Anaesthesiol Clin Pharmacol*. 2019;35:S5–13.
10. Teixeira UF, Fontes PR, Conceição CW, et al. Implementation of enhanced recovery after colorectal surgery (ERAS) protocol: Initial results of the first Brazilian experience. *Arq Bras Cir Dig*. 2019;32:4–7.
11. Teixeira UF, Goldoni MB, Waechter FL, et al. Recuperação otimizada (ERAS) após cirurgia hepática: estudo comparativo de um centro terciário brasileiro. *Arq Bras Cir Dig*. 2019;32:e1424.
12. Gustafsson UO, Hause J, Thorell A, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg*. 2011;146:571–7.
13. Pisarska M, Pędziwiatr M, Małczak P, et al. Do we really need the full compliance with ERAS protocol in laparoscopic colorectal surgery? A prospective cohort study. *Int J Surg*. 2016;36:377–82.
14. Cavallaro P, Bordeianou L. Implementation of an ERAS Pathway in Colorectal Surgery. *Clin Colon Rectal Surg*. 2019;32:102–8.
15. Gharabeih A, Koppikar SJ, Bonilla-Escobar F. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) in the International Journal of Medical Students. *Int J Med Students*. 2014;2:36–7.
16. Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): Revised publication guidelines from a detailed consensus process. *BMJ Qual Saf*. 2016;25:986–92.
17. Gianotti L, Fumagalli Romario U, et al. Association Between Compliance to an Enhanced Recovery Protocol and Outcome After Elective Surgery for Gastric Cancer. Results from a Western Population-Based Prospective Multicenter Study. *World J Surg*. 2019;43:2490–8.
18. Zaouter C, Oses P, Assatourian S, et al. Reduced Length of Hospital Stay for Cardiac Surgery—Implementing an Optimized Perioperative Pathway: Prospective Evaluation of an Enhanced Recovery After Surgery Program Designed for Mini-Invasive Aortic Valve Replacement. *J Cardiothorac Vasc Anesth*. 2019;33:3010–9.
19. Arrick L, Mayson K, Hong T, et al. Enhanced recovery after surgery in colorectal surgery: Impact of protocol adherence on patient outcomes. *J Clin Anesth*. 2019;55:7–12.

20. Williams JB, McConnell G, Allender JE, et al. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *J Thorac Cardiovasc Surg.* 2019;157:1881–8.
21. Małczak P, Wysocki M, Twardowska H, et al. Impact of Adherence to the ERAS® Protocol on Short-term Outcomes after Bariatric Surgery. *Obes Surg.* 2020;30:1498–505.
22. Pisarska M, Torbicz G, Gajewska N, et al. Compliance with the ERAS Protocol and 3-Year Survival After Laparoscopic Surgery for Non-metastatic Colorectal Cancer. *World J Surg.* 2019;43:2552–60.
23. Petrick AT, Still CD, Wood CG, et al. Feasibility and impact of an evidence-based program for gastric bypass surgery. *J Am Coll Surg.* 2015;220:855–62.
24. Kjølhede P, Bergdahl O, Borendal WN, et al. Effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy: An open-label randomised trial. *BMJ Open.* 2019; 9:1–10.
25. Scott MJ, Miller TE. Pathophysiology of major surgery and the role of enhanced recovery pathways and the anesthesiologist to improve outcomes. *Anesthesiol Clin.* 2015; 33:79–91.
26. Myles PS, Devereaux PJ. Pros and cons of composite endpoints in anesthesia trials. *Anesthesiology.* 2010;113:776–8.



ORIGINAL INVESTIGATION

**Compliance with Enhanced Recovery After Surgery
(ERAS) protocol recommendations for bariatric surgery
in an obesity treatment center**



Júlia Gonçalves Zandomenico *, Fabiana Schuelter Trevisol , Jean Abreu Machado

Universidade do Sul de Santa Catarina, Tubarão, SC, Brasil

Received 30 May 2021; accepted 2 October 2021

Available online 25 December 2021

KEYWORDS

Bariatric surgery;
Enhanced recovery
after surgery;
Perioperative care

Abstract

Introduction: The higher risk of perioperative complications associated with obesity has made anesthesiologists increasingly concerned with the management of obese patients. Measures that improve bariatric surgery patient safety have become essential. The implementation of ERAS protocols in several surgical specialties has made it possible to achieve appropriate outcomes as to surgery safety. The aim of this study was to evaluate patient compliance with the recommendations of an ERAS protocol for Bariatric Surgery (ERABS) at a hospital specialized in obesity treatment.

Methods: Cross-sectional study, using a medical record database, in a hospital certified as an International Center of Excellence in Bariatric and Metabolic Surgery. The definition of the variables to be assessed was based on the most recent ERABS proposed by Thorell et al. Results were analyzed using descriptive epidemiology.

Results: The study evaluated all patients undergoing bariatric surgery in 2019. Mean compliance with the recommendations per participant was 42.8%, with a maximum of 55.5%, and was distributed as follows: 22.6% of compliance with preoperative recommendations, 60% to intraoperative recommendations, and 58.1% to postoperative recommendations. The anesthesiologist is the professional who provides most measures for the perioperative optimization of bariatric surgery patients. In our study we found that anesthesiologists complied with only 39.5% of ERABS recommendations.

Conclusions: Mean compliance with ERABS recommendations per participant was 42.8%. Considering that the study was carried out at a hospital certified as an international center of excellence, the need for introducing improvements in the care of patients to be submitted to bariatric surgery is evident.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. 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: juzandomenico@gmail.com (J.G. Zandomenico).

Introduction

Obesity is a public health problem whose incidence has progressively increased.^{1,2} Due to the higher risk of perioperative complications associated with obesity, anesthesiologists are increasingly concerned about the management of obese patients. Consequently, improving bariatric surgery safety has become essential.³ This explains the current trend toward implementing clinical protocols to optimize the perioperative management of obese patients, such as the Enhanced Recovery After Surgery (ERAS) protocol, aiming to improve outcomes.

The ERAS protocol comprises evidence-based recommendations seeking to reduce perioperative stress triggered by surgical trauma.⁴ ERAS recommendations include patient commitment, reduction of surgery-related physiological stress, reduction in postoperative complications, and increase in postoperative recovery rates.⁵ The measures are associated with decrease in morbidity, faster recovery, and shorter length of stay.⁶ Using ERAS protocols in bariatric surgery patients is associated with significant decrease in postoperative complications and length of stay, and subsequent reduction in hospital costs.⁷

The aim of this study was to assess patient compliance with the recommendations of an ERAS protocol for Bariatric Surgery (ERABS) at a hospital certified as an International Center of Excellence in Bariatric and Metabolic Surgery by the Surgical Review Corporation.

Methods

Design

After approval by the Research Ethics Committee of the institution, CAAE 38295620.0.0000.5369 and opinion 4.356.054, a cross-sectional study was carried out using a database, and both paper and electronic format patient medical charts.

Participants

We evaluated patients submitted to bariatric surgery using gastric bypass or sleeve gastrectomy techniques in 2019, totaling 150 patients. The study included patients over 18 years of age, regardless of sex, submitted to bariatric surgery at the hospital evaluated. No patients were excluded from the study.

Variables

We defined the variables to be evaluated based on the most recent ERABS protocol.⁴ They comprised sociodemographic characteristics; pre-existing comorbidities and medications in use; American Society of Anesthesiologists (ASA) classification performed by the anesthesiologist; presence of multidisciplinary team; occurrence of preoperative counseling performed by a psychologist; smoking cessation; difficult airway diagnosed by the anesthesiologist; measurement of preoperative fasting time for clear liquids and solid foods performed by the anesthesiologist; time and type of preoperative medications administered; preoperative oral carbohydrate conditioning; airway device used during surgery;

surgery technique; use of Train Of Four (TOF) and Bispectral Index (BIS) monitors intraoperatively; medications used for analgesia and Postoperative Nausea and Vomiting (PONV) prophylaxis; combination of different postoperative analgesia techniques; use of postoperative Nasogastric Tube (NGT); performance of thromboprophylaxis and therapeutic regimen ordered; time liquid diet was initiated; and time participant was discharged. Additionally, we analyzed the immediate complications considering any manifestation reported by the participant or the data entered into the medical chart. We also evaluated hospital readmission within 30 days after surgery, comprising the reason for readmission and its outcome.

Statistical analysis

Categorical variables are presented as absolute frequencies and proportions, and continuous variables as means and standard deviation. The percentage of compliance per participant was calculated using simple arithmetic mean.

Results

Perioperative risk assessment was performed considering sociodemographic characteristics, such as sex, age, comorbidities, medications in use and the anesthesiologist's preanesthesia assessment. Data are presented in Table 1. Mean BMI was 41.9 kg.m^{-2} , with minimum and maximum values of 31.4 and 63.2, respectively. Mean age was 37 years (SD 10 years), with minimum and maximum age of 19 and 67 years, respectively.

Regarding the distribution of the multidisciplinary team professionals, a psychologist was present for 95.3% of the participants ($n = 143$), a nutritionist for 87.3% ($n = 131$), physical therapist for 78% ($n = 117$), and a psychiatrist for 3.3% ($n = 5$). Preoperative psychologist counseling was provided at the hospital for 40.7% of participants ($n = 61$). None of the participants ($n = 0$) received instructions regarding hospital discharge on the first postoperative day. Twelve participants were smokers and smoking cessation advice was given to 41.6% ($n = 5$). Among participants receiving smoking cessation advice, all of them ($n = 5$) continued to smoke up to the surgical procedure.

Before hospital admission the anesthesiologist performed preanesthesia assessment in 100% of the participants ($n = 150$) and airway assessment was registered on the medical chart for 72.7% of the participants ($n = 109$). Of these, 44% ($n = 48$) did not show any abnormal finding. Among abnormal findings after airway assessment, we registered Mallampati 1 in 55% ($n = 60$) and Mallampati > 2 in 44.9% ($n = 49$), neck circumference > 40 cm in 32.1% ($n = 35$), thyromental distance < 6 cm in 10% ($n = 11$) and interincisal distance < 3 cm in 3.6% ($n = 4$). We found the presence of more than one abnormal finding in 22% of participants ($n = 24$).

Mean fasting time for both clear liquids and solid foods verified by the anesthesiologist was 8 hours. The administration of anesthesia premedication was decided for 40.7% of the participants ($n = 61$), in decreasing order of prevalence: alpha-2-agonist in 57.3% ($n = 35$), antiemetic in 44.2% ($n = 27$), benzodiazepine in 42.6% ($n = 26$), and H2 antagonist

Table 1 Perioperative risk assessment of the patients submitted to bariatric surgery (n = 150).

	n	%
Sex		
Male	41	27.3
Female	109	72.7
Age		
19–30 years	43	28.7
31–50 years	87	58.0
> 50 years	20	13.3
BMI		
30–34.9	9	6.0
35–39.9	48	32.0
≥ 40	93	62.0
Comorbidities		
Arterial hypertension	50	33.3
Liver steatosis	37	24.7
OSAHS	34	22.7
Diabetes mellitus	29	19.3
GERD	26	17.3
Esophageal hernia	21	14.0
Psychiatric disorder	20	13.3
Dyslipidemia	8	5.3
Others	30	20.0
Medications in use		
Anti-hypertensive	47	31.3
Hypoglycemic	17	11.3
Lipid-lowering drugs	7	4.7
Platelet Antiaggregant	5	3.3
Anticoagulant	1	0.7
Psychotropics	35	23.3
Oral contraceptive	43	28.7
Habits		
Smoking	12	8.0
Alcohol consumption	23	15.3
Not applicable	118	78.7
ASA physical status		
I	3	2.0
II	89	59.3
III	58	38.7

OSAHS, Obstructive Sleep Apnea Hypopnea Syndrome; GERD, Gastroesophageal Reflux Disease; ASA, American Society of Anesthesiologists.

in 40.9% (n = 25). Mean time of premedication administration was 111 minutes before surgery. Preoperative oral carbohydrate conditioning was performed in 2% of the participants (n = 3), and the carbohydrate chosen was maltodextrin (n = 3).

Orotracheal intubation combined with the laparoscopic approach was used for 100% of participants (n = 150). TOF and BIS monitor devices were never used (n = 0), thus monitoring of neuromuscular blockade or depth of anesthesia was absent in all participants. Notwithstanding the latter, neuromuscular blockade reversal was performed in 74% of participants (n = 111) using neostigmine in 91% (n = 101) and sugammadex in 9% (n = 10). We were unable to evaluate protective mechanical ventilation strategies as they were not registered on medical charts.

Multimodal PONV prophylaxis was administered to 95% of participants (n = 141). On the other hand, multimodal analgesia was ordered for 74% of participants (n = 111). Dipyrone was administered to 94.7% of participants (n = 142), and non-steroidal anti-inflammatory drugs to 92% (n = 138), opioids to 88% (n = 132), alpha-2-agonist to 60% (n = 90), magnesium sulfate to 34.7% (n = 52) and ketamine to 33.3% (n = 50). Only three participants (2%) received another drug combination for postoperative analgesia, and surgical wound infiltration was performed in these cases.

Opioids for postoperative analgesia were used in 88% (n = 132) of participants and morphine was the opioid of choice for all of them, with a mean administered dose of 9.6 mg. Rescue medication for postoperative pain control was required for 24% of participants (n = 36). To manage this scenario, 17.3% of participants (n = 26) received opioids such as morphine or methadone, with a mean administered dose of 7.8 mg. Instead, 6.7% of participants (n = 10) received 100 mg tramadol.

None of the patients required a nasogastric tube postoperatively (n = 0). Mechanical methods for thromboprophylaxis were performed in all (n = 150) participants. As to pharmacological thromboprophylaxis, low molecular weight heparin was administered to 91.3% of participants (n = 137) and unfractionated heparin to 8% (n = 12).

The mean time to start the restricted liquid diet was 24.3 hours, and to be discharged from hospital was 2.03 days. **Table 2** depicts the prevalence of immediate complications, outcome, and readmission within 30 days. Only one participant (0.6%) required revision surgery during readmission.

Figure 1 presents variables regarding compliance with the measures that are strongly recommended by the ERABS protocol. Mean compliance with the recommendations was 42.81% per participant, with a minimum of 26.32% and a maximum of 55.56%, distributed as follows: 22.6% of compliance with preoperative, 60% to intraoperative and 58.1% to postoperative recommendations.

In addition, we registered the compliance rate with the recommendations according to the professionals involved in patient care. Anesthesiologists are the caregivers with the

Table 2 Perioperative characteristics of patients submitted to bariatric surgery.

	n	%
Immediate complications	86	57.3
Abdominal pain	61	40.7
Nausea	32	21.3
Respiratory distress	4	2.6
Bleeding	2	1.3
Allergy	2	1.3
Fall	1	0.6
Others	6	4.0
Readmission reason	11	7.3
Abdominal pain	10	6.6
Sudden malaise	1	0.6
Outcome		
Discharge	149	99.4
Death	1	0.6

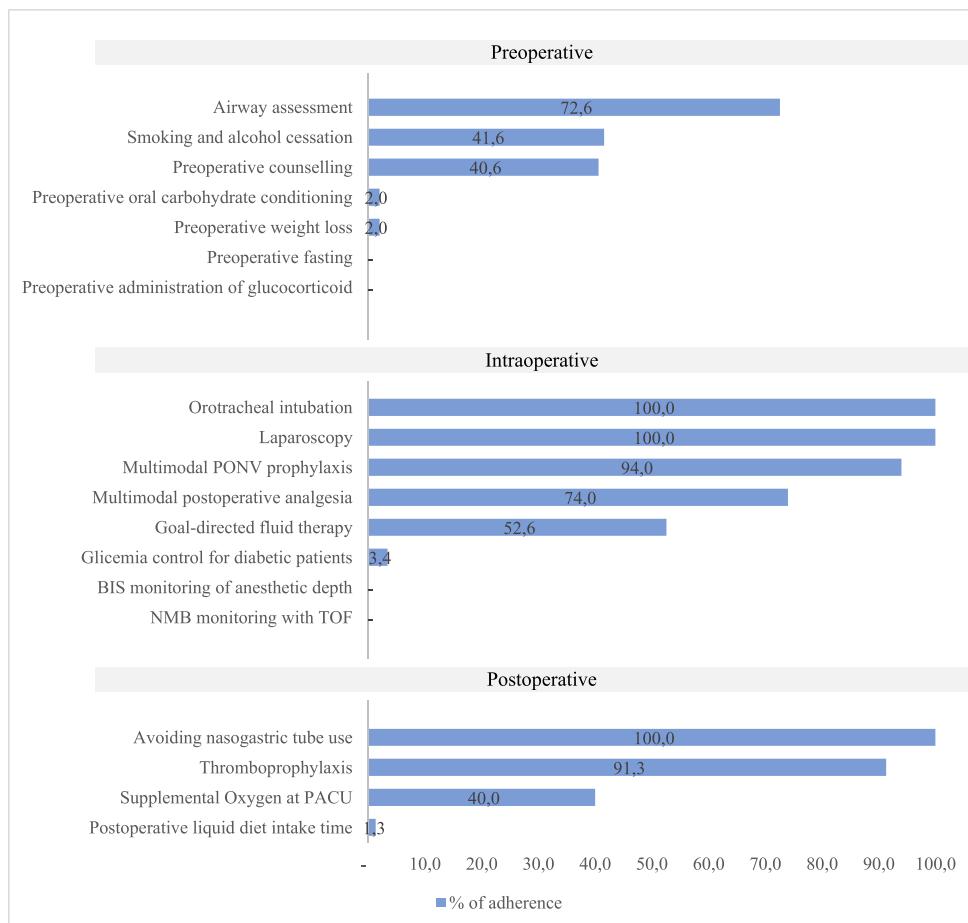


Figure 1 Compliance to measures strongly recommended in the ERAS protocol for bariatric surgery. PONV, Postoperative Nausea and Vomiting; BIS, Bispectral Index; NMB, Neuromuscular Blockade; TOF, Train-Of-Four; PACU, Postanesthetic Care Unit.

highest percentage of recommendations to be complied with, which is 61.1%. In this study, anesthesiologists complied with only 39.1% of the recommendations they were accountable to. Surgeons were the caregivers that achieved the highest rate of compliance with recommendations, or 73.1%.

Discussion

Interest in ERAS protocols have recently increased considerably worldwide. Deficits in teaching and training hospital staff have been revealed,⁵ and lack of compliance with existing recommendations is a health concern.⁸ The interval between arrival of scientific evidence and its implementation in clinical practice is 15 years on average.⁹ Conversely, benefits to patients and institutions are immediate. Therefore, implementing evidence-based recommendations has become the best practice in medicine.

Since 2015, the hospital evaluated in this study has been one of 11 hospitals in Brazil, and the only one in State of Santa Catarina to be certified as an International Center of Excellence in Bariatric and Metabolic Surgery by the Surgical Review Corporation. Despite accreditation and professionals

committed to improving their practice and hospital outcomes, implementing recommendations is often challenging.

Patients are followed by a multidisciplinary team from the beginning of treatment at the bariatric surgery unit of the hospital studied. Indeed, multidisciplinary care is crucial to improve surgical outcomes as it facilitates the interaction among intra-hospital processes.⁵ Preoperative counselling performed at the hospital was given to less than half of participants. This contrasts with several reports^{4,7,10} that have emphasized that preoperative counselling is key to lesser anxiety and improves compliance with postoperative instructions, postoperative recovery, length of stay and long-term outcome.⁴ Our study also revealed that the most absent professional in the multidisciplinary team was the physical therapist. This finding contrasts with current recommendations^{4,11,12} that emphasize physical therapy as an essential element in the management of surgical patients. This scenario may reveal a transitional period for patient care at the hospital assessed, and at other centers,¹¹ as the multidisciplinary approach has been gradually appreciated and implemented in surgical patient management.

Smoking cessation was recommended to all smokers. However, less than half of smokers complied with the recommendation. The current recommendation is to stop smoking

at least four weeks before surgery.⁴ Continuing to smoke during the preoperative period is associated with both greater morbidity and mortality.^{4,13} Particularly in bariatric surgery, there is evidence that smokers have a higher risk of anastomotic ulceration in Roux-en-Y gastric bypass.^{7,14}

Preoperative fasting instructions are provided during the preanesthetic consultation. Although we did not register a relevant percentage of compliance, this measure has been already endorsed by anesthesiology societies that currently recommend two hours of fasting for clear liquids and six hours for solid foods in healthy and obese patients.¹⁵ Longer fasting time has a negative effect on overall patient recovery, triggering, for instance, increase in insulin resistance and metabolic consequences.¹⁶ Therefore, it is wise to promote efforts to attain adequate fasting time for the obese patient.¹¹ However, standardizing and achieving appropriate fasting time is challenging, mainly due to the variability of operating room lists and schedules. Therefore, the goal can be accomplished by an effort to schedule bariatric surgery in the first time slot of the day in the operating room list.

The anesthesiologist is also advised to perform preoperative oral carbohydrate conditioning. This measure is well established for major elective abdominal surgeries and has a strong grade of recommendation.⁴ However, further studies are required to evaluate this measure both in bariatric surgery patients with gastroesophageal reflux disease, due to the possible increased risk of bronchial aspiration during anesthetic induction, and in patients presenting diabetes,⁷ which may explain the low compliance with the measure in this study and in other centers.⁷

During hospitalization, most of the participants in our study received preanesthetic medication, in disagreement to current protocols^{4,7} which emphasize not using premedication, especially benzodiazepines, which represented 42.6% of the pre-medication ordered in this study. The likely key factor explaining this behavior is the resistance to change of professionals, already reported in other centers.⁹ Professionals should be encouraged not to order preanesthetic medication, replacing it by other modalities of preoperative anxiety management, such as the preoperative visit performed by a health professional involved in patient care.

PONV prophylaxis is pivotal, especially if one considers the studied population, which presents a high risk for post-operative nausea and vomiting.^{4,17} The population studied presents an additional PONV risk factor, that is high prevalence of using inhaled anesthetic agents for anesthesia maintenance and opioids for postoperative analgesia. Similar to other pre-ERAS studies,^{3,18} we did not observe compliance with the ERABS⁴ protocol recommendation of preoperative glucocorticoid administration. Possibly, the major determining factor is the operational challenge in delivering this measure. Thus, studies to evaluate implementation have decided to include the administration of glucocorticoids during anesthetic induction.^{3,7}

Anesthetic care in the perioperative period is not limited to providing anesthesia, but also comprises postoperative pain management.¹⁶ Consequently, multimodal analgesia is another recommendation described. Despite having found a high compliance rate of 74%, the recommendation is to provide postoperative analgesia whenever possible.⁴ The main objective is to reduce the consumption of narcotics,^{7,19} which was not found in this study, as both the rate of opioid use and the mean dose

per participant were high. We reported a lower prevalence use of other groups of drugs, such as alpha-2-agonists, ketamine, and magnesium sulfate. Indeed, despite the disadvantages of opioid administration and the emergence of scientific evidence advising to use other drugs, opioids have not yet been completely replaced in the treatment of moderate to severe acute postoperative pain,²⁰ justifying the high prevalence of use. Consequently, a current attempt is being made to combine techniques, such as surgical wound infiltration or transverse abdominal plane block.^{4,16,20}

Another extremely important element of perioperative optimization is the intraoperative monitoring of anesthetic depth and neuromuscular blockade. The hospital studied does not have the equipment to carry out this monitoring, explaining the non-compliance with this recommendation. The barriers our hospital administration met for implementing new technologies were costs, technical support and maintenance, and resistance to change, like those observed in other centers.²¹

In this study the ERABS compliance rate per participant is considered low and comparable to the rate found elsewhere.^{8,22} As the ERABS protocol spreads and efforts are made to incorporate its elements into clinical practice, a significant increase in ERABS compliance is expected. It is essential that health institutions assess behaviors and outcomes to subsequently analyze and correct errors to enhance their outcomes. The most complex recommendations to be implemented depend on the integration and support of the hospital administration, reflecting, in part, professionals' challenges to match their practices with current evidence. Considering that this study was carried out at a hospital certified as a center of international excellence, the need to introduce improvements in the care of patients undergoing bariatric surgery becomes evident.

Anesthesiologists are the chief players and proponents of those changes inside hospital organization. In addition to being accountable for the highest number of elements in perioperative optimization of bariatric surgery patients, the anesthesiologist is also responsible for the patient's overall recovery and, thus, plays a role as a modifier of hospital outcomes. Studies evaluating the implementation of perioperative optimization protocols in colorectal surgery²³ have shown that anesthesiologists are essential to promote perioperative optimization, and their main measures independently associated with reduction in hospital stay are multimodal PONV prophylaxis, standardized use of non-steroidal anti-inflammatory drugs for postoperative analgesia, and strict compliance with a postoperative opioid administration protocol. These are everyday acts and, therefore, they often become trivialized, underestimating their relevance to patient recovery. Anesthesiologists' role can be extended to several aspects of surgical patient care and should not be circumscribed to delivering anesthesia. Thus, the need to include anesthesiologists more in several elements of surgical patient management is evident.

This study reveals how challenging it is to implement perioperative optimization measures in the bariatric surgery clinical pathway. One limitation of the study was the use of secondary data; thus, it is essential to proceed with further analysis using primary data. As a reference center for bariatric surgery, the service receives patients from different locations, which is a bias for the analysis of some variables, such

as preoperative care and hospital readmission, which may have occurred in facilities other than the hospital studied.

Conclusion

The mean ERABS compliance rate per participant was 42.8%. Considering that the study was carried out at a hospital certified as an international center of excellence, the need for improvement in the care of patients to be submitted to bariatric surgery is evident. The anesthesiologist is the professional accountable for most of the measures that impact the perioperative optimization of bariatric surgery patients, and should be seen, increasingly, as a protagonist in the management of these patients.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.bjane.2021.10.018](https://doi.org/10.1016/j.bjane.2021.10.018).

References

1. Bentham J, Di Cesare M, Bilano V, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;390:2627–42.
2. Malik VS, Willett WC, Hu FB. Nealy a decade on - trends, risk factors and policy implications in global obesity. *Nat Rev Endocrinol*. 2013;9:13–27.
3. Barreca M, Renzi C, Tankel J, et al. Is there a role for enhanced recovery after laparoscopic bariatric surgery? Preliminary results from a specialist obesity treatment center. *Surg Obes Relat Dis*. 2016;12:119–26.
4. Thorell A, MacCormick AD, Awad S, et al. Guidelines for perioperative care in bariatric surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. *World J Surg*. 2016;40:2065–83.
5. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery a review. *JAMA Surg*. 2017;152:292–8.
6. Currie A, Burch J, Jenkins JT, et al. The impact of enhanced recovery protocol compliance on elective colorectal cancer resection: results from an international registry. *Ann Surg*. 2015;261:1153–9.
7. Dang JT, Szeto VG, Elnahas A, et al. Canadian consensus statement: Enhanced Recovery After Surgery in bariatric surgery. *Surg Endosc*. 2020;34:1366–75.
8. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348:2635–45.
9. Lassen K, Hannemann P, Ljungqvist O, et al. Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. *Br Med J*. 2005;330:1420–1.
10. Taylor J, Canner J, Cronauer C, et al. Implementation of an enhanced recovery program for bariatric surgery. *Surg Endosc*. 2020;34:2675–81.
11. Trotta M, Ferrari C, D'Alessandro G, et al. Enhanced Recovery After Bariatric Surgery (ERABS) in a high-volume bariatric center. *Surg Obes Relat Dis*. 2019;15:1785–92.
12. Duymaz T, Karabay O, Ural IH. The effect of chest physiotherapy after bariatric surgery on pulmonary functions, functional capacity, and quality of life. *Obes Surg*. 2020;30:189–94.
13. Mills E, Eyawo O, Lockhart I, et al. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. *Am J Med*. 2011;124:144–54.
14. Spaniolas K, Yang J, Crowley S, et al. Association of long-term anastomotic ulceration after roux-en-y gastric bypass with tobacco smoking. *JAMA Surg*. 2018;153:862–4.
15. Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011;28:556–69.
16. Horosz B, Nawrocka K, Malec-milewska M. Anaesthetic perioperative management according to the ERAS protocol. *2016;48:49–54*.
17. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131:411–48.
18. Derderian SC, Rove KO. Enhanced Recovery After Surgery among adolescents undergoing bariatric surgery. *Semin Pediatr Surg*. 2020;29:150885.
19. Ziemann-Gimmel P, Hensel P, Koppman J, et al. Multimodal analgesia reduces narcotic requirements and antiemetic rescue medication in laparoscopic Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis*. 2013;9:975–80.
20. Rawal N. Current issues in postoperative pain management. *Eur J Anaesthesiol*. 2016;33:160–71.
21. Kruse CS, Kristof C, Jones B, et al. Barriers to electronic health record adoption: a systematic literature review. *J Med Syst*. 2016;40.
22. Loughlin SM, Alvarez A, Falcão LFDR, et al. The history of ERAS (Enhanced Recovery After Surgery) Society and its development in Latin America. *Rev Col Bras Cir*. 2020;47:1–8.
23. Grant MC, Roda CMP, Canner JK, et al. The impact of anesthesia-influenced process from an Enhanced Recovery After Surgery for colorectal surgery cohort. *Anesth Analg*. 2019;128:68–74.

ORIGINAL INVESTIGATION

Early versus late sphenopalatine ganglion block with ropivacaine in postdural puncture headache: an observational study



Nelson S. Santos *, Joana M. Nunes, Maria L. Font, Cristina Carmona, Maria M. Castro

Hospital Professor Dr. Fernando Fonseca, Department of Anesthesiology and Pain Medicine, Amadora, Portugal

Received 10 May 2020; accepted 23 January 2021

Available online 21 March 2021

KEYWORDS

Postdural puncture headache;
Sphenopalatine ganglion block;
Timing;
Ropivacaine

Abstract

Background: Postdural puncture headache (PDPH) is a common complication of neuraxial techniques which delays patients' discharge. Sphenopalatine ganglion block (SPGB) is a safe bedside technique with comparable efficacy to Epidural Blood Patch, the gold-standard treatment. There is no evidence on the ideal timing for SPGB performance. We aimed to evaluate the difference between early versus late SPGB concerning efficacy, symptom recurrence and hospital length of stay.

Methods: We present an observational study with 41 patients diagnosed with PDPH who were submitted to SPGB with ropivacaine 0,75%. The study sample ($n = 41$) was divided in two groups: an early (less than 24 hours after diagnosis) and a late (more than 24 hours after diagnosis) SPGB group. Pain was evaluated 15 minutes after the block and follow up occurred daily until patients were discharged. Patients' demographic characteristics, neuraxial technique, timing of SPGB, qualitative pain relief and post-SPGB length of stay were registered and analyzed with SPSS statistics (v26) software.

Results: Early SPGB resulted in a significant reduction in length of stay ($p = 0,009$) and symptom recurrence ($p = 0,036$), showing equally effective pain relief, compared to late SPGB.

Conclusions: SPGB was equally effective in both groups. Data showed that early SPGB reduces length of hospital stay and symptom recurrence, which potentially allows early resumption of daily activities and a reduction in total health costs.

© 2021 Published by Elsevier Editora Ltda. 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/>).

* Corresponding author.

E-mail: nelson.santos@hff.min-saude.pt (N.S. Santos).

Introduction

Postdural puncture headache (PDPH) is a common complication of neuraxial techniques with an incidence of 1–2%.¹ It is classified by the International Classification of Headache Disorders 3rd edition (ICHD-3) as a headache attributed to low cerebrospinal fluid (CSF) pressure, caused by loss of CSF exceeding its production rate.² PDPH can be debilitating, with severe implications affecting daily activities, delaying recovery, and extending hospital stay with associated health care costs.^{3,4} Common symptoms include severe frontal and occipital postural headache, often accompanied by neck stiffness, hearing and visual disturbances, nausea, vomiting or tinnitus.³ The standard treatment is still epidural blood patch (EBP) with a success rate of 68 to 90%.⁵ Although, this is an invasive technique susceptible to complications, such as bleeding, infection, and neurological impairment.^{3,5}

The sphenopalatine ganglion (SPG), also known as Meckel's ganglion, is located 2–3 mm underneath the posterior nasal mucosa, in the pterygopalatine fossae. It is a junction of sympathetic, parasympathetic and sensory innervations that overlap in a small area, mediating pain due to various causes.⁶ Topical transnasal SPG block (SPGB) is a noninvasive treatment first described in 1908 by Sluder,⁷ which since then has been used for the treatment of headaches due to several etiologies.⁴ The procedure is safe, easy to learn, and can be accurately performed in the emergency room.⁶

Literature evidence on the SPGB analgesic efficacy on PDPH is limited and is mainly available in the form of case reports and case series, most using lidocaine and limited to the obstetric population. None of the available studies refer to the ideal timing of SPGB performance after the diagnosis of PDPH.

We conducted an observational study to evaluate the difference between early (less than 24 hours) and late (more than 24 hours) performance of SPGB after PDPH diagnosis, using ropivacaine 0,75%. Our main hypothesis was that the early application of SPGB would allow effective pain control, with faster recovery and earlier discharge.

Methods

We conducted an observational retrospective study approved by the ethics committee of our institution, in accordance with the Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects. According to the ICHD-3 criteria², all the patients diagnosed with PDPH between March 2018 and December 2019 were enrolled. An individual written informed consent for participation was obtained from each patient enrolled. The PDPH diagnostic delay was no more than 48 hours after the beginning of the symptoms. Exclusion criteria were: patient's age under 18 years, SPGB refusal or the existence of contraindications to the technique (coagulopathy, nasal septal deviation, nasal polyps, epistaxis history, or allergy to local anesthetics).

Of 67 eligible patients, 26 did not receive SPGB, hence were excluded. Twenty-five of these patients received conservative treatment and one an EBP, according merely to the anesthesiologist's experience. Anesthesiologists' approach

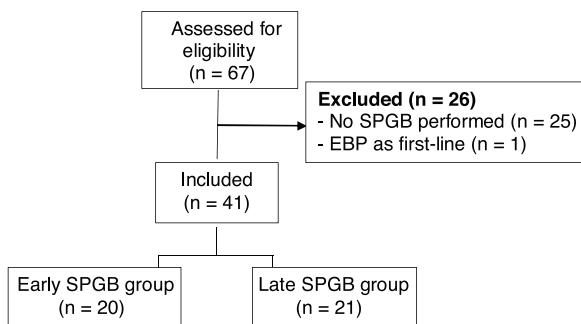


Figure 1 Flow Chart.

to PDPH differ significantly in our hospital, both in terms of treatment options offered and timing of SPGB performance. We aimed to standardize the department's practice with this study but still encountered significant differences in timing of SPGB performance. Hence, as shown in Figure 1, the enrolled patients (n = 41) were divided in two main groups according to the SPGB timing, which was determined exclusively by the anesthesiologist's preference: an early SPGB group that received the block less than 24 hours after diagnosis (n = 20); and a late SPGB group that received the block more than 24 hours after diagnosis (n = 21).

The SPGB technique was performed with the patient supine, in sniffing position. A cotton swab soaked with ropivacaine 7,5 mg.mL⁻¹ was introduced in each nostril until resistance was encountered. Additionally, 1 mL of local anesthetic was applied in each nostril through the shaft. The swabs remained in place for 15 minutes, after which they were removed. All the patients without contraindication also received intravenous analgesia with paracetamol 1 g q6/6 h, a non-steroid anti-inflammatory (metamizole 1 g q8/8 h) and tramadol 100 mg q8/8 h as rescue analgesia. Pain relief was assessed 15 minutes after the block with 45° head of bed elevation. A simplified quantitative pain scale was used, asking the patients to rate their pain relief as "No relief", "Minor relief", "Moderate relief", or "Total relief". Follow up occurred daily with evaluation of pain control, treatment side-effects and symptom recurrence. Upon discharge all patients were instructed to contact their attending doctor or the emergency department if they had recurrence of symptoms. We emphasize that, in our sample, PDPH was the only medical concern prolonging the hospital stay.

The variables registered were the demographic characteristics of the patients, type of neuraxial technique executed, timing of SPGB application, qualitative pain relief, and post-SPGB length of hospital stay.

Our primary endpoint was to evaluate differences in efficacy between early (< 24 h) versus late SPGB (> 24 h). Our secondary outcomes were to evaluate differences in symptom recurrence and post-SPGB length of stay between the two groups. Data were expressed as median or mean ± standard deviation (SD), or number where appropriate. All analyses were performed with IBM SPSS statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Normalization was tested using the Shapiro-Wilk test. Association between categorical variables was evaluated using χ^2 test and the association between continuous variables was eval-

Table 1 Patients' characteristics. Results presented as number (% of total).

Variables	Total (n = 41)	SPGB		p-value
		Early (n = 20)	Late (n = 21)	
Mean age-years (SD)	33.5	35.1 (\pm 9.1)	31.9 \pm 7.9	0.231
Gender				
Male	5	2 (10.0%)	3 (14.3%)	1.000
Female	36	18 (90.0%)	18 (85.7%)	
Surgical specialty				
Obstetric	24	11 (55.0%)	13 (61.9%)	0.756
Others (General Surgery, Urology, Gynecology, and Orthopedics)	17	9 (45.0%)	8 (38.1%)	
Neuraxial technique				
Spinal (Quincke-25 or 27G)	37	18 (90.0%)	19 (90.5%)	1.000
Combined spinal-epidural or epidural	4	2 (10%)	2 (9.5%)	

Table 2 Early versus Late SPGB outcomes. Results presented as mean or number (%).

Variables	Total (n = 41)	SPGB		p-value
		Early (n = 20)	Late (n = 21)	
Pain relief at 15 minutes				
“Total relief”	35	17 (85.0%)	18 (85.7%)	1.000
“No relief”, “minimal” or “moderate relief”	6	3 (15.0%)	3 (14.3%)	
Symptom recurrence	10	2 (10.0%)	8 (38.1%)	0.036
Post-SPGB length of stay (days)		2 \pm 1.6	3.2 \pm 1.5	0.009

uated using Student's *t*-test and Mann-Whitney test. A *p*-value < 0.05 was considered statistically significant.

Results

Forty-one patients were included in the analysis. Patients' characteristics, type and context of neuraxial techniques are presented in **Table 1**. There were no statistically significant differences in these characteristics between both groups.

SPGB was equally effective for pain relief in both groups (85% vs. 85.7%, *p* = 1) as seen in **Table 2**. Twelve patients were discharged home on the same day or in less than 24 hours after the SPGB, without recurrence of symptoms. No SPGB side effects were reported.

Early SPGB was associated with a statistically significant reduction in symptom recurrence (*p* = 0.036) and length of stay after the block (*p* = 0.009), as seen in **Table 2**. Nine patients (45%) in the early SPGB group were discharged home in less than 24 hours after the block. Patients in the late SPGB group had a higher rate of symptom recurrence (38.1% vs 10%, *p* < 0.05). Only two patients with symptom recurrence required rescue therapy due to persistent severe symptoms, one received a second SPGB and the other an EBP. After hospital discharge, there were no patients with recurrence of symptoms.

Discussion

The SPG is an extracranial parasympathetic ganglion, composed of multiple autonomic, sensory, and motor neural

connections. For many years it has been accepted that PDPH results from the disruption of CSF homeostasis.⁸

Low CSF pressure causes the loss of the brain's buoyant support, which is thought to allow it to sag in the upright position, resulting in traction on pain sensitive structures in the cranium. However, the actual means by which CSF hypotension generates headache is debatable. It is currently described as a bimodal mechanism involving both loss of intracranial support and cerebral vasodilation mediated by parasympathetic nerve fibers travelling through the SPG. SPGB is believed to be effective in PDPH pain reduction by blocking these preganglionic parasympathetic nerve fibers.⁹

To our knowledge, this is the first observational study comparing different timing for SPGB performance in PDPH. In our sample, SPGB showed equal effectiveness in pain reduction between the early and late SPGB groups. Early performance of SPGB showed a statistically significant reduction in length of stay and symptom recurrence. One could speculate that, as a first-line therapy, SPGB could result in better outcomes, allow earlier resumption of daily activities, improve patients' satisfaction and potentially reduce health care costs.

When comparing SPGB to EBP in a study with 20 obstetric patients with resistant PDPH, after a course of 7 days on conservative therapy, Nitu et al.⁵ concluded that SPGB produced faster analgesia than EBP or conservative measures. Although the effectiveness in pain relief was evident, the authors did not report data on symptom recurrence or time to discharge.

In our study, rescue analgesic therapy after the SPGB performance was only required in two patients (10%). Comparing to the results obtained by Cohen et al.,¹⁰ this is a significantly lower recurrence rate, which may be related

to possible diagnostic or treatment delays, which were not specified by this author in the manuscript. This difference may also be related to variations in the pharmacokinetics of the local anesthetic used. However, the ideal local anesthetic and the subsequent duration of the analgesic effect remain poorly defined, as stated by Furtado et al.¹¹

Over the years, several PDPH therapies ranging from conservative to invasive procedures have been tried, with insufficient literature support.¹⁰ There is no evidence that conservative measures like bed rest, supplemental intravenous fluid or intravenous analgesics help improve PDPH.³ Despite this, many practitioners still use these conservative therapies and wait spontaneous recovery of PDPH. Compared to the gold-standard treatment with EBP, SPGB is safer, easier to learn, can be performed in an uncontrolled setting like the emergency department and has a low incidence of complications.⁴

Very few studies on the application SPGB for PDPH exist and most have small unrepresentative patient samples limited to the obstetric population.^{10–13} Our findings are in agreement with recent case reports, case series, and retrospective reviews on the efficacy of SPGB in PDPH treatment.^{10–12,14,15} However, compared to our study, the former were limited to obstetric population, lidocaine was the local anesthetic of choice, and outcomes like length of stay or timing of SPGB application were not registered or evaluated. Hence, data on the optimal timing of SPGB application is still lacking.

Several limitations prevent us from generalizing our results. We used a small convenience sample and patients were not randomized between groups, which could have introduced bias in the results. Our study's results would have been stronger if we conducted it as a randomized prospective clinical trial with a larger sample size. Although SPGB involves a simple technique which we tried to standardize in our department, individual performance discrepancies between physicians may have occurred. These variations can impair the reproducibility of these results in other institutions. Also, small variations in the intravenous analgesic regimens applied might have introduced bias in the results. The exact quantification of pain before the application of the block was not uniformly collected by all physicians involved, which can also lead to bias when evaluating results. Also, the low literacy level of the patients in both cohorts and their associated social context limited the application of a validated pain numeric scale, which would better characterize the analgesic efficacy of SPGB.

This study motivated us to design a prospective randomized controlled trial in our institution to better characterize the importance of SPGB timing in its analgesic effect in PDPH treatment.

Conclusions

SPGB showed similar analgesic efficacy when applied earlier or later than 24 hours after the diagnosis of PDPH. The earlier SPGB application showed a reduction in patients'

length of hospital stay and symptom recurrence. We speculate that the early SPGB application potentially allows a faster resumption of daily activities and a reduction in total health costs. In the future, prospective and randomized controlled trials are needed to confirm these findings.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth.* 2003;91:718–29.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd Edition. *Cephalgia.* 2013;33:629–808.
- Sachs A, Smiley R. Post-dural puncture headache: the worst common complication in obstetric anesthesia. *Semin Perinatol.* 2014;38:386–94.
- Robbins MS, Robertson CE, Kaplan E, et al. The sphenopalatine Ganglion: Anatomy, Pathophysiology and therapeutic targeting in headache. *Headache.* 2016;56:240–58.
- Nitu P, Sunil R, Anish M, et al. Sphenopalatine ganglion block for treatment of post-dural puncture headache in obstetric patients: An observational study. *Indian J Anaesth.* 2018;62:972–7.
- Abhijit S, Nair AS, Rayani BK. Sphenopalatine ganglion block for relieving postdural puncture headache: technique and mechanism of action of block with a narrative review of efficacy. *Korean J Pain.* 2017;30:93–7.
- Sluder G. The role of the sphenopalatine ganglion in nasal headaches. *N Y State J Med.* 1908;27:8–13.
- Mohamed B, Eman A, Eslam S, et al. Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache. *Pain Res Treat.* 2018:2516953.
- Neal JM, Rathmell JP. Complications in Regional Anesthesia. 2nd ed. Philadelphia: Wolters Kluwer–LWW; 2013.
- Cohen S, Levin D, Mellender S, et al. Topical sphenopalatine ganglion block compared with epidural blood patch for postdural puncture headache management in postpartum patients—a retrospective review. *Reg Anesth Pain Med.* 2018;43:880–4.
- Furtado I, Lima IF, Pedro S. Ropivacaine use in transnasal sphenopalatine ganglion block for post dural puncture headache in obstetric patients—case series. *Rev Bras Anestesiol.* 2018;68:421–4.
- Kent S, Mehaffey G. Transnasal sphenopalatine ganglion block for the treatment of posdural pucture headache in obstetric patients. *J Clin Anesth.* 2016;34:194–6.
- Patel P, Zhao R, Cohen S. Sphenopalatine ganglion block (SPGB) versus epidural blood patch (EBP) for accidental postdural puncture headache (PDPH) in obstetric patients: a retrospective observation. In: Poster presented at: 32nd Annual Meeting of the American Academy of Pain Medicine. 2016. p. 18.
- Cohen S, Sakr A, Katyal S, et al. Sphenopalatine ganglion block for postdural puncture headache. *Anaesthesia.* 2009;64:574–5.
- Gonçalves LM, Godinho PM, Durán FJ, et al. Sphenopalatine ganglion block by transnasal approach in post-dural puncture headache. *J Clin Anesth.* 2018;48:50.



