BJAN

Vol. 74, N. 5 | Sep-Oct 2024 | ISSN 0104-0014

bjan-sba.org

ELSEVIER

BJAN
Brazilian Journal of Anesthesiology

Brazilian Journal of ANESTHESIOLOGY

Pediatric Anesthesia



Brazilian Journal of Anesthesiology

Vol. 74 N. 5 | September/October 2024

SciELO

SBA Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

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

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

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

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

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

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

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

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

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

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

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

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

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

69°CBA

BRAZILIAN CONGRESS
OF ANESTHESIOLOGY

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

November 13-16

MINAS CENTRO
BELO HORIZONTE, MG

Organization
SBA Brazilian Society of Anesthesiology



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

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

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

MORE INFO: WWW.CBA2024.COM.BR

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

ISSN 0104-0014 • Volume 74 • Number 5 • September—October 2024

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

Editorial

844544 **Mind the gap between low- and middle-income countries (LMICs) and high-income countries (HICs): fostering pediatric anesthesia globally**
Vinícius Caldeira Quintão, Ricardo Vieira Carlos, Gabriel Soares de Sousa, and Maria José Carvalho Carmona

844535 **Advancing pediatric anesthesia in Brazil: reflections on research and education**
Norma Sueli Pinheiro Módolo, Débora de Oliveira Cumino, Luciana Cavalcanti Lima, and Guilherme Antonio Moreira de Barros

844525 **Challenges of organizing pediatric anesthesia in low and middle-income countries**
Anelise Schifino Wolmeister, Tom G. Hansen, and Thomas Engelhardt

Original Investigations

744380 **Efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric laparoscopic surgery: a randomized clinical trial**
Seham Mohamed Moeen, Ola Mahmoud Wahba, Ahmed Mohamed Mandour, Noha Abdel Ghany, Mohamed AbdelKader Osman, Tarek Abdelazeem Sabra, Mohammed Hamada Takrouney, and Ahmed Mohamed Moeen

744178 **Comparison of the lateral sagittal and costoclavicular approaches for ultrasound-guided infraclavicular block in pediatric patients: a prospective randomized study**
Ahmet Murat Yayik, Sevim Cesur, Figen Ozturk, Erkan Cem Celik, Muhammet Emin Naldan, and Ali Ahiskalioglu

744114 **Pediatric emergence delirium is linked to increased early postoperative negative behavior within two weeks after adenoidectomy: an observational study**
Anne Houben, Shahab Ghamari, Andreas Fischer, Claudia Neumann, Torsten Baehner, and Richard K. Ellerkmann

844541 **Preoperative gastric volume assessment using ultrasound in cerebral palsy pediatric patients: a prospective observational study**
Jiwon Han, Hyo-Seok Na, Seihee Min, and Hyun-Jung Shin

844540 **Pediatric Early Warning Score (PEWS) in predicting prognosis of critical pediatric trauma patients: a retrospective study**
Abdulrahman Özel, Ulkem Kocoglu Barlas, Servet Yüce, Cansu Günerhan, and Meltem Erol

744169 **Using the Perfusion Index to predict changes in the depth of anesthesia in children compared with the A-line Autoregression Index: an observational study**
Hala Saad Abdel-Ghaffar, Amani Hassan Abdel-Wahab, and Mohammed Mahmoud Roushdy

744261 **End-tidal carbon dioxide measurements as a surrogate to arterial carbon dioxide during pediatric laparoscopic surgeries: a prospective observational cohort study**
Hala Saad Abdel-Ghaffar, Mohammed Abdel-Moneim Bakr, Mohamed Abdel-Kadr Osman, Sarah George Labib Hanna, and Wesam Nashat Ali

744443 **Posterior transversus abdominis plane block versus lateral quadratus lumborum block in children undergoing open orchiopexy: a randomized clinical trial**
Özgecan P. Zanbak Mutlu, Ayşe Ç. Tütüncü, Pınar Kendigelen, and Beril Kara Esen

844533 **Virtual parental presence with coaching for reducing preoperative anxiety in children: a feasibility and pilot randomized controlled trial**
Clyde T. Matava, Martina Bordini, Ben O' Sullivan, Gabriela Alcaraz Garcia-Tejedor, Nan Gai, Guy Petroz, Conor Mc Donnell, Fahad Alam, Katie Brazel, and Monica Caldeira-Kulbakas

844548 **Effectiveness of intracuff alkalinized lidocaine associated with intravenous dexamethasone in reducing laryngotracheal morbidity in children undergoing general anesthesia for tonsillectomy: a randomized controlled trial**
Morenna Ramos e Oliveira, Norma S.P. Modolo, Paulo Nascimento Jr., Rodrigo M. Lima, Devin Stirling, Glenio B. Mizubuti, Leopoldo Muniz da Silva, and Lais H. Navarro

Review Articles

844519 **An update on the mechanisms and risk factors for anesthesia-related cardiac arrest in children: a narrative review**
Leandro Gobbo Braz, Jose Reinaldo Cerqueira Braz, Teofilo Augusto Araújo Tiradentes, Daniela de Sa Menezes Porto, Cristiano Martins Beserra, Luiz Antonio Vane, Paulo do Nascimento Junior, Norma Sueli Pinheiro Modolo, and Mariana Gobbo Braz

844520 **Comparison of intranasal dexmedetomidine versus oral midazolam for premedication in pediatric patients: an updated meta-analysis with trial-sequential analysis**
Eduardo Maia Martins Pereira, Tatiana Souza do Nascimento, Mariana Gaya da Costa, Eric Slawka, and Carlos Galhardo Júnior

844543 **The effect of nalbuphine on prevention of emergence delirium in children: a systematic review with meta-analysis**
Ka Ting Ng, Wei En Lim, Wan Yi Teoh, and Mohd Fitry Bin Zainal Abidin

Case Reports

744368 **Real-time ultrasound-guided epidural catheter placement in infants: a case series**
Manoj Kamal, Mritunjay Kumar, Pooja Bihani, Tanya Mital, Geeta Singariya, and Pradeep Bhatia

744233 **Ultrasound-guided popliteal sciatic nerve block in a pediatric patient with complex regional pain syndrome: a case report**
Patrícia Milena Souza Vinent, Eduardo José Silva Gomes de Oliveira, Caio Márcio Barros de Oliveira, Ed Carlos Rey Moura, Elizabeth Teixeira Noguera Servin, Lyvia Maria Rodrigues de Sousa Gomes, and Plinio da Cunha Leal

744339 **Transfusion-related acute lung injury and treatment with high-flow oxygen therapy in a pediatric patient: a case report**
Cengiz Sahutoglu, Cansu Balci, and Taner Balcioglu

Letters to the Editor

844521 **Development and evaluation of an educational comic leaflet for pediatric anesthesia care**
Fabiano Soares Carneiro, Juliana Lacerda de Oliveira Campos, Stephanie Bruna Camilo Soares de Brito, Flávia Marques de Melo, and Eliane Cristina de Souza Soares

844546 **The effect of gestational age on short- and long-term complications following primary esophageal atresia repair**
Mathias Johansen, Samuel Wasserman, Dan Poenaru, Jean Martin Laberge, Sam J. Daniel, and Thomas Engelhardt

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



EDITORIAL

Mind the gap between low- and middle-income countries (LMICs) and high-income countries (HICs): fostering pediatric anesthesia globally



Pediatric anesthesia is a critical specialty within the broader field of anesthesiology, essential for ensuring the safety and effectiveness of surgical and procedural care for children. This domain is distinguished by its unique challenges and complexities, demanding specialized training and a profound understanding of pediatric physiology and pharmacology. Despite its importance, there are significant disparities in the training and practice of pediatric anesthesia, especially between low- and middle-income countries (LMICs) and high-income countries (HICs),[1] and addressing them is crucial to improve global pediatric care and its outcomes.

The practice of pediatric anesthesia requires an intricate approach due to the physiological differences between children and adults. Children's anatomical and physiological characteristics, such as their airway size, cardiovascular function, and metabolic rate, need tailored anesthetic techniques and drug dosages.[2] Additionally, pediatric patients often have distinct psychological needs, which can impact their response to anesthesia and their overall perioperative experience.[3]

Inadequate training in pediatric anesthesia can lead to significant challenges. Insufficient exposure and education during residency may contribute to the discomfort and uncertainty anesthesiologists might feel when managing pediatric cases. This lack of confidence can compromise patient safety and the effectiveness of anesthesia, particularly in high-complexity scenarios involving critically ill or high-risk pediatric patients.

The disparity between LMICs and HICs training in pediatric anesthesia is significant. In many LMICs, such as Brazil, pediatric anesthesia is not recognized as a formal subspecialty.[4,5] Medical residency programs in these countries are often shorter when compared to most HICs, with limited time dedicated to pediatric anesthesia. Módolo et al. highlight that in Brazil, for instance, the relatively short duration of residency programs results in limited training focused on pediatric anesthesia, often confined to the third year of residency.[4] This shortfall in training can severely impact the quality of care provided to pediatric patients, posing significant risks to their safety and the efficacy of surgical procedures.