ORIGINAL INVESTIGATION

Minimal fresh gas flow sevoflurane anesthesia and postoperative acute kidney injury in on-pump cardiac surgery: a randomized comparative trial



Eric Benedet Lineburger ^{a,*}, Norma Sueli Pinheiro Módolo ^b, Leandro Gobbo Braz ^b, Paulo do Nascimento Junior ^b

^a Hospital São José, Anestesiologia e Controle da Dor, Criciúma, SC, Brazil

^b Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), Faculdade de Medicina de Botucatu, Departamento de Especialidades Cirúrgicas e Anestesiologia, São Paulo, SP, Brazil

Received 10 February 2021; accepted 13 November 2021

Available online 28 November 2021

KEYWORDS

Acute kidney injury;
Sevoflurane;
Anesthesia;
Occupational health

Abstract

Background: Compound A is generated by sevoflurane when it reacts with carbon dioxide absorbers with strong bases at minimal fresh gas flow (FGF) and is nephrotoxic in animals. No conclusive data has shown increased risk in humans. The aim of this study was to investigate if minimal FGF promotes an increase in the incidence of acute kidney injury (AKI) when compared to high FGF in patients undergoing on-pump cardiac surgery under sevoflurane anesthesia.

Methods: Two hundred and four adult patients scheduled for on-pump cardiac surgery under sevoflurane anesthesia were randomly allocated to two groups differentiated by FGF: minimal FGF ($0.5 \text{ L} \cdot \text{min}^{-1}$) or high FGF ($2.0 \text{ L} \cdot \text{min}^{-1}$). Baseline creatinine measured before surgery was compared daily to values assayed on the first five postoperative days, and 24-hour urinary output was monitored, according to the KDIGO (Kidney Disease Improving Global Outcomes) guideline to define postoperative cardiac surgery-associated acute kidney injury (CSA-AKI). Creatinine measurements were also obtained 20 and 120 days after hospital discharge.

Results: Postoperative AKI occurred in 55 patients, 26 patients (29.5%) in the minimal FGF group and 29 patients (31.5%) in the high FGF group ($p = 0.774$). Twenty days after discharge, 11 patients (6.1%) still had CSA-AKI and 120 days after discharge only 2 patients (1.6%) still had CSA-AKI.

Conclusions: When compared to high FGF, minimal FGF sevoflurane anesthesia during on-pump cardiac surgery is not associated with increased risk of postoperative AKI in this population at high risk for renal injury.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. 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: lineburger@unesp.br (E.B. Lineburger).

Introduction

Sustainable anesthesia involves the use of low fresh gas flow (FGF), avoiding waste anesthetic gases, reducing environmental pollution and promoting cost savings.¹ Low FGF also keeps inhaled gases moist and warm, limiting heat loss from the respiratory system. The use of carbon dioxide (CO₂) absorbers with strong bases (sodium hydroxide, potassium hydroxide), when combined with low FGF, increases canister temperature and reduces the amount of water in the absorber.² Under these conditions, sevoflurane is degraded into a vinyl ether metabolism product, Compound A, which causes dose-dependent nephrotoxicity in rats.³ Newer CO₂ absorbers employ calcium hydroxide rather than strong bases and only produce Compound A when desiccated, while, to date, no conclusive data has shown increased risk associated with low FGF sevoflurane anesthesia in humans.⁴ Despite this, the American Food and Drug Administration (FDA) determines that sevoflurane should not exceed 2 minimum alveolar concentration-hours (2 MAC-hours) at flow rates of 1 to < 2 L·min⁻¹ and to avoid FGF < 1 L·min⁻¹.⁵ The authorities in Brazil have made no such formal recommendation.

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a major complication that leads to poor outcomes and has an incidence up to 40%.⁶ The pathophysiology of CSA-AKI is a matter of intense debate and includes multiple etiologic factors such as inflammation, hypotension during cardiopulmonary bypass (CPB), blood transfusions, and contrast-induced nephropathy prior to surgery. There are several risk factors for CSA-AKI including age, hypertension, preoperative serum creatinine, peripheral vascular disease, respiratory system disease, diabetes, cerebral vascular disease, CPB duration, aortic clamping duration, use of an intra-aortic balloon pump, infection, reoperation, emergency surgery, low cardiac output and type of surgical procedure.⁷

In view of the FDA recommendation on the use of fresh gas flow in anesthesia with sevoflurane but the lack of solid evidence regarding postoperative renal function in anesthesia with this anesthetic agent in minimal fresh gas flow, especially in patients with higher risk, we decided to investigate if there is a difference in the post-operative renal function of patients submitted to cardiac surgery with extracorporeal circulation anesthetized with sevoflurane when comparing a fresh gas flow of 0.5 L·min⁻¹ versus 2 L·min⁻¹.

Methods

Study design and participants

This manuscript followed applicable CONSORT guidelines. After approval by the local ethics committee (São José Hospital, Criciúma, Santa Catarina, Brazil, protocol number 1.540.412), the trial was registered prior to patient enrollment on May 11th, 2016 (CAAE, number 55620516.3.0000.5364; Brazilian Clinical Trials Registry, number RBR-28br3m) and with written informed consent obtained from all subjects participating in the trial, from June 2016 to September 2018 we prospectively screened adult ASA (American Society of Anesthesiologists) physical

status II and III patients of both sexes who were scheduled for on-pump cardiac surgery. Patients with baseline serum creatinine greater than 1.3 mg.dL⁻¹, undergoing emergency surgery, with an intra-aortic balloon pump, with restrictive diastolic dysfunction (type III), or with left ventricular ejection fraction (LVEF) of less than 40% were excluded.

Anesthesia

A standard anesthesia technique was employed with all patients. After 8 hours of fasting for solid food and 4 hours for liquids, patients had a 14G peripheral intravenous (IV) catheter placed in the cephalic vein and infusion of 6 mL·kg⁻¹ lactated Ringer's solution was initiated. Patients were initially monitored with an indwelling arterial catheter, pulse oximetry, electrocardiography (DII, V4 and V5 leads) and bispectral index (BIS, Model A 2000®, software Version 2.21, Aspect Medical Systems, Boston, MA, USA). Patients were given active conductive warming using an adult circulating water mattress fed from a warming device (Medi-Therm III, Model MTA 6900, Gaymar Industries Inc., Orchard Park, NY, USA) with temperature initially set at 38°C.

Following a 3-minute period of preoxygenation (FiO₂ of 1), induction of anesthesia was performed with sufentanil, 0.3 to 0.5 µg·kg⁻¹ IV (intravenous), propofol, 1.5 to 2.0 mg·kg⁻¹ IV, and rocuronium, 0.6 mg·kg⁻¹ IV, administered to facilitate tracheal intubation with a cuffed tube. Maintenance of anesthesia was achieved with age-adjusted minimum alveolar concentration sevoflurane values of 0.3–0.7, end-tidal sevoflurane concentration values of 0.3–1.6 vol% and BIS-guided anesthesia targeting values of 40–60. Continuous IV infusion of remifentanil in the range of 0.2 to 0.5 µg·kg⁻¹·min⁻¹, using a computer-controlled infusion pump (Perfusor® compact, BBraun, Melsungen, Germany) was titrated throughout the procedure to maintain mean arterial pressure (MAP) and heart rate (HR) at baseline values ± 20%. Values of MAP exceeding preoperative baseline values by more than 20% and/or HR exceeding preoperative baseline values by more than 20% were treated by increasing the rate of continuous infusion of remifentanil. When necessary, an infusion of nitroglycerine (0.8–1.5 µg·kg⁻¹·min⁻¹ IV) was initiated. Mean arterial pressure values lower than 20% below baseline values and unresponsive to remifentanil infusion reduction were evaluated with transesophageal echocardiography (TEE) and treated with boluses of fluids or with ephedrine, 5–10 mg IV. Inotropes and vasodilators were carefully titrated in case of ventricular dysfunction.

Lungs were ventilated mechanically with a volume-controlled mode using a Dräger Primus anesthesia workstation (Dräger Medical, Lübeck, Germany) or Aisys® Cs2 carestation (GE Datex-Ohmeda, München, Germany). Inspiratory pressure was set to maintain tidal volume between 6–8 mL·kg⁻¹. The respiratory rate was adjusted to maintain an end-tidal pressure of carbon dioxide close to 35 mmHg. The end-tidal sevoflurane concentration, end-tidal pressure of oxygen, end-tidal pressure of carbon dioxide, nasopharyngeal and rectal temperatures, BIS and ventilation parameters were monitored with the built-in monitors on the Primus or GE workstations.

Blood glycemia control was evaluated with a glucose monitoring device (Optium Xceed, Abbott Diabetes Care Inc.

Alameda, CA, USA). Glucose values were obtained every 20 minutes and treated if $\geq 150 \text{ mg.dL}^{-1}$. The CPB circuit was primed with 1200 mL of lactated Ringer's solution with the addition of heparin (300 U.kg^{-1}) to achieve an activated clotting time greater than 450 seconds. Cardiac arrest was achieved with cold crystalloid cardioplegia. The central temperature during CPB was maintained at a minimum of 34°C , MAP controlled at 60–80 mmHg and lowest permissible hemoglobin level set at 8 g.dL^{-1} during maximal hemodilution. Total CPB and aorta clamping times were recorded. In both groups, during CPB, inhalational anesthesia was maintained with sevoflurane.

Postoperative analgesia was provided 15 minutes before the end of surgery with metamizole, 2 g IV, and patient-controlled analgesia was delivered through an infusion pump (Infusomat® Space, B. Braun, Melsungen, Germany, 2010) with morphine (2 mg bolus IV) and S (+) ketamine (0.2 mg. kg^{-1} bolus IV), programmed with a 10-minute lockout interval. Dexamethasone, 8 mg IV, and ondansetron, 8 mg IV, were administered to prevent nausea and vomiting. Patients were transferred to the ICU on mechanical ventilation and with IV propofol (25 to 50 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$).

Groups and protocol

The groups were differentiated by FGF, with the minimal FGF group on 0.5 L.min^{-1} in FiO_2 of 1 and the high FGF group on 2.0 L.min^{-1} in FiO_2 of 1 according to the Baker⁸ classification of FGF. In the minimal FGF group, for the first 15 minutes of anesthesia, FGF of 5 L.min^{-1} with an FiO_2 of 1 was used to promote denitrogenation of the patient's circuit and tissues. After this period, the FGF was reduced to 0.5 L.min^{-1} with an FiO_2 of 1. Every 20 minutes, an FGF of 2 L.min^{-1} , was administered for one minute, to remove possible accumulation of other gases from patient metabolism to the respiratory system.^{9,10} In the high FGF group, FGF was maintained throughout the procedure at 2 L.min^{-1} with an FiO_2 of 1. The CO_2 absorber (Atriasorb®, São Paulo, SP, Brazil) in the anesthesia workstation canister was calcium hydroxide and sodium hydroxide for both groups. Randomization was performed electronically using a mobile device program (Randomizer for Clinical Trial version 2.3, Medsharing SARL, Copyright 2012, France) with block size of 8 and 2 arms, just before anesthesia induction.

Outcomes

The primary outcome was the incidence of acute kidney injury according to the KDIGO guideline,¹¹ as measured by serum creatinine during the first five days after the surgery and compared to preoperative values, and 24-hour postoperative urinary output. Secondary outcomes were renal function 20 and 120 days after discharge, according to preoperative creatinine values and values 20 and 120 days after discharge.

Statistical analysis

Quantitative variables were described using mean and standard deviation. Categorical variables were presented as counts and percentages. Means were compared using *t*-tests and counts using likelihood ratio chi-square tests. Urinary

volume data were analyzed by generalized estimation equation (GEE) model using a matrix of exchangeable type including group factors (with and without CSA-AKI), time and interaction.

We used a logistic regression model to evaluate the association between FGF and the occurrence of CSA-AKI, adjusting for the effects of CPB time, diabetes, age, baseline creatinine, sex, and blood transfusion. Results were expressed as odds ratios and 95% confidence intervals (CI). *P*-values below 0.05 were deemed statistically significant. Data were analyzed using SPSS version 22.0.

Sample size calculations

We calculated that the enrollment of 154 patients in 1:1 rate of distribution (77 patients each group) would provide the trial with a power of 85% to detect a two-fold increase in the occurrence of AKI among patients using minimal FGF when compared to those under high FGF, considering a pooled AKI baseline rate of 22.6%⁶ and a two-sided significance level of 0.05.

Results

A total of 277 patients were initially eligible to participate in the study. After exclusions, 204 patients were included in the final randomization. Patient recruitment and flow are summarized in Figure 1. After losses to follow-up from the randomized groups, the final sample for analysis was 180 patients (92 in the high FGF group and 88 in the minimal FGF group). As shown in Table 1, there were no statistically significant differences between the groups in relation to demographic data, preoperative clinical data or intraoperative parameters. Most operations were coronary artery bypass grafts (CABG) (80.5%). Estimated glomerular filtration rate was calculated according to the CKD-EPI creatinine equation.¹²

Primary outcome: postoperative CSA-AKI in the first 5 postoperative days

The type of FGF used was not related to a statistically significant difference in the occurrence of CSA-AKI (odds ratio, 0.91; 95% CI, 0.48 to 1.71; *p* = 0.774) as demonstrated by the univariate analysis shown in Table 2. Baseline preoperative creatinine of patients with CSA-AKI was 0.93 ± 0.18 (*p* = 0.049) and prevalence of diabetes mellitus was 41.8% (*p* = 0.017) as demonstrated by the univariate statistical analysis of occurrence of CSA-AKI in the postoperative period (up to five days after the operation) according to the KDIGO criteria (Table 3). Out of the 180 patients analyzed, 55 (30.5%) had CSA-AKI in this period. Of these 55 patients, 39 patients (70.9%) were diagnosed with CSA-AKI exclusively on the basis of diuresis below $0.5 \text{ mL.kg}^{-1}.\text{h}^{-1}$ in less than 6–12-hours. Data obtained from the generalized estimation equation (GEE) showed a statistically significant difference between the groups in cumulative urine outputs at 6, 12 and 24 hours (*p* = 0.044). Eight patients (14.5%) were diagnosed with CSA-AKI only because of increases over baseline creatinine, with diuresis within the minimum limits of normality. Likewise, eight patients (14.5%) were diagnosed with CSA-

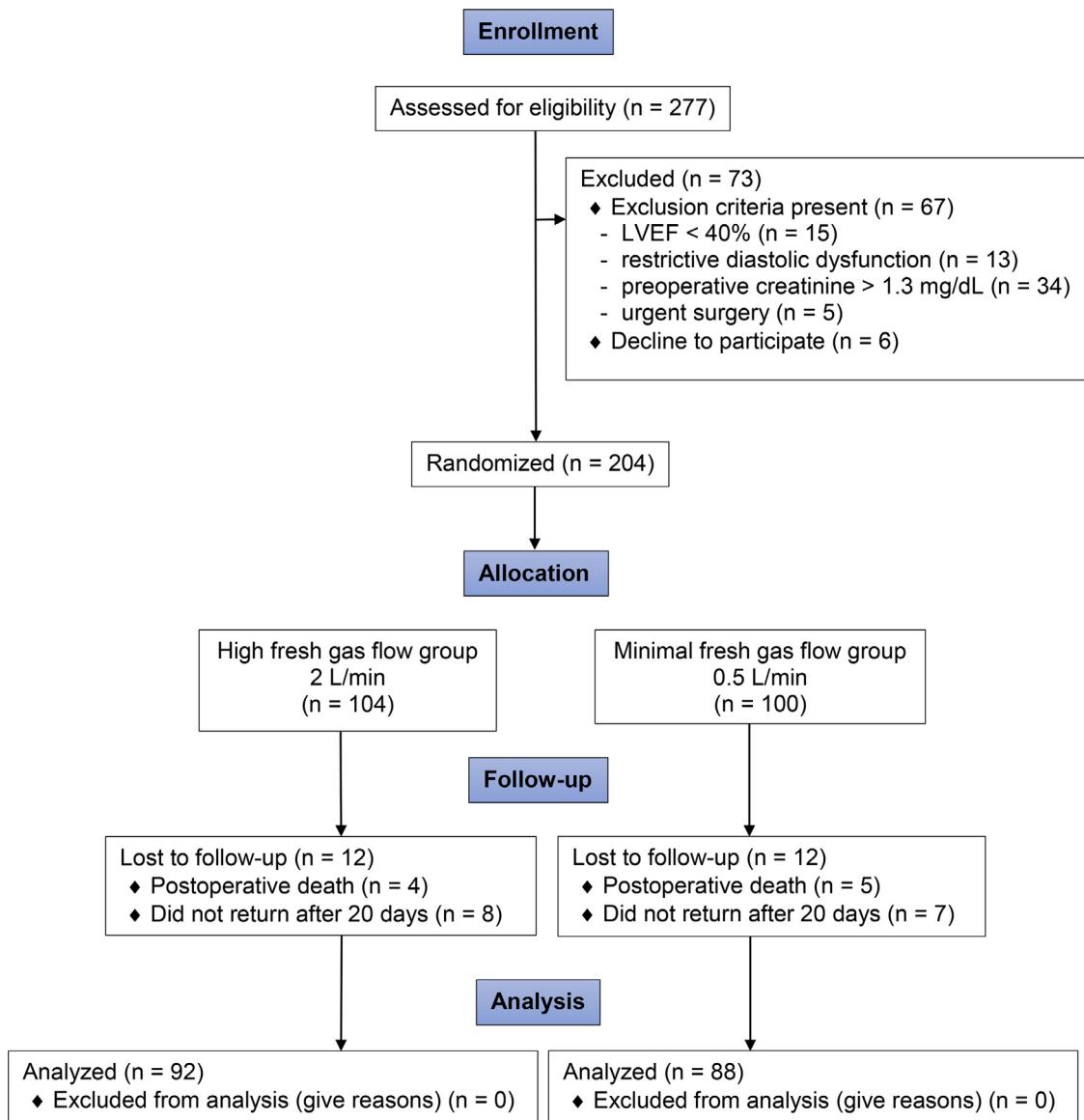


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

AKI on the basis of both increase over baseline creatinine and low diuresis according to the KDIGO criteria. There were no statistical differences in patient demographics, type of operation, CPB time or use of vancomycin as a prophylactic antibiotic. The analysis of the primary outcome by intention-to-treat, considering all the 204 randomized patients, was similar to the per protocol analysis reported above (odds ratio, 1.14; 95% CI, 0.63 to 2.07; $p = 0.672$).

Secondary outcome: CSA-AKI 20 days and 120 days after Hospital Discharge

A total of 180 patients returned within 20 days after hospital discharge to measure serum creatinine. Of these, 11 had CSA-AKI (6.1%) and all of them were patients who had had CSA-AKI during the first 5 postoperative days, showing that these patients had not recovered from kidney injury, according to the KDIGO guideline. A large

proportion of these patients were from the high FGF group, with a total of 9 patients. Once more, fresh gas flow type had no influence on this outcome in the univariate analysis (odds ratio, 0.21; 95% CI, 0.05 to 1.02; $p = 0.053$). Creatinine measurements were only obtained for 121 patients (67.2%) at 120 days after hospital discharge, because of a high incidence of losses to follow up. Of these patients, only 2 (1.6%) still had CSA-AKI according to the KDIGO guideline.

Data from logistic regression for primary and secondary outcomes, 5 and 20 days after surgery, calculated by multivariate analysis and adjusted for CPB time, diabetes mellitus, age, baseline preoperative creatinine, sex and transfusion of packed red blood cells are shown in Table 2. We did not include data from patients seen 120 days after discharge in the logistic regression model because of the low rate of occurrence of CSA-AKI at this point.

Table 1 Patient Demographics, Preoperative Clinical Data and Intraoperative Parameters. Data are mean \pm SD or number of patients (%).

Characteristic	Groups	
	Minimal Fresh Gas Flow (0.5 L.min $^{-1}$) n = 88	High Fresh Gas Flow (2 L.min $^{-1}$) n = 92
Age (years)	61.2 \pm 9.0	60.0 \pm 8.4
Female sex	35 (39.8%)	31 (33.7%)
Body mass index (kg.m $^{-2}$)	27.6 \pm 4.2	27.7 \pm 3.8
Hypertension	75 (85.2%)	79 (85.9%)
Diabetes mellitus	27 (30.7%)	26 (28.3%)
Chronic obstructive pulmonary disease	22 (25.0%)	24 (26.1%)
Preoperative hemoglobin (g.dL $^{-1}$)	12.8 \pm 1.6	13.3 \pm 1.3
Preoperative creatinine (mg.dL $^{-1}$)	0.9 \pm 0.2	0.9 \pm 0.2
Estimated GFR (mL.min $^{-1}$ /1.73 m 2)	83.9 \pm 16.9	85.4 \pm 17.3
Preoperative BUN (mg.dL $^{-1}$)	39.5 \pm 11.5	37.3 \pm 10.3
Prophylactic Antibiotic		
Cephazolin	66 (76.7%)	67 (72.8%)
Vancomycin	20 (23.3%)	25 (27.2%)
Operation		
CABG	70 (79.5%)	75 (81.5%)
AVR	8 (9.1%)	6 (6.5%)
MVR	3 (3.4%)	7 (7.6%)
AVR + CABG	3 (3.4%)	2 (2.2%)
MVR + CABG	0 (0.0%)	2 (2.2%)
Adult Congenital	3 (3.4%)	0 (0.0%)
Bentall	1 (1.1%)	0 (0.0%)
Anesthesia time (min)	293.4 \pm 53.8	285.5 \pm 58.3
Cardiopulmonary bypass time (min)	61.9 \pm 19.3	59.8 \pm 20.6
Aortic cross clamp time (min)	39.2 \pm 16.1	39.3 \pm 16.0
Packed red blood cells transfusion	20 (22.7%)	14 (15.2%)

GFR, glomerular filtration rate; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; AVR, aortic valve replacement or repair; MVR, mitral valve replacement or repair; AVR + CABG, aortic valve replacement or repair with coronary artery bypass graft; MVR + CABG, mitral valve replacement or repair with coronary artery bypass graft.

Discussion

Reducing FGF in modern anesthesia practice is a goal to be achieved on a large scale. Unfortunately, issues related to the safety of this practice, especially when associated with the inhalational anesthetic sevoflurane and the risk of AKI related to the accumulation of Compound A, limit full use of the technique.¹³ The safety of minimal and low FGF with sevoflurane in relation to renal function has already been tested in non-cardiac surgeries.¹⁴ Our study shows the safety

of administration of minimal FGF in a population at high risk of perioperative AKI using sevoflurane associated with the common and longstanding CO₂ absorber sodium hydroxide, which is a strong base known to produce Compound A, mainly when lower long-term FGF is used.¹⁵ Short time regular intervals with high FGF were used as part of the classic minimal FGF technique and rarely cause significant impact on the accumulation of Compound A in the circuit.^{9,10,16} In a recent meta-analysis, sevoflurane was shown not to increase creatinine and blood urea nitrogen (BUN) in healthy patients

Table 2 Univariate and Logistic Regression Analysis for Cardiac Surgery Associated Acute Kidney Injury (CSA-AKI).

Outcome	Minimal Fresh Gas Flow (0.5 L.min $^{-1}$) n = 88	High Fresh Gas Flow (2 L.min $^{-1}$) n = 92	Unadjusted		Adjusted	
			OR (95% CI)	p	OR (95% CI)*	p
CSA-AKI first 5 days	26 (29.5)	29 (31.5)	0.91 (0.48 – 1.71)	0.774	0.88 (0.45 – 1.72)	0.699
CSA-AKI after 20 days	2 (2.3)	9 (9.8)	0.21 (0.05 – 1.02)	0.053	0.18 (0.03 – 0.97)	0.046

* odds ratio (OR) and 95% confidence interval (CI) obtained in logistic regression model adjusting for cardiopulmonary bypass time, diabetes, age, baseline creatinine, sex, and blood transfusion.

Table 3 Univariate analysis for the occurrence of cardiac surgery associated acute kidney injury (CSA-AKI) in the first 5 postoperative days.

Characteristic	CSA-AKI (n = 55)	no CSA-AKI (n = 125)	P
Age (years)	62.1 ± 8.2	59.9 ± 8.9	0.112
Female sex	18 (32.7%)	48 (38.4%)	0.465
Body mass index ($\text{kg} \cdot \text{m}^{-2}$)	27.4 ± 4.2	27.7 ± 3.9	0.662
Hypertension	48 (87.3%)	106 (84.8%)	0.661
Diabetes mellitus	23 (41.8%)	30 (24.0%)	0.017
Chronic obstructive pulmonary disease	16 (29.1%)	30 (24.0%)	0.474
Preoperative hemoglobin ($\text{g} \cdot \text{dL}^{-1}$)	13.1 ± 1.6	13.1 ± 1.5	0.929
Preoperative creatinine ($\text{mg} \cdot \text{dL}^{-1}$)	0.93 ± 0.18	0.86 ± 0.20	0.049
Preoperative blood urea nitrogen ($\text{mg} \cdot \text{dL}^{-1}$)	39.4 ± 10.6	38.0 ± 11.1	0.419
Vancomycin use	14 (25.9%)	31 (25.0)	0.896
Coronary artery bypass graft	46 (83.6%)	99 (79.2%)	0.483
Anesthesia time (min)	290.2 ± 55.8	289.0 ± 56.5	0.896
Cardiopulmonary bypass time (min)	57.5 ± 21.6	62.3 ± 19.0	0.132
Aortic cross clamp time (min)	38.2 ± 18.0	39.8 ± 15.2	0.539
Packed red blood cells transfusion	13 (23.6%)	21 (16.8%)	0.288
6-hour Urinary output (mL)	869.8.7 ± 437.1	1009.2 ± 412.9	0.042
12-hour Urinary output (mL)	1224.5 ± 565.3	1348.9 ± 501.8	0.142
24-hour Urinary output (mL)	1683.6 ± 718.6	1939.5 ± 694.7	0.025

Data are mean ± SD or number of patients (%).

after elective surgeries with low FGF.⁴ We therefore provide indirect (we did not measure Compound A) but reinforcing evidence that AKI associated with Compound A in humans is not clinically evident in clinical practice, even in the case of minimal FGF anesthesia.

We used simple measures for identification of AKI, i.e., creatinine and urinary output. From a clinical perioperative point of view, indications for renal replacement therapy and postoperative renal care are mainly based on these parameters. We found an incidence of CSA-AKI in the first five postoperative days of 30.5%, which is consistent with previous studies.⁶ This percentage decreased significantly after twenty days, falling to just 6.1%. Although a large number of patients were lost to follow-up, we obtained serum creatinine measurements at 3 months after hospital discharge for 121 patients, only 1.6% of whom had values exceeding 1.5x the preoperative values. These data are consistent with AKI related to cardiac surgery as described.⁶

A number of risk factors for CSA-AKI demonstrated in previous studies, such as the nature of the surgical procedure, duration of surgery, duration of CPB, duration of aortic cross-clamping and blood transfusion were not statistically significant in our study, which favored the analysis of the type of flow used. On the other hand, modest differences with respect to preoperative creatinine (0.93 ± 0.18 for CSA-AKI vs. 0.86 ± 0.20 for no CSA-AKI patients, $p = 0.049$) were related to the primary outcome. Although hypertension was not directly shown to be a predictor of CSA-AKI in our study, higher preoperative creatinine values could be a consequence of hypertensive nephrosclerosis and thus indirectly be related to postoperative kidney injury, just as it was demonstrated with diabetes mellitus. Including known risk factors for CSA-AKI such as CPB duration, diabetes mellitus, age, baseline creatinine, sex and blood transfusion in a logistic regression did not reveal evidence of differences in the primary outcome between the groups over the first five

postoperative days (odds ratio, 0.88, 95% CI, 0.45 to 1.72, $p = 0.699$). However, in the same analytical model, 20 days after hospital discharge there was statistical significance for CSA-AKI in the high FGF group (odds ratio, 0.18, 95% CI, 0.03 to 0.97, $p = 0.046$), which can be explained by the low number of patients (only 11 patients had AKI 20 days after discharge).

The fact that there are currently CO₂ absorbers that do not produce compound A does not detract from the importance of this study for two reasons:¹⁷ Firstly, the new CO₂ absorbers are more expensive and have a lower absorption capacity than sodium hydroxide, which results in anesthesia of questionable cost-effectiveness;^{18,19} and secondly, the FDA recommends using higher FGF even with these expensive and modern absorbers, which could lead to increased costs and additional environmental pollution.

Waste anesthetic gases are responsible for occupational exposure of health personnel and are also a source of atmospheric pollution. Chronic exposure to isoflurane, sevoflurane, desflurane and nitrous oxide can lead to cytotoxicity and genome instability, according to evaluation of cells from buccal mucosa.²⁰ Other genetic alterations have also been demonstrated in anesthesiologists, surgeons, nurses and technicians chronically exposed to inhaled anesthetics.^{21,22} While some countries have established limits for operating room waste anesthetic gases,²³ several underdeveloped countries still lack regulation of occupational exposure to inhalational anesthetics. Low FGF anesthesia is clearly consistent with reducing occupational exposure to waste anesthetic gases.

Some authors consider that one risk factor for AKI is hypotension. For this reason, one possible limitation of our study is that we did not analyze MAP intraoperatively or compare it between groups, even though we strictly followed methodology for maintenance of normotension.²⁴ Another potential limitation of the study was that we did not analyze

patients with serum creatinine values higher than 1.3 mg.dL⁻¹, but other studies with non-cardiac surgeries show that sevoflurane is safe at low FGF in patients with creatinine values higher than 1.5 mg.dL⁻¹.²⁵

We conclude that, when compared to a high FGF (2.0 L.min⁻¹), the use of minimal (0.5 L.min⁻¹) FGF anesthesia with sevoflurane is not associated with increased incidence of postoperative AKI in on-pump cardiac surgery. Therefore, this practice should be routinely implemented and encouraged, not least considering the reduction in occupational exposure.^{26,27} The present study reinforces the evidence showing that we can provide sustainable and cost-effective anesthesia in a population at high risk for AKI using sevoflurane at minimal FGF.

Prior presentations

Preliminary results at Anesthesiology 2018, San Francisco. Control/Tracking Number: 18-SA-5085-ASAHQ. Activity: Scientific Abstract. Title: Minimal Fresh Gas Flow Sevoflurane Anesthesia Is Not Associated with Postoperative Acute Kidney Injury In On-pump Cardiac Surgery Patients: A Randomized Controlled Trial. A2205, October 14, 2018, 1:00 PM - 3:00 PM. Room North, Hall D, Area B.

Clinical trial number

Local ethics committee (São José Hospital, Criciúma, Santa Catarina, Brazil, on 11 May 2016, protocol number 1.540.412, CAAE 55620516.3.0000.5364; Brazilian Registry of Clinical Trials [www.ensaiosclinicos.gov.br] number RBR-28br3m).

Funding

Support was provided solely from local institutional sources: São José Hospital, Criciúma, Brazil.

Authors' contributions

EBL: elaboration of the scientific project, randomization and anesthesia, data collection, preparation of the manuscript and statistical analysis; NSPM: preparation of the manuscript; LGB: preparation of the manuscript; PNJ: elaboration of the scientific project, preparation of the manuscript and statistical analysis.

Conflicts of interests

The authors declare no conflicts of interest.

Acknowledgements

The authors thank the collaborators Edson M. Durães, M.D.¹ (randomization and anesthesia), Fernando V. Ghedin, M.D.² (randomization and anesthesia), Mário B. Wagner, M.D., Ph.

D.³ (statistical analysis), Roseleine Borges⁴ (data collection), Sabrina L. Duminelli⁵ (data collection) and all members of the Cardiovascular Surgery Department at São José Hospital, Criciúma, Brazil.

^{1,2}Staff Anesthesiologists from the Anesthesiology and Pain Management Department at São José Hospital, Criciúma, Brazil.

³Professor of Clinical Statistics at Faculty of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

⁴Cardiovascular Surgery Department Perfusionist

⁵Outpatient Clinic Secretary at São José Hospital, Criciúma, Brazil.

References

- Ryan S, Sherman J. Sustainable anesthesia. *Anesth Analg*. 2012;114:921–3.
- Higuchi H, Adachi Y, Arimura S, et al. Compound A concentrations during low-flow sevoflurane anesthesia correlate directly with the concentration of monovalent bases in carbon dioxide absorbents. *Anesth Analg*. 2000;91:434–9.
- Morio M, Fujii K, Satoh N, et al. Reaction of sevoflurane and its degradation products with soda lime. Toxicity of the byproducts. *Anesthesiology*. 1992;77:1155–64.
- Ong Sio LCL, Dela Cruz RGC, Bautista AF. Sevoflurane and renal function: a meta-analysis of randomized trials. *Med Gas Res*. 2017;7:186–93.
- Feldman JM. Managing fresh gas flow to reduce environmental contamination. *Anesth Analg*. 2012;114:1093–101.
- Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol*. 2017;30:60–5.
- Yi Q, Li K, Jian Z, et al. Risk Factors for Acute Kidney Injury after Cardiovascular Surgery: Evidence from 2,157 Cases and 49,777 Controls - A Meta-Analysis. *Cardiorenal Med*. 2016;6:237–50.
- Baker AB. Low flow and closed circuits. *Anaesth Intensive Care*. 1994;22:341–2.
- Calvancanti IL, Vane LA. Inhalation Anesthesia. Rio de Janeiro: Brazilian Society of Anesthesiology; 2007. 156 p.
- Morita S, Latta W, Hambro K, et al. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. *Anesth Analg*. 1985;64:343–7.
- Khawaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179–84.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–12.
- Eger 2nd El, Koblin DD, Bowland T, et al. Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. *Anesth Analg*. 1997;84:160–8.
- Goeters C, Reinhardt C, Gronau E, et al. Minimal flow sevoflurane and isoflurane anaesthesia and impact on renal function. *Eur J Anaesthesiol*. 2001;18:43–50.
- Fang ZX, Kandel L, Laster MJ, et al. Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. *Anesth Analg*. 1996;82:775–81.
- Fang ZX, Eger 2nd El. Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit. *Anesth Analg*. 1995;81:564–8.
- Murray JM, Renfrew CW, Bedi A, et al. Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. *Anesthesiology*. 1999;91:1342–8.
- Epstein RH, Dexter F, Maguire DP, et al. Economic and Environmental Considerations During Low Fresh Gas Flow Volatile Agent Administration After Change to a Nonreactive Carbon Dioxide Absorbent. *Anesth Analg*. 2016;122:996–1006.

19. Higuchi H, Adachi Y, Arimura S, et al. The carbon dioxide absorption capacity of Amsorb is half that of soda lime. *Anesth Analg.* 2001;93:221–5.
20. Souza KM, Braz LG, Nogueira FR, et al. Occupational exposure to anesthetics leads to genomic instability, cytotoxicity and proliferative changes. *Mutat Res.* 2016; 791–2. 42-8.
21. El-Ebiary AA, Abuelfadl AA, Sarhan NI, et al. Assessment of genotoxicity risk in operation room personnel by the alkaline comet assay. *Hum Exp Toxicol.* 2013;32:563–70.
22. Izdes S, Sardas S, Kadioglu E, et al. DNA damage, glutathione, and total antioxidant capacity in anesthesia nurses. *Arch Environ Occup Health.* 2010;65:211–7.
23. Aun AG, Golim MA, Nogueira FR, et al. Monitoring early cell damage in physicians who are occupationally exposed to inhalational anesthetics. *Mutat Res.* 2018;812:5–9.
24. Gaffney AM, Sladen RN. Acute kidney injury in cardiac surgery. *Curr Opin Anaesthesiol.* 2015;28:50–9.
25. Conzen PF, Kharasch ED, Czerner SF, et al. Low-flow sevoflurane compared with low-flow isoflurane anesthesia in patients with stable renal insufficiency. *Anesthesiology.* 2002;97:578–84.
26. Baum JA. Low-flow anaesthesia. *Eur J Anaesthesiol.* 1996;13: 432–5.
27. Ishizawa Y. Special article: general anesthetic gases and the global environment. *Anesth Analg.* 2011;112:213–7.



ORIGINAL INVESTIGATION

Early mobilization after total hip or knee arthroplasty: a substudy of the POWER.2 study

Javier Ripollés-Melchor ^{a,b,c,d,*}, César Aldecoa ^{b,c,d}, Raquel Fernández-García ^{c,e}, Marina Varela-Durán ^{c,f}, Norma Aracil-Escoda ^{a,c}, Daniel García-Rodríguez ^{c,g}, Lucia Cabezudo-de-la-Muela ^{c,h}, Lucía Hormaechea-Bolado ^{c,i}, Beatriz Nacarino-Alcorta ^{c,e}, Rolf Hoffmann ^{c,j}, Juan V. Lorente ^{c,k}, José M. Ramírez-Rodríguez ^{b,c,l}, Ane Abad-Motos ^{a,b,c,d}, on behalf of The POWER2 Study Investigators Group for the Spanish Perioperative Audit and Research Network (RedGERM-SPARN)

^a Infanta Leonor University Hospital, Department of Anesthesia and Perioperative Medicine, Madrid, Spain

^b Spanish Perioperative Audit and Research Network (REDGERM), Zaragoza, Spain

^c Grupo Español de Rehabilitación Multimodal (GERM), Zaragoza, Spain

^d Rio Hortega University Hospital, Department of Anesthesia and Critical Care, Valladolid, Spain

^e Móstoles University Hospital, Department of Anesthesia and Critical Care, Móstoles, Spain

^f Complejo Hospitalario De Montecelo, Department of Anesthesia and Critical Care, Pontevedra, Spain

^g Hospital de La Cruz Roja, Department of Anesthesia and Perioperative Medicine, Gijón, Spain

^h La Fe University Hospital, Department of Anesthesia and Perioperative Medicine, Valencia, Spain

ⁱ Puerta de Hierro University Hospital, Department of Anesthesia and Perioperative Medicine, Majadahonda, Spain

^j Hospital de la Santa Creu i Sant Pau, Department of Anesthesia and Perioperative Medicine, Barcelona, Spain

^k Juan Ramón Jimenez University Hospital, Department of Anesthesia and Perioperative Medicine, Huelva, Spain

^l Lozano Blesa University Hospital, Department of Surgery, Zaragoza, Spain

Received 12 November 2020; accepted 22 May 2021

Available online 10 June 2021

KEYWORDS

Total hip arthroplasty;
Total knee arthroplasty;
Enhanced Recovery After Surgery (ERAS);
Early mobilization;
Local anesthesia

Abstract

Background: Early mobilization after surgery is a cornerstone of the Enhanced Recovery After Surgery (ERAS) programs in total hip arthroplasty (THA) or total knee arthroplasty (TKA). Our goal was to determine the time to mobilization after this surgery and the factors associated with early mobilization.

Methods: This was a predefined substudy of the POWER.2 study, a prospective cohort study conducted in patients undergoing THA and TKA at 131 Spanish hospitals. The primary outcome was the time until mobilization after surgery as well as determining those perioperative factors associated with early mobilization after surgery.

* Corresponding author.

E-mail: ripo542@gmail.com (J. Ripollés-Melchor).

Results: A total of 6093 patients were included. The median time to achieve mobilization after the end of the surgery was 24 hours [16–30]. 4,222 (69.3%) patients moved in ≤ 24 hours after surgery. Local anesthesia [OR = 0.80 (95% confidence interval [CI]: 0.72–0.90); $p = 0.001$], surgery performed in a self-declared ERAS center [OR = 0.57 (95% CI: 0.55–0.60); $p < 0.001$], mean adherence to ERAS items [OR = 0.93 (95% CI: 0.92–0.93); $p < 0.001$], and preoperative hemoglobin [OR = 0.97 (95% CI: 0.96–0.98); $p < 0.001$] were associated with shorter time to mobilization.

Conclusions: Most THA and TKA patients mobilize in the first postoperative day, early time to mobilization was associated with the compliance with ERAS protocols, preoperative hemoglobin, and local anesthesia, and with the absence of a urinary catheter, surgical drains, epidural analgesia, and postoperative complications. The perioperative elements that are associated with early mobilization are mostly modifiable, so there is room for improvement.

© 2021 Published by Elsevier Editora Ltda. 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

Primary total hip arthroplasty (THA) is projected to grow 71%, to 635,000 procedures by 2030 and primary total knee arthroplasty (TKA) is projected to grow 85%, to 1.26 million procedures by 2030 in the USA.¹ As this implies an increase in health expenditure, in recent years the THA and TKA process has been focused as a short or ultra-short stay process, and has adhered to the principles of Enhanced Recovery After Surgery (ERAS), whose aim is to improve patient recovery in order to shorten length of stay (LOS) without increasing complications or readmissions.² Vendittoli et al. recently demonstrated that the implementation of a short-stay ERAS protocol was associated to a significant reduction in the complication rate by 50% when achieving ambulatory THA and < 24 hours LOS for TKA.³ Early function and mobilization are key factors for success of a short stay program, and recent ERAS guidelines recommend that patients should be mobilized as soon as possible following surgery.⁴ As perioperative care continues to become more expedited and health systems aim to implement programs to speed recovery and reduce costs, it is important to identify barriers to early mobilization. In addition to reducing LOS,⁵ early mobilization programs integrated in ERAS protocols reduce postoperative complications. The POWER.2 study⁶ showed that patients treated in self-declared ERAS centers, and who had multidisciplinary clinical pathways for THA/TKA had fewer postoperative complications and shorter LOS; in addition, postoperative complications were inversely related to adherence to the perioperative ERAS items. Importantly, patients who were mobilized early had significantly fewer complications.⁶

Although mobilization during the postoperative period is related to the center where the THA/TKA procedure is performed,³ there are additional factors. Early mobilization can be considered both as an outcome and as a perioperative item within the ERAS program. The main goal of this substudy was to determine factors associated with an early mobilization after surgery.

Methods

Study design and participants

The POWER.2 study was a prospective 2-month multicenter cohort study. The study was approved by the Instituto Aragonés de Ciencias de la Salud Ethics Committee (Zaragoza, Spain) (C.P.-C.I. PI18/135; on 23 May 2018), and by the Spanish Medical Agency, and was registered prospectively in an international trial registry (NCT03570944). The study protocol⁷ and the main results have been published.⁶ Ethics committees or institutional review boards at each site reviewed and approved the protocol. Written informed consent was obtained from all participants. This Substudy is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE).⁸

Participants

Inclusion and exclusion criteria were previously described. In brief, patients were eligible for inclusion if they were 18 years old or older and undergoing elective primary THA or TKA – regardless of whether they were treated in a self-declared ERAS center or not – and were recruited during a single period of two months between October and December 2018 in each participating center. Individual data on 16 ERAS items were collected prospectively for each patient. The definition of the individual ERAS components was based on the EM Soffin and JT YaDeau recommendations.⁹

Data included patient characteristics (American Society of Anesthesiologists – ASA physical status, age, sex, smoking status, body mass index, Rockwood clinical frailty score,¹⁰ and comorbidities), procedure performed, surgical approach, perioperative interventions, ERAS items adherence and outcomes (including postoperative complications, time to achieve targeted mobility, LOS, and 30-day mortality). Complications were defined and graded as mild, moderate, or severe according to international recommendations, and were included if occurring within 30 days after

surgery. Data validation was conducted by specific validators at each site.

Outcomes

The primary outcome for this substudy was the time until mobilization after surgery (i.e., time when patients walked, including any partial or full weight-bearing activities such as walking on the spot, bed-to-chair and bed-to-toilet) as well as determining those perioperative factors associated with early mobilization after surgery.

Statistical analysis

Simple descriptive statistics, including means, medians, quartiles, and proportions, were used to describe the overall and TKA-THA cohorts. The discrete and continuous variables were described as number and percentage and median (interquartile range [IQR]), and their differences analyzed using the Fisher exact or Pearson and Wilcoxon Rank sum tests. For exploratory purposes we split the cohort in patients who moved less than 24 hours after surgery and those who did it after this period.

Statistical methods that allowed simultaneous consideration of multiple factors with an outcome of interest were used to identify associations between covariates and mobilization outcomes. Quasi-Poisson regression was used as the primary outcome was count data. All patient and surgery related variables were included in regression analysis: age (divided into quartiles), body mass index (BMI) (according to categories used to grade obesity [$< 25 \text{ kg.m}^{-2}$, $25\text{--}29.9 \text{ kg.m}^{-2}$, $30\text{--}34.9 \text{ kg.m}^{-2}$ and $> 35 \text{ kg.m}^{-2}$]), ASA physical status, frailty score, comorbidities, preoperative hemoglobin, preoperative creatinine, general anesthesia, spinal or epidural block, regional nerve block, local anesthesia, urinary drain, time of surgery, drains, red blood cell (RBC) transfusion, bleeding, tranexamic acid administration, compliance with the ERAS individual items, presence of ERAS protocol, postoperative hemoglobin, postoperative complications, postoperative level of care, postoperative red blood cell transfusion, and LOS. This analysis was performed for the THA and TKA subgroups. Age was categorized into quartiles to provide more clinically meaningful information, as statistical analysis calculated the risk ratio (RR) to determine the quantitative effects of each covariate. As age is normally a continuous variable, the RR would refer to an increment of one single year, which is less meaningful in a clinical setting. Similar reasons applied to categorizing other numerical variables, such as BMI, for statistical analysis.