In contrast, many HICs have established longer and more specialized training programs that provide a comprehensive education in pediatric anesthesia.[6] These programs are designed to cover all aspects of pediatric anesthesiology, ensuring that practitioners are well-prepared to manage children's unique needs. They not only enhance the proficiency of anesthesiologists but also contribute to better perioperative outcomes for pediatric patients. As a valuable educational tool, Braz et al. presented an update on the mechanisms and risk factors of anesthesia-related cardiac arrest in pediatric surgical patients in countries with different human development indexes and over time. This study promotes a better understanding of these events and differences between countries.[7]

Recent advancements in pediatric anesthesia have brought significant improvements in practice. Innovations in techniques and approaches have enhanced the safety and effectiveness of pediatric anesthetic care. For instance, Abdel-Chaffar et al. analyzed the relationship between $EtCO_2$ and $PaCO_2$ over time in elective pediatric laparoscopic surgeries to maintain normocapnia in children. However, they found that capnography as a trend monitor in pediatric laparoscopic surgeries may not reliably indicate $PaCO_2$ levels, highlighting the need for further research into noninvasive monitoring of $PaCO_2$.[8] In this special issue, Oliveira et al. demonstrated that the use of intracuff lidocaine associated with intravenous dexamethasone can be effective in reducing sore throat 24 hours after tonsillectomy and adenoidectomy when compared to the use of air to inflate the cuff.[9]

Another area of advancement is regional anesthesia. Peripheral nerve blocking in children is recently growing in evidence. Kamal et al. demonstrated the efficacy of real-

https://doi.org/10.1016/j.bjane.2024.844544
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

time ultrasound-guided epidural catheter placement in infants.[10] This technique allows for more precise placement of epidural catheters, which can improve pain management and procedural outcomes in young patients. Still, deciding which block is most effective in specific surgical scenarios can be challenging. Mutlu et al. compared the posterior transversus abdominis plane block versus lateral quadratus lumborum block in children undergoing open orchiopexy, offering more insight into pain management in this frequently performed surgery.[11] Yayik et al. showed that the costoclavicular approach to the brachial plexus is as effective as the lateral sagittal approach, with the advantage of shorter time to perform the block.[12] Similarly, Vinent et al. explored the use of ultrasound-guided nerve blocks in pediatric patients with complex regional pain syndrome, showcasing how technological advancements can improve pain management and overall patient outcomes.[13]

Another important progress is the comparison of premedication strategies. Pereira et al. conducted a comprehensive meta-analysis comparing intranasal dexmedetomidine and oral midazolam for premedication in pediatric patients.[14] Their findings provide valuable insights into which premedication method may offer better efficacy and safety, thereby helping refine preoperative practices and reduce anxiety in pediatric patients. Another innovative approach to reducing anxiety examined the feasibility of the virtual presence of parents during anesthetic induction. This method has been shown to significantly reduce preoperative anxiety, offering a new possibility to add comfort for pediatric patients.[15] Following the same reasoning, Carneiro et al. showed that information prior to surgery regarding the anesthetic act may be well accepted by children and caregivers when presented as a comic strip leaflet.[16] Still looking for a better patient experience, Ng et al. presented a meta-analysis in which the administration of nalbuphine is associated with a significant decrease in the incidence of emergence delirium and postoperative pain scores among children undergoing surgery.[17]

The role of advanced techniques in pediatric anesthesia is further highlighted by Sahutoglu et al., who reported on the management of transfusion-related acute lung injury using high-flow oxygen therapy in a pediatric patient.[18] This case underscores the importance of innovative solutions in addressing complex clinical scenarios that can arise during pediatric anesthesia. Han et al. also contributed to the field by investigating preoperative gastric volume assessment using ultrasound in cerebral palsy pediatric patients, offering new insights into optimizing preoperative care.[19] In the same way, Abdel-Ghaffar et al. evaluated the perfusion index derived from pulse oximetry as a tool for assessing anesthetic depth in comparison with the index derived from evoked potentials, demonstrating possible new use for an already known parameter.[20]

To bridge the gap in pediatric anesthesia training, it is essential to adopt a global perspective and address systemic challenges. Mumphansha et al. explored the influence of power and privilege in pediatric anesthesia, showing these factors can affect training opportunities and access to advanced care.[21] Their analysis highlights the need for more equitable distribution of resources and training opportunities to make sure all practitioners, regardless of their location, have access to high-quality education and support.

Matava and Kurth provide valuable insights into global perspectives on pediatric anesthesia, emphasizing the importance of international collaboration and knowledge exchange.[6] Their editorial highlights the benefits of integrating best practices from HICs and adapting them to the local context in LMICs. By fostering international partnerships, LMICs can enhance their training programs, improve care quality, and ultimately achieve better perioperative outcomes for pediatric patients. Similarly, Johansen et al. carried out a retrospective study that analyzed the impact of gestational age on gastroesophageal and respiratory complications. In addition to suggesting that gastrointestinal complications might be related to gestational age, they also propose that multicenter collaborations are essential for this type of condition.[22]

The role of international collaborations is crucial in addressing the disparities in pediatric anesthesia training. Sharing expertise, resources, and experiences across borders can help develop standardized guidelines and protocols that improve the overall quality of pediatric anesthesia care. These collaborations, especially observational and pragmatic studies, can also facilitate the exchange of innovative techniques and approaches, further advancing in the field and enhancing patient safety.

To effectively bridge the gap in pediatric anesthesia training and practice, several strategies should be implemented. First, developing and implementing comprehensive, specialized training programs for pediatric anesthesia is essential. These programs should offer extensive hands-on experience and exposure to a variety of pediatric cases, ensuring that practitioners are well-prepared to manage complex scenarios.

Second, fostering international collaborations and partnerships, especially between HICs and LMICs, can play a pivotal role in improving pediatric anesthesia training. By sharing knowledge, resources, and best practices, anesthesiologists from different regions can learn from each other and adopt effective strategies to enhance their own training programs and clinical practices.

Third, investing in research and innovation is crucial for advancing pediatric anesthesia practices, given that there is relatively less innovation in pediatric anesthesia compared to adult medicine. Continued research can provide valuable insights into new techniques, technologies, and approaches that can improve patient outcomes and safety. Encouraging and supporting research initiatives in both HICs and LMICs can help drive progress and address the challenges faced in pediatric anesthesia. As an example, Özel et al. study on the Pediatric Early Warning Score (PEWS) highlights the potential for predictive tools to improve the prognosis of critical pediatric trauma patients, furthering this research agenda.[23]

This Pediatrics Special Issue of the *Brazilian Journal of Anesthesiology* serves as an important platform for addressing the current state of pediatric anesthesia training and practice, particularly in LMICs. This issue brings together a diverse collection of articles that highlight advances, challenges, and needs within the field. By promoting comprehensive discussions and offering valuable insights, it aims to contribute to the improvement of pediatric anesthesia training and practice.

The articles featured in this edition provide a broad perspective on the state of pediatric anesthesia, ranging from innovative techniques and approaches to systemic challenges and global perspectives. These contributions are instrumental in advancing the field and addressing the disparities that exist between LMICs and HICs.

In conclusion, addressing the disparities in pediatric anesthesia training and practice is crucial for ensuring the safety and well-being of pediatric patients. Developing specialized training programs, fostering international collaborations, and investing in research and innovation are essential steps in enhancing the quality of pediatric anesthesia care. By bridging the gap between low- and middle-income countries and high-income countries, we can improve perioperative outcomes and guarantee that children worldwide receive the highest standard of care. The ongoing efforts to advance pediatric anesthesia, as highlighted in this special issue of the *Brazilian Journal of Anesthesiology*, are vital for achieving these goals. Through continued collaboration, research, and the implementation of best practices, the field of pediatric anesthesia can evolve to meet the needs of patients across the globe and improve the overall quality of care for children.

Declaration of competing interest

Vinícius Caldeira Quintão and Maria José Carvalho Carmona serve as Associate Editors of the Brazilian Journal of Anesthesiology. The other authors declare no conflicts of interest.