Independent variables individually associated with the outcome with a p -value of < 0.05 on univariate analysis were selected for a multivariable regression model. A two-tailed p -value of < 0.05 was considered significant. OR was calculated in the multivariable regression with 95% confidence intervals (CI) to determine the quantitative effects of each covariate. THA and TKA patients were analyzed separately. We analyzed the variables associated with early mobilization (defined as equal or less than 24 hours) or delayed (greater than 24 hours) by means of a logistical univariate analysis including demographic characteristics, surgery, adherence to ERAS protocol, and postoperative journey.

All analysis were performed using the R software packages. A p -value < 0.05 was considered as statistically significant.

Results

Participants

In POWER.2 study 6146 patients were recruited in 131 Spanish hospitals. Of these, there were complete data about their mobilization in 6093, which were analyzed in this substudy (Fig. 1).

Of the patients, 2280 (37.4%) underwent THA, while 3813 (62.6%) underwent TKA. According to the hospitals where the surgery was performed, 1558 patients (25.6%) were treated in self-proclaimed ERAS centers. The median compliance with the ERAS items was 8 (7–10 IQR), the majority of patients 4101 (67.3%) had ASA physical status II; the median frailty was 3 (2–3). The median preoperative hemoglobin was 14 g.dL^{-1} (13.1–15 IQR). Most patients received spinal anesthesia 5629 (92.4%). 673 (11%) patients had postoperative complications and the median hospital stay was 4 days (3–6) (Table 1).

Outcome data

The median time to achieve mobilization after the end of the surgery was 24 hours (16–30). 4222 (69.3%) patients moved in the first 24 hours after surgery, while 1871 (30.7%) moved after the first 24 hours. 1538 (67.5%) patients undergoing THA and 2684 (70.4%) undergoing TKA moved in the first 24 hours after surgery.

Factors associated with early mobilization

Patient characteristics, surgical and anesthetic factors, and compliance with ERAS items associated with time to mobilization on uni or multivariate analysis are shown in Table 2. For the entire cohort, local anesthesia [OR = 0.80 (95% confidence interval [CI]: 0.72–0.90); $p = 0.001$] and surgery performed in a self-declared ERAS center [OR = 0.57 (95% CI: 0.55–0.60); $p < 0.001$] were associated with shorter time to mobilization. In patients undergoing THA, male sex [OR = 0.94 (95% CI: 0.89–0.99); $p = 0.038$], and surgery performed in a self-declared ERAS center [OR = 0.60 (95% CI: 0.56–0.65); $p < 0.001$] were associated with shorter time to mobilization (Table 2). In the TKA subgroup, local anesthesia [OR = 0.83 (95% CI: 0.74–0.93); $p = 0.001$] and surgery performed in a self-declared ERAS center [OR = 0.55 (95% CI: 0.52–0.59); $p < 0.001$] were associated with shorter time to mobilization; on the contrary, ASA III patients, patients with vascular disease, epidural anesthesia, urinary drain, surgical drains, postoperative complications [OR = 1.28 (95% CI: 1.18–1.38); $p < 0.001$], postoperative stay at ICU level one or ICU level two, and LOS were associated with delayed mobilization (Table 2).

Stratification of the entire cohort among patients who moved before or after the first 24 hours after surgery showed that smoking, preoperative hemoglobin [OR = 0.94 (95% CI: 0.90–0.97); $p < 0.001$], local anesthesia [OR =

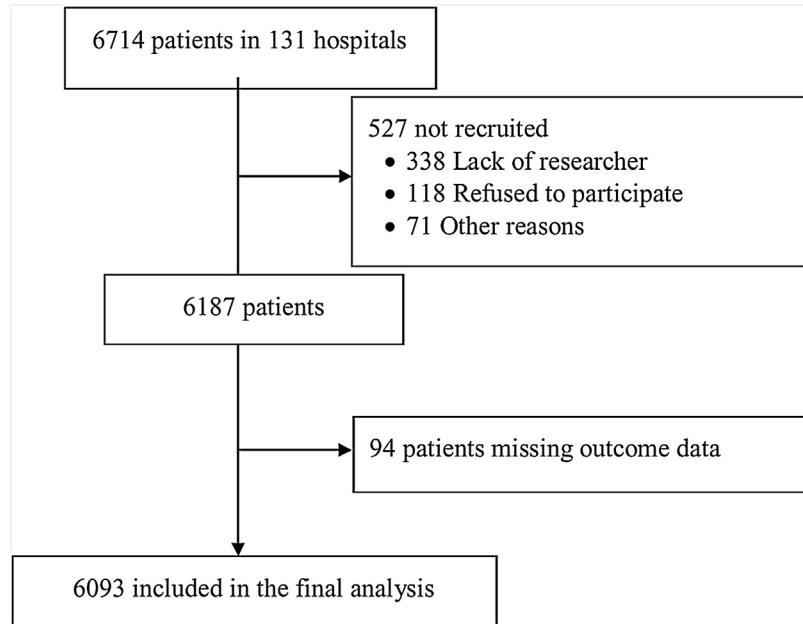


Figure 1 CONSORT flow diagram for included patients.

0.38 (95% CI: 0.26–0.54); $p < 0.001$], intraoperative tranexamic acid administration [OR = 0.70 (95% CI: 0.63–0.79); $p < 0.001$], being treated in an ERAS center [OR = 0.18 (95% CI: 0.15–0.21); $p < 0.001$], mean compliance with ERAS items [OR = 0.80 (95% CI: 0.78–0.82); $p < 0.001$], and postoperative hemoglobin [OR = 0.91 (95% CI: 0.88–0.94); $p < 0.001$] were significantly associated with early mobilization (< 24 hours) (Table 3). In the subgroup of patients who underwent THA, men [OR = 0.77 (95% CI: 0.65–0.92); $p < 0.001$], a BMI of 25–30 [OR = 0.76 (95% CI: 0.60–0.95); $p < 0.001$], preoperative hemoglobin, administration of tranexamic acid, belonging to a self-declared ERAS center [OR = 0.17 (95% CI: 0.13–0.23); $p < 0.001$], the median compliance with ERAS, and postoperative hemoglobin were the variables significantly associated with early mobilization (Table 3); while other variables detailed in Table 3 were associated with an increase in hours up to mobilization after surgery. In the TKA subgroup of patients, local anesthesia [OR = 0.39 (95% CI: 0.26–0.56); $p < 0.001$], preoperative hemoglobin, administration of tranexamic acid, belonging to a self-declared ERAS center, the median compliance with ERAS [OR = 0.79 (95% CI: 0.77–0.88); $p < 0.001$], were significantly associated with early mobilization (Table 3).

The distribution of the entire cohort and the time to mobilization according to whether or not they belonged to an ERAS center is shown in Figure 2. Figure 3 shows the distribution of patients and their mobilization according to the presence or not of postoperative complications.

Discussion

This study provides a snapshot of current practice in a large number of centers on how early mobilization is performed after THA or TKA and explores what factors may influence early or late mobilization. The median time to mobilization

after the end of surgery was 24 hours, moving 69% of patients on the first 24 hours after the end of surgery.

Interestingly, being treated in an ERAS center was the factor most strongly associated with early mobilization, both in patients undergoing THA and TKA. This reflects the importance of hospital protocols, as it indicates that ERAS centers deliberately mobilized patients as soon as possible according to ERAS recommendations, while non-ERAS centers did not. In addition, with each ERAS implemented item, the time until mobilization was reduced by 7%. The median compliance with the ERAS items was 8 of the 16 items that made up the ERAS protocol evaluated in POWER.2 study. This indicates that there is room for improvement in these patients.

Contrary to previous studies in which it was found that age and ASA score were not associated with time until mobilization after THA or TKA,^{3,11} our study found that there are patient related factors associated with mobilization time: in the multivariate analysis we found that a higher ASA score was associated with longer time until mobilization in all patients; in addition, patients older than 76 years, and patients with higher frailty score were unable to move on the first postoperative day. These patients, despite the improvements provided by ERAS programs, should be considered as at-risk patients, and expectations for the postoperative journey should be adjusted.

Since most patients undergoing THA/TKA can be optimized before surgery,¹² it is important to highlight the preoperative factors that influenced the time until postoperative mobilization. Although the median preoperative hemoglobin in our cohort was 14 g.dL⁻¹, for each increase in one gram of hemoglobin, the time to mobilization decreased by 8%. Preoperative anemia was associated with increased risk of receiving RBC transfusion during admission¹³ and, similar to other studies, RBC transfusion^{3,14} and anemia have been associated with both delayed mobilization and postoperative complications.^{6,13} Most patients undergoing

Table 1 Baseline characteristics of patients.

	[ALL] n = 6093	THA n = 2280	TKA n = 3813
Age n, %			
(18,63)	1535 (25.2%)	894 (39.2%)	641 (16.8%)
(63,71)	1762 (28.9%)	540 (23.7%)	1222 (32.0%)
(71,76)	1324 (21.7%)	377 (16.5%)	947 (24.8%)
(76,95)	1472 (24.2%)	469 (20.6%)	1003 (26.3%)
Sex n, %			
Female	3556 (58.4%)	1035 (45.4%)	2521 (66.1%)
Male	2537 (41.6%)	1245 (54.6%)	1292 (33.9%)
BMI kg.m ⁻² , n, %			
(15.9,25)	921 (15.5%)	517 (23.3%)	404 (10.9%)
(25,30)	2341 (39.5%)	955 (43.0%)	1386 (37.4%)
(30,35)	1787 (30.1%)	526 (23.7%)	1261 (34.0%)
(35,110)	883 (14.9%)	224 (10.1%)	659 (17.8%)
ASA Score n, %			
ASA I	388 (6.4%)	233 (10.2%)	155 (4.1%)
ASA II	4101 (67.3%)	1486 (65.2%)	2615 (68.6%)
ASA III	1561 (25.6%)	534 (23.4%)	1027 (26.9%)
ASA IV	42 (0.7%)	26 (1.1%)	16 (0.4%)
Ex-smoker n, %	996 (16.4%)	425 (18.7%)	571 (15.0%)
Smoker n, %	695 (11.4%)	375 (16.5%)	320 (8.4%)
Frailty median, IQR	3.0 [2.0;3.0]	3.0 [2.0;3.0]	3.0 [3.0;4.0]
Hypertension n, %	3614 (72.8%)	1126 (67.5%)	2488 (75.5%)
Ischemic heart disease n, %	356 (7.2%)	117 (7.0%)	239 (7.3%)
Heart failure n, %	156 (2.6%)	56 (2.5%)	100 (2.6%)
Cirrhosis n, %	52 (1.0%)	19 (1.1%)	33 (1.0%)
Stroke n, %	287 (5.8%)	106 (6.4%)	181 (5.5%)
Atrial fibrillation n, %	416 (6.8%)	147 (6.4%)	269 (7.1%)
COPD n, %	690 (13.9%)	261 (15.6%)	429 (13.0%)
Chronic kidney disease n, %	328 (6.6%)	102 (6.1%)	226 (6.9%)
Peripheral vasculopathy n, %	280 (4.6%)	103 (4.5%)	177 (4.6%)
Dementia n, %	66 (1.1%)	20 (0.9%)	46 (1.2%)
Preoperative hemoglobin g.dL ⁻¹ (Median, IQR)	14.0 [13.1;15.0]	14.3 [13.3;15.2]	13.9 [13.0;14.8]
Preoperative creatinine mg.dL ⁻¹ (Median, IQR)	0.8 [0.7;1.0]	0.8 [0.7;1.0]	0.8 [0.7;0.9]
Preoperative RBC transfusion n, %	7 (0.1%)	6 (0.3%)	1 (< 0.1%)
General anesthesia n, %	456 (7.5%)	258 (11.3%)	198 (5.2%)
Epidural anesthesia n, %	386 (6.3%)	60 (2.6%)	326 (8.5%)
Regional anesthesia n, %	925 (15.2%)	156 (6.8%)	769 (20.2%)
Local anesthesia n, %	233 (3.8%)	14 (0.6%)	219 (5.7%)
Spinal anesthesia n, %	5629 (92.4%)	2039 (89.4%)	3590 (94.2%)
Intrathecal morphine administration n, %	435 (7.7%)	158 (7.7%)	277 (7.7%)
Urinary drain n, %	1388 (22.8%)	533 (23.4%)	855 (22.4%)
Surgical drains n, %	4290 (70.4%)	1454 (63.8%)	2836 (74.4%)
Time of surgery, minutes (Median IQR)	90.0 [75.0;110.0]	90.0 [70.0;110.0]	90.0 [75.0;110.0]
Tourniquet time, minutes (Median, IQR)	80.0 [65.0;95.0]	. [.;.]	80.0 [65.0;95.0]
Intraoperative RBC transfusion n, %	60 (1.0%)	47 (2.1%)	13 (0.3%)
Bleeding, mL (Median IQR)	200.0	300.0	150.0 [50.0;300.0]
Tranexamic acid administration	[100.0;350.0]	[200.0;500.0]	
ERAS center n, %	4495 (74.1%)	1591 (70.2%)	2904 (76.4%)
ERAS mean compliance (Median, IQR)	1558 (25.6%)	577 (25.3%)	981 (25.7%)
Postoperative hemoglobin, g.dL ⁻¹ (Median, IQR)	8.0 [7.0;10.0]	8.0 [7.0;10.0]	9.0 [7.0;10.0]
Postoperative complications n, %	11.5 [10.5;12.5]	11.5 [10.4;12.6]	11.5 [10.6;12.5]
Moderate-severe postoperative complications n, %	673 (11.0%)	272 (11.9%)	401 (10.5%)
Level of care after surgery			
Ward/ Post-anesthetic care unit n, %	5692 (93.4%)	2160 (94.7%)	3532 (92.6%)

Table 1 (Continued)

	[ALL] n = 6093	THA n = 2280	TKA n = 3813
ICU level 1 n, %	373 (6.1%)	110 (4.8%)	263 (6.9%)
ICU level 2 n, %	28 (0.5%)	10 (0.4%)	18 (0.5%)
Postoperative RBC transfusion n, %	438 (7.2%)	209 (9.2%)	229 (6.0%)
LOS, days, (Median, IQR)	4.0 [3.0;6.0]	4.0 [3.0;6.0]	4.0 [3.0;6.0]

ASA, American Society of Anesthesiologists; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; RBC, Red blood cell; ERAS, Enhanced recovery after surgery; ICU, Intensive care unit; LOS, Length of stay; THA, total hip arthroplasty; TKA, total knee arthroplasty.

The Level of care after surgery was defined as: Surgical Ward/ Post-anesthetic care unit (Level 0): Normal ward care without Level 1 or 2 capabilities. Critical care Level 1: May include advanced cardiorespiratory monitoring (e.g., invasive arterial/central venous monitoring) and basic organ support (e.g., noninvasive ventilation and inotropic/vasoactive drug administration) Critical care Level 2: Includes advanced organ support, for example, invasive ventilation and renal replacement therapy.

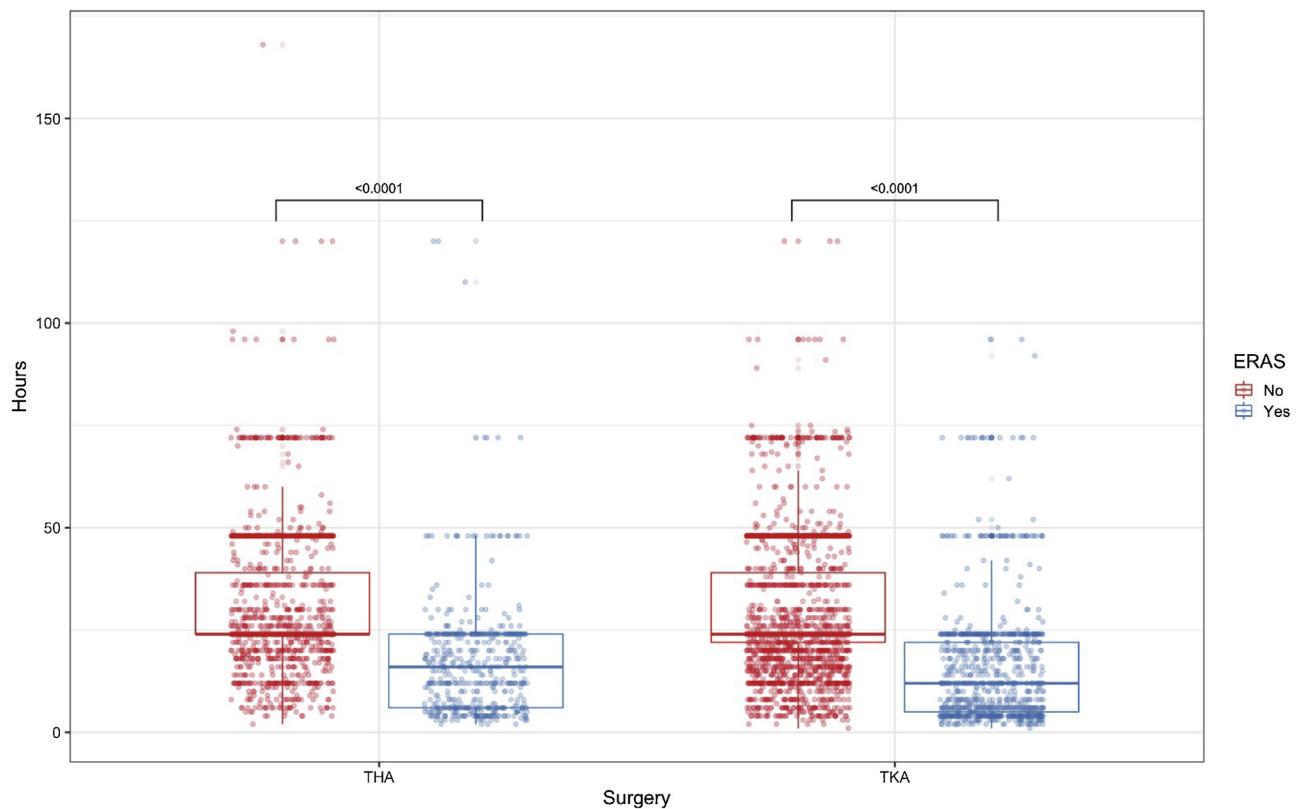


Figure 2 Distribution of hours of mobilization. ERAS, Enhanced recovery after surgery; IQR, Interquartile range; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Dots represent number of hours of mobilization according to ERAS and surgery. Box lines represent median and IQR. By using quasi-poison regression, *p*-values were obtained between the ERAS and non-ERAS groups for THA and TKA.

THA/TKA have iron deficiency anemia¹⁵; however, despite international recommendations,¹⁶ not all centers have an established Patient Blood Management program for these patients¹⁷ in order to treat anemia before surgery.

Epidural analgesia is not frequent in THA/TKA, and it was performed in 2.6% and 8.5% of patients, respectively; however, its use was associated with an increase in time until mobilization after surgery. Nonetheless, the administration of local infiltration analgesia (LIA) was significantly associated with a decrease in hours until mobilization, both in THA and in TKA. A recent meta-analysis showed that LIA

was associated with a reduction of LOS compared to epidural anesthesia finding no differences in postoperative pain in patients undergoing TKA.¹⁸ On the contrary, the effectiveness of the LIA in patients undergoing THA is not clear, and LIA may have limited additional analgesic efficacy in THA when combined with a multimodal analgesic regimen.¹⁹ Similarly, we found that it was the patients undergoing TKA who presented an early mobilization associated with LIA, while not those undergoing THA. LIA with administration of local anesthetic in various combinations with epinephrine, non-steroidal anti-inflammatory drugs, opioids, steroids, or all

Table 2 Univariate and multivariate analysis for mobilization.

Time to mobilization (hours)	ALL				THA				TKA					
	Median (IQR)	OR (uni-variable)	OR (multi-variable)		Median (IQR)	OR (uni-variable)	OR (multi-variable)		Median (IQR)	OR (uni-variable)	OR (multi-variable)			
60	Age	[18,63]	24.00 (16.00 to 28.00)	•	•	[18,63]	24.00 (18.00 to 28.00)	•	•	[18,63]	24.00 (13.00 to 28.00)	•	•	
		(63,71]	24.00 (15.00 to 30.00)	1.004 (0.962- 1.007) 1.048, p = 0.8441)	1.007 (0.962- 1.055, p = 0.7581)	(63,71]	24.00 (18.00 to 30.00)	1.019 (0.955- 1.086, p = 0.5764)	1.028 (0.959- 1.101, p = 0.4435)	(63,71]	24.00 (13.00 to 30.00)	1.021 (0.960- 1.086, p = 0.5143)	1.018 (0.956- 1.083, p = 0.5820)	
		(71,76]	24.00 (17.00 to 30.25)	1.047 (1.001- 1.096, p = 0.0470)	1.031 (0.982- 1.083, p = 0.2128)	(71,76]	24.00 (20.00 to 36.00)	1.103 (1.028- 1.184, p = 0.0064)	1.112 (1.029- 1.200, p = 0.0069)	(71,76]	24.00 (16.00 to 30.00)	1.049 (0.984- 1.119, p = 0.1450)	1.016 (0.952- 1.084, p = 0.6411)	
		(76,95]	24.00 (16.00 to 32.00)	1.047 (1.001- 1.094, p = 0.0448)	1.019 (0.971- 1.071, p = 0.4432)	(76,95]	24.00 (20.00 to 30.00)	1.063 (0.994- 1.136, p = 0.0726)	1.029 (0.953- 1.110, p = 0.4708)	(76,95]	24.00 (15.00 to 34.50)	1.062 (0.997- 1.132, p = 0.0636)	1.028 (0.963- 1.098, p = 0.4088)	
		Sex	Female	24.00 (16.00 to 30.00)	•	•	Female	24.00 (20.00 to 35.50)	•	•	Female	24.00 (14.00 to 30.00)	•	•
		Male	24.00 (16.00 to 29.00)	0.971 (0.941- 1.003, p = 0.0720)	0.973 (0.938- 1.008, p = 0.1331)	Male	24.00 (18.00 to 28.00)	0.935 (0.890- 0.982, p = 0.0071)	0.941 (0.889- 0.997, p = 0.0385)	Male	24.00 (15.00 to 29.00)	0.976 (0.935- 1.019, p = 0.2719)	0.970 (0.926- 1.017, p = 0.2062)	
	BMI	[15.9,25)	24.00 (16.00 to 30.00)	•	•	[15.9,25)	24.00 (20.00 to 32.00)	•	•	[15.9,25)	24.00 (12.00 to 27.00)	•	•	
		[25,30)	24.00 (16.00 to 30.00)	0.984 (0.939- 1.032, p = 0.5038)	•	[25,30)	24.00 (18.00 to 28.50)	0.951 (0.893- 1.014, p = 0.1212)	•	[25,30)	24.00 (15.00 to 30.00)	1.045 (0.973- 1.123, p = 0.2260)	•	
		[30,35)	24.00 (16.00 to 30.00)	0.980 (0.933- 1.029, p = 0.4131)	•	[30,35)	24.00 (19.00 to 30.00)	0.958 (0.892- 1.030, p = 0.2455)	•	[30,35)	24.00 (15.00 to 30.00)	1.041 (0.969- 1.120, p = 0.2743)	•	

Table 2 (*Continued*)

Time to mobilization (hours)	ALL			THA			TKA				
	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)		
ASA	[35,110)	24.00 (18.00 to 36.00) 1.022 (0.966-1.082, p = 0.4425)	•	[35,110)	24.00 (20.00 to 36.00) 1.004 (0.916-1.100, p = 0.9264)	•	[35,110)	24.00 (16.00 to 36.00) 1.088 (1.005-1.178, p = 0.0370)	•		
	ASA I	24.00 (12.00 to 24.00) •	•	ASA 1	24.00 (12.00 to 24.00) •	•	ASA 1	22.00 (11.00 to 24.00) •	•		
	ASA II	24.00 (16.00 to 29.00) 1.135 (1.060-1.217, p = 0.0003) 1.505 (1.171-1.978, p = 0.0022)	1.135 (1.060-1.217, p = 0.0003) 1.505 (1.171-1.978, p = 0.0022)	ASA 2	24.00 (19.00 to 30.00) 1.149 (1.053-1.255, p = 0.0019) 1.546 (1.110-2.240, p = 0.0148)	1.149 (1.053-1.255, p = 0.0019) 1.546 (1.110-2.240, p = 0.0148)	ASA 2	24.00 (14.00 to 28.00) 1.161 (1.041-1.300, p = 0.0087) 1.442 (1.007-2.166, p = 0.0602)	1.161 (1.041-1.300, p = 0.0087) 1.442 (1.007-2.166, p = 0.0602)		
	ASA III	24.00 (19.00 to 36.00) 1.248 (1.161-1.342, p < 0.0001) 1.570 (1.219-2.068, p = 0.0008)	1.248 (1.161-1.342, p < 0.0001) 1.570 (1.219-2.068, p = 0.0008)	ASA 3	24.00 (23.00 to 36.00) 1.261 (1.147-1.388, p < 0.0001) 1.643 (1.174-2.389, p = 0.0061)	1.261 (1.147-1.388, p < 0.0001) 1.643 (1.174-2.389, p = 0.0061)	ASA 3	24.00 (18.00 to 36.00) 1.280 (1.143-1.438, p < 0.0001) 1.490 (1.038-2.242, p = 0.0417)	1.280 (1.143-1.438, p < 0.0001) 1.490 (1.038-2.242, p = 0.0417)		
	ASA IV	24.00 (24.00 to 48.00) 1.409 (1.170-1.684, p = 0.0002) 1.587 (1.170-2.183, p = 0.0036)	1.409 (1.170-1.684, p = 0.0002) 1.587 (1.170-2.183, p = 0.0036)	ASA 4	26.00 (24.00 to 48.00) 1.411 (1.122-1.753, p = 0.0025) 1.606 (1.084-2.443, p = 0.0219)	1.411 (1.122-1.753, p = 0.0025) 1.606 (1.084-2.443, p = 0.0219)	ASA 4	24.00 (24.00 to 36.00) 1.402 (1.020-1.882, p = 0.0303) 1.510 (0.945-2.466, p = 0.0908)	1.402 (1.020-1.882, p = 0.0303) 1.510 (0.945-2.466, p = 0.0908)		
	Ex-smoker	24.00 (16.00 to 30.00) 0.987 (0.946-1.030, p = 0.5544) •	0.987 (0.946-1.030, p = 0.5544) •	Exsmoker	24.00 (18.00 to 30.00) 0.990 (0.928-1.055, p = 0.7527)	0.990 (0.928-1.055, p = 0.7527)	Exsmoker	24.00 (15.00 to 28.00) 0.975 (0.921-1.033, p = 0.3941)	0.975 (0.921-1.033, p = 0.3941)		
	Smoker	24.00 (16.00 to 26.00) 0.948 (0.901-0.997, p = 0.0387)	0.948 (0.901-0.997, p = 0.0387)		24.00 (18.00 to 28.00) 0.928 (0.865-0.994, p = 0.0343)	0.928 (0.865-0.994, p = 0.0343)		24.00 (15.00 to 26.00) 0.947 (0.878-1.020, p = 0.1518)	0.947 (0.878-1.020, p = 0.1518)		
	Frailty	[1,8]	24.00 (16.00 to 30.00) 1.017 (1.001-1.033, p = 0.0352) 0.998 (0.980-1.015, p = 0.7967)	1.017 (1.001-1.033, p = 0.0352) 0.998 (0.980-1.015, p = 0.7967)	[1,7]	24.00 (18.00 to 30.00) 1.040 (1.017-1.062, p = 0.0005) 1.010 (0.983-1.036, p = 0.4767)	1.040 (1.017-1.062, p = 0.0005) 1.010 (0.983-1.036, p = 0.4767)	[1,8]	24.00 (14.00 to 30.00) 1.000 (0.979-1.022, p = 0.9707) 0.985 (0.961-1.008, p = 0.1963)	1.000 (0.979-1.022, p = 0.9707) 0.985 (0.961-1.008, p = 0.1963)	
	Hypertension	24.00 (16.00 to 30.00) 1.027 (0.988-1.068, p = 0.1841)	1.027 (0.988-1.068, p = 0.1841)		24.00 (20.00 to 30.00) 0.983 (0.926-1.043, p = 0.5626)	0.983 (0.926-1.043, p = 0.5626)		24.00 (15.00 to 30.00) 1.066 (1.013-1.122, p = 0.0148)	1.066 (1.013-1.122, p = 0.0148)		

Table 2 (Continued)

	ALL	THA				TKA			
		Time to mobilization (hours)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)
Ischemic heart disease		24.00 (20.75 to 36.00)	1.086 1.157, <i>p</i> = 0.0125)	1.011 1.074, <i>p</i> = 0.7360)	24.00 (24.00 to 36.00)	1.113 1.234, <i>p</i> = 0.0452)	1.018 1.125, <i>p</i> = 0.7248)	24.00 (20.00 to 36.00)	1.072 1.162, <i>p</i> = 0.0934)
Heart Failure		24.00 (18.00 to 31.25)	1.059 1.164, <i>p</i> = 0.2444)	•	24.00 (18.00 to 28.25)	1.008 1.176, <i>p</i> = 0.9221)	•	24.00 (17.50 to 36.00)	1.091 1.228, <i>p</i> = 0.1614)
Cirrhosis		24.00 (19.75 to 28.00)	0.965 1.141, <i>p</i> = 0.6880)	•	24.00 (20.00 to 28.00)	0.850 1.117, <i>p</i> = 0.2652)	•	24.00 (19.00 to 36.00)	1.033 1.271, <i>p</i> = 0.7656)
Stroke		24.00 (18.50 to 36.00)	1.044 1.121, <i>p</i> = 0.2476)	•	24.00 (22.25 to 45.00)	1.070 1.195, <i>p</i> = 0.2331)	•	24.00 (18.00 to 36.00)	1.024 1.124, <i>p</i> = 0.6237)
Atrial Fibrillation		24.00 (18.00 to 36.00)	1.071 1.137, <i>p</i> = 0.0253)	0.992 1.052, <i>p</i> = 0.7969)	24.00 (21.00 to 42.00)	1.068 1.176, <i>p</i> = 0.1822)	0.964 1.058, <i>p</i> = 0.4398)	24.00 (17.00 to 36.00)	1.075 1.159, <i>p</i> = 0.0647)
CPOD		24.00 (18.00 to 28.00)	1.012 1.063, <i>p</i> = 0.6246)	•	24.00 (20.00 to 28.00)	1.007 1.087, <i>p</i> = 0.8511)	•	24.00 (17.00 to 28.00)	1.011 1.078, <i>p</i> = 0.7386)
Chronic kidney disease		24.00 (17.75 to 36.00)	1.047 1.120, <i>p</i> = 0.1845)	1.054 1.124, <i>p</i> = 0.1097)	24.00 (24.00 to 47.50)	1.173 1.305, <i>p</i> = 0.0042)	1.105 1.225, <i>p</i> = 0.0630)	24.00 (12.00 to 36.00)	0.990 1.078, <i>p</i> = 0.8116)
Peripheral vascular disease		24.00 (19.75 to 37.00)	1.092 1.173, <i>p</i> = 0.0155)	1.062 1.134, <i>p</i> = 0.0713)	24.00 (24.00 to 29.50)	1.019 1.144, <i>p</i> = 0.7496)	0.985 1.094, <i>p</i> = 0.7864)	24.00 (18.00 to 48.00)	1.138 1.245, <i>p</i> = 0.0050)
Dementia		24.00 (12.00 to 29.50)	0.947 1.102, <i>p</i> = 0.4919)	•	25.50 (24.00 to 31.50)	1.112 1.413, <i>p</i> = 0.4067)	•	24.00 (12.00 to 24.00)	0.877 1.062, <i>p</i> = 0.1924)

Table 2 (Continued)

Time to mobilization (hours)	ALL				THA				TKA			
	Median (IQR)	OR (uni-variable)	OR (multi-variable)		Median (IQR)	OR (uni-variable)	OR (multi-variable)		Median (IQR)	OR (uni-variable)	OR (multi-variable)	
Preoperative hemoglobin (g.dL^{-1})	[8,18.7]	24.00 (16.00 to 30.00) 0.992, $p = 0.0006$	0.981 (0.970-0.986- 30.00) 1.012, $p = 0.8374$	0.999 (0.986- = 0.0006)	[8,18.7]	24.00 (19.00 to 30.00) 0.987, $p = 0.0004$	0.971 (0.956- 30.00) 1.024, $p = 0.7258$	1.004 (0.984- = 0.0004)	[8.7,18.7]	24.00 (15.00 to 30.00) 1.000, $p = 0.0528$	0.985 (0.971- 30.00) 1.014, $p = 0.7811$	0.998 (0.981- = 0.0006)
Preoperative Creatinine (mg.dL^{-1})	[0.15,14.3]	24.00 (16.00 to 30.00) 1.077, $p = 0.1071$	1.035 •		[0.28,3.72]	24.00 (18.00 to 30.00) 1.173, $p = 0.2024$	1.065 •		[0.15,14.3]	24.00 (14.00 to 30.00) 1.076, $p = 0.2584$	1.028 •	
Preoperative RBT transfusion		48.00 (48.00 to 48.50) 2.561, $p = 0.0003$	1.860 (1.300- 48.50) 1.654, $p = 0.2329$	1.216 (0.870- = 0.0003)		48.00 (48.00 to 48.75) 2.859, $p < 0.0001$	2.088 (1.471- = 0.0001) 1.837, $p = 0.0736$	1.344 (0.961- = 0.0736)		2.00 (2.00 to 2.00) 1.050, $p = 0.2624$	0.078 (NA- 2.00) 1.050, $p = 0.1898$	0.070 (0.000- = 0.2624)
General anesthesia		24.00 (18.00 to 30.00) 1.093, $p = 0.2953$	1.032 •			24.00 (19.00 to 29.50) 1.074, $p = 0.8813$	0.994 •			24.00 (17.00 to 36.00) 1.151, $p = 0.2467$	1.054 •	
Epidural anesthesia		31.00 (24.00 to 48.00) 1.512, $p < 0.0001$	1.433 (1.357- 48.00) 1.343, $p < 0.0001$	1.271 (1.203- < 0.0001)		30.00 (24.00 to 48.00) 1.627, $p < 0.0001$	1.434 (1.258- < 0.0001) 1.568, $p = 0.0001$	1.362 (1.177- 0.0001)		31.00 (24.00 to 48.00) 1.559, $p < 0.0001$	1.467 (1.380- < 0.0001)	1.285 (1.207- < 0.0001)
Regional anesthesia		24.00 (18.00 to 36.00) 1.061, $p = 0.4769$	1.016 (0.973- 36.00) 1.024, $p = 0.3888$	0.981 (0.939- = 0.4769)		24.00 (24.00 to 48.00) 1.278, $p = 0.0008$	1.168 (1.066- = 0.0008) 1.240, $p = 0.0171$	1.126 (1.020- = 0.0171)		24.00 (16.00 to 30.00) 1.048, $p = 0.8950$	0.997 (0.947- = 0.8950)	0.974 (0.926- = 0.3009)
Local anesthesia		7.00 (5.00 to 24.00) 0.604, $p < 0.0001$	0.543 (0.487- 24.00) 0.894, $p = 0.0001$	0.805 (0.722- = 0.0001)		7.00 (4.25 to 23.75) 0.812, $p = 0.0052$	0.547 (0.347- = 0.0052) 1.263, $p = 0.4750$	0.862 (0.558- = 0.4750)		8.00 (5.00 to 24.00) 0.614, $p < 0.0001$	0.549 (0.490- = 0.0001)	0.830 (0.739- = 0.0014)
Spinal anesthesia		24.00 (16.00 to 30.00) 0.988, $p = 0.0167$	0.933 (0.881- 30.00) 1.035, $p = 0.4207$	0.976 (0.922- = 0.4207)		24.00 (18.00 to 30.00) 1.038, $p = 0.2963$	0.959 (0.887- = 0.2963) 1.156, $p = 0.1590$	1.062 (0.977- = 0.1590)		24.00 (14.00 to 30.00) 1.002, $p = 0.0517$	0.921 (0.848- = 0.0517)	0.952 (0.878- = 0.2295)

Table 2 (Continued)

Time to mobilization (hours)	ALL			THA			TKA		
	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)
Urinary drain	24.00 (22.00 to 48.00) 1.252 (1.209- 1.296, p < 0.0001) = 0.0004)	1.068 (1.029- 1.107, p < 0.0001)	1.070 (1.008- 1.136, p < 0.0001) = 0.0270)	24.00 (24.00 to 48.00) 1.225 (1.160- 1.293, p < 0.0001)	1.070 (1.008- 1.136, p < 0.0001)	1.070 (1.008- 1.136, p < 0.0001)	24.00 (20.00 to 48.00) 1.268 (1.213- 1.327, p < 0.0001) = 0.0050)	24.00 (20.00 to 48.00) 1.268 (1.213- 1.327, p < 0.0001) = 0.0050)	1.069 (1.020- 1.119, p = 0.0050)
Surgical drains	24.00 (20.00 to 36.00) 1.372 (1.324- 1.423, p < 0.0001) = 0.0001)	1.203 (1.158- 1.249, p < 0.0001)	1.300 (1.228- 1.377, p < 0.0001) = 0.0001)	24.00 (24.00 to 39.75) 1.377 (1.307- 1.451, p < 0.0001)	1.300 (1.228- 1.377, p < 0.0001)	1.300 (1.228- 1.377, p < 0.0001)	24.00 (18.00 to 36.00) 1.395 (1.328- 1.467, p < 0.0001) = 0.0001)	24.00 (18.00 to 36.00) 1.395 (1.328- 1.467, p < 0.0001) = 0.0001)	1.163 (1.105- 1.224, p = 0.0001)
Time of surgery (minutes)	[30,300] [30,270] 24.00 (16.00 to 30.00) 1.002 (1.002- 1.003, p < 0.0001) = 0.0415)	1.001 (1.000- 1.001, p = 0.0028)	1.001 (1.000- 1.001, p = 0.2445)	24.00 (18.00 to 30.00) 1.002 (1.001- 1.003, p < 0.0001)	1.001 (1.000- 1.001, p = 0.1544)	1.001 (1.000- 1.001, p = 0.1544)	[35,300] 24.00 (15.00 to 30.00) 1.002 (1.002- 1.003, p < 0.0001) = 0.0688)	[35,300] 24.00 (15.00 to 30.00) 1.002 (1.002- 1.003, p < 0.0001)	1.001 (1.000- 1.001, p = 0.0688)
64	RBC transfusion	24.00 (12.00 to 48.00) 1.242 (1.074- 1.427, p = 0.0028)	1.089 (0.940- 1.255, p = 0.2445)	24.00 (24.00 to 48.00) 1.351 (1.160- 1.562, p = 0.0001)	1.068 (0.910- 1.247, p = 0.4103)	1.068 (0.910- 1.247, p = 0.4103)	6.00 (4.00 to 21.00) 0.717 (0.462- 1.051, p = 0.1106)	6.00 (4.00 to 21.00) 0.717 (0.462- 1.051, p = 0.1106)	0.930 (0.629- 1.316, p = 0.6986)
	Bleeding (mL)	[0,2640] [0,2640] 24.00 (17.00 to 32.00) 1.000 (1.000- 1.000, p = 0.7483)	•	24.00 (20.00 to 31.00) 1.000 (1.000- 1.000, p = 0.5721)	1.000 (1.000- 1.000, p = 0.5721)	1.000 (1.000- 1.000, p = 0.5721)	[0,1800] 24.00 (15.00 to 36.00) 1.000 (1.000- 1.000, p = 0.0938)	24.00 (15.00 to 36.00) 1.000 (1.000- 1.000, p = 0.0938)	•
	Tranexamic acid administration	24.00 (15.00 to 28.00) 0.898 (0.868- 0.930, p < 0.0001) = 0.4369)	1.015 (0.978- 1.053, p < 0.0001) = 0.4369)	24.00 (18.00 to 30.00) 0.896 (0.850- 0.944, p < 0.0001)	1.030 (0.973- 1.091, p = 0.3122)	1.030 (0.973- 1.091, p = 0.3122)	24.00 (14.00 to 28.00) 0.906 (0.865- 0.949, p < 0.0001)	24.00 (14.00 to 28.00) 0.906 (0.865- 0.949, p < 0.0001)	1.014 (0.967- 1.063, p = 0.5678)
	ERAS center	12.00 (6.00 to 24.00) 0.540 (0.518- 0.562, p < 0.0001) = 0.0001)	0.573 (0.547- 0.601, p < 0.0001)	16.00 (6.00 to 24.00) 0.566 (0.531- 0.603, p < 0.0001)	0.608 (0.564- 0.654, p < 0.0001)	0.608 (0.564- 0.654, p < 0.0001)	12.00 (5.00 to 22.00) 0.524 (0.496- 0.552, p < 0.0001)	12.00 (5.00 to 22.00) 0.524 (0.496- 0.552, p < 0.0001)	0.556 (0.523- 0.590, p < 0.0001)
ERAS adherence	2,16 2,16	24.00 (16.00 to 30.00) 0.927 (0.922- 0.933, p < 0.0001)	•	24.00 (18.00 to 30.00) 0.945 (0.936- 0.954, p < 0.0001)	•	24.00 (18.00 to 30.00) 0.945 (0.936- 0.954, p < 0.0001)	24.00 (15.00 to 30.00) 0.916 (0.908- 0.923, p < 0.0001)	•	

Table 2 (Continued)

Time to mobilization (hours)		ALL			THA			TKA			
		Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	Median (IQR)	OR (uni-variable)	OR (multi-variable)	
Postoperative Hemoglobin	[1,17.3]	24.00 (16.00 to 30.00)	0.969 (0.959- 0.978, <i>p</i> < 0.0001)	•	[1.4,17]	24.00 (19.00 to 30.00)	0.951 (0.937- 0.966, <i>p</i> < 0.0001)	•	[1,17.3]	24.00 (14.75 to 30.00)	0.980 (0.968- 0.993, <i>p</i> = 0.0019)
Postoperative complications		24.00 (24.00 to 48.00)	1.331 (1.254- 1.411, <i>p</i> < 0.0001)	1.213 (1.137- 1.293, <i>p</i> < 0.0001)	24.00 (24.00 to 48.00)	1.267 (1.158- 1.383, <i>p</i> < 0.0001)	1.096 (0.985- 1.217, <i>p</i> = 0.0895)	24.00 (24.00 to 48.00)	1.374 (1.269- 1.484, <i>p</i> < 0.0001)	1.281 (1.181- 1.387, <i>p</i> < 0.0001)	
Level of care	Ward	24.00 (16.00 to 30.00)	•	•	24.00 (18.00 to 30.00)	•	•	24.00 (14.00 to 28.00)	•	•	
	Level 1 Critical care	24.00 (24.00 to 40.00)	1.164 (1.095- 1.237, <i>p</i> < 0.0001)	1.091 (1.026- 1.159, <i>p</i> = 0.0055)	24.00 (24.00 to 36.00)	1.146 (1.028- 1.274, <i>p</i> = 0.0130)	1.065 (0.952- 1.188, <i>p</i> = 0.2624)	24.00 (20.00 to 40.00)	1.181 (1.096- 1.271, <i>p</i> < 0.0001)	1.113 (1.033- 1.198, <i>p</i> = 0.0046)	
	Level 2 critical care	28.50 (23.75 to 48.00)	1.445 (1.184- 1.743, <i>p</i> = 0.0002)	1.274 (1.035- 1.548, <i>p</i> = 0.0182)	38.00 (24.00 to 48.00)	1.534 (1.118- 2.044, <i>p</i> = 0.0053)	1.252 (0.898- 1.693, <i>p</i> = 0.1633)	28.50 (22.25 to 48.00)	1.396 (1.074- 1.776, <i>p</i> = 0.0092)	1.304 (0.997- 1.671, <i>p</i> = 0.0435)	
	Postoperative RBC transfusion	24.00 (24.00 to 48.00)	1.272 (1.204- 1.343, <i>p</i> < 0.0001)	1.074 (1.010- 1.142, <i>p</i> = 0.0225)	24.00 (24.00 to 48.00)	1.269 (1.174- 1.369, <i>p</i> < 0.0001)	1.072 (0.974- 1.179, <i>p</i> = 0.1519)	24.00 (24.00 to 48.00)	1.262 (1.168- 1.362, <i>p</i> < 0.0001)	1.078 (0.994- 1.167, <i>p</i> = 0.0680)	
LOS	[1,30]	24.00 (16.00 to 30.00)	1.014 (1.011- 1.016, <i>p</i> < 0.0001)	•	[1,30]	24.00 (18.00 to 30.00)	1.014 (1.010- 1.017, <i>p</i> < 0.0001)	[1,30]	24.00 (14.00 to 30.00)	1.014 (1.011- 1.017, <i>p</i> < 0.0001)	

ASA, American Society of Anesthesiologists; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; RBC, Red blood cell; ERAS, Enhanced recovery after surgery; ICU, Intensive care unit; LOS, Length of stay; THA, total hip arthroplasty; TKA, total knee arthroplasty.