References

1. Schifino Wolmeister A, Hansen TG. Engelhardt T. Challenges of organizing pediatric anesthesia in low and middle-income countries. Braz J Anesthesiol. 2024;74:844525.
2. Moeen SM, Wahba OM, Mandour AM, et al. Efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric laparoscopic surgery: a randomized clinical trial. Braz J Anesthesiol. 2022;74:744380.
3. Houben A, Ghamari S, Fischer A, Neumann C, Baehner T, Ellerkmann RK. Pediatric emergence delirium is linked to increased early postoperative negative behavior within two weeks after adenoidectomy: an observational study. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.03.008. Online ahead of print.
4. Módolo NSP, Cumino D de O, Lima LC, Barros GAM. Advancing pediatric anesthesia in Brazil: reflections on research and education. Braz J Anesthesiol. 2024;74:844535.
5. Quintão VC, Concha M, Argüello LAS, Cavallieri S, Cortinez LI, de Sousa GS, et al. Pediatric anesthesiology in Brazil, Chile, and Mexico. Paediatr Anaesth. 2024. https://doi.org/10.1111/pan.14886. Online ahead of print.
6. Matava CT, Kurth D. Global perspectives on pediatric anesthesia. Paediatr Anaesth. 2024. https://doi.org/10.1111/pan.14956. Online ahead of print.
7. Braz LG, Braz JRC, Tiradentes TAA, et al. An update on the mechanisms and risk factors for anesthesia-related cardiac arrest in children: a narrative review. Braz J Anesthesiol. 2024;74:844519.
8. Abdel-Ghaffar HS, Bakr MAM, Osman MAK, Hanna SGL, Ali WN. End-tidal carbon dioxide measurements as a surrogate to arterial carbon dioxide during pediatric laparoscopic surgeries: a prospective observational cohort study. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.07.036. Online ahead of print.
9. Oliveira M, Lima R, Modolo NS, et al. Effectiveness of intracuff alkalinized lidocaine associated with intravenous dexamethasone in reducing laryngotracheal morbidity in children undergoing tonsillectomy: randomized clinical trial. Braz J Anesthesiol. 2024;74.
10. Kamal M, Kumar M, Bihani P, Mital T, Singariya G, Bhatia P. Real-time ultrasound-guided epidural catheter placement in infants: a case series. Braz J Anesthesiol. 2022. https://doi.org/10.1016/j.bjane.2022.03.004. Online ahead of print.
11. Mutlu ÖPZ, Tütüncü AÇ, Kendigelen P, Kara Esen B. Posterior transversus abdominis plane block versus lateral quadratus lumborum block in children undergoing open orchiopexy: a randomized clinical trial. Braz J Anesthesiol. 2023;74:744443.
12. Yayik AM, Cesur S, Ozturk F, Celik EC, Naldan ME, Ahiskalioglu A. Comparison of the lateral sagittal and costoclavicular approaches for ultrasound-guided infraclavicular block in pediatric patients: a prospective randomized study. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.05.005. Online ahead of print.
13. Vinent PMS, Oliveira EJSG, Oliveira CMB, et al. Ultrasound-guided popliteal sciatic nerve block in a pediatric patient with complex regional pain syndrome: a case report. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.07.012. Online ahead of print.
14. Pereira EMM, Nascimento TS do, da Costa MG, Slawka E, Júnior CG. Comparison of intranasal dexmedetomidine versus oral midazolam for premedication in pediatric patients: an updated meta-analysis with trial-sequential analysis. Braz J Anesthesiol. 2024;74:844520.
15. Matava CT, Bordini M, Sullivan BO, et al. Virtual parental presence with coaching for reducing preoperative anxiety in children: a feasibility and pilot randomized controlled trial. Braz J Anesthesiol. 2024;74:844533.
16. Carneiro FS, Campos JL de O, Brito SBCS de, Melo FM de. Soares EC de S. Development and evaluation of an educational comic leaflet for pediatric anesthesia care. Braz J Anesthesiol. 2024;74:844521.
17. Ka Ting Ng, Wei En Lim, Wan Yi Teoh, Abidin Mohd Fitry Bin Zainal. The effect of nalbuphine on prevention of emergence delirium in children: a systematic review with meta-analysis. Braz J Anesthesiol. 2024;74:844543.
18. Sahutoglu C, Balci C, Balcioglu T. Transfusion-related acute lung injury and treatment with high-flow oxygen therapy in a pediatric patient: a case report. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.12.001. Online ahead of print.
19. Han J, Na HS, Min S, Shin HJ. Preoperative gastric volume assessment using ultrasound in cerebral palsy pediatric patients: A prospective observational study. Braz J Anesthesiol. 2024. https://doi.org/10.1016/j.bjane.2024.844541. Online ahead of print.
20. Abdel-Ghaffar HS, Abdel-Wahab AH, Roushdy MM. Using the Perfusion Index to predict changes in the depth of anesthesia in children compared with the A-line Autoregression Index: an observational study. Braz J Anesthesiol. 2021. https://doi.org/10.1016/j.bjane.2021.04.030. Online ahead of print.
21. Mumphansha H, Bould MD, Asnake BM. Power and privilege in pediatric anesthesia. Paediatr Anaesth. 2024. https://doi.org/10.1111/pan.14957. Online ahead of print.
22. Johansen M, Wasserman S, Poenaru P, Laberge JM, Daniel S, Engelhardt T. The effect of gestational age on short- and long-term complications following primary esophageal atresia repair. Braz J Anesthesiol. 2024;74.
23. Özel A, Barlas UK, Yüce S, Günerhan C, Erol M. Pediatric Early Warning Score (PEWS) in predicting prognosis of critical pediatric trauma patients: a retrospective study. Braz J Anesthesiol. 2024;74:844540.

Vinícius Caldeira Quintão [a,b,*], Ricardo Vieira Carlos[a,b], Gabriel Soares de Sousa[a,b], Maria José Carvalho Carmona[b]

[a] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Instituto da Criança e do Adolescente, São Paulo, Brazil*

[b] *Universidade de São Paulo, Faculdade de Medicina (FMUSP), Disciplina de Anestesiologia, São Paulo, SP, Brazil*

[*] Corresponding author.
E-mail: vinicius.quintao@hc.fm.usp.br (V.C. Quintão).

Brazilian Journal of Anesthesiology 2024;74(5): 844535



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Advancing pediatric anesthesia in Brazil: reflections on research and education



Conducting research is a complex task. In pediatrics, in particular, there are obstacles that further complicate its execution, considering that the pediatric population presents particularities in physiology and development that, consequently, are reflected in pharmacodynamics and pharmacokinetics.[1-4] In addition to the fact that a child is not a miniature adult, there are other difficulties that include and surpass regulatory issues and impose restrictions on studies.[1]

There are technical aspects that hinder the recruitment of children, such as the small number of individuals with serious medical problems that justify the conduction of specific studies, the need for appropriate outcome evaluation for different ages, and the required adaptations in procedures and research environments to accommodate different levels of physical, cognitive, and emotional development. There are also few researchers specialized in various areas of pediatrics, with the knowledge and qualifications necessary to carry out age-appropriate procedures for participants. It is worth noting that there is limited infrastructure in research centers, including the limited availability of materials, equipment, and techniques, such as the use of small volumes in sample tests and the availability of validated monitors for children.[5]

Research in children also involves highly relevant ethical issues, which can be grouped into two dimensions: morality and legality.[6] Ethical regulations in research were created to guide researchers' conduct and protect research subjects. These regulations were implemented in response to research involving children with intentional exposure to risks, without any benefit or clarification of potential unfavorable outcomes to their guardians. Thus, the primary objective of regulations is the protection of research participants, especially those belonging to vulnerable populations, such as children.[4]

The first international regulation created was the Nuremberg Code in 1947, in response to the research conducted in concentration camps. This was followed by the Declaration of Helsinki in 1964, which made it possible for vulnerable individuals to participate, provided their legal representative gave official consent. In 1993, the International Ethical Guidelines for Biomedical Research Involving Human Subjects were published, mandating the attainment of informed consent from all research participants and regulating risk-benefit evaluation, data confidentiality, and ethical and scientific review by committees.[6,7]

In Brazil, Resolution 196/1996 of the National Health Council regulated research involving human subjects and referred to children as a vulnerable population. This was repealed and replaced by Resolution 466/2012, which emphasizes the need for research to adhere to the principles of autonomy, beneficence, nonmaleficence, justice, and equity. Thus, the risks to which children may be subjected to as research subjects must be well defined and clearly communicated to their legal guardians and to the children themselves if they have sufficient cognitive development. The Research Ethics Committee must rigorously evaluate protocols involving children, including the requirement of obtaining the Assent Term from the participating child.[6,8]

On the other hand, children are considered therapeutic orphans due to the lack of drugs developed for this age group and the absence of age-appropriate formulations and administration routes that allow for accurate, safe, and palatable use. Specific research in pediatrics is needed because it is difficult to predict the ideal dose, route of administration, absorption, metabolism, elimination, and toxicity, among other characteristics of a drug, before conducting the first clinical trial.[1-5] However, there has always been a preference for recruiting adult participants in research.[2,9]

For these reasons, many techniques and drugs used in daily pediatric practice are off-label.[10] There is little financial interest from the pharmaceutical industry in developing medications for the pediatric age group because, unlike adults, children are mostly healthy, with diseases that can be controlled by inexpensive medications. Additionally, they require greater monitoring and more individuals involved in research, implying higher costs, and if the result is unfavorable, the repercussions will be negative and there is a risk of

https://doi.org/10.1016/j.bjane.2024.844535
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

legal proceedings. If there is a need to repair harm, this will take much longer than in research recruiting adults.[3,5]

At the time of recruitment, legal representatives need to be convinced that the benefits outweigh the risks, and many of them feel uncomfortable allowing participation in the research. For children who have a greater understanding, the Assent Form must also be obtained and explained in simple and easily understandable language.[8] Other factors that negatively impact recruitment include the fear of needles, blood collection, the taste of the medication, and the disruption of normal activities, such as attending school.[3]

We need to discipline ourselves to see things from various perspectives. It is necessary to understand all sides of the issue when admitting, or not, the use of off-label drugs in pediatric anesthesia, which depends on the likely advantages or risks of their use. From the child's perspective, off-label drugs can represent a more current and effective therapeutic option. From the parents' perspective, they may represent untested and unknown risks, which can concern and make them hesitant. From the federal authority's perspective, they represent serious concerns based, in part, on unknown risks and complications from the use of drugs that the regulatory agency does not control. From the industry's perspective, off-label drugs substantially increase annual sales without investment in research. From the anesthesiologist's perspective, these drugs can establish a standard of care with minimal risks or even improve it with greater safety, based on the best available scientific evidence.[11]

Educational efforts, supporting research, and promoting collaboration among physicians, patients' families, and professionals are essential. In this regard, we currently observe remarkable national and international multi-institutional collaborations that allow for information exchange, large amounts of data collection, guideline development, and practice changes that drive the specialty forward. These collaborations are important for continuous improvement in the care of children.[4] However, innovations to improve clinical care, greater investments in pediatric anesthesia research, and training and education of professionals specializing in child care are still required.[12]

In this context, specialization in pediatric anesthesia is dedicated to improving patient safety in this vulnerable population. Every day, pediatric anesthesiologists care for fragile children and their families during difficult times, striving to promote safety and quality in anesthetic procedures, perioperative care, and pain management. Various improvements have contributed to reduced anesthesia-related mortality rates over the past 50 years. However, children are known to be at greater risk for anesthetic complications during the perioperative period.[13] In particular, anesthesia in neonates and infants poses challenges even for experienced anesthesiologists, especially for premature infants or those with comorbidities.[14]