The Level of care after surgery was defined as: Surgical Ward/ Post-anesthetic care unit (Level 0): Normal ward care without Level 1 or 2 capabilities. Critical care Level 1: May include advanced cardiorespiratory monitoring (e.g., invasive arterial/central venous monitoring) and basic organ support (e.g., noninvasive ventilation and inotropic/vasoactive drug administration) Critical care Level 2: Includes advanced organ support, for example, invasive ventilation and renal replacement therapy.

Table 3 Postoperative mobilization after surgery grouped by time after mobilization.

	All			THA			TKA			p. ratio		
	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	
	n = 4222	n = 1871			n = 1538	n = 742			n = 2684	n = 1129		
Age												
[18,63]	1090 (25.8%)	445 (23.8%)	Ref.	Ref.	630 (41.0%)	264 (35.6%)	Ref.	Ref.	460 (17.1%)	181 (16.0%)	Ref.	Ref.
(63,71]	1239 (29.3%)	523 (28.0%)	1.03 [0.89;1.20]	0.664	367 (23.9%)	173 (23.3%)	1.13 [0.89;1.42]	0.319	872 (32.5%)	350 (31.0%)	1.02 [0.83;1.26]	0.856
(71,76]	902 (21.4%)	422 (22.6%)	1.15 [0.98;1.34]	0.095	234 (15.2%)	143 (19.3%)	1.46 [1.13;1.88]	0.004	668 (24.9%)	279 (24.7%)	1.06 [0.85;1.33]	0.599
(76,95]	991 (23.5%)	481 (25.7%)	1.19 [1.02;1.39]	0.029	307 (20.0%)	162 (21.8%)	1.26 [0.99;1.60]	0.059	684 (25.5%)	319 (28.3%)	1.18 [0.95;1.47]	0.125
Sex												
Female	2435 (57.7%)	1121 (59.9%)	Ref.	Ref.	666 (43.3%)	369 (49.7%)	Ref.	Ref.	1769 (65.9%)	752 (66.6%)	Ref.	Ref.
Male	1787 (42.3%)	750 (40.1%)	0.91 [0.82;1.02]	0.102	872 (56.7%)	373 (50.3%)	0.77 [0.65;0.92]	0.004	915 (34.1%)	377 (33.4%)	0.97 [0.84;1.12]	0.679
BMI												
[15.9,25)	620 (15.2%)	301 (16.4%)	Ref.	Ref.	328 (21.9%)	189 (26.0%)	Ref.	Ref.	292 (11.2%)	112 (10.1%)	Ref.	Ref.
[25,30)	1640 (40.1%)	701 (38.1%)	0.88 [0.75;1.04]	0.128	665 (44.5%)	290 (39.9%)	0.76 [0.60;0.95]	0.016	975 (37.6%)	411 (36.9%)	1.10 [0.86;1.41]	0.455
[30,35)	1251 (30.6%)	536 (29.1%)	0.88 [0.74;1.05]	0.153	361 (24.1%)	165 (22.7%)	0.79 [0.61;1.03]	0.077	890 (34.3%)	371 (33.3%)	1.09 [0.85;1.40]	0.515
[35,110)	581 (14.2%)	302 (16.4%)	1.07 [0.88;1.30]	0.494	142 (9.5%)	82 (11.3%)	1.00 [0.72;1.39]	0.987	439 (16.9%)	220 (19.7%)	1.31 [1.00;1.72]	0.053
ASA												
Score												
ASA 1	293 (6.9%)	95 (5.1%)	Ref.	Ref.	176 (11.5%)	57 (7.7%)	Ref.	Ref.	117 (4.4%)	38 (3.4%)	Ref.	Ref.
ASA 2	2882 (68.3%)	1219 (65.2%)	1.30 [1.03;1.67]	0.028	1019 (66.3%)	467 (62.9%)	1.41 [1.03;1.96]	0.030	1863 (69.4%)	752 (66.6%)	1.24 [0.86;1.83]	0.256
ASA 3	1023 (24.2%)	538 (28.8%)	1.62 [1.26;2.10]	0.001	< (21.4%)	329 (27.6%)	1.92 [1.36;2.73]	< 0.001	694 (25.9%)	333 (29.5%)	1.47 [1.01;2.20]	0.046
ASA 4	23 (0.5%)	19 (1.0%)	2.54 [1.31;4.89]	0.006	13 (0.8%)	13 (1.8%)	3.07 [1.33;7.13]	0.009	10 (0.4%)	6 (0.5%)	1.86 [0.59;5.43]	0.280
Ex-smoker	706 (16.7%)	290 (15.5%)	0.89 [0.77;1.04]	0.137	290 (18.9%)	135 (18.2%)	0.91 [0.72;1.15]	0.443	416 (15.5%)	155 (13.7%)	0.85 [0.70;1.04]	0.119
	503	192	0.83	0.038	268	107	0.78	0.053	235	85	0.83	0.154
Smoker	(11.9%)	(10.3%)	[0.69;0.99]		(17.5%)	(14.5%)	[0.61;1.00]		(8.8%)	(7.5%)	[0.64;1.07]	

Table 3 (Continued)

	All			THA			TKA				p. ratio	
	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	
	n = 4222	n = 1871			n = 1538	n = 742			n = 2684	n = 1129		
Frailty	3.0 [2.0;3.0]	3.0 [2.0;4.0]	1.06 [1.01;1.12]	0.031	3.0 [2.0;3.0]	3.0 [2.0;4.0]	1.15 [1.06;1.24]	0.001	3.0 [2.0;4.0]	3.0 [3.0;4.0]	1.00 [0.93;1.08]	0.963
Hyper-tension	2483 (72.6%)	1131 (73.3%)	1.04 [0.91;1.19]	0.566	755 (68.1%)	371 (66.4%)	0.93 [0.75;1.15]	0.481	1728 (74.7%)	760 (77.3%)	1.15 [0.97;1.38]	0.111
Ischemic heart disease	229 (6.7%)	127 (8.2%)	1.25 [1.00;1.57]	0.053	69 (6.2%)	48 (8.6%)	1.42 [0.96;2.07]	0.079	160 (6.9%)	79 (8.0%)	1.18 [0.89;1.55]	0.259
Heart failure	109 (2.6%)	47 (2.5%)	0.97 [0.68;1.37]	0.883	39 (2.5%)	17 (2.3%)	0.91 [0.50;1.59]	0.737	70 (2.6%)	30 (2.7%)	1.02 [0.65;1.56]	0.920
Cirrhosis	35 (1.0%)	17 (1.1%)	1.08 [0.59;1.92]	0.788	13 (1.2%)	6 (1.1%)	0.93 [0.32;2.39]	0.881	22 (1.0%)	11 (1.1%)	1.19 [0.55;2.42]	0.650
Stroke	196 (5.7%)	91 (5.9%)	1.03 [0.80;1.33]	0.803	67 (6.0%)	39 (7.0%)	1.17 [0.77;1.75]	0.460	129 (5.6%)	52 (5.3%)	0.95 [0.67;1.31]	0.748
Atrial fibrillation	281 (6.7%)	135 (7.2%)	1.09 [0.88;1.35]	0.424	92 (6.0%)	55 (7.4%)	1.26 [0.89;1.78]	0.196	189 (7.0%)	80 (7.1%)	1.01 [0.76;1.32]	0.955
COPD	488 (14.3%)	202 (13.1%)	0.91 [0.76;1.08]	0.274	183 (16.5%)	78 (14.0%)	0.82 [0.61;1.09]	0.176	305 (13.2%)	124 (12.6%)	0.95 [0.76;1.19]	0.659
	219 (6.4%)	109 (7.1%)	1.11 [0.87;1.41]	0.380	59 (5.3%)	43 (7.7%)	1.48 [0.98;2.23]	0.061	160 (6.9%)	66 (6.7%)	0.97 [0.72;1.30]	0.840
Chronic kidney disease												
Peripheral vascular disease	181 (4.3%)	99 (5.3%)	1.25 [0.97;1.60]	0.087	70 (4.6%)	33 (4.4%)	0.98 [0.63;1.48]	0.920	111 (4.1%)	66 (5.8%)	1.44 [1.05;1.96]	0.025
Dementia	45 (1.1%)	21 (1.1%)	1.06 [0.62;1.76]	0.833	9 (0.6%)	11 (1.5%)	2.55 [1.04;6.42]	0.041	36 (1.3%)	10 (0.9%)	0.67 [0.31;1.30]	0.242
Preoperative Hemoglobin	14.1 [13.2;15.0]	14.0 [13.0;14.9]	0.94 [0.90;0.97]	0.001	14.4 [13.4;15.3]	14.1 [13.0;15.0]	0.89 [0.84;0.94]	<0.001	14.0 [13.1;14.9]	13.9 [13.0;14.8]	0.97 [0.92;1.02]	0.187
Preoperative creatinine	0.8 [0.7;1.0]	0.8 [0.7;1.0]	1.06 [0.91;1.24]	0.466	0.8 [0.7;1.0]	0.8 [0.7;1.0]	1.02 [0.72;1.45]	0.924	0.8 [0.7;0.9]	0.8 [0.7;1.0]	1.07 [0.90;1.28]	0.451
Preoperative RBC	1 (< 0.1%)	6 (0.3%)	12.15 [2.00;314.42]	0.005	0 (0.0%)	6 (0.8%)	. [.;.]	.	1 (< 0.1%)	0 (0.0%)	. [.;.]	.

Table 3 (Continued)

	All			THA			TKA			p. ratio		
	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	
	n = 4222	n = 1871			n = 1538	n = 742			n = 2684	n = 1129		
General anesthesia	310 (7.3%)	146 (7.8%)	1.07 [0.87;1.31]	0.527	177 (11.5%)	81 (10.9%)	0.94 [0.71;1.24]	0.681	133 (5.0%)	65 (5.8%)	1.17 [0.86;1.59]	0.310
Epidural anesthesia	184 (4.4%)	202 (10.8%)	2.66 [2.16;3.27]	0.000	30 (2.0%)	30 (4.0%)	2.12 [1.26;3.56]	0.005	154 (5.7%)	172 (15.2%)	2.95 [2.35;3.72]	0.000
Regional anesthesia	614 (14.5%)	311 (16.6%)	1.17 [1.01;1.36]	0.038	93 (6.0%)	63 (8.5%)	1.44 [1.03;2.01]	0.033	521 (19.4%)	248 (22.0%)	1.17 [0.98;1.38]	0.074
Local anesthesia	199 (4.7%)	34 (1.8%)	0.38 [0.26;0.54]	0.001	12 (0.8%)	2 (0.3%)	0.37 [0.05;1.36]	0.147	187 (7.0%)	32 (2.8%)	0.39 [0.26;0.56]	< 0.001
Spinal anesthesia	3911 (92.6%)	1718 (91.8%)	0.89 [0.73;1.09]	0.272	1371 (89.1%)	668 (90.0%)	1.10 [0.83;1.47]	0.523	2540 (94.6%)	1050 (93.0%)	0.75 [0.57;1.00]	0.053
Intrathecal morphine	258 (6.6%)	177 (10.3%)	1.63 [1.33;1.99]	< 0.001	98 (7.1%)	60 (9.0%)	1.28 [0.91;1.79]	0.150	160 (6.3%)	117 (11.1%)	1.86 [1.45;2.39]	< 0.001
Urinary drain	827 (19.6%)	561 (30.0%)	1.76 [1.55;1.99]	0.000	311 (20.2%)	222 (29.9%)	1.68 [1.38;2.06]	< 0.001	516 (19.2%)	339 (30.0%)	1.80 [1.54;2.11]	< 0.001
Surgical drains	2802 (66.4%)	1488 (79.5%)	1.97 [1.73;2.24]	0.000	896 (58.3%)	558 (75.2%)	2.17 [1.79;2.64]	< 0.001	1906 (71.0%)	930 (82.4%)	1.91 [1.60;2.27]	< 0.001
Time of surgery	90.0 [72.0;110.0]	90.0 [75.0;120.0]	1.01 [1.00;1.01]	< 0.001	90.0 [70.0;110.0]	90.0 [75.0;118.0]	1.01 [1.00;1.01]	< 0.001	90.0 [75.0;110.0]	95.0 [80.0;120.0]	1.01 [1.00;1.01]	< 0.001
Tourniquet time	78.0 [63.0;92.0]	80.0 [68.0;99.0]	1.01 [1.01;1.01]	< 0.001	78.0 [63.0;92.0]	80.0 [68.0;99.0]	1.01 [1.01;1.01]	< 0.001
Intraoperative RBC	35 (0.8%)	25 (1.3%)	1.62 [0.96;2.71]	0.072	25 (1.6%)	22 (3.0%)	1.85 [1.02;3.31]	0.041	10 (0.4%)	3 (0.3%)	0.74 [0.16;2.46]	0.643
Bleeding	200.0 [100.0;350.0]	200.0 [100.0;350.0]	1.00 [1.00;1.00]	0.789	300.0 [200.0;500.0]	300.0 [200.0;500.0]	1.00 [1.00;1.00]	0.963	150.0 [50.0;300.0]	120.0 [50.0;300.0]	1.00 [1.00;1.00]	0.088

Table 3 (Continued)

	All			THA			TKA						
	≤ 24		> 24	OR	p. ratio	≤ 24	> 24	OR	p. ratio	≤ 24	> 24	OR	p. ratio
	n = 4222	n = 1871			n = 1538	n = 742			n = 2684	n = 1129			
Tranexamic acid administration	3203 (76.3%)	1292 (69.2%)	0.70 [0.62;0.79]	< 0.001	1108 (72.8%)	483 (65.1%)	0.70 [0.58;0.84]	< 0.001	2095 (78.4%)	809 (71.8%)	0.70 [0.60;0.83]	< 0.001	
ERAS center	1406 (33.3%)	152 (8.1%)	0.18 [0.15;0.21]	0.000	517 (33.6%)	60 (8.1%)	0.17 [0.13;0.23]	0.000	889 (33.1%)	92 (8.1%)	0.18 [0.14;0.22]	0.000	
ERAS mean compliance	9.0 [7.0;11.0]	8.0 [6.0;9.0]	0.80 [0.78;0.82]	0.001	9.0 [7.0;11.0]	7.0 [6.0;9.0]	0.82 [0.79;0.85]	< 0.001	9.0 [8.0;11.0]	8.0 [6.0;9.0]	0.79 [0.77;0.82]	< 0.001	
Postoperative hemoglobin, g.dL ⁻¹ (mean, IQR)	11.6 [10.6;12.6]	11.3 [10.3;12.4]	0.91 [0.88;0.94]	0.001	11.6 [10.5;12.7]	11.2 [10.0;12.3]	0.85 [0.80;0.90]	0.001	11.6 [10.6;12.5]	11.4 [10.4;12.4]	0.95 [0.91;0.99]	0.027	
Postoperative complications	403 (9.5%)	270 (14.4%)	1.60 [1.35;1.88]	0.001	150 (9.8%)	122 (16.4%)	1.82 [1.41;2.35]	< 0.001	253 (9.4%)	148 (13.1%)	1.45 [1.17;1.80]	0.001	
Moderate to severe post-operative complications	193 (4.6%)	154 (8.2%)	1.87 [1.50;2.33]	0.001	85 (5.5%)	64 (8.6%)	1.61 [1.15;2.26]	0.006	108 (4.0%)	90 (8.0%)	2.07 [1.54;2.76]	< 0.001	
Postoperative care:													
Ward	3984 (94.4%)	1708 (91.3%)	Ref.	Ref.	1468 (95.4%)	692 (93.3%)	Ref.	Ref.	2516 (93.7%)	1016 (90.0%)	Ref.	Ref.	
ICU level 1	227 (5.4%)	146 (7.8%)	1.50 [1.21;1.86]	0.001	66 (4.3%)	44 (5.9%)	1.42 [0.95;2.09]	0.087	161 (6.0%)	102 (9.0%)	1.57 [1.21;2.03]	0.001	
ICU level 2	11 (0.3%)	17 (0.9%)	3.59 [1.68;7.97]	0.001	4 (0.3%)	6 (0.8%)	3.14 [0.87;12.82]	0.081	7 (0.3%)	11 (1.0%)	3.86 [1.50;10.68]	0.005	
Postoperative RBC	240 (5.7%)	198 (10.6%)	1.96 [1.61;2.39]	0.001	106 (6.9%)	103 (13.9%)	2.18 [1.63;2.90]	< 0.001	134 (5.0%)	95 (8.4%)	1.75 [1.33;2.29]	< 0.001	
LOS	4.0 [3.0;6.0]	5.0 [4.0;7.0]	1.03 [1.02;1.04]	0.001	4.0 [3.0;6.0]	5.0 [4.0;7.0]	1.03 [1.01;1.04]	< 0.001	4.0 [3.0;6.0]	5.0 [4.0;7.0]	1.02 [1.01;1.04]	< 0.001	

ASA, American Society of Anesthesiologists; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; RBC, Red blood cell; ERAS, Enhanced recovery after surgery; ICU, Intensive care unit; LOS, Length of stay; THA, total hip arthroplasty; TKA, total knee arthroplasty.

The Level of care after surgery was defined as: Surgical Ward/ Post-anesthetic care unit (Level 0): Normal ward care without Level 1 or 2 capabilities. Critical care Level 1: May include advanced cardiorespiratory monitoring (e.g., invasive arterial/central venous monitoring) and basic organ support (e.g., noninvasive ventilation and inotropic/vasoactive drug administration) Critical care Level 2: Includes advanced organ support, for example, invasive ventilation and renal replacement therapy.

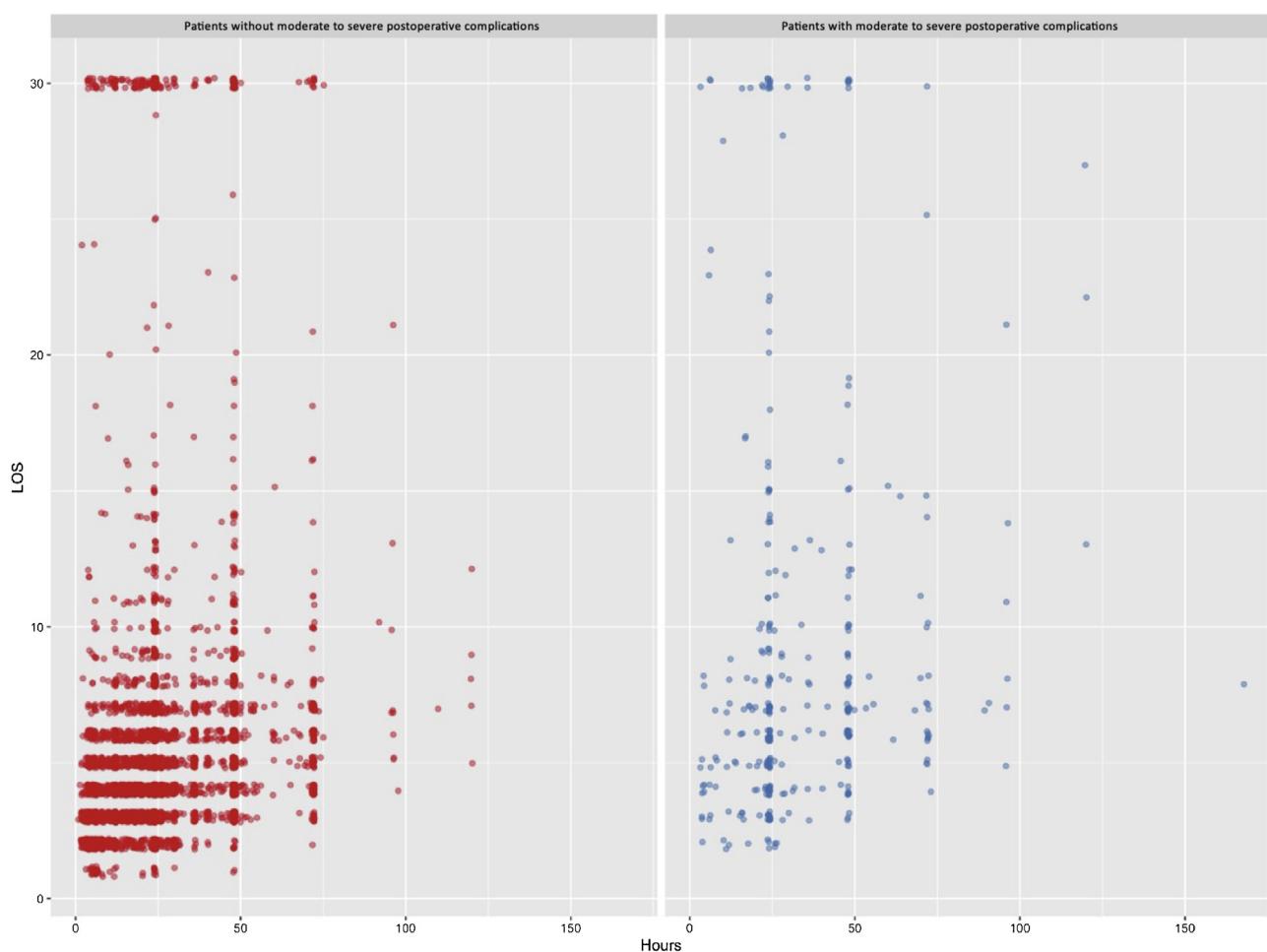


Figure 3 Scatter plot. Relation between hours of mobilization and length of stay (LOS) stratified by postoperative complications.

to the wound is a simple and safe technique for the treatment of postoperative pain; despite that, its use in patients included in POWER.2 was less than 4%, mainly patients undergoing TKA, while only 14 (0.6%) patients undergoing THA received LIA, so this substudy cannot provide new evidence in these patients.

Both the use of surgical drains and urinary drains were discouraged in the ERAS guidelines,⁴ and both of them were associated with an increase in hours until mobilization in POWER2. A 2019 meta-analysis showed that urinary catheterization during THA/TKA can increase postoperative urinary tract infection without reducing the incidence of postoperative urinary retention risk ratio.²⁰ The results of this substudy reinforce the ERAS recommendations,²¹ it is logical that unselected urinary catheterization does not provide benefits and delays mobilization. Similarly, postoperative treatment in intensive care units delayed mobilization in patients in our study.

Our study has certain limitations: although LOS in several countries has been reported to be short,²² the aim is to improve recovery to be able to go directly home and not via another institution.²³

Our study shows that although mobilization was early in most cases, it was not related to reduced LOS, even in patients without complications (Fig. 3). Nor have we

evaluated whether early mobility was associated with the participation of physiotherapists or rehabilitation physicians in the process. Finally, this study was not specifically designed to assess the causes of delayed mobilization, so there are certain circumstances such as orthostatic hypotension, postoperative pain or urinary retention that were not evaluated and are nonetheless important.²⁴

Conclusions

The majority of patients with THA and TKA are mobilized early in Spanish hospitals. Early time to mobilization was associated with the compliance with ERAS protocols, preoperative hemoglobin and LIA, and with the absence of a urinary catheter, surgical drains, epidural analgesia and postoperative complications. The perioperative elements that are associated with early mobilization are mostly modifiable, so there is room for improvement in patients undergoing THA/TKA.

Funding

Support was provided solely from institutional and/or departmental sources. The POWER.2 study and this substudy were supported by the Spanish Perioperative Audit

and Research Network (REDGERM) <www.grupogerm.es>. REDGERM had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

This article is not based on a previous communication to a society or meeting.

Conflicts of interest

JRM reports personal fees from Edwards Lifesciences, Fresenius Kabi, MSD and Dextera Medical outside the submitted work; CA reports personal fees from Fresenius Kabi and Octapharma outside the submitted work; MVD reports personal fees from MSD, Pfizer, Astellas, Ferrer y Fresenius Kabi outside the submitted work; JV reports personal fees Edwards Lifesciences, Fresenius Kabi and Biomerieux outside the submitted work. RGF, NAE, DGR, LCM, LHB, BNA, JMRR and AAM nothing to disclose.

Acknowledgements

We are willing to make the data, analytical methods, and study materials available to other researchers. Such material will be available upon request to the author of correspondence.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: <https://doi.org/10.1016/j.bjane.2021.05.008>.

References

1. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am.* 2018;100:1455–60.
2. Kehlet H. Enhanced Recovery After Surgery (ERAS): good for now, but what about the future? *Can J Anaesth.* 2015;62:99–104.
3. Vendittoli P-A, Pellei K, Desmeules F, et al. Enhanced recovery short-stay hip and knee joint replacement program improves patients outcomes while reducing hospital costs. *Orthop Traumatol Surg Res.* 2019;105:1237–43.
4. Wainwright TW, Gill M, McDonald DA, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Acta Orthop.* 2020;91:3–19.
5. Tayrose G, Newman D, Slover J, et al. Rapid mobilization decreases length-of-stay in joint replacement patients. *Bull Hosp Jt Dis.* 2013;71:222–6.
6. Ripollés-Melchor J, Abad-Motos A, Díez-Remesal Y, et al. Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Total Hip and Knee Arthroplasty in the Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol in Elective Total Hip and Knee Arthroplasty Study (POWER2). *JAMA Surg.* 2020;155:e196024.
7. Ripollés-Melchor J, Abad-Motos A, Logrono-Egea M, et al. Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol in Elective Total Hip and Knee Arthroplasty. *POWER.2 Study: Study Protocol for a Prospective, Multicentre, Observational Cohort Study. Turkish J Anaesthesiol Reanim.* 2019;47:179–86.
8. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg.* 2014;12:1495–9.
9. Soffin EM, Yadeau JT. Enhanced recovery after surgery for primary hip and knee arthroplasty: A review of the evidence. *Br J Anaesth.* 2016;117:iii62–72.
10. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005;173:489–95.
11. Chen AF, Stewart MK, Heyl AE, et al. Effect of immediate post-operative physical therapy on length of stay for total joint arthroplasty patients. *J Arthroplasty.* 2012;27:851–6.
12. Hansen TB, Bredtoft HK, Larsen K. Preoperative physical optimization in fast-track hip and knee arthroplasty. *Dan Med J.* 2012;59:A4381.
13. Jans O, Jorgensen C, Kehlet H, et al. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. *Transfusion.* 2014;54:717–26.
14. Petersen MK, Madsen C, Andersen NT, et al. Efficacy of multimodal optimization of mobilization and nutrition in patients undergoing hip replacement: a randomized clinical trial. *Acta Anaesthesiol Scand.* 2006;50:712–7.
15. Kearney B, To J, Southam K, et al. Anaemia in elective orthopaedic surgery - Royal Adelaide Hospital, Australia. *Intern Med J.* 2016;46:96–101.
16. Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth.* 2011;106:13–22.
17. Abad-Motos A, Ripollés-Melchor J, Jerico C, et al. Patient Blood Management for primary hip and knee replacement. A survey among POWER.2 study researchers. *Rev Esp Anestesiol Reanim (Engl Ed).* 2020;67:237–44.
18. Li C, Qu J, Pan S, Qu Y. Local infiltration anesthesia versus epidural analgesia for postoperative pain control in total knee arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res.* 2018;13:112.
19. Andersen LO, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. *Br J Anaesth.* 2014;113:360–74.
20. Ma Y, Lu X. Indwelling catheter can increase postoperative urinary tract infection and may not be required in total joint arthroplasty: a meta-analysis of randomized controlled trial. *BMC Musculoskeletal Disord.* 2019;20:11.
21. Wald HL, Ma A, Bratzler DW, Kramer AM. Indwelling urinary catheter use in the postoperative period: Analysis of the national surgical infection prevention project data. *Arch Surg.* 2008;143(6):551–7.
22. Kehlet H. Fast-track hip and knee arthroplasty. *Lancet (London, England).* 2013;381:1600–2.
23. Cram P, Landon BE, Matelski J, et al. Utilization and Short-Term Outcomes of Primary Total Hip and Knee Arthroplasty in the United States and Canada: An Analysis of New York and Ontario Administrative Data. *Arthritis Rheumatol (Hoboken, NJ).* 2018;70:547–54.
24. Kehlet H. History and future challenges in fast-track hip and knee arthroplasty. *Orthopade.* 2020;49:290–2.

ORIGINAL INVESTIGATION

**Bilateral versus unilateral erector spinae plane block
for postoperative analgesia in laparoscopic
cholecystectomy: a randomized controlled study**



Sevim Cesur ^b, Hadi Ufuk Yörükoglu ^{a,*}, Can Aksu ^b, Alparslan Kuş ^b

^a Bitlis Tatvan State Hospital, Clinic of Anesthesiology and Reanimation

^b Kocaeli University, School of Medicine, Department of Anesthesiology and Reanimation, Kocaeli, Turkey

Received 12 May 2020; accepted 2 April 2021

Available online 28 April 2021

KEYWORDS

Nerve Block;
Ultrasound Imaging;
Erector Spinae Plane
Block;
Laparoscopic
Cholecystectomy;
Analgesia

Abstract

Introduction: Laparoscopic cholecystectomy (LC) is the common surgical intervention for benign biliary diseases. Postoperative pain after LC remains as an important problem, with two components: somatic and visceral. Trocar entry incisions lead to somatic pain, while peritoneal distension with diaphragm irritation leads to visceral pain. Following its description by Forero et al., the erector spinae plane (ESP) block acquired considerable popularity among clinicians. This led to the use of ESP block for postoperative pain management for various operations.

Materials and methods: This study was conducted between January and June 2019. Patients aged between 18 and 65 years with an American Society of Anesthesiologists (ASA) physical status I-II, scheduled for elective laparoscopic cholecystectomy were included in the study. All the patients received bilateral or unilateral ESP block at the T8 level preoperatively according to their groups.

Results: There was no significant difference between the groups in terms NRS scores either at rest or while coughing at any time interval except for postoperative 6th hour ($p = 0.023$). Morphine consumption was similar between the groups but was significantly lower in group B at 12 and 24 hours ($p = 0.044$ and $p = 0.022$, respectively). Twelve patients in group A and three patients in group B had shoulder pain and this difference was statistically significant ($p = 0.011$).

Discussion: In conclusion, bilateral ESP block provided more effective analgesia than unilateral ESP block in patients undergoing elective LC. Bilateral ESP block reduced the amount of opioid consumption and the incidence of postoperative shoulder pain.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. 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: ufukyorkoglu@gmail.com (H.U. Yörükoglu).

Introduction

Laparoscopic cholecystectomy (LC) is the common surgical intervention for benign biliary diseases. Postoperative pain after LC remains as an important problem,¹ with two components, somatic and visceral. Trocar entry incisions lead to somatic pain, while peritoneal distension with diaphragm irritation causes visceral pain.²

Following its description by Forero et al.,³ the erector spinae plane (ESP) block acquired considerable popularity among clinicians for its effectiveness, ease of application, and relatively low risk of complications. This has led to the use of ESP block for postoperative pain management for various operations.⁴

In contrast to many other interfacial plane blocks, there is some evidence that the ESP block is effective both against visceral and somatic pain.⁵ Several studies have shown that the ESP block provides adequate postoperative analgesia for LC.^{6,7} However, it is unclear whether the block needs to be performed bilaterally, as some authors believe that the major component of postoperative pain after LC derives from the tissue trauma during gall bladder resection that can be prevented using a unilateral regional anesthesia technique.⁸

The aim of the study was to compare the analgesic efficacy of unilateral versus bilateral ESP block in patients undergoing LC. The primary outcome measure was morphine consumption at the postoperative 24th hour. Secondary outcome measure was to compare pain scores, incidences of shoulder pain, nausea and vomiting, and patient's satisfaction.

Methods

This study was conducted between January and June 2019. It was approved by the Kocaeli University Clinical Trials Ethical Committee (KIA 2018/488) and registered with clinicaltrials.gov (NCT03781687). Written informed consent was obtained from the patients.

Patients aged between 18 and 65 years, with an American Society of Anesthesiologists (ASA) physical status I-II, and scheduled for elective laparoscopic cholecystectomy were included in the study. Patients with obesity (body mass index > 35 kg.m⁻²), infection of the skin at the site of needle puncture area, known allergies to any of the study drugs, coagulopathy, recent use of opioid drugs, or inability to communicate with the investigators were excluded from the study.

Patients were randomly allocated to two groups: Group A (Unilateral) and Group B (Bilateral). The sequence was done using www.random.org and the allocation sequence was concealed in sealed opaque envelopes, which indicated the treatment to be assigned to the patient. All the patients received preoperative bilateral or unilateral ESP block at the T8 level preoperatively according to their groups. All the blocks have been done 20 minutes before the surgery in a separate block room. All blocks were performed by experienced anesthesiologists with no involvement in patients' perioperative follow-up and data collection processes.



Figure 1 Ultrasound image of erector spinae plane block. ESM, erector spinae muscle.

ESP technique

All patients were premedicated with midazolam 0.03 mg.kg⁻¹ IV (intravenous). Blocks were performed in the prone position with standard monitoring. An Esaote My Lab 6 US machine (Florence, Italy) with a convex probe (1–8 MHz) and a 22G, 80-mm, insulated facet type needle (B Braun Sonoplex, Melsungen, Germany) were used for all block applications.

After appropriate skin disinfection, the probe was placed longitudinally 3 cm lateral to the T8 level. Following identification of the transverse process and erector spinae muscle, the needle was inserted with in-plane approach from cranial to caudal direction (Fig. 1). Bupivacaine 0.25% (20 mL) was administered on the right side in group A patients and bilaterally at the T8 level in group B patients. The spread of the injectate beneath the erector spinae muscle was visualized in both the cranial and caudal directions.

General anesthesia

Following monitoring of SpO₂, ECG and noninvasive blood pressure, anesthesia was induced with propofol (2–3 mg.kg⁻¹), fentanyl (1 mcg.kg⁻¹) and rocuronium (0.6 mg.kg⁻¹). Desflurane in combination with nitrous oxide in oxygen at a ratio of 2:1 was used for anesthesia maintenance. Pneumoperitoneum was created with carbon-dioxide and maintained at a range of 10–12 mm Hg. At the end of the surgery, tramadol 100 mg and paracetamol 1 g IV were administered. Ondansetron 8 mg IV was also administered to prevent postoperative nausea and vomiting.

Patients were also provided with a patient controlled analgesia (PCA) device containing 0.5 mg.mL⁻¹ morphine set to deliver a 1 mg bolus dose, with an 8-minute lock out time and an 1-hour limit of 6 mg. Rescue analgesia using tenoxicam 20 mg IV was planned if NRS was > 3.

Table 1 Demographic data.

	Group A (n = 45)	Group B (n = 45)	p
Age (year)	52.2 ± 12.5	53.31 ± 10.17	0.868
Sex (M/F)	13/32	14/31	0.819
Height (cm)	163.68 ± 8.44	163.35 ± 8.25	0.977
Weight (kg)	77.17 ± 15.26	81.2 ± 14.15	0.242
ASA status (I/II)	24/21	23/22	0.834
Duration of surgery (min)	64.55 ± 15.44	69 ± 21.91	0.420

Data are presented as mean ± SD and patient numbers.

Table 2 NRS scores in rest and while coughing at the postoperative 1st, 6th, 12th, 24th hour.

	Group A (n = 45)	Group B (n = 45)	p ^a
NRS scores in rest			
1 st hour	2.00 (0.00-4.00)	2.00 (1.00-4.00)	0.889
3 rd hour	2.00 (0.00-2.00)	1.00 (0.00-2.00)	0.334
6 th hour	1.00 (0.00-2.00)	1.00 (0.00-2.00)	0.643
12 th hour	0.00 (0.00-1.00)	0.00 (0.00-1.50)	0.505
24 th hour	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.809
NRS scores while coughing			
1 st hour	2.00 (1.00-5.00)	3.00 (2.00-4.00)	0.440
3 rd hour	2.00 (1.00-4.00)	2.00 (0.00-2.50)	0.228
6 th hour	1.00 (0.00-2.00)	0.00 (0.00-1.50)	0.048 ^a
12 th hour	0.00 (0.00-2.00)	0.00 (0.00-2.00)	0.442
24 th hour	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.909

Data are presented as median (25–75 percentile).

^a p < 0.05, (Mann-Whitney U test).

Morphine consumptions and NRS scores both at rest and while coughing were recorded at postoperative hours 1, 3, 6, 12 and 24. The incidences of shoulder pain, nausea, and vomiting in the postoperative first 24 hours were also recorded. Patients were asked if they were satisfied with the anesthesia technique using a 6-point satisfaction score system (0 = not at all satisfied, 5 = very satisfied) and whether or not they would choose this technique again. A blinded pain nurse performed postoperative follow-up of patients and collected the data. Analyses of all data were performed by other researchers that were blinded to the groups.

Statistical analysis

In a previous study conducted in our clinic, mean morphine consumption among patients undergoing unilateral ESP block for LC at the T8 level was 7.5 ± 5.8 mg (6). We calculated that for 80% power and an error of 0.05, the required sample size to detect a 40% difference in morphine consumption at 24 hours after the surgery would 43 patients per group. We finally included 46 patients in each group in case of dropouts.

All statistical analyses were performed using the IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA) software. Kolmogorov-Smirnov test was used to assess the assumption of normality.

Continuous variables were presented depending on normal distribution with either mean ± standard deviation or (in case of no normal distribution) median (25th-75th

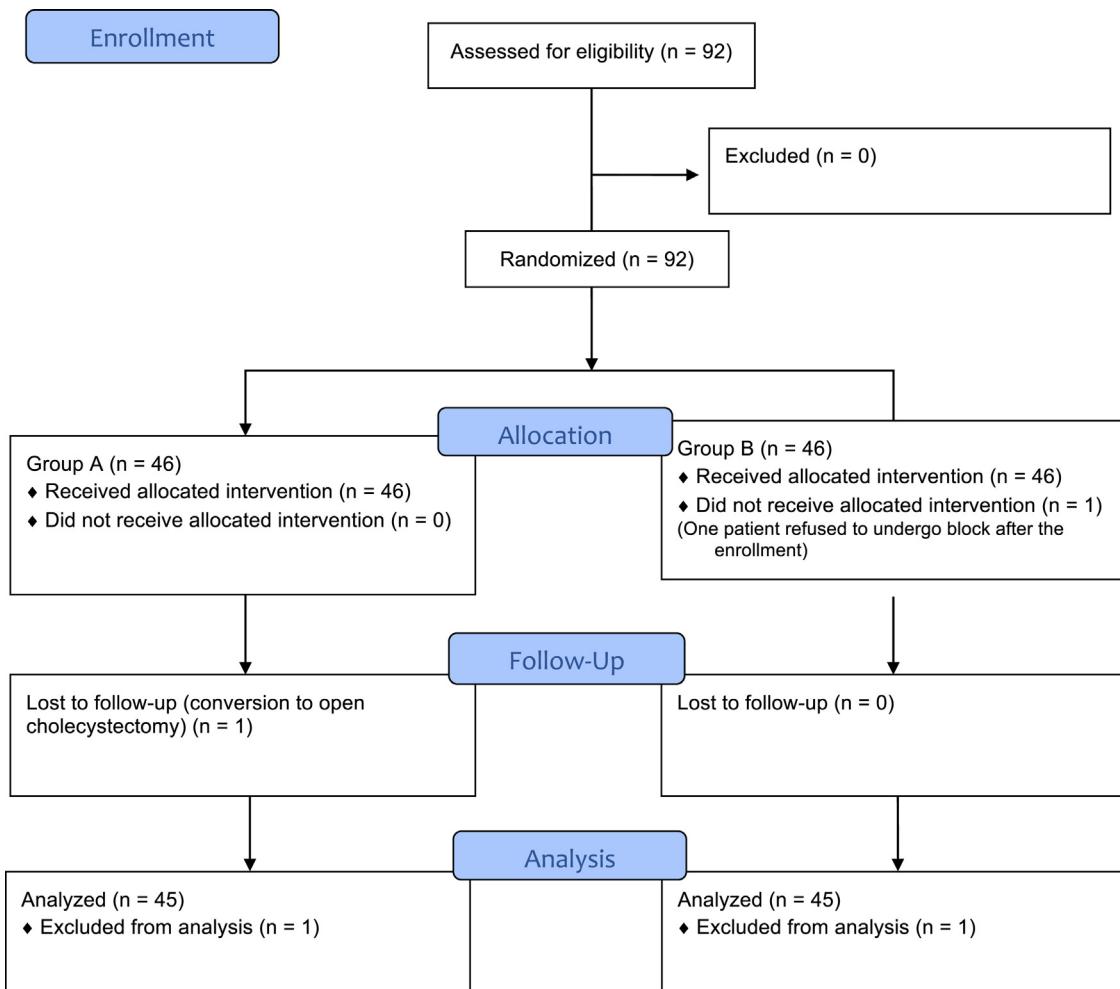
percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were carried out using independent samples t-test/ Mann-Whitney U test, whichever was appropriate. Association between two categorical variables was examined by Chi-square test. A value of p < 0.05 was considered statistically significant.

Results

Figure 2 shows the Consort diagram of enrollment for this study. Ninety-two patients were randomly assigned to either group A or B. Two patients were excluded from the study. One patient refused to undergo block after the enrollment and one patient was excluded due to conversion to open cholecystectomy.

The groups were comparable in terms of demographic data and duration of surgery (Table 1).

There was no significant difference between the groups in terms NRS scores either at rest or while coughing at any time interval except for the postoperative 6th hour (p = 0.023) (Table 2). Morphine consumption was similar between the groups but was significantly lower in group B at 12 and 24 hours (p = 0.044 and p = 0.022, respectively) (Table 3). Twelve patients in group A and three patients in group B had shoulder pain, and this difference was statistically significant (p = 0.011) (Table 4). Nausea and vomiting were similar between the groups (Table 4).

**Figure 2** Consort flow diagram.**Table 3** Morphine consumptions at the postoperative 1st, 6th, 12th, 24th hour.

	Group A (n = 45)	Group B (n = 45)	p
Morphine consumption (mg)			
1 st hour	1.11 ± 0.57	1.15 ± 0.79	0.280
3 rd hour	2.77 ± 1.67	2.73 ± 2.01	0.617
6 th hour	4.95 ± 3.32	3.82 ± 2.87	0.431
12 th hour	6.68 ± 4.86	5.08 ± 3.37	0.044*
24 th hour	8.28 ± 5.79	6.08 ± 3.66	0.022*

Data are presented as mean ± SD.

* 0.05, (Mann-Whitney U test).

No complications related to block procedures were observed.

eral ESP block reduced the incidence of shoulder pain ($p = 0.011$).

Laparoscopic technique for cholecystectomy is becoming more popular than open technique as it leads to less surgical trauma, better tissue healing, and faster recovery. Although it is a minimally invasive surgery, pain after LC still stands as a problem to solve and has multiple components like surgical manipulations, visceral pain, subdiaphragmatic irritation.⁹ There is also a somatic component due to abdominal thoracars. The PROSPECT Working Group recommends the use of non-steroidal inflammatory drugs (NSAIDs), paracetamol

Discussion

The study findings showed that the bilateral ESP block reduced total morphine consumption at postoperative hours 12 and 24, while total morphine consumption decreased by 26% compared to the unilateral block. Furthermore, bilat-

Table 4 Incidences of shoulder pain, nausea and vomiting, and patients' satisfaction scores.

	Group A (n = 45)	Group B (n = 45)	p
Shoulder pain, n (%)			
Yes	12 (80.0)	3 (20.0)	0.011 ^a
No	33 (44.0)	42 (56.0)	
Nausea, n (%)			
Yes	11 (57.9)	8 (42.1)	0.441
No	34 (47.9)	37 (52.1)	
Vomiting, n (%)			
Yes	7 (58.3)	5 (41.7)	0.756
No	38 (48.7)	40 (51.3)	
Satisfaction scores, n (%)			
0	0 (0.0)	0 (0.0)	0.955
1	2 (4.4)	2 (4.4)	
2	2 (4.4)	0 (0.0)	
3	4 (8.9)	6 (13.3)	
4	8 (17.9)	8 (17.9)	
5	29 (64.4)	29 (64.4)	
Total	45 (100.0)	45 (100.0)	

Data are presented number of patients and %.

^a p < 0.05, (Chi-square test).

and local anesthetic infiltration to the port insertion site for routine analgesia, and opioid drugs for rescue analgesia.¹⁰ However, according to the results of a recently published meta-analyses about the pharmacological methods used for analgesia after LC, effectiveness of paracetamol and NSAIDs has low quality of evidence while intravenous ketamine, opioids and pregabalin has moderate to high quality evidence.⁹ Either way, regional anesthesia techniques should be performed as a component of multimodal analgesia to prevent inadequate treatment of postoperative pain, if possible.¹⁰ Studies have investigated the use of the transversus abdominis plane (TAP) block with different techniques in LC.^{11,12} However, the results are inconsistent. With the TAP block, cutaneous fibers and sometimes also parietal components of the parietal peritoneum are blocked. This technique is therefore not effective for visceral pain, and its use is still controversial.