The rates of cardiac arrest attributable to anesthesia in children are inversely related to the Human Development Index (HDI) of the country. However, regardless of the HDI, the rate of anesthesia-related cardiac arrest is higher in children under one year of age, indicating that safety has not improved for this population. On the other hand, the 24-hour survival rate after cardiac arrest increases as the HDI of the country increases. This progress can be attributed to advances in pharmacology, improvements in education and training in pediatric anesthesiology, increased availability of neonatal and pediatric intensive care services, centralization of care in specialized pediatric services, and investment in research directed at children. These facts highlight the need to fill this growing gap in anesthetic care for children.[15]

In developed countries, pediatric anesthesia is often a subspecialty of anesthesiology. Conversely, in underdeveloped and developing countries, the subspecialty scarcely exists, and anesthesiologists with little experience in pediatric anesthesia are often responsible for the care provided to children.[15]

In Brazil, significant differences in pediatric anesthesia training are observed, primarily due to the lack of recognition of the subspecialty, as well as the poor distribution or even nonexistence of specialized services in various regions of this extensive country.[16] During anesthesiology training, pediatric anesthesia training is limited and consequently inadequate in terms of knowledge, competency, and use of the latest technology for administering safe anesthesia.[17]

For these reasons, programs that encourage the education of pediatric anesthesia and the work of individuals trained to handle children in resource-limited countries, such as ours, should be supported, as they play an important role in promoting safe anesthesia for children.[15,16] Being trained and accredited as a specialist by a recognized institution is the foundation for the future of perioperative care for this vulnerable population.[17]

In Brazil, in the early 1990s, two major pediatric hospitals, Pequeno Príncipe and Joana de Gusmão, were pioneers in offering one-year theoretical and practical training in the subspecialty of pediatric anesthesiology. In recent decades, there has been a growing interest in sub specialization. Currently, we have a few fellowship programs (Pequeno Príncipe, Instituto da Criança-USP, Hospital de Base de São José do Rio Preto, Instituto Nacional da Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, among others)[16] and two optional fourth-year residency programs in pediatric anesthesiology recognized by the Ministry of Education (Instituto de Medicina Integral Prof. Fernando Figueira and Hospital Infantil Sabará), an important step in the certification of professionals dedicated to this additional training.

Other important forms of training include workshops, where participants can practice specific skills and competencies for the pediatric population. In 2010, the Pediatric Anesthesia Immersion Course (CIAPED) was created by pediatric anesthesiologists from different regions of the country, with support from the Pernambuco State Society of Anesthesiology (SAEPE), which pioneered the training of practical skills and crisis management with realistic simulation. This course is itinerant, reaching all regions of Brazil and other Latin American countries, with an average of five CIAPEDs held per year and having trained approximately 2500 anesthesiologists to date. More recently, the São Paulo State Society of Anesthesiology (SAESP) created the Advanced Pediatric Anesthesia Support (SAAPed), a workshop offered periodically focusing on crisis situations in pediatric anesthesia through lectures, high-fidelity simulators, and scenario debriefing.

What future measures should be taken to improve education and research in pediatric anesthesia in Brazil?

We believe it is essential to define a minimum curriculum that includes the necessary competencies and skills to safely perform pediatric anesthesia and, similarly, to promote the creation of research networks among specialized professionals. It is undeniable that specialized anesthesiologists can conduct higher-quality research, which directly impacts anesthetic care, increases safety and contributes to better outcomes for this vulnerable population. There is clearly room for improvement, and we owe it to future generations.[18] Public health policymakers are also expected to consider the needs of children in developing the necessary infrastructure and availability of sufficient research funding.

Conflicts of interest

The authors declare no conflict of interests. The Curie Artificial Intelligence (https://www.aje.com/br/curie/) was used for English editing purpose.

References

1. Naka F, Strober B, Shahriari M. Clinical trials: Kids are not just little people. Clin Dermatol. 2017;35:583—93.
2. Wilson JT. An Update on the Therapeutic Orphan. Pediatrics. 1999;104(Supplement_3):585—90.
3. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015;79:357—69.
4. Fialho FA, Palacios M. A participação de crianças em protocolos de pesquisa: uma revisão de literatura. Rev Bras Bioet. 2014;10 (1—4):77—91.
5. Kipper DJ. Ética em pesquisa com crianças e adolescentes: à procura de normas e diretrizes virtuosas. Rev Bioetica. 2016;24:37—48.
6. Gaiva M. Pesquisa envolvendo crianças: aspectos éticos. Rev Bioet. 2009;17:135—46.
7. World Medical Association Declaration of Helsinki. JAMA [Internet]. 2013 Nov 27;310(20):2191.. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.281053.
8. Conselho Nacional de Saúde. RESOLUÇÃO No. 466 [Internet]. Brasil; 2012. Available from: https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf
9. Shirkey H. Therapeutic orphans. Pediatrics. 1999;104:583—4.
10. Schrier L, Hadjipanayis A, Stiris T, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr. 2020;179:839—47.
11. Smith MC, Williamson J, Yaster M, Boyd GJC, Heitmiller ES. Off-Label Use of Medications in Children Undergoing Sedation and Anesthesia. Anesth Analg. 2012: 1151148—54.
12. Fehr J. SPA: A Growing Society Serving Our Most Vulnerable Patients. ASA Monit. 2023;87:33.
13. Walters C, Kynes J, Reddy S, Crockett C, Lovejoy H, Lorinc A. Pediatric Anesthesia Specialty Societies and Multi-Institutional Collaborations. Children. 2020;7:233.
14. Disma N, Veyckemans F, Virag K, et al. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). Br J Anaesth. 2021;126:1157—72.
15. Tiradentes TAA, Einav S, Braz JRC, et al. Global anaesthesia-related cardiac arrest rates in children: a systematic review and meta-analysis. Br J Anaesth. 2023;131:901—13.
16. Quintão VC, Concha M, Argüello LAS, et al. Pediatric anesthesiology in Brazil, Chile, and Mexico. Pediatr Anaesth. 2024. https://doi.org/10.1111/pan.14886. Online ahead of print.
17. Sen I, Dave N, Bhardwaj N, Juwarkar C, Beegum S. Specialised training in paediatric anaesthesia: Need of the hour. Indian J Anaesth. 2021;65:17.
18. de Graaff JC, Frykholm P, Engelhardt T, et al. Pediatric anesthesia in Europe: Variations within uniformity. Pediatr Anesth. 2024. https://doi.org/10.1111/pan.14873. Online ahead of print.

Norma Sueli Pinheiro Módolo [a,*], Débora de Oliveira Cumino [b,c,d], Luciana Cavalcanti Lima [e,f], Guilherme Antonio Moreira de Barros [a]

[a] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu (FMB), Departamento de Especialidades Cirúrgicas e Anestesiologia, Botucatu, SP, Brazil*

[b] *Sabará Hospital Infantil, São Paulo, SP, Brazil*

[c] *Serviço de Anestesiologia Pediátrica/SAPE, Brazil*

[d] *Hospital Municipal Menino Jesus, São Paulo, SP, Brazil*

[e] *Instituto Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil*

[f] *Faculdade Pernambucana de Saúde, Recife, PE, Brazil*

[*] Corresponding author.
E-mail: norma.p.modolo@unesp.br (N.S. Módolo).

Brazilian Journal of Anesthesiology 2024;74(5): 844525



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Challenges of organizing pediatric anesthesia in low and middle-income countries



"Children have the right to enjoy the highest attainable standard of health. Specialist pediatric anesthesia care should be provided for all children. Particularly children aged less than three years should be treated by experienced staff that follows continuous education, regular training and updates to maintain their competencies. Children who have significant comorbidity and those who require highly specialized or major surgery benefit from specialized anesthetic care in dedicated pediatric centers."

The Safe Anesthesia For Every Tot initiative

Pediatric anesthetists are recognized as highly specialized professionals, tasked with the complex responsibility of taking care of a vulnerable population. This expertise requires a delicate balance between scientific mastery, precision, and steady commitment to the safety of the young ones. However, the dynamics of this profession, and the pursuit of safety within, can vary significantly across the globe. From the individual level — regarding standards, requirements, and training opportunities — to the environmental characteristics — settings and resources — there is a significant difference in the quality of the pediatric anesthesia provided worldwide. Achieving and maintaining institutional competencies as delineated by the Safe Anesthesia for Every Child (Safetots) initiative (www.safetots.org)[1] (Table 1), poses significant challenges in Low- and Middle-Income (LMIC) countries such as Brazil and the wider South America.

According to The Lancet Commission on Global Surgery, the distribution of the specialist surgical workforce is measured by the density of specialist surgeons, anesthetists, and obstetricians per 100,000 population and correlates with specific health outcomes. For example, countries with a higher density of providers per 100,000 population have lower maternal mortality. In 2015, the recommendation of specialist surgeons, anesthetists, and obstetricians was 20 per 100,000 population with the goal of 20 to 40 by 2030. Not surprisingly, shortages and maldistributions of these professionals are seen within and among LMIC leading to serious inequity. Specialists are frequently concentrated in urban areas with higher surgical infrastructure and working in better-equipped tertiary care centers, leaving the rural areas neglected.[2]

Following this same pattern, the Brazilian reality is illustrated by the 2023 demographic data of 13.7 anesthesiologists per 100,000 population varying from 4.2 in the province of Acre to 30.6 in the Federal District, and 68.5 in the south and southeast of the country.[3] This is in stark contrast to the USA for example where an average of 5.4 pediatric anesthesiologists per 100,000 are available for children alone.[4]

Training a new anesthesia workforce takes time and is unlikely to be achieved by 2030. In High-Income Countries (HICs) the training for anesthesia varies between 4 to 5 years and the requirements include pediatric anesthesia exposure in the early years of training under the direct supervision of a pediatric anesthetist. Most European countries have an additional organized society for pediatric anesthetists committed to continuing education in pediatric anesthesia. The regular anesthesia residency program in Brazil is 3 years and residents only rotate in pediatric anesthesia during their last year of residency. Currently, five centers in Brazil offer a four-year training in pediatric anesthesia. Pediatric anesthesia as a structured and recognized subspecialty, however, is not organized and hence has limited national representation. A direct consequence is that there are no public available data on the pediatric anesthesia workforce in Brazil.