Thoracic paravertebral block (TPVB) may be another alternative regional anesthesia technique for postoperative analgesia. Studies have reported the successful use of bilateral TPVB with both US guidance and nerve stimulation in LC.^{13,14} However, TPVB is an advanced technique, either with US guidance or with nerve stimulation, because of the proximity of the pleura to the paravertebral space and the potential risk of hemodynamic complications. This particularly accounts for the popularity of the ESP block and its use by many clinicians as a replacement for TVPB. The ESP block affects both visceral and somatic pain fibers.⁵ On the other hand, lower potential risks of complications make this technique preferable for LC. Tulgar et al.⁷ reported that bilateral ESP block at the T9 level provided effective analgesia in LC. Similarly, a previous study from our clinic, showed that adequate analgesia was provided with unilateral ESP block at

the T8 level.⁶ Additionally, effective analgesia with bilateral ESP block after LC in pediatric patients has also been reported in literature.¹⁵

In laparoscopic abdominal surgeries, nerve fibers responsible for the somatic pain arises from T6-L2, and visceral pain derives from the structures involved in the surgery.² According to cadaver studies of ESP block, the injection of 20 mL of drug may result in a widespread from T1 to L1.^{16,17} De Cassai et al.¹⁸ reported that the injection spread in the ESP block requires different volumes of injection according to the site of injection. In the thoracic region 3.3 (radiological studies) and 3.5 (cadaveric dissection) mL were needed when ESP block was performed, 5 mL of injectate was needed to cover a vertebral level in the lumbar region.

It is expected that performing ESP block at T8 with 20 mL of local anesthetic will be sufficient for laparoscopy. However, the major component of postoperative pain after LC may be tissue trauma during gall bladder resection that can be prevented with a unilateral regional anesthesia technique.⁸ In this study, patients were satisfied with the analgesia provided by unilateral injection. Nevertheless, bilateral ESP block was more effective than unilateral injection. Bilateral block may be painful for some patients, but bilateral ESP block can be performed with a single needle entry from the midline to reduce this pain.¹⁹

High pneumoperitoneum pressures may increase the incidence of postoperative shoulder pain.¹⁰ Aspirating residual gas at the end of the operation has also been shown to reduce postoperative shoulder pain.¹⁰ In this study, pneumoperitoneum was maintained at a range of 10–12 mm Hg. Pneumoperitoneum gas was aspirated after completion of the operative procedures. A previous study from our clinic,⁶ reported that unilateral ESP block reduced postoperative shoulder pain, and the present study shows that bilateral ESP block is more effective in reducing postoperative shoulder pain.

There are a number of limitations to this study. No sham block was performed on at the contralateral side in the unilateral group patients, and the placebo effect is unclear. As discussed previously, the mechanism of the ESP block still remains unclear. It has also been reported that unilateral ESP block may result in bilateral sensory blockade,²⁰ and performing sham block on the contralateral side would have affected the drug spread or concentration.

In conclusion, bilateral ESP block provided more adequate analgesia than unilateral ESP block in patients undergoing elective LC. Bilateral ESP block also reduced the amount of opioid consumption and the incidence of postoperative shoulder pain.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Informed consent was obtained from all individual participants included in the study.

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with

the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Rosero EB, Joshi GP. Hospital readmission after ambulatory laparoscopic cholecystectomy: incidence and predictors. *J Surg Res.* 2017;219:108–15.
2. Chin KJ, McDonnell JG, Carvalho B, et al. Essentials of our current understanding: abdominal wall blocks. *Reg Anesth Pain Med.* 2017;42:133–83.
3. Forero M, Adhikary SD, Lopez H, et al. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. *Reg Anesth Pain Med.* 2016;41:621–7.
4. De Cassai A, Bonvicini D, Correale C, et al. Erector spinae plane block: a systematic qualitative review. *Minerva Anestesiol.* 2019;85:308–19.
5. Chin KJ, Adhikary S, Sarwani N, et al. The analgesic efficacy of pre-operative bilateral erector spinae plane (ESP) blocks in patients having ventral hernia repair. *Anesthesia.* 2017;72:452–60.
6. Aksu C, Kus A, Yorukoglu HU, et al. The effect of erector spinae plane block on postoperative pain following laparoscopic cholecystectomy: a randomized controlled study. *Anestezi Derg.* 2019;27:9–14.
7. Tulgar S, Kapaklı MS, Senturk O, et al. Evaluation of ultrasound-guided erector spinae plane block for postoperative analgesia in laparoscopic cholecystectomy: a prospective, randomized, controlled clinical trial. *J Clin Anest.* 2018;49:101–6.
8. Ekstein P, Szold A, Sagie B, et al. Laparoscopic surgery may be associated with severe pain and high analgesia requirements in the immediate postoperative period. *Ann Surg.* 2006;1:41–6.
9. Eftekhariyazdi M, Ansari M, Darvishi-Khezri H, et al. Pharmacological methods of postoperative pain management after laparoscopic cholecystectomy: a review of meta-analyses. *Surg Laparosc Endosc Percutan Tech.* 2020;30:534–41.
10. Barazanchi AWH, MacFater WS, Rahiri JL, et al. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. *Br J Anaesth.* 2018;121:787–803.
11. Ortiz J, Suliburk JW, Wu K, et al. Bilateral transversus abdominis plane block does not decrease postoperative pain after laparoscopic cholecystectomy when compared with local anesthetic infiltration of trocar insertion sites. *Reg Anesth Pain Med.* 2012;37:188.
12. Ma N, Duncan JK, Scarfe AJ, et al. Clinical safety and effectiveness of transversus abdominis plane (TAP) block in post-operative analgesia: a systematic review and meta-analysis. *J Anesth.* 2017;31:432–52.
13. Aydin G, Aydin O. The efficacy of ultrasound-guided paravertebral block in laparoscopic cholecystectomy. *Medicina.* 2018;54:75.
14. Naja ZM, El-Rajab M, Ziade F, et al. Preoperative vs. postoperative bilateral paravertebral blocks for laparoscopic cholecystectomy: a prospective randomized clinical trial. *Pain Pract.* 2011;11:509–15.
15. Aksu C, Gurkan Y. Ultrasound-guided bilateral erector spinae plane block could provide effective postoperative analgesia in laparoscopic cholecystectomy in paediatric patients. *Anaesth Crit Care Pain Med.* 2019;38:87–8.
16. Adhikary SD, Bernard S, Lopez H, et al. Erector spinae plane block versus retrolaminar block: a magnetic resonance imaging and anatomical study. *Reg Anesth Pain Med.* 2018;43:756–62.
17. Ivanusic J, Konishi Y, Barrington MJ. A Cadaveric Study Investigating the mechanism of action of erector spinae blockade. *Reg Anesth Pain Med.* 2018;43:567–71.
18. De Cassai A, Andreatta G, Bonvicini D, et al. Injectate spread in ESP block: a review of anatomical investigations. *J Clin Anesth.* 2020;61:109669.
19. Yorukoglu HU, Aksu C, Kilic CT, et al. Bilateral erector spinae plane block with single injection. *J Clin Monit Comput.* 2019;33:1145–6.
20. Tulgar S, Selvi O, Ahiskalioglu A, et al. Can unilateral erector spinae plane block result in bilateral sensory blockade? *Can J Anesth.* 2019;66:1001–2.



ORIGINAL INVESTIGATION

Inkk Trial – Intraoperative ketamine for perioperative pain management following total knee endoprosthetic replacement in oncology: a double-blinded randomized trial



V. Susan Paulin ^{a,*}, Sumitra G Bakshi ^a, Prateek C. Hegde ^b, Akanksha Rathod ^a, Ashish Gulia ^b, Ajeeta M. Kulkarni ^c, Vincent S. Paramanandam ^c

^a Tata Memorial Hospital and Homi Bhabha National Institute, Department of Anaesthesia, Critical Care and Pain, Mumbai, India

^b Tata Memorial Hospital and Homi Bhabha National Institute, Department of Surgical Oncology, Orthopedic Oncology, Mumbai, India

^c Tata Memorial Hospital and Homi Bhabha National Institute, Department of Physiotherapy, Mumbai, India

Received 5 October 2020; accepted 10 July 2021

Available online 28 July 2021

KEYWORDS

Ketamine;
Post-operative pain;
Orthopedic
rehabilitation
surgery;
Total knee
replacement

Abstract

Background: There has been a growing interest in the use of ketamine following orthopedic surgeries. We hypothesized that low dose intravenous ketamine during surgery would help in mobilization following total knee replacement (TKR) in oncology patients as assessed by the timed to up and go (TUG) test at 72 hours post-surgery. Our secondary objectives were to compare the opioid requirement at the end of 72 hours, pain scores, satisfaction with pain management, adverse effects, range of joint movement achieved in the post-operative period and the functional recovery at the end of 1 month.

Methods: After the ethics committee approval, registration of the trial with the Clinical Trial Registry - India (CTRI), and informed consent, this double-blinded trial was conducted. Using computer generated randomization chart, an independent team randomized the patients into ketamine group which received at induction, a ketamine bolus dose of $0.5 \text{ mg} \cdot \text{kg}^{-1}$ before the incision followed by $10 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \text{min}^{-1}$ infusion which was maintained intraoperatively till skin closure and the saline group received an equivalent volume of saline. Postoperatively, patient controlled morphine pumps were attached and the pain score with morphine usage were recorded for 72 hours. The TUG tests and range of motion were assessed by the physiotherapists until 72 hours.

* Corresponding author.

E-mail: susanvercetti@gmail.com (V.S. Paulin).

Results: Fifty-two patients were enrolled in the trial. Demographics were comparable. No significant intraoperative hemodynamic changes and post-operative adverse events were noted between the groups. A decrease in the TUG test, along with decreased opioid usage with a better range of movements was noted in the ketamine group, but this was not statistically significant. Day of discharge, patient satisfaction score, and functional recovery assessed by Oxford Knee Score (OKS) were comparable between the groups.

Conclusion: In conclusion, low dose intraoperative ketamine infusion does not provide clinical benefit in perioperative pain management and postoperative rehabilitation following total knee endoprosthetic replacement in oncology.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction and rationale

A pain-free postoperative period is imperative following total knee replacement (TKR) surgeries as it aids in early rehabilitation and faster recovery.¹ Currently available analgesic interventions during TKR include epidural analgesia, peripheral nerve block and opioids.² Epidural analgesia has failed to gain popularity because of incidences of hypotension, urinary retention, pruritis, motor weakness and increased transfusions and fluid requirements.^{3,4} The use of opioids through intravenous patient-controlled analgesia (IV PCA) is associated with side effects including nausea, vomiting, constipation, sedation, and urinary retention⁵. Intra-articular local anesthetic infiltration has not gained popularity in our hospital. Additionally, peripheral nerve blocks are not favored as there is the risk of femoral quadriceps weakness leading to increased risk of fall. There are documentations of few cases of neuritis and femoral neuropathy following peripheral blocks. All of which can affect postoperative rehabilitation.⁶ Hence, arose a need to have a suitable multi-modal analgesic regimen for these patients.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been used in few orthopedic surgeries, including knee and spine surgeries, with results suggesting a decrease in opioid requirement perioperatively. The literature is inconclusive about the optimum dose and duration for the continuation of ketamine infusion in the peri-operative period.^{7,8} Also, there is a lack of data on whether ketamine is equally effective in endoprosthetic knee replacement surgeries, which involve a longer procedure with more soft tissue and neurovascular dissection. Here, normal soft tissues are excised to achieve negative surgical margins resulting in large structural defects which are reconstructed by tumor endoprosthesis.⁹ As tissue handling and trauma is maximum during any surgery, we aimed to study the benefit of intraoperative use of ketamine in rehabilitation following endoprosthetic TKR, and we hypothesized that a low dose of intravenous ketamine during surgery would help in mobilization following endoprosthetic TKR in oncology patients as assessed by the timed to Up and Go (TUG) test.^{7,10,11}

Our primary objective was to compare functional recovery using the TUG test at the end of 72 hours. Our secondary objectives were to compare the opioid requirement at the end of 72 hours, pain scores, satisfaction with pain management, the incidence of adverse effects and range of joint

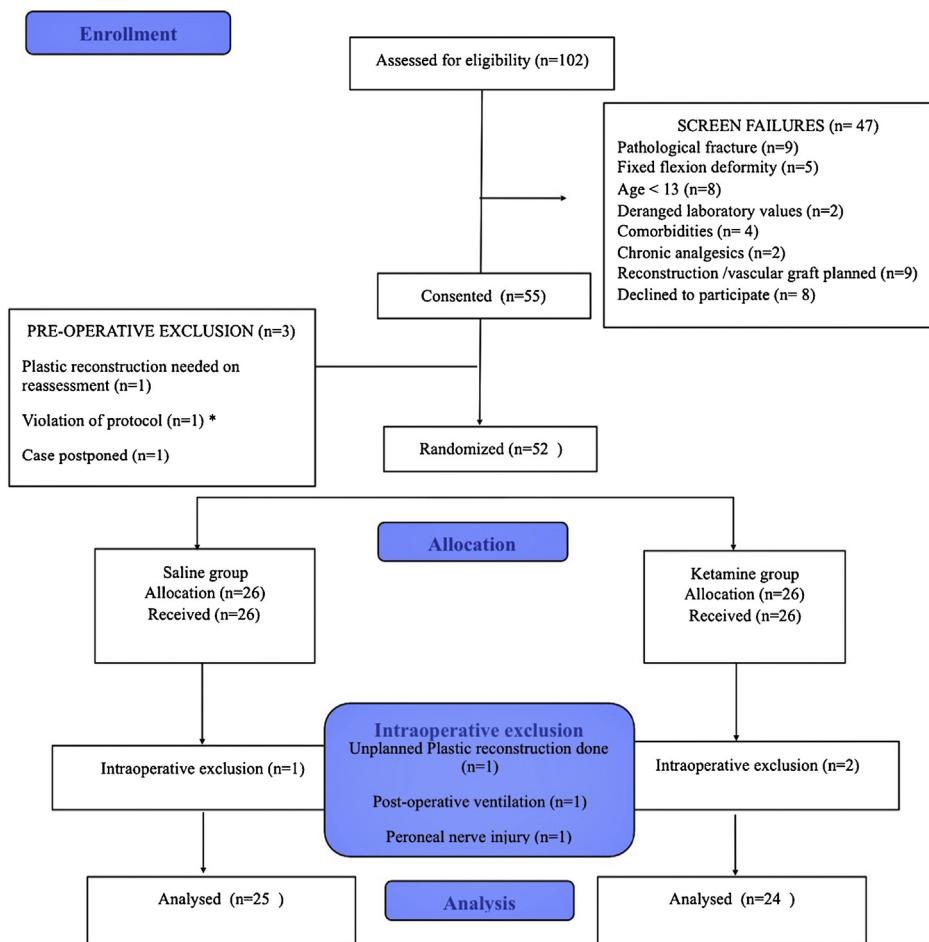
movement achieved in the postoperative period. We also compared the functional recovery at the end of one month.

Methods

This prospective double-blinded randomized control trial was conducted in our hospital from September 2017 till October 2018. After the Institutional Ethics Committee approval [IEC approval number: IEC/0817/1855/002], the trial was registered with the clinical trial registry of India [CTRI/2015/08/006130] and written informed consent was obtained from each patient/guardian. Patients with American Society of Anesthesiologists (ASA) physical status I and II, aged above 13 years undergoing total knee replacement for oncological indications were included. Patients undergoing reconstructive surgery with major plastic flaps or on preoperative opioid/drug abuse, on chronic pain medications, with preoperative pathological fracture, muscle weakness of affected limb leading to limitation to mobility, pregnant patients, patients with contraindications to ketamine such as raised intracranial pressure, glaucoma medications, raised intraocular pressure, history of vertigo, auditory/visual hallucinations, or on antipsychotic medications were excluded. Postoperative exclusion criteria included intraoperative common peroneal nerve damage and postoperative ventilation or hemodynamic instability preventing mobilization for more than 24 hours.

Previous observations by the physiotherapy team revealed that patients after endoprosthetic TKR in oncology patients with standard analgesic protocol at our center, take an average of 142 seconds at 72 hours to complete the TUG test. The standard analgesic protocol at our center includes the use of intraoperative opioid along with post-operative morphine PCA pumps (1 mg bolus and 10-minute lockout interval), and either intravenous (IV) paracetamol or diclofenac. Group sample sizes of 20 each was required with 80% power with mean difference of 35.5 (25% reduction in TUG Day 3) and with a significance level (alpha) of 0.05. Permitting a 30% drop out (for postoperative exclusion), 52 was taken as sample size.

Patients were preoperatively educated in the use of patient controlled analgesia (PCA) pumps and familiarized with the use of the Numeric Rating Scale (NRS; 0 to 10 scale where 0 = no pain and 10 = worst pain imaginable) for rating their postoperative pain at rest and movement. On the morning of the surgery, patients were randomized into



* Femoral nerve block given before the induction of anaesthesia

Figure 1 CONSORT Flow Diagram.

ketamine group or saline group. A team of residents, who were not part of the research team, randomized patients in accordance with computer generated randomization chart. This group prepared the study drug, labeled, and handed over the syringes to the concerned anesthesiologist. This ensured that the theatre team, patients, and the study team were blinded to the nature of the study drug. The ketamine group received at induction, a bolus dose of $0.5 \text{ mg} \cdot \text{kg}^{-1}$ followed by $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion, while the saline group received equivalent volume of saline.

Induction of general anesthesia and intraoperative management was standardized. Upon arrival in the operating room, baseline parameters – i.e., heart rate (HR), blood pressure (BP), oxygen saturation were noted. In addition, electrocardiogram was continuously monitored. Patients were induced with either propofol $2-3 \text{ mg} \cdot \text{kg}^{-1}$ or thiopentone sodium $5-7 \text{ mg} \cdot \text{kg}^{-1}$ intravenously; the need for neuromuscular blockade and airway management were decided as per the theatre anesthesiologists. Intraoperative analgesia included fentanyl $2 \mu\text{g} \cdot \text{kg}^{-1}$ IV at induction, followed by morphine, $0.1 \text{ mg} \cdot \text{kg}^{-1}$ (lean body weight) IV after 30–45 minutes. If needed, fentanyl $1-2 \mu\text{g} \cdot \text{kg}^{-1}$ could be repeated as and when required. The study drug bolus was administered after the airway was secured and was followed

by infusion as per instruction given by the unblinded team. The study drug was continued till the completion of skin closure. The procedures were performed by the same surgical team. Perioperatively, steroids, tranexamic acid, and peri-articular anesthetic injections were not used. A single negative suction drain was inserted in all patients.

At the end of surgery, injection paracetamol $500 \text{ mg} \cdot 1\text{g} (> 50 \text{ kg}: 1 \text{ g}, 45-50 \text{ kg}: 750 \text{ mg}, \text{less than } 45 \text{ kg}: 15 \text{ mg} \cdot \text{kg}^{-1} \text{ maximum of } 500 \text{ mg})$ was given intravenously. In the postanesthesia care unit (PACU), the PCA pump with morphine was initiated with a standard setting of 1 mg bolus and lockout interval of 10 minutes. All patients were followed up by acute pain service (APS) and resting pain assessed using NRS scale. The worst pain during exercise was recorded by the physiotherapist at the end of each exercise session. Adverse effects were recorded as follows at 24, 48, and 72 hours. Vomiting was recorded at 24, 48, 72 hours as per vomiting score (0: no nausea, no vomiting; 1: nausea alone; 2: one episode of emesis; and 3: two or more episodes of emesis).¹² Sedation was assessed using the 6-point Ramsay sedation scale (in which 1 = awake, anxious, agitated, restless; and 6 = asleep, no response to light glabellar tap or loud auditory stimulus).¹³

Table 1 General demographics.

Parameters		Saline group	Ketamine group
Age (years) ^a		19.42 ± 6.09	24.62 ± 11.47
Sex	Male (n%) ^b	14 (53.8%)	15 (57.7%)
	Female (n%) ^b	12 (46.2%)	11 (42.3%)
Weight (kilograms) ^a		51.52 ± 11.67	54.98 ± 12.11
ASA	ASA I (n%) ^b	24 (92.3%)	25 (96.2%)
	ASA II (n%) ^b	2 (7.7%)	1 (3.8%)

ASA, American Society of Anesthesiologists physical status.

^a Values as mean \pm standard deviation.^b Number (percentages within the group); $p < 0.05$ is considered significant.**Table 2** Intraoperative details.

Parameters		Saline group	Ketamine group	<i>p</i> -value
Preoperative chemotherapy (n%) ^a		21 (80.8%)	16 (61.6%)	0.2
Heart rate (beats/min) ^b	After bolus	78 [64.50–88]	75.50 [64.50–95]	0.8
	At end of infusion	80.50 [72–97.50]	90 [80–97.25]	0.07
Systolic blood pressure (mmHg) ^b	After bolus	100 [94.50–110.25]	100 [92.75–117.25]	0.3
	At end of infusion	110 [101.50–117.25]	111 [101.50–125]	0.3
Diastolic blood pressure (mmHg) ^b	After bolus	60 [50–65.75]	57.50 [50–70.25]	0.4
	At end of infusion	65 [55–71.75]	67.50 [57.50–77]	0.4
Duration of surgery (minutes) ^c		100.74 ± 6.99	106.4 ± 12.11	0.1
Blood loss (milliliters) ^c		726.92 ± 360.62	890.38 ± 470.32	0.2
Length of resection (centimeters) ^c		16.38 ± 4.18	16.33 ± 4.40	0.7

 $p < 0.05$ is considered significant.^a Number (percentages within the group).^b Values as Median [Inter-quartile range].^c Values as mean \pm standard deviation.

Unpleasant feelings like hallucinations (auditory/visual), dizziness, nightmares were recorded on a score from 1–5, 5 = worst imaginable.¹⁴ At 30-day follow-up in the outpatient department, details of ongoing pain killers and functional recovery were recorded on Oxford Knee Score (OKS), which is a validated 12-item knee questionnaire that scores patients from 12 (best possible) to 60 (worst possible).¹⁵ The scale is available in English language and was administered by the investigator and patients' replies recorded.

The TUG measured the time it takes a patient to rise from an armed chair (at least up to knee length for the given patient), walk 3 meters, turn, and return to sitting in the same chair.¹⁰ Patients were instructed to walk as quickly as they feel safe and comfortable. The use of the arms of the chair was permitted to stand up and sit down. A stopwatch was used to measure the time to complete the TUG within the nearest one-tenth of a second. Walking aids, if needed, were allowed for patients in the immediate postoperative period (24–48 hours) only.

All the raw data were entered and analyzed using SPSS Statistics version 25 software. Demographic data were expressed as mean \pm standard deviation (age, weight, height, duration of surgery, anesthesia, or proportion (sex and ASA physical status). The continuous data were analyzed using Student's independent t-test when normally distributed (fentanyl use, morphine use, degrees of move-

ment), and with Mann–Whitney U test if otherwise (Heart rate [HR], blood pressure [BP], minimum alveolar concentration [MAC] and pain scores). All the analyses were two-tailed and the confidence level was 95%; $p < 0.05$ was considered statistically significant.

Results

A total of 102 patients were screened and 52 patients were randomized; 49 were included for the final TUG analysis, refer to consort diagram (Fig. 1). The general demographics such as age, gender, weight, ASA physical status, duration of surgery and anesthesia were comparable between the two groups (Tables 1 and 2). We found that the functional recovery assessed using TUG test at end of 72 hours was better in the ketamine group with 103.25 ± 30.04 seconds as compared to the saline group with 125.91 ± 49.32 seconds. But this finding was not statistically significant ($p = 0.1$). The results of the TUG tests on each postoperative day along with degrees of flexion achieved are shown in Table 3. The comparison of perioperative opioid requirement is enumerated in Table 4. Interventions were required intraoperatively for six patients for tachycardia and hypertension (2 in the saline group and 4 in the ketamine group). No statistical difference was seen in this regard. There was no discontinuation of the study drug due to any hemodynamic instability intraoperatively. The postoperative pain scores at rest and

Table 3 Postoperative assessment of rehabilitation.

Outcomes	Saline	Ketamine	p
TUG at 24 h (s) ^a	170.58 ± 52.89	135.55 ± 55.12	0.2
TUG at 48 h (s) ^a	139.92 ± 47.69	140.64 ± 64.34	0.8
TUG at 72 h (s) ^a	125.91 ± 49.32	103.25 ± 30.04	0.1
Maximum flexion at 24 h (°) ^a	47.08 ± 19.12	51.25 ± 17.98	0.6
Maximum flexion at 48 h (°) ^a	68.00 ± 20.57	72.92 ± 24.53	0.3
Maximum flexion at 72 h (°) ^a	74.64 ± 18.96	81.15 ± 16.35	0.3

TUG, timed to Up and Go test.

p < 0.05 is considered significant.

^a Values as mean ± standard deviation.**Table 4** Perioperative opioid usage.

Parameters	Saline	Ketamine	p
Intraoperative fentanyl usage (μg) ^a	213.25 ± 76.75	205.00 ± 86.12	0.7
Postoperative morphine usage at 2 h (mg) ^a	4.38 ± 3.07	4.11 ± 3.19	0.6
Post-operative morphine usage at 24 hours (mg) ^a	32.13 ± 19.99	28.52 ± 20.84	0.6
Postoperative morphine usage at 48 h (mg) ^a	48.64 ± 27.19	48.01 ± 30.32	0.6
Postoperative morphine usage at 72 h (mg) ^a	67.59 ± 40.58	61.34 ± 32.93	0.5

μg, micrograms; mg, milligrams.

p < 0.05 is considered significant.

^a Values as mean ± standard deviation.**Table 5** Assessment.

Parameters	Saline	Ketamine	p-value	
Preoperative OKS ^a	Overall Received preoperative chemotherapy No preoperative chemotherapy	25 [24–26] 25 [24–26] 26 [23–27]	26 [22–27] 27 [25–28] 22 [21–24]	0.8 0.07 0.1
Postoperative OKS ^a	Overall Received preoperative chemotherapy No preoperative chemotherapy	34 [32–36] 34 [33–37] 34 [31–35]	33 [30–36] 35 [33–36] 30 [29–32]	0.7 0.8 0.1
Day of discharge (days) ^b	6.35 ± 1.79	5.78 ± 1.41	1.0	
Patient satisfaction score ^c	4 [3–4]	4 [4–4]	0.5	

OKS, Oxford Knee Score.

^a Values as Median [Inter-quartile range].^b Values as mean ± standard deviation; p < 0.05 is considered significant.^c On a Likert scale of 1–5 where 1 = very unsatisfied, and 5 = very satisfied.

during exercise were comparable between the two groups. **Figure 2** shows the trend of postoperative pain scores during exercise. The median pain score at 24 hours during exercise was 7 [5–8] in the saline group and 5 [4–7.5] in the ketamine group ($p = 0.2$). No significant postoperative adverse events such as nausea, vomiting, sedation, and dysphoric symptoms were noted between the groups. Day of discharge, patient satisfaction score and functional recovery assessed by OKS at one month follow up were comparable between the groups (**Table 5**).

Discussion

From this study we found that intraoperative intravenous ketamine infusion at $10 \text{ } \mu\text{g}.\text{kg}^{-1}.\text{min}^{-1}$ following a bolus of $0.5 \text{ mg}.\text{kg}^{-1}$ did not improve post-operative rehabilita-

tion following endoprosthetic TKR in oncology. Though the ketamine group had a better performance with respect to the TUG test at the end of 72 hours, the difference was not statistically significant.

The difference in knee replacement done for tumors as compared to the conventional ones are that the part of the bone involved (femur or tibia) by the tumor is removed, keeping a safe margin with a cover of overlying muscles,¹⁶ while in conventional TKR, only the articular surface is removed and replaced.¹⁷ In tumour reconstruction, emphasis is placed on safe resection and reconstruction is secondary with the ligaments (collateral and cruciate) sacrificed in order to achieve complete resection. Postoperative rehabilitation is a challenge in tumor reconstruction. In distal femur reconstruction patients can be started on full weight bearing and gradual knee flexion. In proximal tibia

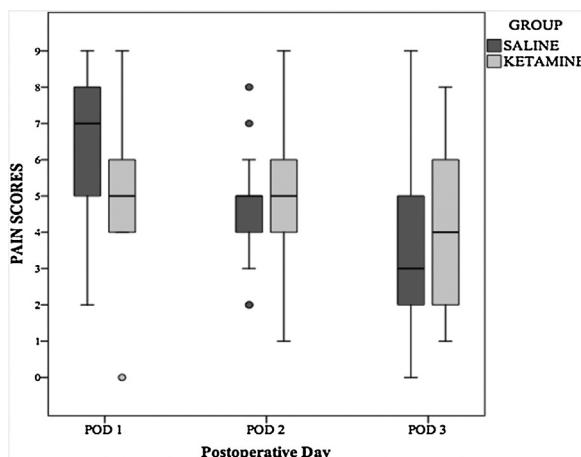


Figure 2 Boxplot of pain score after exercise.

reconstruction, the patients although started on full weight bearing, are advised to delay knee bending up to 6 weeks in order to protect the ligament reconstruction.¹⁸ Nevertheless, despite the site of tumor, we presumed that the better functional scores at 48–72 hours could be translated in better prolonged rehabilitation which is most needed following these surgeries due to extensive tissue dissection. Hence, a review of functional recovery was done again at the end of one month for all trial patients. We found no difference between the two groups with respect to functional recovery as assessed by OKS.

Previous studies^{19–21} suggest that perioperative use of ketamine may benefit in postoperative rehabilitation. Adam et al.¹⁹ had demonstrated better knee flexion in the study group which was statistically significant when ketamine was used along with continuous femoral nerve block. In the above trial, the ketamine infusion was continued 48 hours postoperatively at $1.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ after an intraoperative infusion run at $3 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with no serious adverse effects. Two continuous infusions along with a PCA pump for post-operative pain management can be seen as cumbersome and not practical in all scenarios. The role of ketamine in preventing or reducing central sensitization due to tissue damage has been well established.^{22,23} Since the tissue damage is maximum during the intra-operative period of any surgery, we rationalized that ketamine infusion during this period should work. In our trial, the ketamine group consistently had better degree of flexion on all assessments postoperatively till 72 hours, although this was not statistically significant.

Similarly significant opioid sparing and analgesic effects have been observed with ketamine infusion in orthopedic surgeries and many of these studies^{19,24–27} continued the ketamine infusion postoperatively for varied periods of time with a maximum recorded duration of 48 hours and at different dosages. There remains a chance of dosing errors with continuous infusions,²⁸ and hence as a policy ketamine infusions are not used inpatient wards at our hospital. Cengiz et al.²⁶ had recorded a reduction of morphine consumption up to 45% with an intraoperative ketamine infusion at $6 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in total knee replacement surgeries. In our trial, the intraoperative fentanyl ($205.00 \pm 86.12 \text{ } \mu\text{g}$ vs. $213.25 \pm 76.75 \text{ } \mu\text{g}$) and the first 24 hours postoperative mor-

phine requirement ($28.52 \pm 20.84 \text{ mg}$ vs. $32.13 \pm 19.99 \text{ mg}$) recorded in the ketamine group were lower though not significant. Similarly the pain scores in ketamine group was lower than of saline group and of a different severity (moderate versus severe in case of saline, however this was not statistically significant). Similar to the other trials,^{19,25,26} there were no adverse effects of ketamine such as hallucinations and delusions observed postoperatively. Thus, the question on the role of continuing ketamine infusion into the postoperative period to obtain opioid sparing with better analgesic effects and to improve rehabilitation still remains. The intraoperative hemodynamic parameters were higher, though not significant, in the ketamine group; whether this is attributable to the increase in blood loss of around 150 ml in the ketamine group, is speculative (Table 1).

Postoperative rehabilitation after TKR surgeries have been assessed using 2-minute walk tests, passive and active knee motion, performance measures such as TUG, IALS (Iowa level of assistance scale) and patient reported outcome measures (PROM).¹¹ We chose TUG test for our assessment. It is one of the most commonly used performance assessment tools. TUG test is quicker, less resource intensive and does not rely on clinician's perception and studies show that PROMs are less reliable than performance measures in the immediate post-surgery period.²⁹ The literature shows that TUG test has predictive values on both short³⁰ and long term¹¹ functional recovery following arthroplasties. Studies suggest that preoperative and acute TUG test is a better predictor of long-term functional outcome on the 6-minute walk test when not adjusted for age, sex, and preoperative functional outcomes. Bade et al.¹¹ also propose that post-operative day 2 range of motion is not a better predictor of long-term functional outcome following total knee arthroplasties for osteoarthritis as against pre-operative ROM. Nevertheless, does this finding apply to TKR with endoprosthesis performed for oncosurgeries is something that needs to be evaluated with a larger sample.

We used the OKS for the PROM assessment.³¹ We found that the cohort of patients who underwent pre-operative chemotherapy had better pain relief and they performed well on the pre-operative OKS (26 [24–27] in patients who received preoperative chemotherapy vs 22 [21–26]) though there was no statistical significance on this ($p = 0.3$). Postoperatively, as expected, at one month follow up, the cohort which received preoperative chemotherapy had a median OKS of 35 [33–36] as compared to the non-receivers 32 [30–34] ($p = 0.007$). Items, such as ability to kneel and feeling of sudden "give way" were not applicable to all the patients. Literature shows that preoperative chemotherapy can lead to decrease in inflammation of tissues surrounding the tumors leading to actual reduction of the size of the lesion while responders to chemotherapy were found to have decrease or complete remission of pain and a decreased vascularity of the tumor. This could translate into better surgical margins and hence outcomes.³²

There were limitations to the trial, ketamine infusion was restricted to the intraoperative period when tissue handling and trauma is maximum. The impact of this intervention was assessed by clinical parameters inclusive of rehabilitation and pain scores. We could have also looked at inflammatory markers to have a complete understanding of the role ketamine played in the body's response to surgical trauma.

In summary, we infer that intraoperative intravenous ketamine infusion at $10 \mu\text{g}.\text{kg}^{-1}.\text{min}^{-1}$ following a bolus of $0.5 \text{ mg}.\text{kg}^{-1}$ does not improve postoperative rehabilitation following total knee endoprosthetic replacement surgeries in oncological settings.

Funding

Homi Bhabha National Institute thesis fund. IRB: IEC/0817/1855/002. Clinical trial registration: CTRI/2015/08/006130.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Husted H, Lunn TH, Troelsen A, et al. Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop.* 2011;82:679–84.
2. Korean Knee Society. Guidelines for the management of post-operative pain after total knee arthroplasty. *Knee Surg Relat Res.* 2012;24:201–7.
3. Patel N, Solovyova O, Matthews G, et al. Safety and efficacy of continuous femoral nerve catheter with single shot sciatic nerve block vs epidural catheter anesthesia for same-day bilateral total knee arthroplasty. *J Arthroplasty.* 2015;30: 330–4.
4. Ahmed A, Baig T. Incidence of lower limb motor weakness in patients receiving postoperative epidural analgesia and factors associated with it: An observational study. *Saudi J Anaesth.* 2016;10:149–53.
5. Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. *Pain Physician.* 2008;11:S105–20.
6. Sharma S, Iorio R, Specht LM, et al. Complications of femoral nerve block for total knee arthroplasty. *Clin Orthop Relat Res.* 2010;468:135–40.
7. Jouguet-Lacoste J, La Colla L, Schilling D, et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med.* 2015;16:383–403.
8. Xu B, Wang Y, Zeng C, et al. Analgesic efficacy and safety of ketamine after total knee or hip arthroplasty: a meta-analysis of randomised placebo-controlled studies. *BMJ Open.* 2019;9:e028337.
9. Anagnostatos K, Kohn D. Megaprostheses of the knee joint. *Der Orthopade.* 2010;39:949–59.
10. Givens DL, Eskildsen S, Taylor KE, et al. Timed up and go test is predictive of patient-reported outcomes measurement information system physical function in patients awaiting total knee arthroplasty. *Arthroplasty Today.* 2018;4: 505–9.
11. Bade MJ, Kittelson JM, Kohrt WM, et al. Predicting functional performance and range of motion outcomes after total knee arthroplasty. *Am J Phys Med Rehabil/Assoc Acad Psychiatry.* 2014;93(7):579.
12. Kannan TR, Saxena A, Bhatnagar S, et al. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *J Pain Symptom Manage.* 2002;23:60–5.
13. McGrane S, Pandharipande PP. Sedation in the intensive care unit. *Miner Anesthesiol.* 2012;78:369–80.
14. Allen CA, Ivester JR Jr. Ketamine for pain management—side effects & potential adverse events. *Pain Manage Nurs.* 2017;18:372–7.
15. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Jt Surg Br Vol.* 1998;80:63–9.
16. Puri A. Limb salvage in musculoskeletal oncology: Recent advances. *Indian J Plast Surg.* 2014;47:175.
17. Mihalko WM. Arthroplasty of the knee. In: Azar FM, Beaty JH, Canale ST, editors. *Campbell's operative orthopaedics.* 13th ed. Philadelphia: Elsevier; 2017. p. 396–468.
18. Oren R, Zagury A, Katirz O, et al. Principles of rehabilitation after limb-sparing surgery for cancer. In: *Musculoskeletal cancer surgery.* Dordrecht: Springer; 2004. p. 583–93.
19. Adam F, Chauvin M, Du Manoir B, et al. Small dose ketamine improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Anesth Analg.* 2005;100(2):475.
20. Menigaux C, Fletcher D, Dupont X, et al. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. *Anesth Analg.* 2000;90:129–35.
21. Menigaux C, Guignard B, Fletcher D, et al. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. *Anesth Analg.* 2001;93:606–12.
22. Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg.* 2003;97:1108–16.
23. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain.* 1999;82:111–25.
24. Aveline C, Gautier JF, Vautier P, et al. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. *Eur J Pain.* 2009;13:613–9.
25. Kim SH, Im Kim S, Ok SY, et al. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. *Korean J Anesthesiol.* 2013;64:524.
26. Cengiz P, Gokcinar D, Karabeyoglu I, et al. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. *J Coll Physicians Surg Pak.* 2014;24:299–303.
27. Remérand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg.* 2009;109:1963–71.
28. Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. *Anesthesiology.* 1992;76:362–7.
29. McAuley C, Westby MD, Hoens A, et al. A survey of physiotherapists' experience using outcome measures in total hip and knee arthroplasty. *Physiother Can.* 2014;66:274–85.
30. Poitras S, Wood KS, Savard J, et al. Predicting early clinical function after hip or knee arthroplasty. *Bone Jt Res.* 2015;4:145–51.
31. Stratford PW, Kennedy DM. Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *J Clin Epidemiol.* 2006;59:160–7.
32. Bacci G, Picci P, Ruggieri P, et al. Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities the istituto rizzoli experience in 127 patients treated preoperatively with intravenous methotrexate (high versus moderate doses) and intraarterial cisplatin. *Cancer.* 1990;65:2539–53.



ORIGINAL INVESTIGATION

Effect of preoperative anxiety level on postoperative pain, analgesic consumption in patients undergoing laparoscopic sleeve gastrectomy: an observational cohort study



Yonca Ozvardar Pekcan ^{ID} ^{a,*}, Bahattin Tuncalı ^{ID} ^a, Varlık Erol ^{ID} ^b

^a Başkent University School of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey

^b Medicana Hospital Izmir, Department of General Surgery, Izmir, Turkey

Received 6 May 2021; accepted 13 November 2021

Available online 27 November 2021

KEYWORDS

Laparoscopy;
Pain management;
Postoperative pain;
Preoperative anxiety

Abstract

Background: This prospective observational cohort study aimed to investigate the relationship between preoperative anxiety levels and postoperative pain and analgesic requirement in patients undergoing laparoscopic sleeve gastrectomy.

Methods: Forty two female patients with body mass index ≥ 35 , who underwent laparoscopic sleeve gastrectomy for treatment of obesity were included in the study. Spielberger's state and trait anxiety scales were used in this study. Demographic data of the patients, anesthetic and analgesic drugs during the surgery, pain levels measured with verbal analog scale at the postoperative 1st, 4th, 12th, and 24th hour, sedation levels measured with the Ramsay sedation scale, and the amount of analgesic consumed were recorded. Anesthesiologist, surgeon, and patient were not informed of the anxiety level results. The relationship between preoperative anxiety and postoperative pain and analgesic consumption was evaluated by Spearman's correlation analysis. Stepwise multiple linear regression analysis was applied. Normal Distribution control was performed by applying the Shapiro-Wilk test to residual values obtained from the final model.

Results: There was no relationship between trait anxiety level and postoperative pain and analgesic consumption. A correlation was found between state anxiety level and pain level up to 24 hours and analgesic consumption ($p < 0.05$). According to the obtained model it had been observed that the university graduates consumed more analgesic compared to other education level groups.

Conclusion: In this study, a relationship was found between preoperative state anxiety level and 24-hour pain scores and analgesic consumption in patients who underwent laparoscopic sleeve gastrectomy under general anesthesia.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. 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: yncapek@gmail.com (Y.O. Pekcan).

Introduction

Preoperative anxiety is a psychological problem that exists in patients before surgery. It, is used to express anxiety associated with the planned surgery and/or after the surgery, and its incidence is reported to be approximately 11–80%.^{1,2} Similarly, there are studies reporting that concomitant psychiatric problems, such as anxiety disorder, may be as high as 48% in patients undergoing bariatric surgery.^{3,4}

Studies examining the relationship between preoperative anxiety level and postoperative pain report conflicting results. Various studies have reported that high preoperative anxiety levels increase postoperative pain and analgesic consumption in patients undergoing operations, such as orthopedic surgery, laparoscopic cholecystectomy, abdominal hysterectomy, and breast surgery.^{5–16} On the other hand, there are studies showing that there is no relationship between preoperative anxiety level and postoperative pain.^{17–21} During our literature review, we did not find any study examining the relationship between preoperative anxiety levels and postoperative pain in patients undergoing laparoscopic bariatric surgery. The relationship between anxiety and postoperative pain and analgesic consumption could be revealed more clearly in this patient group with a detailed preoperative psychological assessment and low postoperative pain expectation compared to open surgery.

The aim of this study was to investigate the relationship between preoperative anxiety levels and postoperative pain and analgesic requirement in patients undergoing laparoscopic sleeve gastrectomy.

Methods

This study was carried out in accordance with the Declaration of Helsinki. After obtaining permission from the Clinical Research Ethics Committee (approval no KA17 / 24, Turkey, 12.04.2017), this study was conducted with 42 female patients aged between 18 and 65 years, who underwent laparoscopic sleeve gastrectomy, with an American Society of Anesthesiologists (ASA) physical status \leq III, body mass index (BMI) \geq 35, as a prospective, double-blind, and single-center observational cohort study, and was also registered in the Clinicaltrials.gov clinical trials registry (n°NCT04432558). Written informed consent was obtained from all patients. The STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) guidelines were followed when reporting this study. As preoperative anxiety levels of female patients were found to be higher compared to male patients in various studies, we preferred to conduct the study in female patients in order to eliminate the difference arising from gender.^{22,23} Patients with any psychiatric or neurological disease, those who used psychiatric drugs (antidepressants, anxiolytics), chronic alcohol users, those who were allergic to the drugs used in the study, and illiterate patients were excluded from the study.

The state (STAI-I) and trait (STAI-II) anxiety scales, which were developed by Spielberger et al. in 1970, were used to measure preoperative anxiety. This scale is a 4-point Likert self-report scale consisting in a total of 40 items, 20 of which allocated in the state (STAI-I) and 20 in the trait (STAI-II) anxiety subscales. In particular, STAI-I measures the current

state of anxiety and the STAI-II, the general state of anxiety. All items are followed by a 4-point scale rating the frequency of feelings from “not at all” to “very much” and scoring from 1 to 4. The score ranged from 20 to 80 points, and higher scores indicated higher levels of anxiety.²⁴ The questionnaire form was given to the patients in a closed envelope by the anesthesiologist on the date of their preoperative examination, and they were asked to open the envelope and answer the questions one day before the operation between 9.00 and 10.00 ppm. When the patient was discharged, the envelope was delivered to the anesthesiologist. The total scores were calculated with the manual scoring system and recorded on the form. If a patient did not respond to more than three statements, the filled-out form was planned to be considered invalid. The anesthesiologist, surgeon and patient all were unaware of the preoperative anxiety score before the discharge of the patient.

Demographic data including age, height, body weight, BMI, ASA physical status, and schooling (Primary School = Low, Secondary-High School = Middle, University = High) of the patients who were taken to the operating room were recorded. Following standard monitoring, which included electrocardiography (ECG), noninvasive blood pressure, body temperature, and peripheral oxygen saturation (SpO₂), standard anesthesia protocol was applied to all patients. After anesthesia induction with intravenous (IV) 0.02 mg.kg⁻¹ midazolam, 1 µgr.kg⁻¹ fentanyl, 2 mg.kg⁻¹ propofol, endotracheal intubation was provided with 1 mg.kg⁻¹ rocuronium. A 2–3% concentration of sevoflurane in oxygen and nitrous oxide (50–50%) was used for maintenance of anesthesia. After the operation started, 10 mg.kg⁻¹ paracetamol was administered via intravenous infusion for 15 minutes for analgesia and 1 mg.kg⁻¹ tramadol HCL was administered via intravenous bolus at the end of the operation. For postoperative nausea/vomiting prophylaxis, 10 mg metoclopramide and 8 mg ondansetron were administered via IV injection. Ideal body weight was taken into consideration while adjusting drug doses. The number of analgesic drugs used during the operation and the duration of the operation were recorded.

During the preoperative evaluation, the patients were informed about patient-controlled analgesia (PCA). For postoperative analgesia, tramadol HCL was prepared as 2 mg.mL⁻¹ in 100 mL isotonic saline solution. After the patient was awakened, PCA was initiated with 10 mg.h⁻¹ infusion, 20 mg bolus, 15-minute lockout interval, and a 4-hour limit of 200 mg while leaving the operating room according to the modified Aldrete criteria.²⁵ In the postoperative period, patients were followed up in the post-anesthesia care unit and were transported to the service within 1–3 hours. The verbal analog scale (VAS, 0 = no pain, and 10 = unbearable pain) was used to evaluate the pain level at the 1st, 4th, 12th, and 24th postoperative hours, and the Ramsay sedation scale was used to evaluate the sedation level.²⁶ If the VAS pain score was > 4 , and 4 hours had passed from the first paracetamol dose, 10 mg.kg⁻¹ paracetamol IV infusion was administered, if 4 hours had not passed, diclofenac sodium 1–3 mg.kg⁻¹ intramuscular (IM) was administered and the VAS score was reevaluated after 1 hour. The maximum daily dose of diclofenac sodium was administered not exceeding 150 mg and the paracetamol dose not exceeding 4 g. The amount of analgesic administered for 24 hours in the postoperative period was recorded.

Table 1 - Demographic characteristics of the participants.

Variables	n	%
Age (years)		
18–35	22	52.3
36–50	14	33.3
51–65	6	14.2
Schooling		
Low (Primary school)	11	26.1
Middle (Middle and high school)	15	35.7
High (University)	16	38.0
BMI		
35–42	20	47.6
43–50	17	40.4
51–58	4	9.5
59–65	1	2.3
Time (min)		
0–120	27	64.2
121–240	14	33.3
241–360	1	2.3

BMI, Body mass index ($\text{kg} \cdot \text{m}^{-2}$).

Table 2 - Relationship between state and trait anxiety scores with VAS and analgesic consumption.

	VAS 24h	Tramadol (consumed 24h with PCA)	Total Tramadol (PCA + IV consumed 24h)
STAI-I	r = 0.378 <i>p</i> = 0.014	r = 0.416 <i>p</i> = 0.006	r = 0.436 <i>p</i> = 0.004
STAI-II	r = 0.169 <i>p</i> = 0.284	r = 0.160 <i>p</i> = 0.160	r = 0.165 <i>p</i> = 0.297

r, Spearman's correlation coefficient; VAS, verbal analog scale; STAI-I, state anxiety score; STAI-II, trait anxiety score.

During or after surgery, if the heart rate was < 50, IV atropine ($10 \mu\text{gr} \cdot \text{kg}^{-1}$) was administered, if the heart rate was $\geq 100 \text{ beats} \cdot \text{minute}^{-1}$ or if the blood pressure was 20% above

the basal blood pressure value, fentanyl ($50 \mu\text{gr} \text{ IV}$) was administered, if the Ramsay score exceeded 4 in the postoperative period, the tramadol HCL infusion rate was reduced by half and reevaluation was planned after 30 minutes.

Statistical analysis

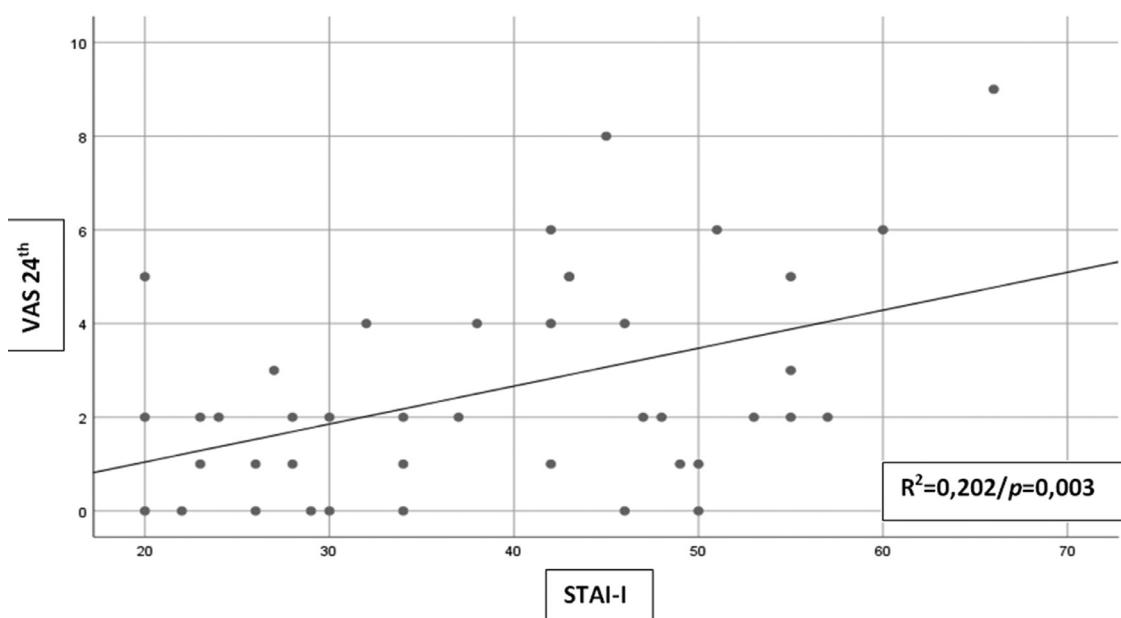
Statistical analysis of the data obtained in the study was carried out with the IBM SPSS Statistics for Windows, Version 25.0 (Released 2017, Armonk, NY: IBM Corp.) package program. A power analysis based on correlation analysis was used to determine the linear relationship between postoperative pain and analgesia consumption and anxiety level. Stepwise multiple linear regression analysis was applied, and normal distribution control was performed by applying Shapiro-Wilk test to residual values obtained from the final model.

At least 37 volunteers were calculated as being sufficient to find a significant linear relationship between the two variables at a large class effect size ($r = 0.50$) by using two-way hypothesis testing with 90% power at the 0.05 Type-I error level.

Results

A total of 42 female patients were included in the study. Demographic data including age, height, body weight, BMI, and schooling (Primary School = Low, Secondary-High School = Middle, University = High) are summarized in Table 1. No statistically significant difference was found between demographic data and anxiety scores (STAI-I, II) in the analysis performed with Spearman's correlation analysis.

A correlation was found between the state anxiety level and VAS values at the 24th hour, and the total tramadol dose at the 24th hour (Table 2, Figs. 1 and 2). However, no relationship was found between the trait anxiety level and VAS values and analgesic consumption (Table 2).

**Figure 1** Verbal analog scale values at the 24th hour with STAI-I. STAI-I, state anxiety score; VAS, verbal analog scale.

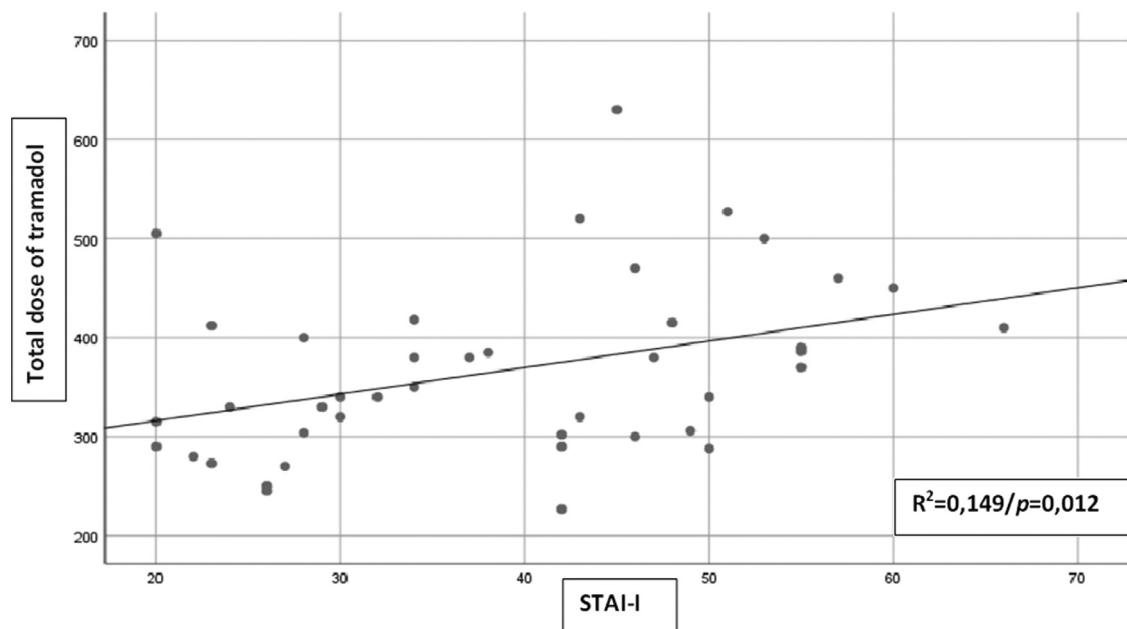


Figure 2 Total dose of tramadol consumed at the 24th hour with STAI-I. STAI-I, state anxiety score.

Age, BMI, operation time, STAI-I, STAI-II variables were used numerically in their original scales.

Schooling was taken as a 2-class categorical variable and coded as 0 (1+2) – 1 (3).

Using these variables, in the Multiple Stepwise Linear Regression analysis applied for the Total Tramadol (mg) variable, firstly the Age variable was entered into the model ($p = 0.009$), and then the model was completed with STAI-I ($p = 0.013$).

According to the obtained model, a 1-year increase in the age variable caused a decrease of 2.973 mg in analgesic consumption, while a 1-unit increase in the STAI-I level resulted in a 2.464 mg increase in analgesic consumption (Table 3).

In the analysis for pain scores (VAS Total), only education level was included in the model ($p = 0.034$).

According to the obtained model it had been observed that the university graduates consumed an average of 3.677 mg more analgesic compared to other schooling groups (Table 4).

Discussion

With this prospective observational cohort study, a correlation was found between the preoperative STAI-I level measured the night before the operation and the pain level at

the postoperative 24th hour and analgesic consumption in patients who underwent laparoscopic sleeve gastrectomy for obesity.

Every patient who is scheduled for surgery experiences anxiety as a physiological and psychological response. The level of anxiety can vary depending on various factors. Although the results of the studies are contradictory, it has been stated that age, gender, characteristics of surgery, ASA physical status, past operational experience, education level, personality, marital status, occupation, health insurance, approach to the disease, cultural and religious beliefs are factors affecting the preoperative anxiety level.^{8,9,11,17,20,26} In our study, a decrease was observed in analgesic consumption with increasing age. This decrease due to the increase in age was attributed to the fatalistic perspective that develops in advanced ages due to cultural and religious beliefs in our society, and patients' reluctance to ask for analgesics because of their comorbidities due to the fear of drug side effects. In addition, in our study, university graduates were observed to consume more analgesics than other level of education groups. In another study; the identifiers of patient satisfaction in pain management after day surgery were investigated, and they were stated as low preoperative pain, no preoperative analgesic consumption, high expected post-operative pain, and low education level.²⁷

It has been stated that preoperative anxiety facilitates the activation of the entorhinal cortex of the hippocampal

Table 3 Relationship between state anxiety scores and age with analgesic consumption (total tramadol).

	B	Std. Error	p
(Constant)	381.272	57.546	< 0.001
Age	-2.973	1.077	0.009
STAI-I	2.464	0.941	0.013

($R^2 = 28.8\%$, $p = 0.001$)

STAI-I, State anxiety score; R^2 , Multiple Stepwise Linear Regression's determination coefficient.

Table 4 - Relationship between VAS and schooling.

	B	Std. Error	p
(Constant)	13.105	1.238	< 0.001
Schooling	3.677	1.674	0.034

($R^2 = 10.8\%$, $p = 0.034$)

R^2 , Multiple Stepwise Linear Regression's determination coefficient; VAS, verbal analog scale.

formation and causes the pain threshold to be lowered and the pain intensity to be perceived as more than it actually is. By showing that there is a positive relationship between postoperative pain and anxiety, it has been reported that increased anxiety and fear cause an increase in pain severity and the need for opioids after surgery, and that patients try to overcome anxiety and tension in this way.^{15,16}

High levels of pain and anxiety, especially in obese patients, can stimulate the neuroendocrine system and cause cardiac complications, respiratory system problems, increase in gastrointestinal symptoms such as nausea and vomiting, and increase in postoperative mortality and morbidity due to the immune system being affected.^{28–31}

Bayrak et al.¹⁶ reported that patients who had laparoscopic cholecystectomy with high anxiety scores measured by the Spielberger anxiety scale had dissatisfaction with intraoperative unstable hemodynamic parameters (arterial pressure, heart rate, peripheral oxygen saturation), increased postoperative pain, and analgesic consumption. In another study, patients with preoperative state anxiety score above 45 and who had cesarean section with general anesthesia had higher pain levels in the first 12 hours, but no correlation was found with analgesic consumption.⁷ In a study conducted by Kain et al⁸ on patients who underwent abdominal hysterectomy, they stated that state anxiety was associated with the patient's sudden postoperative pain, and it was even a positive predictor of postoperative pain. In their study, in which they compared preoperative benzodiazepine with placebo and evaluated cortisol, interleukin 6, T and B lymphocyte values, they stated that the consumption of painkillers decreased within the first four hours after the operation and did not change in total, and they attributed this to the increased pain in abdominal surgeries.²⁰ Yilmaz et al.²¹ could not find a relationship between preoperative and postoperative anxiety levels and postoperative pain levels and analgesic need in their study on septoplasty operations, and they attributed this to low pain due to the minor surgery. Possible reasons for the contradictory results in various studies may be the type of surgery performed, duration of surgery, type of anesthesia, patient groups, and the postoperative analgesia protocol applied. Since this study was a laparoscopic surgery, VAS values may have been found to be low in the first 24 hours. Patients' attitudes toward drugs may also be effective in consumption of analgesics. Although some patients experience pain due to side effects or fear of addiction, some patients may overuse analgesics because they fear pain or restlessness.¹¹ Such situations may make it difficult to determine the relationship between anxiety, pain, and analgesic consumption. In a study conducted on 1,416 non-cardiac and non-brain surgery patients, the anxiety level measured by the Amsterdam Pre-operative Anxiety and Information Scale, not the anxiety level measured by STAI, was found to be more sensitive in predicting postoperative pain; however, it was stated that female gender, young age, preoperative pain score, type of surgery and size of incision are independent predictors of severe postoperative pain.¹⁷ In addition, another study stated that measurements with STAI-I and II were based on subjective anxiety and pain complaints rather than physical indicators, and the evaluation of preoperative pain was recommended for future studies.^{15,19} In a study comparing the scales, it was stated that high values measured by the Pain

Catastrophizing Scale (PCS) may be an indicator of higher postoperative pain scores without increasing opioid use.⁶

This study has several limitations. First, the fact that the preoperative pain, postoperative anxiety score and PCS score were not assessed and this may have caused self-reporting bias (when the patient ranks his anxiety higher than the average person with the same amount of anxiety). The lack of correlation between trait anxiety and pain may be explained by the fact that the available evidence is not strong enough to exclude a consistent self-report bias of patient responses to the criteria used in the study, rather than a causal relationship. The subjective nature of the measurements may have caused a lack of power. Second, preoperative anxiety and postoperative pain assessments were based on self-reporting and not on clinical diagnoses. Objective evaluations could be achieved in patients with measurement of cortisol and noradrenaline in saliva and blood, changes in blood pressure and heart rate, grimace and muscle tone. The third limitation was that patients completed the tests on their own. This problem can be overcome by filling it in by an anesthesia or psychiatrist 1 day before surgery. Thus, newly developed depression can also be diagnosed. Finally, the small number of patients is also a limiting factor in this study.

Conclusion

In this study, no correlation was found between the preoperative trait anxiety score level and postoperative pain and analgesic consumption in patients who underwent laparoscopic sleeve gastrectomy under general anesthesia. However, a significant relationship was found between the state anxiety level and 24-hour analgesic consumption. We conclude that these results may contribute to postoperative pain management in patients undergoing laparoscopic sleeve gastrectomy.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.bjane.2021.11.003](https://doi.org/10.1016/j.bjane.2021.11.003).

References

1. Jawaid M, Mushtaq A, Mukhtar S, et al. Preoperative anxiety before elective surgery. Neurosciences (Riyadh). 2007;12:145–8.
2. Akinsulore A, Owojuigbe A, Faponle A, et al. Assessment of preoperative and postoperative anxiety among elective major surgery patients in a tertiary hospital in Nigeria. Middle East J Anaesthesiol. 2015;23:235–40.
3. de Zwaan M, Enderle J, Wagner S, et al. Anxiety and depression in bariatric surgery patients: A prospective, follow-up study using structured clinical interviews. J Affect Disord. 2011;133:61–8.

4. Edwards-Hampton SA, Madan A, Wedin S, et al. A closer look at the nature of anxiety in weight loss surgery candidates. *Int J Psychiatry Med.* 2014;47:105–13.
5. De Cosmo G, Congedo E, Lai C, et al. Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain.* 2008;24:399–405.
6. Dunn LK, Durieux ME, Fernández LG, et al. Influence of catastrophizing anxiety, and depression on in-hospital opioid consumption, pain, and quality of recovery after adult spine surgery. *J Neurosurg Spine.* 2018;28:119–26.
7. Ozturk Inal Z, Gorkem U, Inal HA. Effects of preoperative anxiety on postcesarean delivery pain and analgesic consumption: general versus spinal anesthesia. *J Matern Fetal Neonatal Med.* 2020;33:191–7.
8. Kain ZN, Sevarino F, Alexander GM, et al. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. *J Psychosom Res.* 2000;49:417–22.
9. Kain ZN, Sevarino F, Pincus S, et al. Attenuation of the preoperative stress response with midazolam: effects on postoperative outcomes. *Anesthesiology.* 2000;93:141–7.
10. Polomano RC, Heffner SM, Reck DL, et al. Evidence for opioid variability, Part 2: Psychosocial influences. *Semin Perioper Nurs.* 2001;10:159–66.
11. Caumo W, Hidalgo MPL, Schmidt AP, et al. Effect of preoperative anxiolysis on postoperative pain response in patients undergoing total abdominal hysterectomy. *Anesthesia.* 2002;57:740–6.
12. Ozalp G, Sarıoğlu R, Tuncel G, et al. Preoperative emotional states in patients with breast cancer and postoperative pain. *Acta Anaesthesiol Scand.* 2003;47:26–9.
13. Feeney SL. The relationship between pain and negative affect in older adults: anxiety as a predictor of pain. *J Anxiety Disord.* 2004;18:733–44.
14. Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain.* 2005;21:439–45.
15. Ip HYV, Abrishami A, Peng PWH, et al. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology.* 2009;111:657–77.
16. Bayrak A, Sagiroğlu G, Copuroglu E. Effects of preoperative anxiety on intraoperative hemodynamics and postoperative pain. *J Coll Physicians Surg Pak.* 2019;29:868–73.
17. Kalkman JC, Visser K, Moen J, et al. Preoperative prediction of severe postoperative pain. *Pain.* 2003;105:415–23.
18. Hashimoto K, Iwayama S, Sano Y, et al. Preoperative anxiety induces no clinically relevant effect on intraoperative nociceptive levels during breast surgery under general anesthesia. *J Anesth.* 2015;29:967–70.
19. Munafò MR, Stevenson J. Selective processing of threat-related cues in day surgery patients and prediction of post-operative pain. *Br J Health Psychol.* 2003;8:439–49.
20. Kain ZN, Sevarino FB, Rinder C, et al. Preoperative anxiolysis and postoperative recovery in women undergoing abdominal hysterectomy. *Anesthesiology.* 2001;94:415–22.
21. Yilmaz Y, Durmus K, Inal FY, et al. The effect of preoperative and postoperative anxiety on postoperative pain and analgesic need in septoplasty operations. *Dicle Med J.* 2014;41: 288–29.
22. Papageorgiou GM, Papakonstantinou A, Mamplekou E, et al. Pre- and postoperative psychological characteristics in morbidly obese patients. *Obes Surg.* 2002;12:534–9.
23. Kim WS, Byeon GJ, Song BJ, et al. Availability of preoperative anxiety scale as a predictive factor for hemodynamic changes during induction of anesthesia. *Korean J Anesthesiol.* 2010;58:328–33.
24. Oner N, Le Compte A. State-Trait Anxiety Inventory Handbook, 1. Print. Istanbul: Bogazici University Publications; 1983. p. 1–26.
25. Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth.* 1995;7:89–91.
26. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadole. *Br Med J.* 1974;2:656–9.
27. Coluzzi F, Bragazzi L, Di Bussolo E, et al. Determinants of patient satisfaction in postoperative pain management following hand ambulatory day-surgery. *Minerva Med.* 2011;102:177–86.
28. Karaman S, Dogru S, Karaman T, et al. Anesthesia management in laparoscopic bariatric surgery: Perioperative complications and outcomes in the third year of practice. *JCEI.* 2014;5:200–5.
29. Vaughn F, Wichowski H, Bosworth G. Does preoperative anxiety level predict postoperative pain? *AORN J.* 2007;85:589–604.
30. Rodrigues HF, Furuya RK, Dantas RAS, et al. Association of preoperative anxiety and depression symptoms with postoperative complications of cardiac surgeries. *Rev Lat Am Enfermagem.* 2018;26:3107.
31. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. *J Clin Anesth.* 2005;17:134–45.



SYSTEMATIC REVIEW

Impact of topical airway anesthesia on immediate postoperative cough/bucking: a systematic review and meta-analysis



Thiago Mamoru Sakae ^{a,*}, Renato Lucas Passos de Souza ^b,
Julio Cesar Mendes Brandão ^{c,d}

^a Clinigastro Medicina Integrada, Post PhD in Health Sciences, Criciúma, SC, Brazil

^b Universidade de São Paulo (USP), Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto, SP, Brazil

^c Postdoctoral Research Fellow, Harvard Medical School, Boston, United States

^d Sociedade Brasileira de Anestesiologia, Brazil

Received 7 July 2020; accepted 16 March 2021

Available online 22 April 2021

KEYWORDS

Airway management;
Topical anesthesia;
Intubation,
intratracheal;
Cough;
Anesthesia recovery
period;
Airway extubation

Abstract

Background: Postoperative cough may occur after tracheal intubation, but it is indistinct which drug is best at diminishing these events. Additionally, airway reflexes are commonly accompanied by severe hemodynamics responses during emergence.

Objectives: To evaluate the role of topical airway anesthesia on immediate post-extubation cough/bucking and extubation time.

Methods: Randomized clinical trials from MEDLINE, EMBASE, CENTRAL, and LILACS published until December 23, 2020 were included. Our primary outcome was postoperative cough/bucking incidence which was compared between local anesthetics and controls. Extubation times were likewise considered. Predisposition appraisal and subgroup, affectability investigations were likewise performed.

Results: The pooled analysis found a 45% reduction in cough incidence after treatment with topical airway local anesthetic ($RR = 0.55$; 95% CI: 0.42 to 0.72; $p < 0.001$). The number needed to treat (NNT) was 4.61. The intervention showed no differences in reduction of the extubation time (mean difference = -0.07; 95% CI: -0.14 to 0.28; $p = 0.49$).

Conclusion: Topical airway anesthesia demonstrated better than placebo or no medication in reducing immediate post-extubation cough/bucking. Further studies could have this objective to combine the different ways to perform better outcomes for patients.

© 2021 Published by Elsevier Editora Ltda. 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/>).

* Corresponding author.

E-mail: thiagosakae@gmail.com (T.M. Sakae).

Introduction

The procedures of intubation and extubation are known to cause pain and discomfort. Postoperative cough, sore throat, hoarseness of voice and laryngospasm are kinds of distressing sequelae after tracheal intubation. In any case, it is hazy which drug is best at diminishing these events. Additionally, airway reflexes are commonly accompanied by severe hemodynamic responses during emergence.¹⁻⁶

Perioperative respiratory adverse events (mainly bucking and coughing) frequently occur during extubation and may lead to negative outcomes, increasing morbidity and mortality of patients. These events can trigger negative pressure pulmonary edema, an abrupt increase in intraocular, intrathoracic, intraabdominal, and intracranial pressure.⁵⁻⁸

Several techniques have been applied to attenuate extubation reaction during rise as intravenous (IV) medications (local anesthetics, opioids, dexmedetomidine),⁹⁻¹¹ jelly medications on endotracheal tube cuff (lidocaine, corticosteroids, water-soluble lubrication, vegetable gum),^{5,6,12} local anesthetics intracuff (local anesthetic, alkalinized or not),¹³⁻¹⁵ nebulized anesthetics or laryngotracheal topicalization^{1,3,4,8,16-21} with anesthetics (local or others),²⁰⁻²² translaryngeal injection, and/or airway nerve blocks.²³

Topical local anesthetic administration reduces the risk of perioperative respiratory adverse events in elective endotracheal intubation. Be that as it may, conclusive proof of its adequacy stays subtle, due, to some degree, to the wide inconstancy in the procedure for showering topical anesthetic.^{3,6,24}

Local anesthetic jelly could have lubricating properties to limit the potential harm to the tracheal mucosa and stifling bucking. Its job in avoidance of postoperative cough, sore throat, and hoarseness is not effective.⁵

Considering assessing the viability of topical airway anesthesia has yielded opposing outcomes. A few investigations have shown great viability of this technique in preventing laryngospasm, sore throat, cough, and agitation as well.^{1-3,18,22} In any case, others found that there is no profit by topical anesthesia and even report an expanded incidence of perioperative airway complications brought about by the incitement from the spray itself.^{8,25,26}

The target of this investigation is to assess the role of topical airway anesthesia on immediate postoperative coughing and extubation time.

Methods

Search methods for identification of reviews

To search in MEDLINE papers with terms: (1) topical anesthesia OR topical airway anesthesia; (2) anesthesia, local/methods OR Anesthetics, Local OR Lidocaine; (3) Intubation OR Intubation, Intratracheal/methods OR Intubation, Intratracheal/adverse effects OR Airway Management/methods OR Extubation OR Cough; (4) 1 AND 2 AND 3. The period searched was between (1966/01/01[Date - Entry]: 2020/12/23[Date - Entry]).

The procedure of information extraction was performed utilizing a convention adjusted from PRISMA statement, counting the investigation, identification information, time of the examination conduction, structure, inclusion and exclusion criteria, demographic characteristics, outcomes measures, statistical analysis, and limitations (Fig. 1).

We looked at the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (1966 to December 2020); EMBASE (1974 to December 2020); and LILACS (1982 to December 2020). We utilized the referred MeSH and free text terms to search MEDLINE and CENTRAL.

Criteria for considering reviews for inclusion

Two review authors autonomously checked on and chose preliminaries from the list items, and surveyed reads for appropriateness, methodology, and quality. Zones of contradiction or vulnerability were arbitrated by different agents. The agreement between two autonomous analysts during the full-content audit was viewed as excellent ($k = 0.89$; 95% CI: 0.82 to 0.96)

The independent variables were the type of local anesthetic, dose, and treatment period. The outcomes researched were incidence of emergence cough/bucking and extubation time.

For studies to be remembered for the meta-analysis, they needed to meet the accompanying criteria: (1) they had to be a clinical trial design; (2) they needed to look at least two groups (local anesthetic vs. control); and (3) they had proportions/relative risk/mean with relating 95% CIs, or with adequate information for calculation.

No confinements were set for members' ages or definition of cough as used in individual studies. Studies with laryngeal mask airways, nasal intubation, and airway nerve block were excluded.

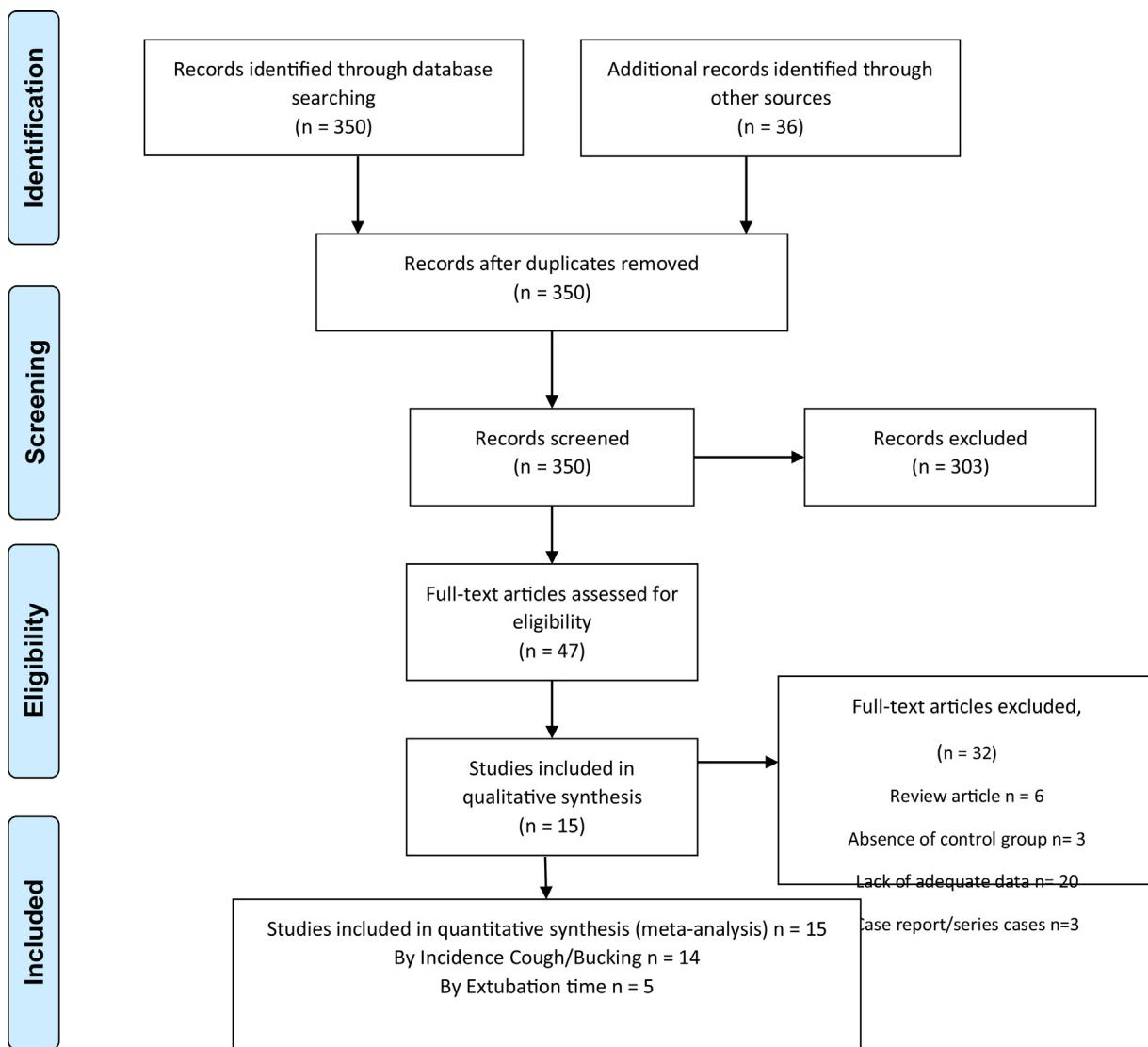
Data collection and analysis

We analysed data using RevMan5.0 software. We pooled the included investigations to yield the relative risks of severe/moderate cough with 95% confidence intervals (CI) or standard errors.

Selection of reviews

Data extraction and management

Data were extracted using a standardized form. Information extracted included: type of design study; age and gender of members; number of members; randomization strategy; type of surgery; surgery duration; ASA (American Society of Anesthesiologists) physical status; incidence and grade of cough during extubation; time to extubation; improvements in parameters: local anesthetic compared with placebo or other drug groups; laryngospasm; airway obstruction severity; adverse events. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool was adopted to evaluate the studies quality of evidence. All the studies presented a moderate to high GRADE certainty ratings. All the studies were clinical trials, most part with double blind evaluation. The extubation

**Figure 1** Flowchart of study selection.

times results demonstrate a low heterogeneity and risk of bias. The indirectness was not a problem because the intervention is low cost, accessible, and has a little execution difficulty.

Assessment of methodological quality of included reviews

Data synthesis

We introduced all point gauges as means \pm SE or risk ratios (RR). We utilized forest plots to show the results. For dichotomous factors, we determined a fixed-effect risk ratio (RR) with 95% confidence intervals (CI) for individual studies.

We measured heterogeneity among the pooled estimates by utilizing the I^2 . We performed affectability investigations contrasting random-effects and fixed-effect models. Potential for publication bias was assessed using the Egger test, Higgins test, and funnel plots (Fig. 2).²⁷

Results

The electronic database looked through of 350 articles. There were 15 articles^{3,4,6,14–16,28–36} that met the inclusion criteria and were included in the analysis (Fig. 1). The features of the included studies are introduced in Table 1. Articles or studies with unpublished or ongoing studies were not included in this meta-analysis.

Incidence of immediate post-extubation cough/bucking

A random effect model was utilized for the examination because high heterogeneity existed among the studies ($Tau^2 = 0.15$; $p < 0.0001$; $I^2 = 74.0\%$). The pooled analysis found a 45% reduction in cough incidence after treatment with topical airway local anesthetic (RR = 0.55; 95% CI: 0.42 to 0.72; $Z = 4.32$; $p < 0.001$) (Fig. 3). The absolute risk reduction (ARR)

Table 1 Description of the studies included in meta-analysis.

Trial	Sample size	Male %	ASA physical status	Duration (min)	Surgery types	Anesthesia maintenance	Intervention/ Comparator	Outcomes
Arslan 2013	54	87.0	I-II	16.4 ± 4.4	Laryngeal microsurgery	Sevoflurane	1 - Lidocaine 10% spray	No reduction in cough incidence and laryngospasm. Agitation lower in lidocaine group.
Bousselmi 2014	80	Sex ratio 1.2 to 2.3	I-III	14.9 ± 5.3 82 ± 34 80 ± 42 72 ± 32 76 ± 36	Not described	Propofol + Remifentanil	2 - Saline spray 1 - Saline instillation + saline cuff 2 - Saline instillation + lidocaine cuff 3 - Lidocaine instillation + saline cuff 4 - Lidocaine instillation + lidocaine cuff	Reduction in cough incidence and sore throat.
D'Aragon 2013	116	0%	I-II	30-120	Elective gynecologic procedure All female	Desflurane	1 - 4% lidocaine 4 mL spray + lidocaine cuff 2 - 4% lidocaine 4 mL spray + NS cuff 3 - NS spray + lidocaine cuff 4 - NS spray + NS cuff	Reduction in cough incidence (NNT 3.05). No influence in sore throat.
Diachun 2001	46	Not described	I-III	Not described	Non ear, nose and throat surgery	Isoflurane +N2O	1 - Lidocaine 2% TT 2 mg.kg ⁻¹ spray 2 - Saline 4 mL 3 - Nothing	Reduction in cough incidence.
Dutta 2016	45	42.2	I-III	Not described	Not decribed	Sevoflurane	1 - Lidocaine 10% TT 1.5 mg.kg ⁻¹ 2- NS i.v + NS spray 3 - Dex 0.3 ug. kg ⁻¹ + NS spray	No reduction in cough and extubation time
Fang 2018	52	25.0	I-II	Until 4 hours	Thyroidectomy	Propofol + Remifentanil	1 - Ropivacaine 0,75% 6 mL	Reduction in cough. No influence on sore throat and extubation time.

Table 1 (Continued)

Trial	Sample size	Male %	ASA physical status	Duration (min)	Surgery types	Anesthesia maintenance	Intervention/Comparator	Outcomes
Gupta 2006	50	Not described	Not described	Not described	Carotid endarterectomy	Volatile	2 - Saline 6 mL 1 - Lidocaine 4% 4 mL TT	Reduction in cough.
Jee 2003	75	70.6	Not described	106.8 ± 44.7 123.4 ± 55.9	Orthopaedic, plastic, lower abdominal surgery	Enflurane	2 - NS 4 mL TT 1 - No drug	Reduction in number of coughs (5 and 10 min).
Lee 2011	55	61.8	I	28.9 ± 7.2 103.6 ± 40.8	Laryngeal microscopic surgery	Sevoflurane + N2O	2 - Lidocaine 2% TT 1 mg.kg⁻¹ spray 5 min before extubation 3 - IV lidocaine 1 mg.mL⁻¹	No reduction in cough incidence, reduction in number of coughs.
Li 2016	322	56.5	I-III	30.1 ± 7.9 90.7 ± 23.6	Urology, otolaryngology, ophthalmologic, orthopedic	Sevoflurane	2 - No treatment Lidocaine 2% TT 4 mg.kg⁻¹	Reduction in cough, laryngospasm, desaturation. No influence on extubation time.
Paltura 2018	64	45.3	I	86.9 ± 30.3 20 to 25 min	Suspension laryngoscopy for benign laryngeal diseases	Sevoflurane	Saline 0,9% 4 mL 1 - Lidocaine 10% spray 7 puffs	No reduction in cough incidence and extubation time. Agitation lower in lidocaine spray group.
Shabnum 2017	60	61.6	I-II	240 ± 18.67	Craniotomies	Isoflurane	2 - Lidocaine 2% 1 mL (cotton swap) 3 - Control (nothing applied)	Reduction in cough incidence. No influence in extubation time.

Table 1 (Continued)

Trial	Sample size	Male %	ASA physical status	Duration (min)	Surgery types	Anesthesia maintenance	Intervention/ Comparator	Outcomes
Soltani 2002	204	57.8	I-II	45 ± 0.6	Cataract surgery	Halothane + N2O	2 intratracheal lignocaine 2% 1.5 mg.kg ⁻¹ + IV placebo 3 - IV + intratracheal placebo 1 - lidocaine 10% spray distal end ETT	I.V. lidocaine promotes reduction in cough incidence. No influence in extubation time.
Yamasaki 2013	60	45.0	I-II	124 ± 52	Tympanoplasty	Propofol + Remifentanil	2 - lidocaine 10% spray laryngopharyngeal structures 3 - 2% lidocaine jelly ETT 4 - i.v. Lignocaine 2% 1.5 mg.kg ⁻¹ at the end of surgery 5 - 2% lidocaine intracuff 6 - normal saline end ETT	Reduction in cough/severe cough.
Zamora Lozano 2007	78	48.7	I-II	226 ± 54 60-120 min	General, gynaecology, orthopedic, ophtalmological, plastic, urological	Volatile	1 - Lidocaine 4% 3 mL transtracheal 2 - No medication 1 - Lidocaine 2% TT 5 mL 2 - Lidocaine 2% IV 5 mL 3 - Saline 0,9% 5 mL 4 - Lidocaine 2% 5 mL intracuff	Reduction in cough.

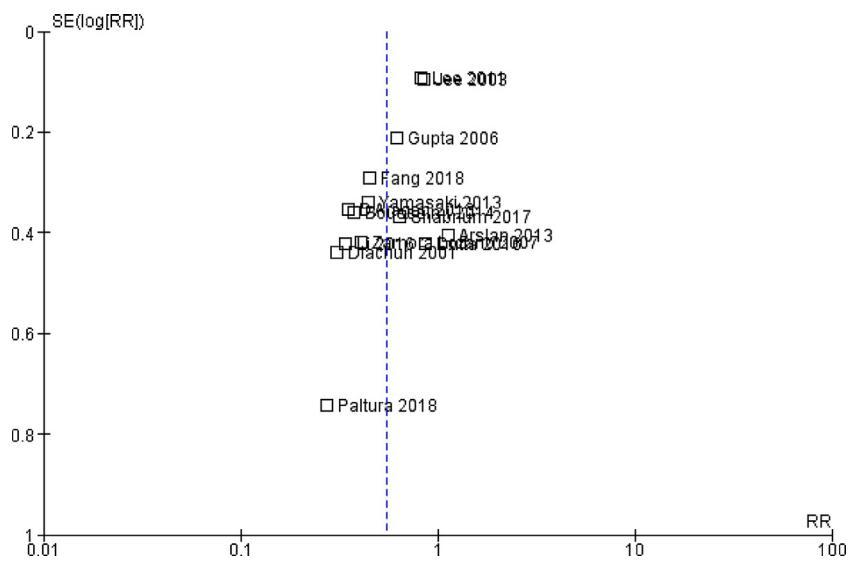


Figure 2 Funnel plot.

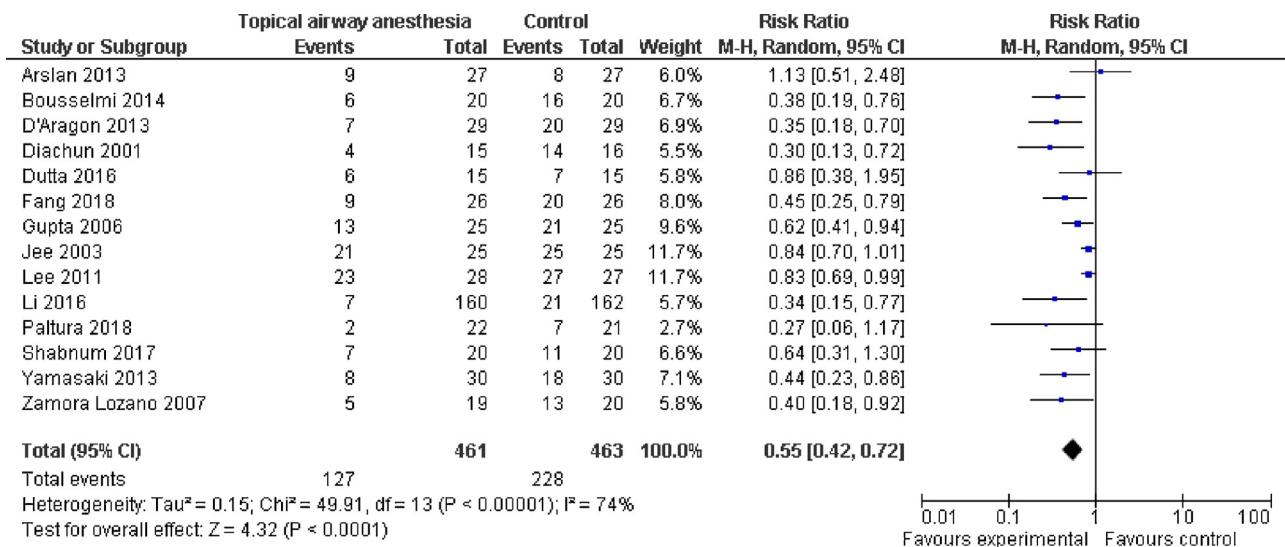


Figure 3 Incidence of immediate post-extubation cough/bucking.

was 21.7%. The number needed to treat (NNT) was 4.61. This analysis included 924 patients in all studies.

Extubation time

We further examined the influence of the topical airway local anesthetic in the extubation time. In this analysis, we used a fixed effect because of low heterogeneity ($\chi^2 = 1.94$; $p = 0.75$; $I^2 = 0.0\%$). The intervention showed no differences in reducing the extubation time (mean difference = -0.07; 95% CI: -0.14 to 0.28; $z = 0.69$; $p = 0.49$) (Fig. 4). This second analysis included 512 participants in all studies.

Discussion

This systematic review demonstrated that the local anesthetics used as topical tracheal would do well to diminish the

rate of periextubation cough/bucking in comparison with either placebo or no medication. It also demonstrated that the local anesthetics used as tracheal or topical application did not influence on the extubation time as well.

There is a meaningful relationship between frequency of cough and the first-hour sore throat.^{1,35,36} There are several morbid and physiological outcomes of development emergence coughing and they have prompted numerous examinations looking at changed drugs to diminish peri-extubation coughing. Lam and colleagues¹³ meta-analysis found that intracuff lidocaine significantly decreased post-operative coughing when contrasted and control groups, fundamentally the same as our discoveries. Also, Rajendram et al.³⁷ meta-analysis determined the intracuff lidocaine to be the most effective at preventing peri-extubation coughing and IV lidocaine was the least effective, among other IV medications. In other recent meta-analyses, Tung et al.¹⁰ found that lidocaine altogether diminished postoper-

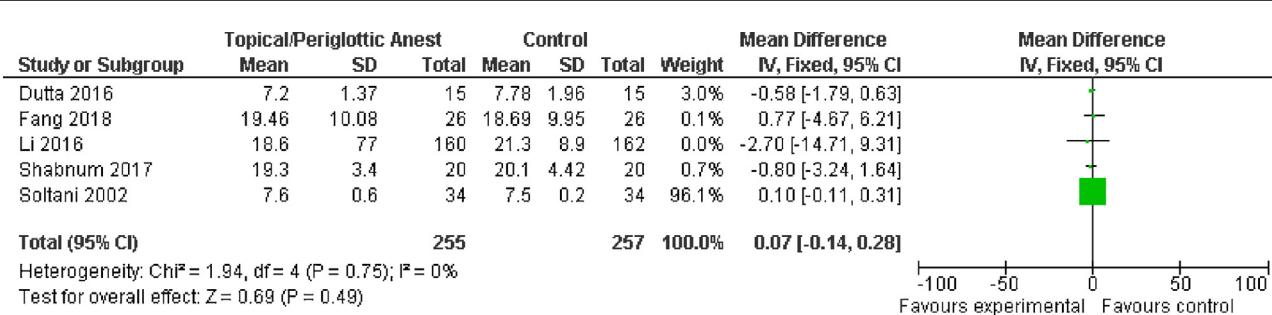


Figure 4 Extubation time in minutes.

ative coughing when contrasted and control groups, like our discoveries as well. In our study we also found local anesthetics to be likely very effective in reducing emergence cough.