Availability of pediatric anesthesia expertise is critical and affects patient outcomes. In 2017, the Anaesthesia PRactice In Children Observational Trial (APRICOT) study analyzed the incidence of severe critical events in children undergoing general anesthesia in Europe, highlighting key concepts of the population's vulnerability and urging targeted education and strategies to improve quality in pediatric anesthesia.[5] The very same observations also hold true in LMICs. A multicenter observational cohort in South Africa evaluated the Severe Anesthesia-Related Critical Incidents (SARCIs). They reported SARCI of almost 16% in a population composed of two-thirds healthy patients of which more than

https://doi.org/10.1016/j.bjane.2024.844525
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Table 1 Institutional competence (adapted from safetots.org).

Who	• Provider: Anesthesiologist with special training in pediatric anesthesia. Residents and fellows are supervised in a 1:1 manner by experienced staff • Patient: Children < 3 years, ASA ≥ III, underlying congenital and metabolic diseases, undergoing major or complex surgery
Where	In pediatric hospitals or in general hospitals with dedicated pediatric areas. Referral pathways to resourced multidisciplinary pediatric environments
What	Highly specialized/ major surgery (cardiac, thoracic, major visceral, major orthopedic, neurosurgical, burns and craniofacial procedures), complex comorbidities and critically ill children must have specialized anesthetic care in dedicated pediatric centers
When	Balance between increased perioperative risks for newborns and infants and impact of procedure delay.
Ho**W**	High Quality and Safe Anesthesia Care. Expertise in pediatric anesthetic techniques guaranteeing optimal care for all children in all situations

half underwent minor surgery. Factors such as young age, urgency of the procedure, severity of the surgery, and level of hospital independently increased the risk for SARCI. Compared with medium to high-income countries the SARCI events were 3 times higher, and the incidence of Perioperative Cardiac Arrests (POCA) was 10 times greater.

These results reinforce the notion that pediatric anesthesia care needs to be provided by staff trained in pediatric anesthesia in particular when it involves infants and neonates.[6] The latter is further underlined by the NECTARINE study.[7] Safety in pediatric anesthesia needs to be addressed urgently, that is evident in the article "Access to Safe Pediatric Anesthesia in LMICs-The Problem Is Clear; It Is Time to Solve It!".[8] Data from a tertiary teaching hospital in Brazil reported at least twice as high incidence of anesthesia-related cardiac arrest (2.81 per 10,000) when compared with HIC (from 0.14 to 1.4 per 10,000). Young age, an American Society of Anesthesiologists (ASA) physical status greater than III as well as difficulties with airway management are the greatest causes of anesthesia-related cardiac arrest and illustrate the need for trained pediatric anesthesia staff with appropriate pediatric resources.[9]

Who and when

Another huge barrier to the improvement of quality and safety in Brazil and South American LMICs is the model of healthcare delivery: The role of the physician is often the central point of care underestimating the real requirement of other well-trained healthcare professionals. The practice of anesthesia is no different, the physician plays a pivotal role in decision-making and the care provision is delivered in a system based on hierarchy. Opposed to that, in high-income countries, the healthcare system has evolved to embrace a multidisciplinary approach and collaborative teamwork, where responsibilities are shared among professionals such as anesthesiologists, nurses, and respiratory specialists.

This comprehensive model of care ensures safety, especially in the context of the pediatric population, where the tasks are more complex and time-critical due to the higher fragility of the patients. Even though Europe and North America have different structured healthcare systems, the overall practice of anesthesia relies heavily on the expertise of the non-medical personnel. Anesthesia is either provided directly by a physician or supervised by a physician in most of the European countries while in the US nurse anesthetists may provide direct care medical guidance. In both, trained nurse anesthetists or anesthesia technicians work together with the physicians, assuming different levels of independence, and focusing on providing excellent clinical care.[10]

This huge discrepancy among the anesthesia workforce worldwide is well documented by the World Federation of Societies of Anesthesiologists (WFSA). For example, the workforce in the US has more than 33,000 nurse anesthesia providers as well as almost 2,000 other anesthesia providers while in Brazil there are no nurse anesthesia providers or other supporting professionals.[11]

Certainly, the transition to a decentered and multidisciplinary system is a difficult task, yet it is based on a fundamental principle: shared expertise leads to improved safety and quality of care.

How

There is no doubt that pediatric anesthesia care for sicker and younger children at a tertiary specialized pediatric center improves patient outcomes. Unfortunately, there is a mismatch between individual patient needs and available clinical resources in LMICs. Nonetheless, any center providing pediatric care must always have staff with expertise in pediatric resuscitation available. In addition, reciprocal relationships need to be in place for the provision of a higher level of care if transfer is deemed necessary.[12]

The development of partnerships between LMIC-LMIC and HIC-LMIC gave rise to the Global Initiative for Children's Surgery (GICS), responsible for the identification of the priorities for surgical children and the development of guidelines for Optimal Resources for Children's Surgery (OReCS).[13] Based on their recommendations, first-level hospitals have the infrastructure and workforce to admit healthy children for common surgical procedures, resuscitation, and emergency surgical care. Sicker children and/ or younger than 1 year old requiring more complicated surgical procedures should receive perioperative treatment in higher levels of care unless emergent. The most experienced available anesthesia providers should be in charge. Secondary and tertiary-level hospitals must have specialists with pediatric experience in anesthesia for the comprehensive care of more complex cases and children with comorbidities. These recommendations are aligned with the World Federation of Societies of WFSA and the Association of Anaesthetists to enhance the quality of children's care by providing training in LMICs.

Programs such as SAFE Paeds — a branch of the Safer Anaesthesia Education (SAFE) initiative have led to improvement in the knowledge, skills, and behavior of anesthesia providers. Opportunities for advanced training in pediatric anesthesia to develop future pediatric anesthesia leaders and educators should be encouraged. The goal is to guarantee that any hospital admitting a pediatric patient has a team of anesthesia providers led by at least one anesthesiologist appropriately trained.[8] Academic training centers, mostly represented by tertiary referral centers, should be staffed with experienced pediatric anesthetists to ensure the quality of education training.

Where and who

Unfortunately, in Brazil pediatric anesthesia encounters challenges based on the lack of either educational or financial incentives for healthcare professionals to pursue additional training. First, there is little or no movement of local staff from smaller institutions to seek additional training at specialized centers. Second, remuneration in pediatric anesthesia is shamefully inferior in comparison with other areas of anesthesia effectively placing the importance, needs, and well-being of children below most. It is important to notice that, most of the time, anesthesia practice occurs in the context of a mixed population varying from geriatric patients to infants in the same hospital on the same operating list. Children are commonly not pooled or cared for in a pediatric friendly environment.

It is well described that caseload and clinical experience are crucial to improve safety in pediatric anesthesia and the number of years of practice being the most common factor influencing the quality of care. Each year of anesthesia experience reduces 1% of respiratory events and 2% of cardiovascular events.[5,14] The dedication of pediatric anesthesia performance of less than 73 days per year is an independent risk factor for the number of cardiac arrests in the operating and postoperative recovery room.[14] In this way, not only the lack of adequate training but also the scarce maintenance of required skills exposes the children in need of anesthesia to suboptimal care in Brazil and in the majority of LMICs in South America.

In HICs, the economic pressure, time constraints, and demands of enhanced productivity conflict with the possibility of healthcare providers prioritizing education. This situation is even more challenging in LMIC.[15] Data from the APRICOT study showed a variable incidence and management of severe perioperative critical events across Europe, raising concerns about pediatric anesthesia training, teams' experience with higher-risk children, resources, and infrastructure.[5] A sub—analysis of the APRICOT, exploring the differences between Scandinavian data (Denmark, Finland, Norway, and Sweden) and the rest of Europe, indicated better outcome regarding the incidence and nature of perioperative critical events.[16] This is not surprising given the unique practice and training in pediatric anesthesia in Scandinavia: the use of medications, anesthetic techniques, and training are uniform, there are always two anesthesia—trained professionals, and in the pediatric recovery room, patients are accompanied by recovery—trained and registered nurses. Aligned with this high standard of care, the Scandinavian countries have had a consistent training program in pediatric anesthesia and intensive care running for over 20 years. There is no doubt that all these factors continue to result in a safer perioperative outcome.[17]

Future directions

Without changes in the investment in extra years of specific pediatric anesthesia training, either by providing financial funding or by standardizing and regulating pediatric anesthesia competencies, the current mixed anesthesia system will continue to disadvantage children in Brazil. In addition to organizing local pediatric specialized care, administrative strategies are necessary to guarantee and optimize the delivery of excellent care. The creation of specific guidelines and flowsheets related to referral criteria are essential, permitting objective decision making. Such strategies should be based on hospital infrastructure and equipment, population age, urgency of the procedure, complexity of anesthesia, postoperative care needs, pain management availability, and the experience of the anesthesia, surgical, and nursing teams involved.

Technological and pharmacological advances in anesthesia play an important role in the reduction of morbidity and mortality in perioperative settings worldwide. Adequate and well-functioning equipment is an elementary requirement for safe anesthesia in children and is extensively described by the World Federation of Societies of Anesthesiologists (WFSA) and the World Health Organization (WHO) Safe Surgery Checklist.[18] Even though access to new technologies is variable in LMICs, improvement of care should not only focus on acquiring equipment but guaranteeing the proper use of the basic equipment by training personnel and maintenance of competence.[15] Gaps in the preparation of appropriately sized pediatric equipment and monitors remain a major obstacle despite the availability of perioperative pediatric anesthesia equipment.[19]

Investing in infrastructure alone will not solve these challenges, developing an institutional competence does.[20] In the pre-pandemic era, the Global Initiative for Children's Surgery stated that the delivery of safe, effective surgical care to children was already critical and neglected. The pandemic has aggravated this scenario posing unprecedented challenges to the healthcare system worldwide. Even though the adult population bore the brunt of the pandemic as reflected in the number of deaths, the impact on the pediatric population cannot be underestimated.[21] The fear of reaching the hospitals resulted in diagnostic as well as therapeutic delays and preventable complications.[22]

Longer surgical waiting lists and diseases that are more advanced have an even bigger impact on pediatric anesthesia practice, exacerbating the existing surgical backlogs and delays for elective, urgent, and emergent cases.[23] Brazil and other South American LMICs need urgent mobilization of resources and focus on strategies to mitigate the already overwhelmed healthcare provision for children. The exponential growth in pediatric surgical need will increase the ratio between mixed-practice anesthetists and pediatric patients. Nonetheless, special efforts must be made to provide long-term strategies to guarantee pediatric anesthesia care.

The morbidity and mortality in the pediatric population undergoing surgery can be significantly improved by

implementing simple strategies. As anesthetists, we should ask ourselves uncomfortable questions: Are we able to provide appropriate care for these children needing surgery? and When will we be ready to put safety into practice? In addition, most importantly: Are we ready to respect the right of the child to enjoy the highest attainable standard of health?

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgement

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

References

1. Weiss M, Vutskits L, Hansen TG, Engelhardt T. Safe Anesthesia For Every Tot - The SAFETOTS initiative. Curr Opin Anaesthesiol. 2015;28:302–7.
2. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386:569–624.
3. Scheffer M, et al. Demografia Médica no Brasil 2023 [Internet]. São Paulo: AMB, FMUSP; 2023 Feb 06 [cited 2023 Oct 17]. Available from: https://amb.org.br/wp-content/uploads/2023/02/DemografiaMedica2023_8fev-1.pdf.
4. Kurth CD, Tyler D, Heitmiller E, Tosone SR, Martin L, Deshpande JK. National pediatric anesthesia safety quality improvement program in the United States. Anesth Analg. 2014;119:112–21.
5. Habre W, Disma N, Virag K, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. Lancet Respir Med. 2017;5:412–25.
6. Cronje L, Torborg AM, Meyer HM, et al. An Evaluation of Severe Anesthetic-Related Critical Incidents and Risks From the South African Paediatric Surgical Outcomes Study: A 14-Day Prospective, Observational Cohort Study of Pediatric Surgical Patients. Anesth Analg. 2022;134:728–39.
7. Disma N, Veyckemans F, Virag K, et al. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). Br J Anaesth. 2021;126:1157–72.
8. Evans FM, Wake PB, Gathuya ZN, McDougall RJ. Access to Safe Pediatric Anesthesia in LMICs-The Problem Is Clear; It Is Time to Solve It!. Anesth Analg. 2022;134:724–7.
9. Gonzalez LP, Braz JR, Modolo MP, de Carvalho LR, Modolo NS, Braz LG. Pediatric perioperative cardiac arrest and mortality: a study from a tertiary teaching hospital. Pediatr Crit Care Med. 2014;15:878–84.
10. Steurer MP. Comparison and contrast of anesthesia practice in Europe and the U.S. ASA Monitor. 2015;79:18-20.
11. World Federation of Anaesthesiologists. Workforce map [Internet]. WFSA2022 [cited 2023 Nov 18]. Available from: https://wfsahq.org/resources/workforce-map/.
12. Subramanyam R, Isserman R, Maddirala S, Kurth CD. Quality Improvement and Safety Analytics can improve perioperative safety for children in developing countries. Paediatr Anaesth. 2019;29:298–9.
13. Global Initiative for Children's Surgery Collaborators. Global Initiative for Children's Surgery: A Model of Global Collaboration to Advance the Surgical Care of Children. World J Surg. 2019;43:1416–25.
14. Habre W. Paediatr Anaesth. after APRICOT (Anaesthesia PRactice In Children Observational Trial): who should do it? Curr Opin Anaesthesiol. 2018;31:292–6.
15. de Graaff JC, Johansen MF, Hensgens M, Engelhardt T. Best practice & research clinical anesthesiology: Safety and quality in perioperative anesthesia care. Update on safety in pediatric anesthesia. Best Pract Res Clin Anaesthesiol. 2021;35:27–39.
16. Hansen TG, Borke WB, Isohanni MH, Castellheim A. APRICOT Study Group of the European Society of Anaesthesiology Clinical Trial Network. Incidence of severe critical events in paediatric anaesthesia in Scandinavia: Secondary analysis of Anaesthesia PRactice In Children Observational Trial (APRICOT). Acta Anaesthesiol Scand. 2019;63:601–9.
17. Hansen TG, Vutskits L, Disma N, Becke-Jakob K, Elfgren J, Frykholm P, et al. Harmonising paediatric anaesthesia training in Europe: Proposal of a roadmap. Eur J Anaesthesiol. 2022;39:642–5.
18. Merry AF, Cooper JB, Soyannwo O, Wilson IH, Eichhorn JH. International Standards for a Safe Practice of Anesthesia 2010. Can J Anaesth. 2010;57:1027–34.
19. Tegegne BA, Lema GF, Fentie DY, Bizuneh YB. The preparedness of preoperative anesthesia equipment's and monitors for pediatric patients. Ann Med Surg (Lond). 2023;85:3423–7.
20. Batista Filho LAC, Randhawa VK, Maciel AT, Coimbra MR. We need to talk about critical care in Brazil. Clinics (Sao Paulo). 2022;77:100096.
21. Borel M, Xie L, Kapera O, Mihalcea A, Kahn J, Messiah SE. Long-term physical, mental and social health effects of COVID-19 in the pediatric population: a scoping review. World J Pediatr. 2022;18:149–59.
22. Katato GK, Situala P, Gupte A, ET Al-Antary. The Impact of COVID-19 on Pediatric Malignancy Diagnosis and Treatment: Never the Same but Lessons Learned. Vaccines (Basel). 2023;11:66.
23. Quarello P, Ferrari A, Mascarin M, Milano GM, Tornesello A, Bertolotti M, et al. Diagnostic Delay in Adolescents with Cancer During COVID-19 Pandemic: A New Price for Our Patients to Pay. J Adolesc Young Adult Oncol. 2022;11:316–9.

Anelise Schifino Wolmeister [a,b,*], Tom G. Hansen[c,d], Thomas Engelhardt[a]
[a] *Montreal Children's Hospital, Department of Anesthesia, Montreal, Canada*
[b] *Hospital de Clínicas de Porto Alegre, Departamento de Anestesia e Medicina Perioperatória, Porto Alegre, RS, Brazil*
[c] *Akershus University Hospital, Department of Anesthesia & Intensive Care, Lørenskog, Norway*
[d] *University of Oslo, Institute of Clinical Medicine, Oslo, Norway*

[*] Corresponding author.
E-mail: anewolmeister@gmail.com (A. Schifino Wolmeister).
Received 14 January 2024; Accepted 10 June 2024

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric laparoscopic surgery: a randomized clinical trial

Seham Mohamed Moeen [a,*], Ola Mahmoud Wahba [a], Ahmed Mohamed Mandour [a], Noha Abdel Ghany [a], Mohamed AbdelKader Osman [b], Tarek Abdelazeem Sabra [b], Mohammed Hamada Takrouney [b], Ahmed Mohamed Moeen [c]

[a] *Assiut University, Faculty of Medicine, Department of Anesthesia, Intensive Care, and Pain Management, Assiut, Egypt*
[b] *Assiut University, Faculty of Medicine, General Surgery Pediatric Division, Assiut, Egypt*
[c] *Assiut University, Faculty of Medicine, Assiut Urology and Nephrology Hospital, Assiut, Egypt*

Received 16 April 2021; accepted 14 May 2022
Available online 23 May 2022

KEYWORDS
Dexmedetomidine;
Magnesium sulfate;
Intraperitoneal analgesia;
Pediatric;
Laparoscopic surgery

Abstract

Background: We evaluated the efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal (IP) bupivacaine in pediatric laparoscopic inguinal herniorrhaphy.

Methods: Ninety-seven male children, ASA I–II, 1–6 years old, undergoing laparoscopic inguinal herniorrhaphy, were randomized to receive before peritoneal insufflation, IP 2 $mg.kg^{-1}$ bupivacaine 0.5% combined with either 1 $\mu g.kg^{-1}$ of dexmedetomidine (Group D), 30 $mg.kg^{-1}$ of magnesium sulfate (Group M), or normal saline (Group C). All tested drugs were diluted to the volume of 10 mL with normal saline. FLACC pain scores, need for rescue analgesics, time to flatus and first stool, emetic events, adverse effects, functional recovery, and parents' satisfaction were recorded for the first 48 h postoperatively.