Topical airway anesthesia is not a recent strategy. Franz Kuhn (1866–1929), a German surgeon, made a noteworthy viable and logical commitment towards the advancement of modern anesthesia and emergency medicine. In 1900, he had developed a metallic endotracheal tube. Kuhn performed tracheal intubation using this method in the alert patient, utilising local anaesthesia – with cocaine – of the upper aviation routes, or under general anesthesia with chloroform.³⁸

The impact of site-coordinated topical airway local anesthetic, splashed by an atomizer straightforwardly onto supraglottic, glottis, and subglottic zones, even direct vision, has a wide variability, and it should be seen as a peripheral blockade. The various strategies for lidocaine spray may significantly affect results. To accomplish ideal impact of topical airway anesthesia, spray over supraglottic, glottis, and subglottic regions is suggested.^{3,39}

It is known that surgical stimuli are not constant during operation. Imagining a graph of surgical stress, the intubation is considered one of the greatest nociceptive stimuli in the perioperative period. This is the reason for using high bolus doses of intravenous agents such as opioids in anesthetic induction. The plasma concentration of an intravenous anesthetic should be titrated to match the need of individual patient.⁴⁰

The conveyance of a spray under direct vision permits focused on the inclusion of key laryngeal structures, as well as subglottic applications. The use of an atomizer seems to be important when compared to the administration via trachea. It seems to be a more effective option to nonatomized conveyance because atomized particles are little, spread a huge surface zone, and may better hold fast to endotracheal layer bringing about progressively powerful medication assimilation. Therefore, the electrical charge of the atomized particle contributes to increased spread throughout the respiratory tract.^{8,24,41}

There are other described ways of topicalization for an application that includes the blind instillation of lidocaine to the back of the mouth, administration directly down the tracheal tube and nebulization. Lidocaine applied indiscriminately into the rear of the mouth has appeared to convey answer to key laryngeal structures in youngsters, yet it is probably going to be less solid than application under direct vision and far-fetched to anesthetize the subglottic district.^{3,8,41}

The use of nebulization is probably going to be less aggravated to the airway than an application with a splash and might be of advantage in methodology requiring a wide dispersion of local anesthesia (e.g., flexible bronchoscopy or fiberoptic intubation), as nebulization enhances the spread of much smaller droplets to the peripheral airways, but nebulization cannot target the local anesthetic to a particular area, delay the time to administer and the dose delivered is still unknown (because part of it could escape exhalation).^{8,39}

The use of topical airway anesthesia had a little influence on extubation time. This keeps the developing patient's tidal volumes well without troublesome rise airway reflexes, which allows employing a ventilator pressure support mode or handbag assisted ventilation.^{4,31,33,42} On the other hand, another meta-analysis⁴³ confirmed that both alkalinised and non-alkalinised intracuff fundamentally delayed spontaneous ventilation time. To what extent intracuff lidocaine expanded the extubation time was not analysed, yet in the event that the objective was productive turnover of the working room, at that point intracuff lidocaine would not be a suggested decision.⁴³

Besides the reduction in perioperative cough,^{1–3,14,15,28–31,33,39,42} sore throat^{1,15,19} and laryngospasm,¹ oropharyngeal instillation of local anesthetic attenuates the cardiovascular responses to intubation^{7,16,31–34,44,45} and postoperative throat pain without influence patients recovery.^{3,4,14,39} D'Aragon et al.,¹⁴ in a multivariate analysis, watched the use of lidocaine spray diminished the rate of cough at extubation (odds ratio = 0.256; $p < 0.001$). In the same study, the utilisation of intracuff alkalinized lidocaine did not affect the event of cough ($p = 0.471$). They found a number need to treat (NNT) with lidocaine spray of 3.05 patients.¹⁴

Considering the efficacy of airway topical anesthesia against an important nociceptive stimulus of the endotracheal tube, we can consider it as regional anesthesia. The use of local anesthesia is a generally common part of any perioperative multimodal analgesia or improved recuperation after medical procedure (ERAS) pathway.⁴⁵ With the assortment of local strategies accessible and the adaptability of these methods in regards to various surgeries, regional anesthesia/analgesia particularly positions the anesthesiologist to have a noteworthy effect in the decrease of narcotics in the perioperative period.^{46,47}

The length of action of topical laryngeal local anesthetic may depend on the type and concentration used. Most of the studies included in this meta-analysis used lidocaine. Lidocaine has a fast onset of action when injected into tissue

at normal physiological pH. Lidocaine has a term of activity of 1–2 hours when used for different regional anesthesia strategies. Other options with longer effect should be considered to reduce the incidence of cough/bucking and others perioperative respiratory adverse events, especially in surgeries with longer anesthesia times.^{1,4,8,39,48,49}

An infusion of the local anesthetic lidocaine is ordinarily utilised as an aid to control intraoperative nociception and postoperative pain. When used in nerve blocks or regional anesthesia, local anesthetics produce antinociception by either repressing excitation of nerve endings or by blocking conduction of activity possibilities in peripheral nerves. A balanced technique of multimodal general anesthesia predicated on picking a mix of specialists, including regional anesthesia, that demonstrated at various focuses in the nociceptive framework to control nociception intraoperatively and pain postoperatively. Since these specialists additionally decline excitement, the portions of hypnotics inhaled ethers needed to control unconsciousness are diminished.^{50,51}

Anesthesiologists adopt a few techniques to diminish pointless narcotic use, narcotic opioid-related adverse events, and reactions in the perioperative period. Multimodal analgesia, upgraded recuperation pathways, and regional anesthesia are key apparatuses as we move in the direction of ideal narcotic stewardship and the perfect of compelling absense of pain without unwanted sequelae.⁴⁷

While the multimodal approach seems to raise the advantage to symptom proportion, a rational strategy for include the topical airway anesthesia is proposed. With the assortment of local methods accessible and the adaptability of these strategies in regard to various surgeries, regional anesthesia/analgesia of pain remarkably positions the anesthesiologist to have a noteworthy effect in the decrease of anesthetic consumption and narcotics in the perioperative period.^{46,50}

The main limitation of this study is that cough/bucking and coughing severity may be a subjective interpretation, raising the issue of between inter-observer variability and bias. Even though contrasting and “nothing”, or no medicine may bring up issues of result appraisal inclination with regards to surveying a subjective outcome, most of the studies utilised blinded assessors apart from the primary anesthesiology group. Another restriction is the enormous level of heterogeneity in medication dosage. This heterogeneity may change the watched impact, particularly whenever included examinations used subtherapeutic doses. We endeavored to outline this impact by leading a subgroup investigation using low, middle, and high doses, however it was not possible due to the sparsity of information.

Considering the choice of local anesthetic, it can interfere with the outcome of cough and postoperative sore throat. There is a need for more studies to show the difference between the different local anesthetics and drugs, and if there are worse adverse events or outcomes to evaluate better interventions. Magnesium sulphate, liquorice, and steroids seem most effectively prevented postoperative sore throat at 24 hours.¹ Also, there are others confounding factors such as total intravenous anesthetic (TIVA) versus volatile, the cumulative rank of opioids effects, tracheal tube size and cuff type, all of which we couldn't evaluate because of lack of information. Several reasons may exist for the distinction in consequences of various researches,

including diverse statistical methods and models for study consideration and avoidance.^{4,10,17}

All study medications exhibited superior to placebo or no medication in diminishing peri-extubation cough, but further studies could have this objective to combine the different ways to perform this kind of anesthesia, such as opioid use, other adjuvant anesthetics, hemodynamics data, and other local anesthetics.

Conclusion

This systematic review showed that the local anesthetics used as topical application would be advised to reduce the frequency of immediate post-extubation cough/bucking in comparison to either placebo or no medication. It also demonstrated that the local anesthetics used as topical tracheal application had better odds to reduce the extubation time as well. The NNT found was 4.61.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Singh NP, Makkar JK, Cappellani RB, et al. Efficacy of topical agents for prevention of postoperative sore throat after single lumen tracheal intubation: a Bayesian network meta-analysis. *Can J Anaesth.* 2020;67:1624–42.
- Mihara T, Uchimoto K, Morita S, et al. The efficacy of lidocaine to prevent laryngospasm in children: A systematic review and meta-analysis. *Anaesthesia.* 2014;69:1388–96.
- Li LW, He L, Ai Y, et al. Site-directed topical lidocaine spray attenuates perioperative respiratory adverse events in children undergoing elective surgery. *J Surg Res.* 2016;203:206–10.
- Fang P, Zong Z, Lu Y, et al. Effect of topical ropivacaine on the response to endotracheal tube during emergence from general anesthesia: A prospective randomized double-blind controlled study. *BMC Anesthesiol.* 2018;18:1–6.
- Liao AHW, Yeoh SR, Lin YC, et al. Lidocaine lubricants for intubation-related complications: a systematic review and meta-analysis. *Can J Anesth.* 2019;66:1221–39.
- Sumathi PA, Shenoy T, Ambareesha M, et al. Controlled comparison between betamethasone gel and lidocaine jelly applied over tracheal tube to reduce postoperative sore throat, cough, and hoarseness of voice. *Br J Anaesth.* 2008;100:215–8.
- Shabnum T, Ali Z, Naqash I, et al. Effects of lignocaine administered intravenously or intratracheally on airway and hemodynamic responses during emergence and extubation in patients undergoing elective craniotomies in supine position. *Anesth Essays Res.* 2017;11:216–22.
- Roberts MH, Gildersleeve CD. Lignocaine topicalization of the pediatric airway. *Paediatr Anaesth.* 2016;26:337–44.
- Clivio S, Putzu A, Tramèr MR. Intravenous Lidocaine for the Prevention of Cough: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Anesth Analg.* 2019;129:1249–55.
- Tung A, Fergusson NA, Ng N, et al. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. *Br J Anaesth.* 2020;124:480–95.
- Yang SS, Wang NN, Postonogova T, et al. Intravenous lidocaine to prevent postoperative airway complications in adults: a systematic review and meta-analysis. *Br J Anaesth.* 2020;124:314–23.

12. Kulkarni LM, Holyachi R, Kurdi MS. Vegetable gum based gel lubrication of endotracheal tube cuffs improves efficacy of alkalinized intracuff lignocaine in preventing postoperative sore throat: a randomized controlled study. *Anaesth, Pain Intensive Care.* 2016;20:422–8.
13. Lam F, Lin Y, Tsai H, et al. Effect of intracuff lidocaine on postoperative sore throat and the emergence phenomenon: a systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2015;10:e0136184.
14. D’Aragon F, Beaudet N, Gagnon V, et al. The effects of lidocaine spray and intracuff alkalinized lidocaine on the occurrence of cough at extubation: A double-blind randomized controlled trial. *Can J Anesth.* 2013;60:370–6.
15. Bousselmi R, Lebbi MA, Bargaaoui A, et al. Bousselmi 2014 Article medicale General anaesthesia. *Tunis Med.* 2014;92:29–33.
16. Lee DH, Park SJ. Effects of 10% lidocaine spray on arterial pressure increase due to suspension laryngoscopy and cough during extubation. *Korean J Anesthesiol.* 2011;60:422–7.
17. Kuriyama A, Aga M, Maeda H. Topical benzylamine hydrochloride for prevention of postoperative sore throat in adults undergoing tracheal intubation for elective surgery: a systematic review and meta-analysis. *Anaesthesia.* 2018;73:889–900.
18. Minogue SC, Ralph J. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. *Anesth Analg.* 2004;99:1253–7.
19. Tanaka Y, Nakayama T, Nishimori M, et al. Lidocaine for preventing postoperative sore throat. *Cochrane Database Syst Rev.* 2015;14:CD004081.
20. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. *Indian J Anaesth.* 2015;59:37–42.
21. Gu W, Xu M, Lu H, et al. Nebulized dexmedetomidine-lidocaine inhalation as a premedication for flexible bronchoscopy: a randomized trial. *J Thorac Dis.* 2019;11:4663–70.
22. Kuriyama A, Maeda H, Sun R. Topical application of magnesium to prevent intubation-related sore throat in adult surgical patients: a systematic review and meta-analysis. *Can J Anesth.* 2019;66:1082–94.
23. Malcharek MJ, Bartz M, Rogos B, et al. Comparison of Enk Fibreoptic Atomizer with translaryngeal injection for topical anaesthesia for awake fibreoptic intubation in patients at risk of secondary cervical injury: A randomised controlled trial. *Eur J Anaesthetol.* 2015;32:615–23.
24. Takaenoki Y, Masui K, Oda Y, et al. The Pharmacokinetics of Atomized Lidocaine Administered via the Trachea: A Randomized Trial. *Anesth Analg.* 2016;123:74–81.
25. von Ungern-Sternberg BS, Boda K, Chambers NA, et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. *Lancet.* 2010;376:773–83.
26. Hamilton ND, Hegarty M, Calder A, et al. Does topical lidocaine before tracheal intubation attenuate airway responses in children? An observational audit. *Paediatr Anaesth.* 2012;22:345–50.
27. Higgins JPT, Thomas J, Chandler J, et al, Available from www.training.cochrane.org/handbook, 2019.
28. Yamasaki H, Takahashi K, Yamamoto S, et al. Yamasaki 2013 Efficacy of endotracheal lidocaine administration with. *J Anesth.* 2013;27:822–6.
29. Zamora-Lozano J, Cruz-Villaseñor JA, Rodríguez-Reyes J, et al. Comparison of topical, intravenous, and intracuff lidocaine for reducing coughing after extubation during emergence from general anesthesia. *Rev Esp Anestesiol Reanim.* 2007;54:596–601.
30. Diachun CAB, Tunink BP, Brock-Utne JG. Suppression of cough during emergence from general anesthesia: Laryngotracheal lidocaine through a modified endotracheal tube. *J Clin Anesth.* 2001;13:447–51.
31. Dutta D, Godara M, Purohit S, et al. Comparison of the effect of intravenous dexmedetomidine and lignocaine spray instilled into the endotracheal tube on extubation response in patients undergoing spine surgery. *J Neuroanaesth Crit Care.* 2016;3:239–44.
32. Jee D, Park SY. Lidocaine sprayed down the endotracheal tube attenuates the airway-circulatory reflexes by local anesthesia during emergence and extubation. *Anesth Analg.* 2003;96:293–7.
33. Paltura C, Güvenç A, Devlioğlu ÖN, et al. Original Research: Aerosolized Lidocaine: Effective for Safer Arousal After Suspension Laryngoscopy. *J Voice.* 2020;34:130–3.
34. Arslan IB, Kose I, Ciger E, et al. Does Topical Anesthesia Using Aerosolized Lidocaine Inhibit the Superior Laryngeal Nerve Reflex? *Laryngol Neurrolaryngology.* 2013;149:466–72.
35. Soltani HA, Aghadavoudi O. The effect of different lidocaine application methods on postoperative cough and sore throat. *J Clin Anesth.* 2002;14:15–8.
36. Gupta S, Heames B, Lampa M. The effect of laryngotracheal lidocaine on coughing after general anesthesia for carotid endarterectomy. *Eur J Anaesthetol.* 2006;23:258.
37. Rajendram R, Joseph A, Ramachandran SK. Pharmacological interventions to prevent cough at extubation: a meta-analysis. *Eur J Anaesthetol.* 2016;33:84.
38. Thierbach A. Franz Kuhn, his contribution to anaesthesia and emergency medicine. *Resuscitation.* 2001;48:193–7.
39. Dhooria S, Chaudhary S, Ram B, et al. A Randomized Trial of Nebulized Lignocaine, Lignocaine Spray, or Their Combination for Topical Anesthesia During Diagnostic Flexible Bronchoscopy. *Chest.* 2020;157:198–204.
40. Struys M, Absalom A, Shafer SL. "Intravenous Drug Delivery Systems" in Miller's Anesthesia. 8th ed. Elsevier; 2014.
41. Woodruff C, Wieczorek PM, Schricker T, et al. Atomised lidocaine for airway topical anaesthesia in the morbidly obese: 1% Compared with 2%. *Anaesthesia.* 2010;65:12–7.
42. Khezri MB, Kayalha H. The effect of combined ephedrine and lidocaine pretreatment on pain and hemodynamic changes due to propofol injection. *Acta Anaesthesiol Taiwan.* 2011;49:54–8.
43. Chen W, Sun P, Yang L, et al. Improving endotracheal tube tolerance with intracufflidocaine: a meta-analysis of randomized controlled trials. *J Med Coll PLA.* 2013;28:302–12.
44. Sun HL, Wu TJ, Ng CC, et al. Efficacy of oropharyngeal lidocaine instillation on hemodynamic responses to orotracheal intubation. *J Clin Anesth.* 2009;21:103–7.
45. Meng YF, Cui GX, Gao W, et al. Local airway anesthesia attenuates hemodynamic responses to intubation and extubation in hypertensive surgical patients. *Med Sci Monit.* 2014;20:1518–24.
46. Grant MC, Sommer PM, He C, et al. Preserved analgesia with reduction in opioids through the use of an acute pain protocol in enhanced recovery after surgery for open hepatectomy. *Reg Anesth Pain Med.* 2017;42:451–7.
47. Koepke EJ, Manning EL, Miller TE, et al. The rising tide of opioid use and abuse: the role of the anesthesiologist. *Perioper Med.* 2018;7:16.
48. Stevens JB, Vories PA, Walker SC. Nebulized tetracaine attenuates the hemodynamic response to tracheal intubation. *Acta Anaesthesiol Scand.* 1996;40:757–9.
49. Wieczorek PM, Schricker T, Vinet B, et al. Airway topicalisation in morbidly obese patients using atomised lidocaine: 2% compared with 4%. *Anaesthesia.* 2007;62:984–8.
50. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. *Anesth Analg.* 2018;127:1246–58.
51. de Boer HD, Carlos RV, Mulier JP. Is the Balance in Anesthesia Right? Multitarget Approach and Alteration of Systemic Inflammation. *Anesth Analg.* 2019;128:e130.



CASE REPORT

Bradycardia in a pediatric population after sugammadex administration: case series

Erica Viviana Guimarães Carvalho *¹, Sandra Maria Carvalho Caldas ,
Dinis Fernando Pereira Pinheiro Machado da Costa, Cristina Maria Graça Peixoto Gomes

Department of Anesthesiology, Hospital de Braga, Braga, Portugal

Received 24 April 2021; accepted 26 December 2021
Available online 1 February 2022



Abstract Sugammadex is a distinctive neuromuscular reversal drug that acts by encapsulating the neuromuscular relaxant molecule and dislodging it from its site of action. Sugammadex has been approved for pediatric patients over 2 years of age. Although arrhythmias have been reported, there is no report of adverse effects in healthy children, such as severe bradycardia requiring intervention. We report two cases of severe bradycardia immediately after the administration of sugammadex in healthy children. Our aim is to alert to the occurrence of one of the most severe adverse effects of sugammadex, in the healthy pediatric population as well.
© 2022 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Sugammadex is a modified γ -cyclodextrin, regularly used to effectively reverse the neuromuscular blockade induced by rocuronium and vecuronium.¹ Sugammadex acts by encapsulating rocuronium or vecuronium molecules, dislodging them from the neuromuscular junction and, consequently, reversing neuromuscular blockade. Since the inception of sugammadex in clinical practice, mild and transient adverse effects have been described, and severe adverse effects such as bradycardia followed by cardiac arrest have been reported in adults. Arrhythmias (3rd degree atrioventricular block, QT interval prolongation, persistent bradycardia, coronary vasospasm),

hypersensitivity and anaphylaxis are among the most prominent severe side effects reported.¹⁻³

In the pediatric population, sugammadex has been approved for patients above 2 years of age, and there are already some studies focusing on the adverse effects of sugammadex in pediatric patients. In most cases, severe bradycardia occurred in patients presenting cardiac comorbidities.⁴ Conversely, we describe two case reports of healthy pediatric patients in which, despite complying with drug administration recommendations, severe bradycardia was diagnosed and reversed only after treatment with atropine.

Case reports

Informed consent for publication was obtained from the parents.

* Corresponding author.
E-mail: erica.vg.carvalho@gmail.com (E.V. Carvalho).

Case 1

Three-year-old female patient, weighing 17 kg, ASA (American Society of Anesthesiologists) physical status I, scheduled for cleft lip and palate repair.

After standard ASA monitoring (pulse oximetry, noninvasive blood pressure, continuous ECG, temperature, and capnography), train-of-four neuromuscular blockade monitoring, bispectral index and urinary output, general anesthesia was induced with intravenous administration of fentanyl 3 $\text{mcg} \cdot \text{kg}^{-1}$, propofol 3 $\text{mg} \cdot \text{kg}^{-1}$, and rocuronium 0.6 $\text{mg} \cdot \text{kg}^{-1}$. Amoxicillin and clavulanic acid (30 $\text{mg} \cdot \text{kg}^{-1}$ intravenously) were administered as antibiotic prophylaxis. Dexamethasone (0.15 $\text{mg} \cdot \text{kg}^{-1}$ intravenously) was administered to prevent nausea and vomiting, and ketorolac (0.5 $\text{mg} \cdot \text{kg}^{-1}$ intravenously) was administered as a multimodal analgesia component. Anesthesia was maintained with a mixture of oxygen and sevoflurane. Boluses of fentanyl (10 mcg) and rocuronium (3 mg) were administered 70 minutes after anesthesia induction. Before wound closure, the remaining multimodal analgesia components (paracetamol 260 mg and tramadol 35 mg both intravenously) and ondansetron 1.7 mg were administered intravenously. The surgery lasted circa 3 hours, was uneventful, and the patient remained hemodynamically stable (Heart Rate [HR] between 103 and 121 beats per minute (bpm) and Mean Arterial Pressure [MAP] between 60 and 62 mmHg). After observing a train-of-four ratio below 0.9, 34 mg (2 $\text{mg} \cdot \text{kg}^{-1}$) of sugammadex was administered intravenously in the following dilution: 100 mg diluted in 10 mL of saline (10 $\text{mg} \cdot \text{mL}^{-1}$). Immediately after administration, marked bradycardia of 53 bpm (Fig. 1), without hemodynamic consequences was observed, and was reversed after the administration of 0.35 mg of atropine. The trachea was extubated uneventfully. The patient was sent to the Post-anesthetic Care Unit (PACU) and was discharged after criteria were met, without any complications registered.

Case 2

Six-year-old male patient, weighing 21 kg, ASA I scheduled for ureter cystoscopy. Standard ASA monitoring (pulse oximetry, non-invasive blood pressure, continuous electrocardiogram, temperature, and capnography), train-of-four neuromuscular blockade monitoring, bispectral index, and urine output was followed. General anesthesia was induced with intravenous administration of fentanyl 2 $\text{mcg} \cdot \text{kg}^{-1}$, propofol 3 $\text{mg} \cdot \text{kg}^{-1}$ and rocuronium 0.6 $\text{mg} \cdot \text{kg}^{-1}$. The patient developed an

episode of bronchospasm with oxygen desaturation and bradycardia (Fig. 2), that was treated with manual ventilation, sevoflurane, inhaled salbutamol plus ipratropium bromide and intravenous hydrocortisone. Anesthesia was maintained with a mixture of oxygen and sevoflurane. Approximately 20 minutes before the end of surgery, paracetamol (320 mg) and ketorolac (10 mg) were administered intravenously for post-operative analgesia. Ondansetron (2 mg) was administered intravenously for nausea and vomiting prophylaxis. The surgery was uneventful with the patient hemodynamically stable (MAP 67–70 mmHg and HR 90–106 bpm). After observing train-of-four ratio below 0.9, 42 mg of sugammadex IV (2 $\text{mg} \cdot \text{kg}^{-1}$) in the following dilution were administered: 100 mg diluted in 10 mL of saline (10 $\text{mg} \cdot \text{mL}^{-1}$). After the administration, bradycardia (55 bpm) with hemodynamic changes (PAM \sim 50 mmHg) was observed and reverted after the administration of 0.45 mg of atropine (Fig. 2). Minutes after resolution, and 90 minutes after the event, blood was drawn for measuring tryptase (both resulted negative). Extubation was uneventful and the patient remained at the PACU until discharge criteria were met, uneventful and without other adverse effects associated with sugammadex.

Discussion

The purpose of these case reports is to alert to the occurrence of one of the most concerning adverse effects associated with sugammadex, severe bradycardia in the healthy pediatric population. There have been cases reported of profound bradycardia culminating in asystole in adults, thus bradycardia is well recognized as a potential adverse effect of sugammadex by the manufacturer.² However, despite the time relationship between sugammadex and bradycardia, no specific pharmacological or physiological mechanism of action has been suggested or established.³ Thus, the only recommendation is to inject sugammadex quickly (10 seconds) and in a single bolus. In addition, in the case of the pediatric population, the manufacturer recommends diluting sugammadex up to 10 $\text{mg} \cdot \text{mL}^{-1}$ to enhance the accuracy of the dose administered.²

Moreover, large-scale studies focusing on this issue are scarce and virtually non-existent in the pediatric population. In 2020, Alsuhebani et al.⁴ reported a study that included 221 children in which sugammadex was administered for neuromuscular blockade reversal. Bradycardia was registered in 18 patients, of whom 7 presented cardiac

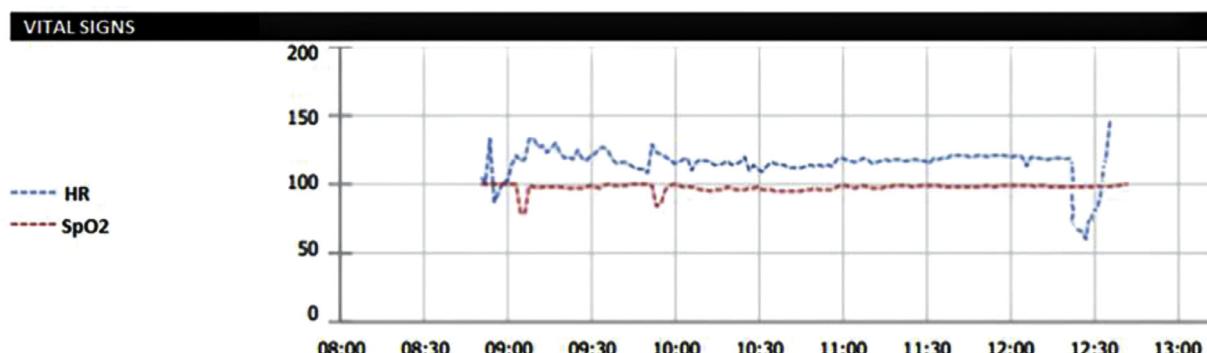


Figure 1 HR and Peripheral Oxygen Saturation (SpO_2) during the intraoperative period.

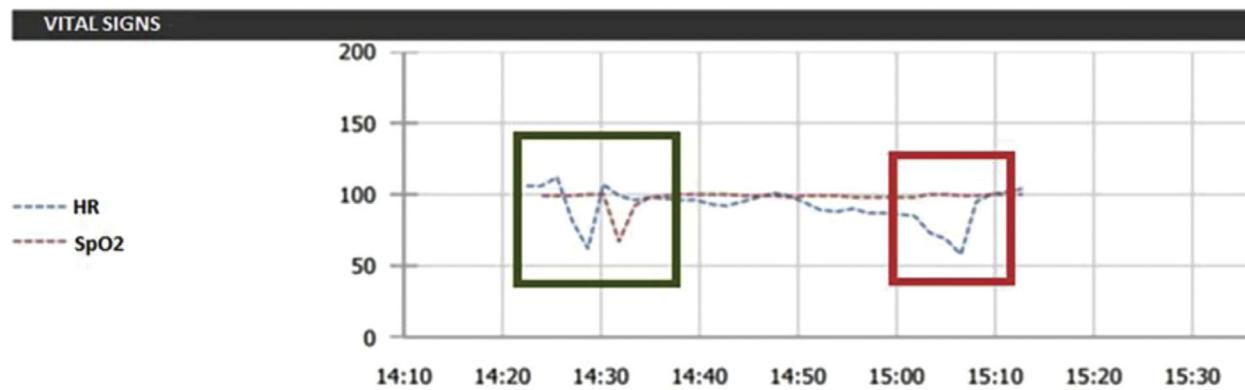


Figure 2 HR and SpO₂ during the intraoperative period. The black square represents bronchospasm at induction, and the red square represents bradycardia after administration of sugammadex.

comorbidities. None of the patients required pharmacological treatment to reverse bradycardia and no clinically significant changes in blood pressure were observed. However, this adverse effect may not always resolve spontaneously, and it may require pharmacological treatment to avoid it evolving to severe arrhythmia or cardiac arrest.

In addition to this adverse effect, anaphylaxis following sugammadex administration has also been described,³ so in Case 2, given the simultaneous hypotension, anaphylaxis was cogitated as a differential diagnosis, and therefore serum tryptase was measured. As serum tryptase levels were negligible (in both samples) and hemodynamic instability reversed after atropine administration, we excluded the diagnosis of anaphylaxis.

Hence, in the absence of further studies on bradycardia in the healthy pediatric population, the clinical report of these cases is an important and valuable source of information. The adverse effect described in these two patients was reported to the manufacturer, and also to the National Medicine and Health Product Authority (INFARMED), the agency responsible for pharmacovigilance in Portugal.

Conclusion

Even when administered at the appropriate dose and according to the manufacturer's recommendations, sugammadex can effectively cause severe bradycardia associated with hemodynamic instability in healthy children, and that may not easily reverse without adequate pharmacological

treatment. Therefore, more studies are required in this specific population.

Learning points

Bradycardia is a well-known adverse effect of sugammadex administration.

More studies focusing on this adverse effect in the pediatric population are required.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*. 2007;104:575–8.
2. Bridion (sugammadex) [prescribing information]. Whitehouse Station, NJ; Merck & Co, Inc: December 2015.
3. Hunter JM, Naguib M. Sugammadex-induced bradycardia, and asystole: how great is the risk? *Br J Anaesth*. 2018;121:8–12.
4. Alsuhebani M, Sims T, Hansen JK, et al. Heart rate changes following the administration of sugammadex in children: a prospective, observational study. *J Anesth*. 2020;34:238–42.



CASE REPORTS

Debridement of axillary necrotizing fasciitis under anesthetic blocks of the serratus plane and supraclavicular brachial plexus: a case report



Leonardo Saraiva Guimarães de Oliveira *, Renata de Andrade Chaves

Hospital Metropolitano Odilon Behrens, Prefeitura Municipal de Belo Horizonte, Departamento de Anestesiologia, Belo Horizonte, MG, Brazil

Received 20 December 2020; accepted 27 February 2021

Available online 19 April 2021

KEYWORDS

Axilla;
Brachial plexus
blocks;
Case reports;
Intermediate back
muscles;
Regional anesthesia;
Thoracic wall

Abstract The regional techniques for axillary analgesia are well established. However, few studies have investigated surgical anesthesia. In this report, extensive debridement of axillary necrotizing fasciitis, including the posteromedial region of the right arm, performed under exclusive regional anesthesia in a patient with probable difficult airway is described. The procedure was accomplished under a Serratus Plane Block (SPB) and supraclavicular brachial plexus block, guided by ultrasound, and with venous sedation. We observed satisfactory anesthesia 15 minutes after the intervention, efficient intraoperative pain control and within the following 24 hours. Surgical axilla anesthesia is feasible with the described blocks.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Interfacial thoracic blocks, including Erector Spinae Plane (ESP), pectoral (PECS I and II), and Serratus Plane Blocks (SPB), are established analgesic techniques for thoracic, breast and axilla surgeries and are less invasive alternatives to Thoracic Epidural (TEB) and Thoracic Paravertebral Blocks (TPVB).^{1–3} However, in the literature, there is no consensus

on the performance of these blocks for anesthetic purposes, especially for axillary surgeries. The axilla is a region of intricate anatomy and innervation, which makes it challenging to induce surgical anesthesia in this compartment.¹

In the present report, the combination of the SPB and supraclavicular brachial plexus block (BPP), guided by ultrasound, was proposed to address extensive axillary necrotizing fasciitis, which included the posteromedial region of the right arm, in a probable difficult airway scenario.

* Corresponding author.

E-mail: saraivaleo@gmail.com (L.S. Oliveira).



Figure 1 A, Sonoanatomy of the serratus plane block (LDM, Latissimus Dorsi Muscle; SAM, Serratus Anterior Muscle). B, Image after surgical debridement. C, Sonoanatomy of supraclavicular brachial plexus block (BP, Brachial Plexus; SCA, Subclavian Artery).

Case report

Voluntary and informed consent was provided by the patient for the inclusion of his data in this report. The patient was a 55-year-old male with a height of 1.75 m and weight of 82 kg; he had diabetes mellitus type II and took 500 mg of metformin/day. The patient was referred to the operating room for emergency surgical debridement with diffuse necrotizing fasciitis and multiple abscesses in the right axilla, which had been ongoing for 10 days due to a probable complication of suppurative hidradenitis (Fig. 1A). The patient had reported fasting for 8 hours. The physical examination revealed that he was conscious, eupneic, and hemodynamically stable. The airway examination revealed that the patient had a Mallampati score of IV, mouth opening of less than 4 cm, upper lip bite test class of II and thyromental distance of less than 6 cm. The axillary inspection showed extensive necrotizing fasciitis affecting the entire anatomical pyramid, extending to the edges of the pectoral muscles and the posteromedial face of the right arm. The laboratory tests showed leukocytosis of 15,000 cell·mm⁻³ with deviation, PCR 259 mg·dL⁻¹, hyperglycemia of 280 mg·dL⁻¹ (corrected to 170 mg·dL⁻¹ with 10 IU of regular insulin) and arterial gasometry showing adequate peripheral perfusion. After standard monitoring, antibiotic therapy with 400 mg of ciprofloxacin and 600 mg of intravenous (IV) clindamycin was instituted. Sedation was started with 1 mcg·kg⁻¹ dexmedetomidine in a 10-minute bolus and 1 mg/kg ketamine and was maintained with 0.7 mcg·kg⁻¹·h⁻¹ dexmedetomidine. Spontaneous ventilation was maintained with O₂ support by a nasal catheter at 2 L·min⁻¹. The blocks were guided by ultrasound (GE LOGIQ V2®; General Electric Company, Wauwatosa, WI) with a linear transducer (6–13 MHz). When performing the SPB, with the patient in supine position and arm abducted, the probe was slid distally and laterally (in sagittal orientation) from the middle portion of the clavicle until 4th and 5th ribs appeared. The probe was reoriented to the coronal plane and tilted backward, identifying the Latissimus Dorsi Muscle (LDM); then, the Serratus Anterior Muscle (SAM) was visualized deep in relation to the LDM and superficial to the ribs. A 50-mm needle (Locoplex® 50 mm, Vygon, Ecouen, France) was inserted from the posterior to anterior direction in the interfacial plane of these muscles, and 20 mL of ropivacaine

0.5% was injected (Fig. 1B). In the BPB, the transducer was positioned in the transverse plane, proximal to the clavicle. The transducer was inclined caudally to visualize the thoracic structures (subclavian artery, 1strib, pleura, and brachial plexus); the plexus was noted as a collection of hyperechoic oval structures posterior and superficial to the artery. The needle was introduced in the same plane, and 15 mL of ropivacaine 0.5% was injected (Fig. 1C). A loss of sensitivity was observed in the lateral thorax wall of T2-T6 in the entire axilla and lateral region of the pectorals as well as in the entire right upper limb during the pinprick test performed 15 minutes after the blocks. A fibrobronchoscope, videolaryngoscope and laryngeal mask n. 5 were prepared in case airway rescue was needed. The procedure lasted 1 hour and 30 minutes, with satisfactory sensorial block and RASS-2 sedation scale scores. Adjuvant therapy with 2 g of dipyrone, 30 mg of ketorolac and 4 mg of ondansetron was administered. There were no pain complaints (score of 0 on the visual analogue scale) within 2 hours in the PACU. Within the following 24 hours, there were also no episodes of pain; 2 g of dipyrone was administered on a fixed schedule every 6 hours, and there was no need for opioids.

Discussion

It is well known that acute and chronic pain can develop after breast and axilla surgery, and regional anesthesia help prevent this. Both TPVB and TEB are traditional techniques for regional chest anesthesia, but they are elaborate and are associated with latent catastrophic complications.^{1,2} With the evolution of ultrasound-guided blocks, new analgesic techniques have emerged for this purpose. Thoracic interfacial blocks such as the ESP, PECS I and II and SPB have appeared as safer and easier alternatives to perform.^{1,3} However, while analgesia in these regions is satisfactory, procedures performed exclusively with peripheral nerve anesthesia are not widely performed. The axilla is a region of complex anatomy and innervation, and it is not simple to induce surgical anesthesia in this compartment (Table 1).¹

Anesthetic blocks were chosen to avoid general anesthesia because of the difficult airway condition. However, it is known that the choice for regional anesthesia is not always the guarantee of safety. In cases of block failure

Table 1 Axillary anatomy.

Walls	Boundaries	Inervation
Medial	External surface of 4 first ribs Serratus anterior muscle Subscapularis muscle	Intercostal nerves Long thoracic Nerve C5-C7 Lower and upper subscapular nerves C5-C6
Posterior	Teres major muscle Latissimus dorsi muscle tendon Pectoralis major muscle	Subscapular nerves Thoracodorsal nerve C8-T1
Anterior	Pectoralis minor muscle Pectoral and clavipectoral fascias	Lateral pectoral nerve C5-C7 and medial pectoral nerve C8-T1
Base	Axillary fascia, adipose layer, and skin	Intercostobrachial nerve T2– T3 Medial brachial cutaneous nerve C8-T1 Lateral cutaneous branches of intercostal nerves T3-T9
Apex	Cervicoaxillary canal	
Lateral	Space between the humerus and the insertions of the muscles of the anterior and posterior walls	

Source: Moore KL, Dalley AF, Agur AM. Clinically Oriented Anatomy Seventh Edition. Lippincott Williams & Wilkins; 2014. p. 851-870.

or complications, the difficult airway would need to be addressed suddenly, adding risks to the situation. Clinicians may choose to perform blocks in this scenario, but it is mandatory to prepare a plan for the airway.⁴

PVTB induces axillary analgesia by accessing ventral thoracic roots, blocking the intercostobrachial and intercostal nerves. However, for anesthetic purposes, theoretically, there is a gap in the coverage of innervation since the medial brachial cutaneous nerve and the medial and lateral pectoral, long thoracic and thoracodorsal nerves originate from the brachial plexus.¹ By blocking similar innervations, the ESP also promotes good axillary analgesia. Nevertheless, the same limitations remain as with the PVTB. De Cassai et al. (2019) proposed the use of the SPB with brachial plexus selective nerve blocks to prevent these issues. The authors accessed the long thoracic, thoracodorsal, medial, and lateral pectoral nerves individually, inducing anesthesia in the region.³

Radiological and cadaveric dissection studies after SPBs have evidenced that solutions spread to the axilla and lateral thoracic wall, stimulating the reproduction of this block in a surgical context.^{1,2} With the SPB, the accessed nerves are responsible for most of the sensitive innervation of the axilla (intercostobrachial and lateral cutaneous branches of intercostal), further the long thoracic and thoracodorsal nerves, responsible for axillary myotomes. All these nerves are located between the fascias of the SAM and LDM.² Sanllorente-Sebastian et al. (2020) reported 2 cases of axillary arteriovenous fistulas being successfully treated under the supraclavicular BPB and SPB (between the SAM and external intercostal muscle at the 2nd rib level). In one case, it was necessary to additionally administer mepivacaine in the incision.⁵ The ability to perform the technique in the supine position in patients with severe pain was the reason why the SPB was chosen over the ESP. The SPB was chosen over the PECS II (pectorals, long thoracic, intercostobrachial, and lateral cutaneous branches of intercostal nerves are reached) because there was an infection that extended towards the anterosuperior chest. The reason that

the BPB was performed was that the debridement extended to the posterior arm region (radial nerve territory) and there was a probable need to address the remaining axillary innervation (medial and lateral pectoral nerves and medial brachial cutaneous nerve).¹

The SPB is a well-explored analgesic technique used in axillary surgeries. However, there is still a lack of strong evidence supporting the use of the SPB for anesthetic purposes in this context. In the present case, we successfully performed extensive axillary debridement with the SPB and supraclavicular BPB. Clinical trials are necessary to validate the presented conclusions as well as to determine the viability of the SPB as a unique technique in these circumstances and the required doses for this technique.

Authors' contributions

Leonardo Saraiva Guimarães de Oliveira: conception and design of the study, data acquisition and interpretation, writing of the article and critical review, final approval.

Renata de Andrade Chaves: conception and design of the study, data acquisition and interpretation, critical review of the article, final approval.

Conflicts of interest

The authors declare no conflicts of interest.

References

- de la Torre PA, Jones JW, Álvarez SL, et al. Axillary local anesthetic spread after the thoracic interfacial ultrasound block – a cadaveric and radiological evaluation. Rev Bras Anestesiol. 2017;67:555–64.
- Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: A novel ultrasound-guided thoracic wall nerve block. Anaesthesia. 2013;68:1107–13.

- [3] De Cassai A, Bonvicini D, Ruol M, Correale C, Furnari M. Erector spinae plane block combined with a novel technique for selective brachial plexus block in breast cancer surgery. *Korean J Anesthesiol.* 2019;72:270–4.
4. Khetarpal R, Chatrath V, Dhawan A, Attri J. Regional anesthesia in difficult airway: The quest for a solution continues. *Anesth Essays Res.* 2016;10:178–83.
5. Sanllorente-Sebastián R, Rodríguez-Joris E, Avello-Taboada R, Fernández-López L, Ayerza-Casas V, Robador-Martínez D. Addition of serratus-intercostal plane block/BRILMA for arteriovenous access surgery. *Rev Esp Anestesiol Reanim.* 2020;67:343–6.

Glossary

BPB: brachial plexus block
ESP: erector spinae plane block
LDM: latissimus dorsi muscle
PECS: pectoralis blocks
RASS: Richmond Agitation Sedation Scale
SAM: Serratus anterior muscle
SPB: serratus plane block
TEB: thoracic epidural block
TPVB: thoracic paravertebral block

CASE REPORT

It's not always postdural puncture headache: a case report and note to the astute anesthesiologist



Ejaz Khan a,* , Rovnat Babazade a , Mohamed Ibrahim a , Michelle Simon a , Lindsay Juarez b , Mandonca Roni b , Vadhera Rakesh a

^a University of Texas Medical Branch at Galveston, Department of Anesthesiology, Galveston, Texas, USA

^b Metropolitan Medical Center, NYCH* Hospitals, Department of Anesthesiology, New York, USA

Received 21 May 2020; accepted 4 June 2021

Available online 24 June 2021

KEYWORDS

Postdural puncture headache;
Epidural blood patch;
Unintended dural puncture;
Endovascular embolization;
Incidental intracranial aneurysm

Abstract Dural puncture is either diagnosed by unexpectedly profound response to medication test dose or development of a postpartum postural headache. Epidural blood patch is the gold standard for treatment of PDPH when conservative management fails. However, postpartum headaches can be resistant to multiple epidural blood patches. In such cases, preexisting intracranial processes should be considered and ruled out. We report here the unique case of a pregnant patient who developed a resistant headache in the postpartum period related to an incidental intracranial aneurysm. Subsequent treatment with endovascular embolization adequately relieved her symptoms. Early surgical consultation and a multidisciplinary team approach involving neurology and neuroimaging is required for successful management of patients such as the one described here.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Epidural labor analgesia complicated by Postdural Puncture Headache (PDPH) as a result of unintended dural puncture is not uncommon.¹ Up to one third of unintended dural puncture events may go unrecognized at the time of procedure, only later identified once the patient has developed a

PDPH.^{2,3} Lumbar epidural blood patch procedures have been shown to provide significant symptomatic relief in up to 93% of patients after first patch placement and 97% of patients after a second patch placement.⁴ Other less common causes of postpartum headache, however, must be considered and ruled out when conventional treatment for PDPH proves ineffective.

The incidence of cerebral aneurysm is about 2% in both the general population and women of childbearing age.⁵ Although the etiology is often unknown, both genetic and environmental factors are likely at play.⁶ The majority of cerebral aneurysms are located in the anterior circulation

* Corresponding author.

E-mail: khane4@nycchc.org (E. Khan).

(80–90%), with a minority being found in the posterior circulation.⁷ Normal physiologic changes during pregnancy may increase the risk of cerebral aneurysm formation, progression, and even rupture.⁸ However, the incidence of unruptured or incidental cerebral aneurysm during pregnancy is not well established.⁵ We present here a unique case of refractory PDPH in a young parturient with an incidental intracranial aneurysm treated with endovascular embolization for ultimate symptomatic relief.