Results: FLACC scores were significantly higher in Group C than in the other two groups at 6, 8, 12, 18, 24, and 48 hours after surgery with no differences between Groups D and M. Rescue analgesia was significantly higher in Group C with none of the children in Groups D and M requiring rescue analgesia ($p = 0.001$). Times to first flatus and stool, emetic events, and adverse effects did not differ among groups. Times to return to normal functional activity were comparable in all groups. Parents' satisfaction was greater in Groups D and M than in Group C ($p = 0.026$).

Conclusion: Dexmedetomidine and magnesium sulfate added to IP bupivacaine improved the analgesia afforded by bupivacaine in the first two postoperative days in children scheduled for laparoscopic herniorrhaphy.

Study conducted at the Faculty of Medicine, Assiut University, Egypt.

* Corresponding author.
E-mail: seham.moeen@aun.edu.eg (S.M. Moeen).

https://doi.org/10.1016/j.bjane.2022.05.003
0104-0014/© 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/).

© 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

Nowadays, in an era of minimally invasive surgery, pediatric laparoscopic inguinal hernia repair has become widely popular replacing the conventional open method and assuming an important place in pediatric surgery.[1]

Laparoscopic surgery has many advantages over open procedures, such as better cosmetics, shorter hospital stay, rapid recovery, and greater capability to visualize and repair a contralateral hernia.[1,2]

Pain after laparoscopy is less intense than after laparotomy, but laparoscopy is not pain free and analgesia after this type of surgery is inadequately studied.[3]

Diaphragmatic irritation with stretching of the peritoneum that accompanies gas insufflation may be the cause of diffuse abdominal pain. However, the exact mechanism of such pain remains uncertain.[4]

Intraperitoneal (IP) instillation/nebulization of local anesthetics has been used as a method for reducing postoperative pain and opioid use following laparoscopy through acting on visceral nociceptors of the peritoneum.[3]

Dexmedetomidine is a selective alpha-2 (α2) adrenergic agonist known to have analgesic and sedative characteristics that can augment the duration of action of local anesthetics.[5] IP instillation of dexmedetomidine with bupivacaine reduced pain and rescue analgesia in children undergoing laparoscopic appendectomy.[6]

Magnesium sulfate ($MgSO_4$) also has been administered via different routes in anesthetic practice for relieving postoperative pain. Besides, it has been used to attenuate the adverse hemodynamic changes that occur with pneumoperitoneum and promote the quality of recovery.[7]

This study aimed to evaluate the efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric elective unilateral laparoscopic inguinal herniorrhaphy.

Methods

This prospective, randomized, double-blinded, controlled clinical trial was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Ethical approval was provided by our Institutional Review Board on March 30, 2016 and the trial was registered at ClinicalTrials.gov. Written informed consent was taken from the parents or legal guardians of all participating children.

This study was done in the period from August 2016 to September 2019. Children aged 1 to 6 years scheduled for elective unilateral laparoscopic inguinal hernia repair were included in this study. Children were excluded if their physical status according to the American Society of Anesthesiologists (ASA) was III or higher (i.e., patients with severe cardiac, respiratory, hepatic, renal, or central nervous system impairment), were on magnesium therapy, received analgesics before surgery, or had an allergy to the study drugs.

The enrolled children were randomly assigned through a computer-generated random number table (www.random.org), by an anesthetist not involved in the study into three equal groups (n = 35).

Group D received 1 μg.kg^{-1} of dexmedetomidine, Group M received 30 mg.kg^{-1} of magnesium sulfate while Group C received normal saline. All the tested drugs were diluted to the volume of 10 mL using normal saline. Before peritoneal insufflation, 2 mg.kg^{-1} bupivacaine 0.5% were instilled into the peritoneal cavity followed by the prepared diluted tested drug in a separate syringe.

On the day of surgery, the group into which children were allocated was revealed via a sealed envelope to an unblinded anesthetist who prepared and diluted the study drugs to a volume of 10 mL using normal saline in identical sterile syringes labeled with the randomly assigned numbers.

The surgeons, anesthesiologists, medical staff in the operating room, the children and their parents or guardians, Postanesthesia Care Unit (PACU) nurses, and ward nurses were blinded to the treatment group.

No premedication was used. A standardized anesthesia protocol was applied to all children. All children were connected to electrocardiography, noninvasive blood pressure, pulse oximetry, and thermometer for routine basic monitoring, and anesthesia was induced via a face mask using 8% sevoflurane in 100% oxygen. An intravenous cannula was inserted and an infusion of dextrose 5% in 0.45 NaCl was begun at 4–6 mL.kg^{-1}.h^{-1}. Anesthesia induction was completed with intravenous (IV) fentanyl 1 μg.kg^{-1}, propofol 2 mg.kg^{-1}, and cisatracurium 0.15 mg.kg^{-1}. After 3 minutes the trachea was intubated, and pressure-controlled ventilation was used to maintain the value of end-tidal CO_2 within a normal range (35–45 mmHg). Anesthesia was maintained with 2–3% sevoflurane in 100% oxygen, IV cisatracurium 0.03 mg.kg^{-1}, and IV fentanyl boluses 1–2 μg.kg^{-1} were titrated to maintain the changes in heart rate and noninvasive mean arterial blood pressure within 20% of basal values.

All enrolled children received IV paracetamol 15 mg.kg^{-1} before starting the surgery. The standardized prophylactic antiemetic was IV granisetron 40 μg.kg^{-1}.

In all groups, laparoscopic surgery was done according to the standard surgical protocol. After the primary trocar was placed through a periumbilical incision, intraperitoneal instillation of 2 mg.kg^{-1} bupivacaine 0.5% followed by the diluted study drugs into the abdominal cavity was performed through the primary trocar outlet. Instillation was performed toward the undersurface of the diaphragm and the patients were shifted to the Trendelenburg position for 5 minutes before returning the operating table to the zero position. Then pneumoperitoneum was performed using non-humidified and non-heated CO_2, with the intra-abdominal pressure maintained around 10 mmHg, and a classical surgical technique was started.

After termination of the surgical procedure, the surgeon removed trocars, and CO_2 was cleared completely from the peritoneal cavity by manual compression of the abdomen. Sevoflurane was discontinued and residual muscle paralysis was reversed with 0.05 $mg.kg^{-1}$ neostigmine and 0.02 $mg.kg^{-1}$ atropine, and extubation of the trachea was done in the left lateral position with the head down.

In the PACU, all children were connected to standard monitoring. Modified Aldrete Score was evaluated every 5 minutes and when children achieved an Aldrete score of 9 or higher they were ready for discharge to the intermediate care unit.

Data collection

Clinical data of participating children, surgery time, and anesthesia time were recorded.

Our primary outcome variable was the intensity of pain following surgery. It was assessed by parents or guardians of participants through the Face, Legs, Activity, Cry, and Consolability (FLACC, 0–10) pain score, where 0 = no pain and 10 = the worst possible pain[8], after explaining the aim and the way to use it to them.[9]

The evaluation of the FLACC scores began immediately after the children were admitted to the PACU (T_0) and then at 1 h (T_1), 2 h (T_2), 4 h (T_4), 6 h (T_6), 8 h (T_8), 12 h (T_{12}), 18 h (T_{18}), 24h (T_{24}), and 48 h (T_{48}) thereafter.

Paracetamol 15 $mg.kg^{-1}$ IV was given as a rescue analgesic when the FLACC pain score was > 3 and then every 6 h until the end of the study. Thirty minutes after the first paracetamol dose, if the FLACC score was still > 3, IV fentanyl 0.5 $\mu g.kg^{-1}$ was administered. Time to a first analgesic request and total dose of rescue analgesia in the first 48 hours was recorded.

The number of children who experienced an emetic episode (defined as a single vomit or retch, or any number of continuous vomits or retches separated by the absence of both vomiting and retching for at least 3 minutes)[9], times until first flatus and the first passage of stool during the first 48 h postoperative were recorded by child's parent or guardian.

The incidence of other adverse effects, including hypotension and bradycardia (defined by the reduction of more than 20% of the baseline mean arterial pressure or heart rate, respectively), respiratory depression, sedation, and urinary retention were controlled and recorded.

The degrees of children's functional limitation were evaluated by their parents (the secondary outcome variable) through the Functional Activity Score (FAS) whereas; (A = no limitation; B = mild limitation; and C = severe limitation)[10] at 6, 12, 18, 24, and 48 hours postoperative, until full functional recovery was achieved. The FAS measures the degree to which children return to their usual activities after surgery.[10]

Parents' satisfaction was assessed by the four-point Likert scale (1 = excellent; 2 = good; 3 = fair; and 4 = poor).

Children were hospitalized for follow-up for 48 h after surgery and were discharged from the hospital, when they were capable of drinking, urination, walking, and after recovery of bowel function.

Sample size calculation and statistical analysis

Our primary outcome variable was the intensity of pain following surgery evaluated by the FLACC pain score. Sample size calculation was based on a previous study[9], with the assumption that there is a true difference of 2.0 in mean FLACC scores at 2 h after surgery among the groups. Assuming a standard deviation of 2.0, with a type I error of 0.05 and power of 90%. A sample size of 29 patients in each group was required. Hence, 35 children per group were then enrolled to compensate for possible protocol violations.

The Kolmogorov-Smirnov test was used for data normality.

Continuous variables were analyzed with analysis of variance (ANOVA) or the Mann-Whitney U-test as appropriate. The $\chi 2$ test or Fisher's exact test was applied for analyzing categorical variables as appropriate. All data are presented as mean (SD), or number (percentage) as appropriate. A p-value < 0.05 was considered as significant.

Statistical analyses were performed by computerized statistical software (SPSS, version 21; SPSS, Chicago, Ill).