Case report

A 28-year-old gravida 5 para 5 at 40 weeks gestation presented to our labor and delivery unit in early labor, with plans for spontaneous vaginal delivery. Her past medical history was unremarkable, and she had reportedly received uneventful epidural labor analgesia for her last delivery. On admission, epidural labor analgesia was requested by the patient and ultimately placed in the L4–L5 intervertebral space with the patient in a sitting position. After preparing an appropriate sterile field, a 17G Tuohy needle was used to identify and enter the epidural space using a loss-of-resistance to saline technique. Loss of resistance was achieved at a depth of 4.5 cm, at which time a 19G multi-orifice epidural catheter was easily threaded and secured at 9 cm at the skin. Aseptic technique was maintained throughout the procedure.

Following negative aspiration from the catheter and a negative test dose with 3 mL 2% lidocaine with 1:200,000 epinephrine, an epidural infusion of 0.1% bupivacaine + 2 mcg.mL⁻¹ fentanyl at 12 mL.h⁻¹ was initiated. The patient received a 4-mL epidural bolus of this solution at the time of infusion initiation with a 4-mL Patient Controlled Epidural Analgesia (PCEA) dose available at a 20-minute lock out. The neuraxial blockade had reached a T4 level bilaterally shortly after the initial bolus, at which time the infusion rate was decreased to 2 mL.h⁻¹ with concern for intrathecal catheter migration. Soon after epidural placement, the patient began to complain of headache, though no signs of unintended dural puncture were appreciated at that time. The headache was occipital in location, throbbing in nature, 5–6/10 in severity and aggravated with the patient in a head-up position. The patient exhibited no focal neurologic deficits. Within a few hours, the patient began to report increased labor pain with physical exam findings consistent with a T12 level of blockade on the right side and T9 level on the left. The asymmetrical levels of neuraxial blockade as well as fading of the epidural block indicated a high likelihood that the catheter was, in fact, in the epidural space. Thusly, a 4-mL bolus dose of the epidural infusion cocktail was administered, and the infusion rate was increased to 10 mL.h⁻¹. The patient reported adequate relief from labor pain but failed to see improvement in her ongoing positional headache. Her labor course proceeded in an uneventful manner, and she delivered a healthy newborn via uncomplicated, spontaneous vaginal delivery.

In the early postpartum period, the patient's headache increased in severity to a 7/10 and was unrelieved by conservative management with intravenous fluids, oral analgesics, and bed rest. An epidural blood patch was performed approximately 24 hours after delivery using 15 mL of autol-



Figure 1 Left supraclinoid, paraophthalmic ICA aneurysm, measuring approximately 9 × 6 mm.

ogous blood. The injection was performed at the L3–L4 intervertebral space, using a 17G Tuohy needle in a midline approach. The patient reported transient symptomatic relief, however the headache returned less than 24 hours later.

A second blood patch was placed 72 hours after the first blood patch, again using 15 mL of autologous blood, injected at the L3–L4 intervertebral space with a midline approach. The patient reported immediate improvement in the severity of her headache from 8/10 to 4/10 following the second blood patch, however her symptoms again returned approximately 24 hours later. Forty eight hours after the second blood patch, a third blood patch was placed, again using 15 mL autologous blood and a 17G Tuohy needle in a midline approach, however this time the injection was made at the L4–L5 intervertebral space under fluoroscopic guidance. Needle placement was confirmed with spread of dye within the epidural space and about the nerve roots. The patient again reported transient relief followed by recurrence within 24 hours. Her headache was not associated with nausea, vomiting, or any focal neurologic deficits. No neck rigidity or compromised cervical mobility was appreciated. Computed Tomography Angiography (CTA) of the patient's head revealed an incidental left supraclinoid, paraophthalmic aneurysm of the Internal Carotid Artery (ICA) measuring 9 × 6 mm (Fig. 1 and 2). The patient subsequently underwent an endovascular pipeline embolization of this aneurysm and reported sustained symptomatic relief at 48 hours post procedure. She was discharged home on oral analgesic medications as needed.

Discussion

Lumbar epidural placement is the gold standard for labor analgesia in most developed countries and is a common practice worldwide. PDPH is a known complication of epidural placement in this setting. The incidence of PDPH following unintended dural puncture with a 17G needle can be as high as 75–85%,⁹ however it is not the only cause of postpartum headache.¹⁰ Table 1 provides a brief summary of differential diagnoses for headache in the postpartum period. PDPH classically presents as a frontal or occipital postural headache,

Table 1 Brief summary of differential diagnoses for headache in the postpartum period, comparing timeline, clinical indicators, and appropriate workup and/or treatment.

Differential diagnosis for PDPH	Timeframe	Clinical clues	Workup/treatment
PDPH	12 hours to 5 days following dural puncture event	Postural in nature "Throbbing" quality Fronto-occipital location	Conservative management with fluids, non-narcotic analgesic medications ± caffeine Epidural blood patch for resistant symptoms
Preexisting intracranial aneurysm	Onset shortly after epidural placement, but can present at any time	Unrelieved by conservative management measures for PDPH	Cerebral angiography Neuroendovascular surgery consultation
Migraine or tension-type headache	Can present at any time	History of migraine or tension-type headaches Sensitivity to light and/or sound Preceding aura	Acetaminophen ± caffeine Trial of ergot alkaloids (i.e., sumatriptan) for persistent symptoms consistent with migraine
Fatigue/dehydration	Can present at any time	Decreased skin turgor Mild cognitive symptoms/"brain fog"	Intravenous fluids Symptomatic management

**Figure 2** Cerebral angiogram showing left supraclinoid, paraophthalmic ICA aneurysm.

throbbing in nature, and can range from mild to severe and incapacitating. The headache onset typically begins within 12–48 hours and rarely more than 5 days after the dural puncture event. Headache soon after epidural placement is more likely related to either pneumocephalus or preexisting intracranial pathology.^{11,12} Our patient, indeed, complained of headache soon after epidural placement – considering that a loss-of-resistance to saline technique was used, the possibility of pneumocephalus was exceptionally low. Although unintended, dural puncture was not recognized at the time of epidural placement, a questionably high level of neuraxial blockade after bolus dose raised suspicion for intrathecal connection.

While the exact cause of PDPH is not entirely known, it's thought to be related to the decrease in cerebrospinal fluid

pressure secondary to volume loss, leading to traction on structures within the cranium.¹³ The initial management of PDPH is bed rest with supportive therapy including oral or intravenous fluids and nonnarcotic analgesic medications. Epidural blood patch is the standard treatment for resistant PDPH and is usually offered after 24 hours of failed conservative management.

Our patient received three blood patches, each followed by symptom recurrence within 24 hours, suggesting that her headache was related to a preexisting intracranial aneurysm, rather than unintended dural puncture. One explanation for this would be an increase in transmural pressure within the aneurysm related to cerebrospinal fluid leak. The transmural pressure of an aneurysm is the difference between the Mean Arterial Pressure (MAP) and Intracranial Pressure (ICP).¹⁴ Dural puncture can affect a clinically significant decrease in ICP, potentially even triggering the rupture of a preexisting aneurysm. Our patient's headache relief following endovascular embolization of the aneurysm supports the increased transmural pressure hypothesis.

The existing literature on unruptured intracranial aneurysms in pregnancy is extremely limited, and therefore guidelines for obstetric anesthetic management do not exist. Epidural labor analgesia, however, is generally considered safe for patients with no evidence to suggest a preexisting intracranial vascular anomaly. Undiagnosed neurovascular conditions rarely first manifest in the postpartum period, however thoughtful clinical evaluation and due consideration of alternative diagnoses is essential in providing timely, appropriate care to these patients.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Gurudatt CL. Unintentional dural puncture and postdural puncture headache – can this headache of the patient as well

- as the anaesthesiologist be prevented? *Indian J Anaesth.* 2014;58:385–7.
2. Davies RG, Laxton CJ, Donald FA. Unrecognised dural punctures. *Int J Obstet Anesth.* 2003;12:142–3.
 3. Sprigge JS, Harper SJ. Accidental dural puncture and post dural puncture headache in obstetric anaesthesia: presentation and management: a 23-year survey in a district general hospital. *Anaesth Rep.* 2008;63:36–43.
 4. Safa-Tisseront V, Thormann F, Malassiné P, Henry M, Riou B, Coriat P, et al. Effectiveness of epidural blood patch in the management of post-dural puncture headache. *Anesthesiology.* 2001;95:334–9.
 5. Kim YW, Neal D, Hoh BL. Cerebral aneurysms in pregnancy and delivery: pregnancy and delivery do not increase the risk of aneurysm rupture. *Neurosurgery.* 2013;72:143–9, discussion 150.
 6. Rinkel GJ. Natural history, epidemiology and screening of unruptured intracranial aneurysms. *J Neuroradiol.* 2008;35:99–103.
 7. Priebe HJ. Aneurysmal subarachnoid haemorrhage and the anaesthetist. *Br J Anaesth.* 2007;99:102–18.
 8. Nelson LA. Ruptured cerebral aneurysm in the pregnant patient. *Int Anesthesiol Clin.* 2005;43:81–97.
 9. Al-Metwali RR. Epidural morphine injections for prevention of post dural puncture headache. *Anaesth Rep.* 2008;63:847–50.
 10. Grant EN, Wang J, Gelpi B, Wortman A, Tao W. Diagnosing and managing peripartum headache. *Proc (Baylor Univ Med Cent).* 2015;28:463–5.
 11. Reddi S, Honchar V, Robbins MS. Pneumocephalus associated with epidural and spinal anesthesia for labor. *Neurol Clin Pract.* 2015;5:376–82.
 12. Stanhope E, Foulds L, Sayed G, Goldmann U. Diagnosing causes of headache within the postpartum period. *J Obstet Gynaecol.* 2018;38:728.
 13. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth.* 2003;91:718–29.
 14. Yao, F. Yao and Artusio's Anesthesiology. 6th edition. 2008-625-629.

CASE REPORTS

Transient median nerve palsy following ultrasound-guided subscapularis plane block: a case report



Syahrul Mubarak Danar Sumantri ^{a,*}, Anna Surgeon Veterini^b

^a Siloam Hospitals Jember, Department of Anaesthesiology & Critical Care, Jember, Indonesia

^b Dr. Soetomo General Hospital, Department of Anaesthesiology & Intensive Therapy, Surabaya, Indonesia

Received 24 July 2020; accepted 2 April 2021

Available online 27 April 2021

KEYWORDS

Case report;
Nerve block;
Adverse effects

Abstract The subscapularis plane block is an effective approach to anesthetize axillary and upper subscapular nerves. There have been no reports regarding brachial plexus paralysis as a potential complication to date. Described here is a case of median nerve palsy following ultrasound-guided subscapularis plane block for awake frozen shoulder manipulation that was performed on a 52-year-old female diagnosed with adhesive capsulitis. The patient could not flex digits two and three, and ipsilateral inner palm numbness occurred shortly after the block commenced, with complete resolution in the next two hours. The local anesthetics spillage towards brachial plexus with possible partial paralysis should always be expected after subscapularis plane block.

© 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Subscapularis plane block (SSPB) has only been reported three times by anesthesiologists who wanted to achieve analgesia over the shoulder region, in addition to the suprascapular and lateral pectoral nerve blocks.^{1–3} Until then, there had been no reports concerning complication associ-

ated with this plane block. We present our experience with one case of median nerve palsy complicating SSPB for awake frozen shoulder manipulation and investigate its possible mechanism.

Case report

A 52-year-old female patient of 50 kg weight and 156 cm height was scheduled to undergo awake frozen shoulder manipulation for her left shoulder's painful adhesive capsulitis. The patient, however, refused her orthopedic sur-

* Corresponding author.

E-mail: caliptra36@gmail.com (S.M. Sumantri).

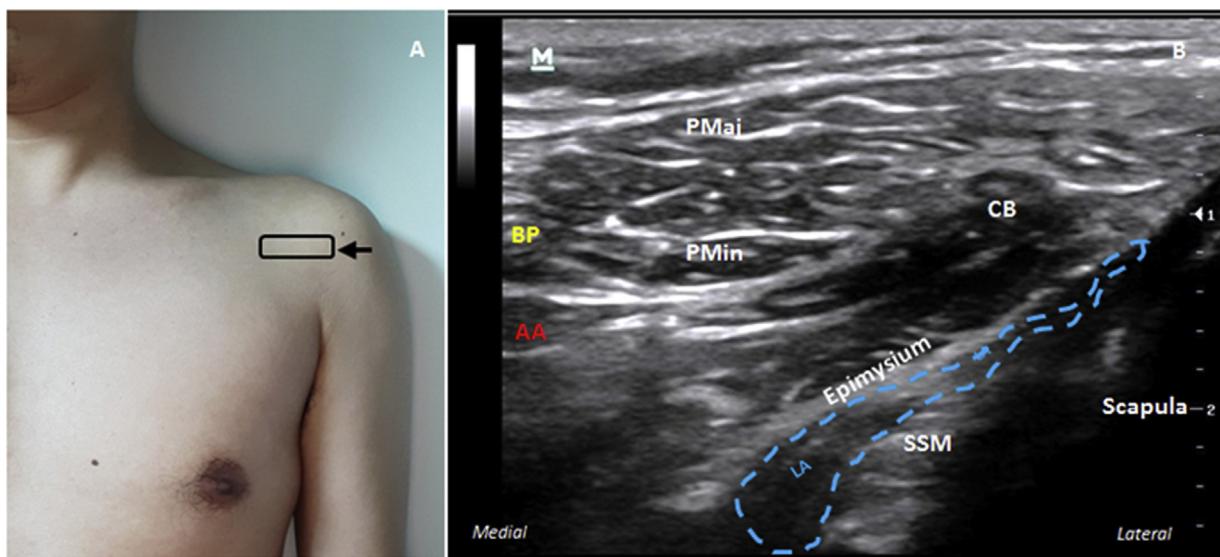


Figure 1 A, Illustration of probe positions and needle directions for subscapularis plane block (SSPB); B, Ultrasound image of local anesthetic (LA) deposited beneath subscapularis muscle (SSM). Brachial plexus (BP) was seen at the medial of the screen above axillary artery (AA). The three layers of muscle at the anterior border of subscapularis plane were coracobrachialis (CB), pectoralis minor (P.Min), and pectoralis major (P.Maj) muscle.

geon's reference for physical rehabilitation through shoulder manipulation, leaving her with worsening pain and limited shoulder movement that went untreated for two weeks. Considering her previous history of recurrent asthma attacks and her objection to potential complication of transient unilateral phrenic nerve that might risk her respiratory status, she refused the option of ipsilateral interscalene brachial plexus (BP) block.

We presented an alternative interfascial plane shoulder block consisting of combined SSPB, pectoral and suprascapular nerve block with careful explanation of its novelty and limited evidence, earning the patient and her relative's consent. The first block given was SSPB by administering 15 ml of 1.5% lidocaine with epinephrine 0.1 mg (5 µg.mL⁻¹), guided by ultrasonography as described by Sondekoppam et al.¹ with the illustrative probe position as shown in Figure 1A.

The probe was positioned at the axial plane of shoulder, where the lesser trochanter of humerus and the subscapularis muscle were well-identified sonographically. After local skin infiltration, a non-stimulating 100-mm-long, 21G, short-beveled needle (Locoplex®, Vygon, Padova, Italy) was inserted in-plane with the ultrasound probe, in a lateral-to-medial direction. The needle was advanced until the tip is positioned in the interfascial plane between the coracobrachialis (CB) and subscapularis muscle (SSM). Color Doppler real-time evaluation during needle insertion is paramount to avoid unintentional puncture to the anterior and posterior circumflex humeral arteries. It is then advanced further, with a small amount of hydrodissection solution (normal saline) being injected carefully until a visible spread of solution dissected SSM away from its epimysium (Fig. 1B). After confirming the correct needle tip position, the author then deposited the desired amount of local anesthetics (LA) exactly beneath the SSM epimysium.

Fifteen minutes after injecting LA, before commencing with the two other blocks, the patient complained of

hypoesthesia at the lateral side of ipsilateral inner palm, followed by the inability to flex digits two and three into a compact fist, corresponding to proximal median nerve palsy. After reassuring the patient that the complication would be transient, two other blocks were given without any significant findings. Shoulder manipulation was uneventful, with a duration of 30 minutes. Two hours after SSPB commenced, symptoms of proximal median nerve palsy had been completely remitted. During the next day's follow-up evaluation by phone, the patient did not mention any complaint nor subsequent problem related to her previous transient median nerve palsy and was satisfied with the intervention.

Discussion

The subscapularis plane is a potential space between the anterior aspect of SSM and pectoralis major muscle (PMM). First described by Sondekoppam et al., this approach focuses on subscapular (SSN) and axillary nerves (AN) as these structures are present on the ventral surface of SSM. Its clinical significance is that these nerves provide sensory supply to anterior and posteroinferior quadrants of the shoulder.^{1,4}

The ideal approach to achieve optimum SSN and AN block is still debatable until recently, since there have only been three papers describing ultrasound-guided fascial block technique related to SSM by employing different methods. Earlier, Sondekoppam et al. and Drake et al. injected LA over the ventral surface of SSM at the intermuscular plane beneath PMM. Later, Tran et al. decided to put LA in the plane between SSM and anterior glenohumeral joint capsule. All authors have effectively blocked SSN and AN with a different volume of LA; 15, 10, and 2 ml, respectively.^{1–3}

Anatomically, lateral approach to SSPB with the medial border of coracobrachialis muscle as stop demarcation line of the needle tip can be considered safe as there is no major structure on the needle path. Also, the presence of

sheath towards the proximal third of the upper arm may theoretically limit LA's spread into BP, causing unwanted upper extremity paralysis.⁵ Positioning the needle tip over the ventral surface of SSM for SSPB is presumed to cause BP involvement as suggested by Drake et al. from their cadaveric dissection that showed posterior cord and radial nerve staining following methylene blue injection.³ Unfortunately, Sondekoppam et al. did not mention any BP involvement in their correspondence.¹ Given the possibility of BP involvement following SSPB from the previous approach, the author decided to inject LA beneath the epimysium of SSM.

It is reasonable that another approach by Tran et al. should instead be performed as it utilizes less volume of LA that is deposited beneath SSM and separated from BP, so then the likelihood of BP involvement would be far lower than the author's approach. Tran et al. performed such an approach merely to stain the anterior capsule of shoulder joint, not specifically targeting SSN and AN like the author did.² On his two lightly embalmed cadaveric shoulders, Tran et al. found that an amount of 3 ml dye could stain the main trunk of AN and articular branch of SSN. However, considering the anatomical variation of nerve branches, one should carefully implement this limited evidence on living subjects as no studies nor reports following said publication recommend the practice.² Nevertheless, due to the limited evidence of median nerve paralysis as a complication of SSPB, the author found patient's complete consent as lacking during the preoperative visit, resulting in patient's temporary disappointment when the unexpected event occurred.

Drake et al. were the first to show how partial BP involvement could occur as the dye might stain the posterior cord and radial nerve as it ran in the same plane where they deposited the injection. They found that the posterior cord of BP ran right on the medial side of subscapularis muscle-tendon junction at the anterior surface of the SSM, overlaid only by subcutaneous tissue.³ Apart from that, the implausibility of median nerve involvement was supported by its position, that was lateral from SSM myotendinous junction and far anterior to the axillary artery (AA). Nevertheless, throughout the extensive literature search, this report may be the first to address such an unusual complication of SSPB involving median nerve paralysis.

The first possible mechanism lies in the debatable presence of BP sheath expanding from the neck to the distal end of the axilla, as it is vital as a proposed mechanical barrier against unintentional spillage of LA from the adjacent interfascial plane block. The conflicting BP sheath anatomy may theoretically explain inadvertent LA spillage towards BP, voiding the likelihood of needle positioning failure as the

author had carefully observed needle tip under ultrasound followed by further normal saline hydrodissection to confirm its position beneath the fascia of SSM before injecting LA. The second aspect of the mechanism of SSPB involving BP paralysis is the volume of LA. There is no defined volume of LA needed for SSPB to completely cover AN and SSN other than what Sondekoppam et al. published, but many other fascial plane blocks were known to have a smaller volume to reduce unintended nerve blocks other than what was targeted.¹

The causes of median nerve paralysis following SSPB can only be hypothesized as there is an insufficient report regarding this complication. Theoretically, it has resulted from LA spillage towards BP from a large volume of LA injections and diffusion through adjacent thoracic structures. Despite its nature as self-limiting perioperative morbidity, the occurrence of BP paralysis may concern patients, in addition to increased length of stay and hospital costs. Further cadaveric and clinical studies are needed to determine the ideal LA technique and volume for SSPB without complicating PB paralysis.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

Published with the written consent of the patient. No external funding or other competing interests declared.

References

1. Sondekoppam RV, Lopera-Velasquez LM, Naik L, et al. Subscapularis and sub-omohyoid plane blocks: an alternative to peripheral nerve blocks for shoulder analgesia. Br J Anaesth. 2016;117:831–2.
2. Tran J, Agur A, Peng P. Deep plane to subscapularis approach for anterior shoulder analgesia: a tribute to Dr Darcy Price. Reg Anesth Pain Med. 2019;44:759–60.
3. Drake R, Vissa D, Johnson M, et al. Subscapularis plane block - a novel phrenic nerve sparing single injection shoulder block - an anatomical study. FASEB J. 2017;31:903–5.
4. Tran J, Peng PWH, Agur AMR. Anatomical study of the innervation of glenohumeral and acromioclavicular joint capsules: implications for image-guided intervention. Reg Anesth Pain Med. 2019;44:452–8.
5. Costabeber I, De Almeida GM, Becker M, et al. Brachial plexus cords: a morphological study. Rev Bras Anestesiol. 2010;60:614.



LETTER TO THE EDITOR

The anesthesiologist thoughts on medical residency in anesthesiology in Brazil



Dear Editor,

The significant role of the anesthesiologist in the management of critical patients has been comprehensively revealed during the COVID-19 pandemic. Theory and technical skills and leadership capacity became evident, showing the resourcefulness that distinguishes anesthesiologists.¹

However, recognition by peers, scientific societies, and patients is a recent fact, given the anesthesiologist is classically described as the unrecognized or even hidden “hero”,² and anesthetics is labelled by non-anesthesiologists as straightforward procedures, merely limited to delivering induction of amnesia and analgesia.²

In fact, the low-profile perception towards anesthesiology practice may result on one hand from the massive advance of the specialty observed in recent decades, leading to an extremely low incidence of anesthetic complications,³ and, on the other, from the almost exclusive dedication of anesthesiologists to perioperative medicine.

In 2010, the Helsinki Declaration on Patient Safety in Anesthesiology clearly stated the anesthesiologist's domains in the areas of anesthesia, intensive care, emergency, and pain.² As such, the resourcefulness of anesthesiologists has resulted not from the acquisition of new skills, but from the mere opportunity to apply already acquired knowledge.

Residency in anesthesiology is a training program that will make a general practitioner competent in the several domains previously described. Thus, institutions/hospitals establish training programs by defining the several skills and knowledge residents ought to master after training completion. Anesthesiology training programs differ from one country to another.⁴

Anesthesiology training in Brazil lasts a minimum of three years, comprising a 60-hour week schedule, and is regulated by the National Commission for Medical Residency (CNRM) with the scientific assistance of the Brazilian Society of Anesthesiology (SBA). The learning program includes the 54 key-point content the resident must master at the end of training.⁵ In total, Brazilian medical residents will have completed at least circa 9300 hours of practical training before being able to obtain the title of anesthesiology specialist.

The resident may choose to attend an extra training year in more specific areas of anesthesiology (fellowship) after completing the residency program, although the option is only available in a minority of training centers.

In comparison, in the European Union (EU), anesthesiology training lasts a minimum of five years⁶ with a schedule of 37 to 45 hours weekly, depending on the country.⁷ The resident will have to master the content established by the European Board and Section of Anesthesiology program, that includes 16 areas of knowledge divided into the four domains of activity of the anesthesiologist. A Portuguese medical resident, for example, ought to complete at least circa 10,400 hours of practical training (based on a 40-hour week schedule).⁸

In practice, the difference between Brazil and the EU regarding the duration of training is almost entirely explained by the fact that the weekly workload of a Brazilian medical resident is 50% greater than of an EU resident. Even though shortening program time allows for quick training of specialists, the heavy weekly workload may lead to greater fatigue and a predisposition to medical error.⁷

After critical analysis of the Brazilian and EU training programs one can realize that the major difference between them lies in the domain of intensive care and medical emergencies. The EU program contemplates the fact that acquisition of knowledge in these two areas is crucial for training residents. Indeed, training residents in these areas enables them to acquire not only important skills for the anesthesia management of critically ill patients, but also plays an important role in the early and late clinical management of the same patients.

A training program that encompasses intensive care and emergency enables the resident to have broader useful medical knowledge, impacts management of patients, and consolidates the fundamental role anesthesiologists can play in the intensive care and emergency units in Brazil. In practice, taking into consideration the number of weekly working hours, introducing these two areas of knowledge would result in a six-month increase in the duration of the Brazilian training program.

Finally, we would like to encourage a reflection on the Brazilian anesthesiology residency program. Considering the role that anesthesiologists may have in Brazil, the following issues should be addressed while elaborating a new curricular program: Should anesthesiology training be given “in bolus or continuous infusion”? Is the implementation of a

curriculum in the domains of intensive care and emergency relevant to training anesthesiologists? Should the duration of the anesthesiology training program be extended?

Declaration of Competing interest

The authors declare no conflicts of interest.

References

1. McCartney CJ, Mariano ER. COVID-19: bringing out the best in anesthesiologists and looking toward the future. *Reg Anesth Pain Med.* 2020;45:586–8.
2. Martin C, De Robertis E, De Hert S. The anaesthesiologist: the unsung hero of peri-operative intensive care. *Eur J Anaesthesiol.* 2019;36:387–9.
3. Mathis MR, Schonberger RB, Whitlock EL, Vogt KM, Lagorio JE, Jones KA, Conroy JM, Kheterpal S. Opportunities Beyond the Anesthesiology Department: broader Impact Through Broader Thinking. *Anesth Analg.* 2022;134:242–52.
4. Yamamoto S, Tanaka P, madsen MV, et al. Comparing anesthesiology residency training structure and requirements in seven different countries on three continents. *Cureus.* 2017;9:e1060.
5. Programa Teórico para Médicos em Especialização. Acessado a 23 de abril de 2022: <https://sbahq.org/programa-me/>.
6. European Training Requirements in anesthesiology. (2018). Acessado a 23 de abril de 2022: https://www.uems.eu/_data/assets/pdf_file/0003/64398/UEMS-2018.17-European-Training-Requirements-in-Anesthesiology.pdf.
7. Temple J. Resident duty hours around the globe: where are we now? *BMC Med Educ.* 2014;14 Suppl 1(Suppl 1):S8.
8. Regime Jurídico da formação médica especializada. (2018). Acessado: 23 de abril de 2022: <https://ordemdosmedicos.pt/wp-content/uploads/2015/05/0107701085.pdf>.

João S. Castedo  ^{a,*}, Vanessa Henriques Carvalho  ^b

^a Unidade Local de Saúde de Matosinhos (ULSM), Departamento de Anestesia, Matosinhos, Portugal

^b Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Departamento de Anestesiologia, Campinas, SP, Brazil

* Corresponding author.

E-mail: joaosercastedo@gmail.com (J.S. Castedo).

Received 19 May 2022; accepted 24 June 2022

Available online 30 July 2022



LETTER TO THE EDITOR

Factors associated with medical errors in perioperative anesthetic practice: cross-sectional study



Dear Editor,

Errors in anesthesia, mainly during drug administration, are significant and common, and have been repeatedly reported in the literature. However, even with improvement in the anesthetic technique and safety protocols, such errors still occur worldwide, and represent a serious health issue.

Anesthesiologists routinely choose, prepare, and administer potent medications in a brief span of time, and often the decision on which drug to use is made by just one anesthesiologist. Thus, the likelihood of an unintentional error is easily understandable, despite the high potential risk of irreparable harm to the patient.

Thereby, analysis of errors in intraoperative drug administration is of major relevance for patient well-being and safety. In view of the scenario, this study focused on understanding the factors related to anesthetic error in the state of Pará, Brazil, aiming to help establish processes and measures for patient protection and higher anesthetic safety.

This cross-sectional study is based on the analysis of a validated electronic questionnaire. The sample consisted of 90 anesthesiologists members of the Anesthesiology Society of the State of Pará (Saepa) in 2020. All anesthesiologists who were members of Saepa were included in the study, although physicians who had not paid their annual membership fee and/or who did not complete data fully and adequately were excluded.

Data were collected from the questionnaire based on Erdman et al., 2016¹ (Table 1), which explores demographic data and the anesthetic practice profile of the respondent.

Of the 90 respondents, 85.6% stated they had made a medication administration error. Among those who had made errors, most had occurred between one and five times (94.8%). The most common error was drug exchange (51.9%) followed by omission (23.4%). Fatigue was the most frequently reported error contributing factor (53.5%), followed by incorrect reading of the label/ ampoule (23.9%). Among the 77 professionals who reported medication errors, 60 administered drugs erroneously in the neuraxis.

Most anesthesiologists answered that there had been no harm to patients (61.0%). The morning shift revealed a higher incidence of severe errors (37.7%). The most severe errors occurred during anesthesia maintenance (54.5%). Concerning the time elapsed for error detection, 83.1% of the anesthesiologists reported that the error was immediately detected. Late error detection was reported in 12 cases (15.6%).

The study showed that most of the participant anesthesiologists had already made some type of error, although most of the reported errors resulted in minimal concerns and low morbidity for the patients. The deaths of two patient (2.6%) were related to medication errors.

Our findings agree with a study assessing Canadian anesthesiologists which revealed that 85.0% of them had already made some kind of error. Additionally, that study reported four deaths directly related to medication errors.² Another study carried out in India aimed to study medication errors reporting the events and preventive measures taken by anesthesiologists. It revealed that more than two thirds of respondents (75.6%, n = 740) experienced medication errors, and 7.7% (57) reported occurrence of severe morbidity and complications.³

The high workload of health professionals causes fatigue, making them more prone to cognitive process failure, leading to error and, consequently, a tendency to deal with errors individually. However, a more comprehensive analysis reveals hidden organizational and administrative conditions contributing to error which must be considered. Consequently, in handling with error one must also include process since the practitioner is the end of a chain and only a part of systematic failure. Thus, the greater effort of practitioners to avoid errors by themselves is not likely to succeed, as implementing more secure processes and systems are also required.

Therefore, prevention is the best method for treating medication errors,⁴ complying with the following measures: reading the medication label of vials or syringes carefully before preparing or injecting medication; improving vials and syringe labels regarding font, size, color, and information included; labeling syringes; avoiding, whenever possible, similar packaging and presentation of medications, which contribute to drug exchange error; dispensing medication in pre-filled syringes, instead of ampoules (for emergency or general use drugs), which should be prepared and

Table 1 Electronic questionnaire based on Erdman et al., 2016

1. How old are you? (years)
2. What is your gender? (Male/Female)
3. How long have you been practicing anesthesia (including residency)? (years)
4. How many hours do you practice weekly?
5. What is your level of specialization?
 - (A) Medical residency in progress
 - (B) Anesthesiologist (holds specialist title)
 - (C) Anesthesiology Title by the Brazilian Society of Anesthesiology (SBA)
6. Have you ever made a medication error? (Yes/No)
7. How many times did you make a medication error?
8. What kind of errors did you make?
 - (A) Omission (drug not administered/ forgotten)
 - (B) Drug repetition
 - (C) Wrong drug (administration of a drug other than the one prescribed).
 - (D) Wrong time (drug administered at wrong time)
 - (E) Wrong dosage (wrong concentration, amount, or rate of infusion)
9. Did any of the factors below contribute to the error?
 - (A) Distraction or fatigue
 - (B) Pressure to execute the procedure
 - (C) Misreading of the label/vial
 - (D) Lack of knowledge or experience with the drug
 - (E) Inadequate storage
 - (F) Wrong programming of the infusion pump
 - (G) Inadequate communication between anesthesiologists
 - (H) Others not specified
10. Have you incorrectly administered medication in the neuraxis? (Yes/No)
11. What was the worst outcome for your patient after your medication error?
 - (A) No harm (error did not result in change in anesthetic plane or increase in recovery time)
 - (B) Lower morbidity with reversible harm (increased time to tracheal extubation or postanesthetic recovery)
 - (C) Increased morbidity with reversible harm (invasive monitoring required for error correction)
 - (D) Increased morbidity with irreversible harm (myocardial infarction, cardiac arrest, or permanent neurological sequelae)
 - (E) Death
12. In which shift of the day did your most severe error occur?
 - (A) Morning
 - (B) Afternoon
 - (C) Night
 - (E) I don't remember
13. At what time of the perioperative period did your most severe error occur?
 - (A) In the preanesthetic period
 - (B) During induction of anesthesia (or early intraoperative period)
 - (C) During anesthesia maintenance
 - (D) During tracheal extubation (or just before tracheal extubation)
 - (E) In the postoperative period
14. How long did it take to detect your most severe error?
 - (A) Immediate detection
 - (B) Late detection
 - (C) Suspected, unconfirmed error

Source: Authors.

labeled by the anesthesiologist responsible for drug administration, avoiding drug repetition, omission, or incorrect dosage.⁵ Accordingly, medication errors related to practitioner fatigue will be minimized.

Despite its relevance, the study has limitations, as data compilation was strongly dependent on participants' memory and truthfulness. We therefore suggest that new studies focusing on the subject should be performed, examining medical and hospital documents to minimize the likelihood of biases.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Erdmann TR, Garcia JHS, Loureiro ML, Monteiro MP, Brunharo GM. Perfil de erros de administração de medicamentos em

- anestesia entre anestesiologistas catarinenses. Rev Bras Anestesiol. 2016;66:105–10.
2. Orser BA, Chen RJ, Yee DA. Medication errors in anesthetic practice: a survey of 687 practitioners. Can J Anaesth. 2001;48:139–46.
 3. Annie SJ, Thirilogasundary MR, Kumar VRH. Drug administration errors among anesthesiologists: The burden in India – A questionnaire-based survey. J Anaesthesiol Clin Pharmacol. 2019;35:220.
 4. Jensen L, Merry A, Webster C, Weller J, Larsson L. Evidence-based strategies for preventing drug administration errors during anaesthesia. Anaesthesia. 2004;59:493–504.
 5. Nanji KC, Merry AF, Shaikh SD, Pagel C, Deng H, Wahr JA, et al. Global PRoMiSe (Perioperative Recommendations for Medication Safety): protocol for a mixed-methods study. BMJ Open. 2020;10:1–8.

João Marcos do Oliveira Junior ^a, Lauro Ferreira dos Santos Neto  ^a, Tiago Braga Duarte  ^b, Bruno Mendes Carmona  ^b, Luís Vinícius Pires da Costa  ^a, Daniela Ferreira Tramontin  ^{a,*}, Deivid Ramos dos Santos  ^a, Lauriana Marques Corrêa  ^c

^a Universidade do Estado do Pará (UPEA), Belém, PA, Brazil

^b Universidade Federal do Pará (UFPA), Belém, PA, Brazil

^c Centro Universitário do Estado do Pará (CESUPA), Belém, PA, Brazil

* Corresponding author.

E-mail: danitramon@gmail.com (D.F. Tramontin).

Received 23 February 2022; accepted 2 July 2022

Available online 30 July 2022



LETTER TO THE EDITOR

Burnout risk among anesthesiology residents in Brazil during the second wave of COVID-19: a cross-sectional survey[☆]



Dear Editor,

Anesthesiology residents are historically at high risk of burnout syndrome,¹ and we hypothesized that the Coronavirus Disease 2019 (COVID-19) pandemic could worsen this scenario. Burnout is a global concern^{2,3} that could reduce residents' ability to cope with stress and is associated with other mental disorders.¹ We performed a study to determine the prevalence of burnout risk among anesthesiology residents in Brazil during the second wave of the COVID-19 pandemic. The secondary objective was to recognize factors that could correlate to the risk of developing burnout. Identifying these factors could lead to building more resilient training centers.

This survey-based nationwide cross-sectional observational study measured burnout risk among anesthesiology residents in Brazil using the Oldenburg Burnout Inventory (OLBI). We collected data through a multi-modal non-probability online survey using both river (social media) and panel (Brazilian Society of Anesthesiology's mailing list) sampling from January 12 to March 2, 2021. All three years of in-training anesthesiologists were invited to participate. Ethical approval was obtained from the institutional review board at Fundação ABC/FMABC before the study started (CAAE number 39505120.7.0000.0082). The study protocol and report followed the STROBE statement. The survey included the Oldenburg Burnout Inventory (OLBI) and 24 additional questions. OLBI's measurement was validated in order to quantify the risk of burnout based on two dimensions: exhaustion and disengagement. The cultural adaptation and validation of OLBI for the Brazilian population resulted in an instrument with 13 questions.⁴ We assumed that a proper cut-off to determine burnout risk should have clinical meaning. A relevant clinical relationship has been previously described by Peterson et al.,² who identified that values of OLBI beyond their national validation mean could prospectively predict future long-term sickness absence. In

parallel, we used the national mean of OLBI as cut-off, as determined by the Brazilian validation. The mean scores found in the Brazilian validation study were 2.33 for exhaustion and 2.4 for disengagement.⁴ Thus, the OLBI's cut-off level 4.73 was defined by adding both dimensions' means. Residents were considered "at-risk" of developing burnout when their score was beyond 4.73, while scores simultaneously beyond the mean for exhaustion and disengagement defined "high risk" of burnout. The following 24 questions of the survey were designed to potentially define factors correlated with the risk of burnout. We tried to minimize sampling bias by inviting residents through methods that allowed participation from all country regions. Lack of validation of the correlation questions was minimized by the input of variables from previous burnout literature. Since the answers relied on a non-probabilistic sampling method, no statistical power calculation was determined. Standard descriptive statistics were used to summarize the results. Baseline characteristics were compared to the target population with a two-sample test of proportion. All 24 correlation questions were analyzed by two logistic regressions, one with the binary outcome "at-risk" and the other with the binary outcome "high risk" of burnout. Significant results from those regressions were included in a final multiple linear regression model with the OLBI score as the dependent variable. Beta coefficients were calculated to standardize the correlations. Beta coefficients above or equal to 0.2 were considered to determine the strength of correlation as moderate to strong, while we assumed values below 0.2 as weaker correlations. Semipartial coefficients of determination were calculated to determine the percentage of association between the OLBI score and each potential predictor. Statistical significance was considered at the level of 0.05 for two-sided hypothesis testing, and confidence intervals were set at 95%. Data were analyzed with STATA 17.0 (StataCorp, 2021). Participants who did not complete all forms were excluded from the analysis.

Answers were completed by 205 participants. The survey completion rate was 91.5%, given that 224 guests signed the e-consent, and the response rate was 9.3%, considering a target population of 2205 residents. The age of participants was 29.9 ± 3.12 . Assuming an equal distribution of residents by training year in the target population (33%), there was no significant difference from our sample. Female participants accounted for 107 (52.2%) residents. All regions of Brazil were represented with a similar proportion to the residents'

[☆] Institutional Research Board Certificate of Ethical Approval: 39505120.7.0000.0082. Study registry: ISRCTN61736991

Table 1 Multiple linear regression for total OBLI score as the dependent variable.

Covariates		n (%)	Mean±SD	OBLI score (Mean±SD)	β	Coef. (95% CI)	Semipartial R ²	p-value
Access to COVID-19 tests through the residency program	Yes	119 (58.0%)	5.06±0.92	5.61±0.86	-0.27	-0.52 (-0.74 to -0.29)	0.072	<0.001 ^a
	No	86 (42.0%)	5.61±0.86					
Alcohol consumption	Yes	159 (77.6%)	5.17±0.93	5.70±0.84	-0.22	-0.49 (-0.75 to -0.29)	0.044	<0.001 ^a
	No	46 (22.4%)	5.70±0.84					
Institutional COVID-19 prevention protocol	Yes	157 (76.6%)	5.16±0.91	5.70±0.91	-0.19	-0.43 (-0.69 to -0.17)	0.037	0.001 ^a
	No	48 (23.4%)	5.70±0.91					
Age		29.9 ±3.12	5.29±0.93		-0.18	-0.05 (-0.09 to -0.01)	0.027	0.005 ^a
Relocation to COVID-19 ICU/ward	Yes	90 (43.9%)	5.26±0.93	5.31±0.95	-0.15	-0.29 (-0.52 to -0.06)	0.020	<0.001 ^a
	No	115 (56.1%)	5.31±0.95					
Year of residency	1	87 (42.4%)	5.23±0.90					
	2	70 (34.1%)	5.31±0.99	0.05	0.97 (-0.15 to 0.35)	0.002	0.446	
	3	48 (23.4%)	5.36±0.92		0.11	0.26 (-0.02 to -0.54)	0.011	0.071
Felt coerced or pushed to assist patients with COVID-19	Yes	99 (48.3%)	5.52±0.85	0.18	0.33 (0.10–0.56)	0.028	0.005 ^a	
	No	106 (51.7%)	5.08±0.97					
Considered abandoning the anesthesiology training due to the pandemic	Yes	49 (23.9%)	5.78±0.90	0.29	0.64 (0.38–0.90)	0.080	<0.001 ^a	
	No	156 (76.1%)	5.14±0.89					

Number of observations: 205; R² = 0.334; F=10.90; p < 0.0001.

β , Beta coefficient represents standardized correlations; $\beta \geq 0.2$ determined moderate to strong correlation. Coef, Regression Coefficient; 95% CI, 95% Confidence Intervals; Semipartial R², represents the proportion of variance in OBLI score that a single variable can explain.

^a p-value < 0.05.

in-training national distribution, except for a higher proportion in the Southeast region (73.2% in a target population of 61.9%). The prevalence of anesthesiology residents at-risk of developing burnout was 73.2%, while it was 57.1% for high risk. During the outbreak of the COVID-19 pandemic, data collected from medical residents in Brazil by Mendonça et al.⁵ showed a 48.6% risk of developing burnout. Compared to our result of 73.2%, it is possible that anesthesiology residents could possibly be at higher risk of burnout than other medical residents in Brazil. While regarding high risk, a study conducted among Brazilian anesthesiology residents in 2018 showed that 29.72% of participants were at high risk of developing burnout.¹ Compared to our observation of 57.1%, an increase in the high risk of developing burnout in anesthesiology residents during the COVID-19 pandemic could be assumed.

Access to diagnostic testing of COVID-19 provided by the residency program was the most important protective factor against burnout risk (Table 1), accounting for 7.2% of its variance. On the other direction, having considered abandoning the anesthesiology training due to the pandemic was the main contributor to burnout risk (Table 1), accounting for 8% of OBLI variation. Such characteristic was also observed among neurosurgery residents in the USA.³ It is likely that the desire to quit anesthesiology training should signal the need for support.

Interpretation of these results should consider that the non-probabilistic sampling could compromise generalizability. A low response rate could imply high non-response bias, although the population demographic was similar to the

target population in most possible comparisons. Also, the lack of validation of the correlation questions could represent imprecision in participants' answers.

In conclusion, anesthesiology residents' risk of burnout in Brazil during the second wave of the COVID-19 pandemic was critical. Providing access to COVID-19 testing was correlated with protection, whereas the desire to quit training was associated with increased risk. Acknowledging the high prevalence and factors related to burnout risk could support training centers' decision-making.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Govêia CS, Cruz TTM, Miranda DB, et al. Associação entre síndrome de burnout e ansiedade em residentes e anestesiologistas do Distrito Federal. Braz J Anesthesiol. 2018;68:442–6.

2. Peterson U, Bergström G, Demerouti E, et al. Burnout Levels and self-rated health prospectively predict future long-term sickness absence: a study among female health professionals. *J Occup Environ Med.* 2011;53:788–93.
3. Khalafallah AM, Lam S, Gami A, et al. A national survey on the impact of the COVID-19 pandemic upon burnout and career satisfaction among neurosurgery residents. *J Clin Neurosci.* 2020;80:137–42.
4. Schuster MS, Dias VV. Oldenburg Burnout Inventory – validação de uma nova forma de mensurar Burnout no Brasil. *Cien Saude Colet.* 2018;23:553–62.
5. Mendonça VS, Steil A, Góis AFT. Mental health and the COVID-19 pandemic: a study of medical residency training over the years. *Clinics (Sao Paulo).* 2021;76:e2907.

Natanael Pietroski dos Santos *, Luisa Emanuela Biseo Henriques , Rafael Pivovar De Camargo Rosa , Rebecca Midory Marques Monteiro , Rafael Vicente Sanches Gonçalves , José Carlos Canga , Desiré Carlos Callegari , Esther Alessandra Rocha 

CET Integrado da Faculdade de Medicina do ABC, Santo André, SP, Brazil

* Corresponding author.

E-mail: pietroski@gmail.com (N. Pietroski dos Santos).

Received 5 October 2021; accepted 3 August 2022

Available online 12 August 2022

BJAN

Brazilian Journal of Anesthesiology

Contact us

✉ editor.bjan@sbahq.org

🌐 www.bjan-sba.org

📞 +55 21 979 770 024