Results

One hundred and five patients were enrolled for eligibility, and eight patients were excluded from the study (Fig. 1). There were no significant differences among all groups regarding patients' characteristics and clinical data (Table 1).

The pain scores were comparable among the three studied groups in the first four hours after surgery ($p > 0.05$). However, they were significantly higher in Group C than in the other two groups later on ($p < 0.001$) (Fig. 2). No significant differences were found between both Groups D and M in mean FLACC scores throughout the study period ($p > 0.05$) (Fig. 2).

Time to first paracetamol dose was significantly earlier and the total dose of administered paracetamol was significantly higher in Group C with no children in Groups D and M requiring paracetamol administration. None of the children in all groups required intraoperative or postoperative fentanyl (μg) administration (Table 1).

The incidence of emetic episodes, time to first flatus (h), and time to first stool (h) after surgery were comparable in three studied groups as illustrated in Table 2.

No patient experienced bradycardia, hypotension, respiratory depression, sedation yielding to delayed hospital discharge, or urine retention needing urethral catheterization in three groups.

Children in Group C returned to full functional activity earlier during the first 6 h postoperative than Groups D and M. By the 12th postoperative hour, all children in Groups D and M had returned to normal activity with no residual functional limitation (Table 3).

The parents' satisfaction scores with analgesia were significantly higher in Groups D and M than in Group C, with no difference between Groups D and M ($p = 0.420$) (Table 3).

All the children studied were successfully discharged home 48 h after the operation.

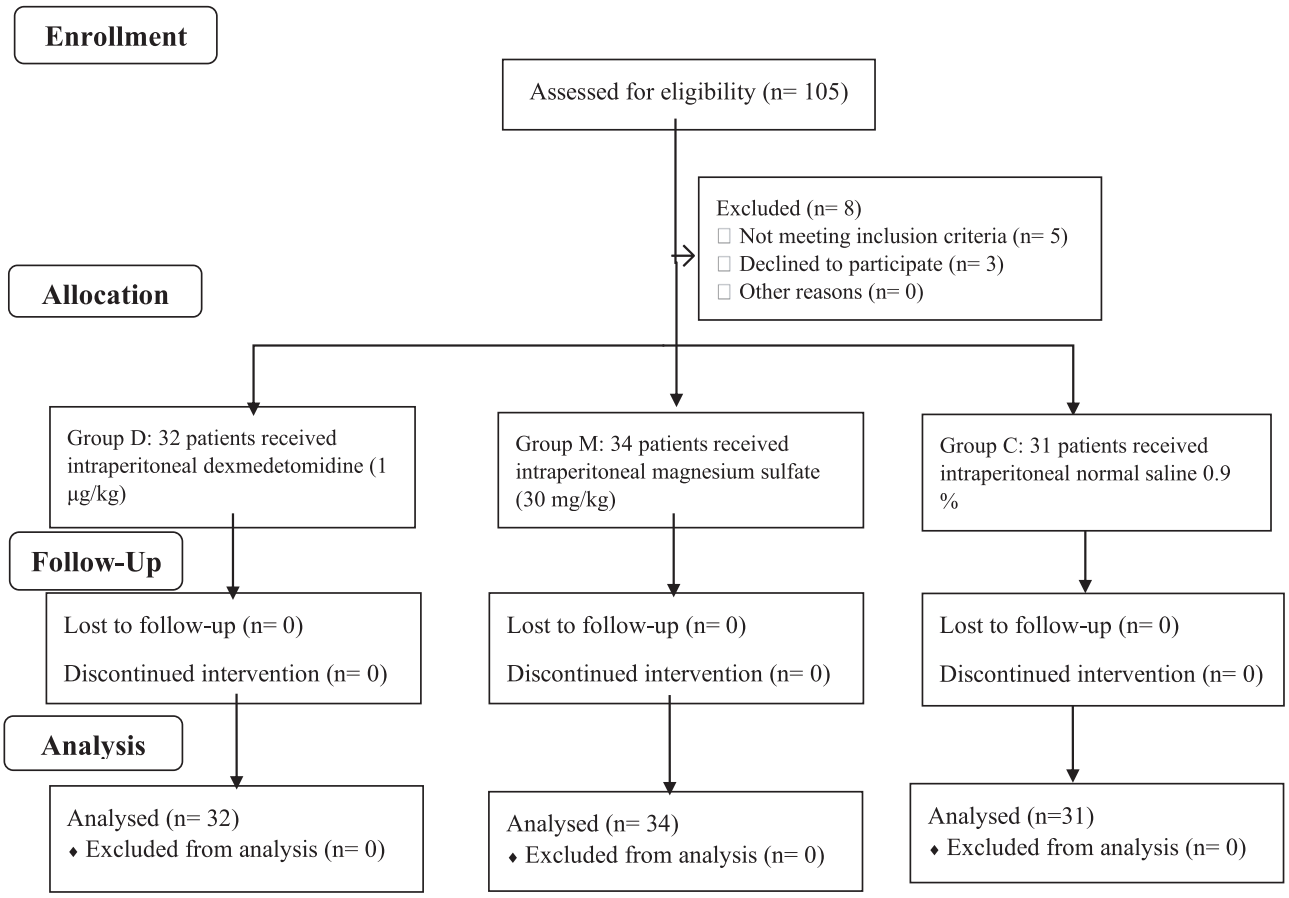


Figure 1 CONSORT flow diagram of participants.

Discussion

The present study demonstrated that the preemptive IP administration of bupivacaine 0.5% plus dexmedetomidine or magnesium sulfate in children scheduled for elective unilateral laparoscopic inguinal hernia repair provided greater analgesic efficacy compared to IP bupivacaine 0.5% alone with no differences in bowel function recovery and time to return to normal activity during the first 48 h postoperative.

Pediatric laparoscopic surgery has found increasing popularity all over the world as its use is safe even in neonates[4] and it allows rapid recovery[9] through effective, uncomplicated analgesia.[3]

Table 1 Characteristics and clinical data of the three groups.

	Group D (n = 32)	Group M (n = 34)	Group C (n = 31)	*p*-value
Age (years)	3.9 (1.7)	4.2 (1.4)	3.8 (1.5)	0.523
Weight (kg)	19.2 (5.5)	16.9 (6.7)	17.4 (6)	0.283
ASA class (I / II)	20 (62.5)/ 12 (37.5)	21 (61.8)/ 13 (38.2)	22 (71)/ 9 (29)	0.695
Operation side (right/left)	13 (40.6)/ 19 (59.4)	15 (44.1)/ 19 (55.9)	11 (35.5)/ 20 (64.5)	0.776
Duration of surgery (min)	46.4 (8.9)	42.7 (7.4)	43.3 (7.1)	0.115
Duration of anesthesia (min)	63.9 (7.6)	65.1(6.3)	62.5 (7)	0.08
Patients required intraoperative fentanyl (μg)	0 (0)	0 (0)	0 (0)	–
Time to first paracetamol dose (h)	–	–	8.97 (2.06)	<0.001
Total dose of postoperative paracetamol consumption (mg)	0 (0)	0 (0)	1850.81 (635.99)	<0.001
Total dose of postoperative fentanyl consumption (μg)	0 (0)	0 (0)	0 (0)	–

Data are presented as mean (SD), or number of patients (%). A *p*-value < 0.05 was considered statistically significant. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group. ASA, American Society of Anesthesiologists.

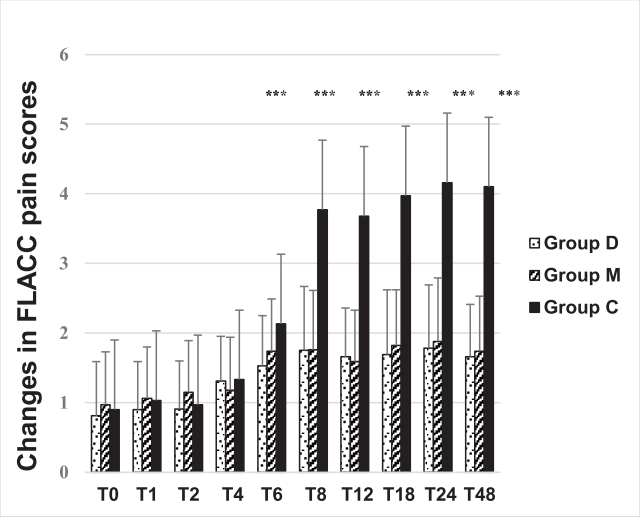


Figure 2 Changes in FLACC pain scores in the three studied groups. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group. ***s indicates $p < 0.001$.

The exact mechanism of pain following laparoscopic surgery remains uncertain, and yet, rapid peritoneal distension, stretching of vessels and phrenic nerves, visceral handling, the existence of residual gas, and inflammatory biomarkers may be responsible for such pain.[4] Pain following laparoscopy is commonly presented by abdominal discomfort and shoulder tip pain in adults, while in pediatrics shoulder tip pain is less frequent.[1]

IP administration of local anesthetics and analgesics has been used recently to improve postoperative analgesia.[9] Tian et al. reported that IP ropivacaine is an effective method to control pain in toddlers undergoing laparoscopic herniorrhaphy.[9] Freilich et al. found that aerosolized bupivacaine given at the beginning of a robotic-assisted pyeloplasty surgery improved the quality of recovery.[11] Zanetta et al. reported that IP bupivacaine decreases opioid consumption after laparoscopic surgery in children.[12] Additionally, El Basha et al. found that IP levobupivacaine improved pain control after pediatric laparoscopic surgeries.[3]

Dexmedetomidine 1 $\mu g.kg^{-1}$ has been used recently intraperitoneally alone or combined with local anesthetics in adult laparoscopic surgeries because of its analgesic and sedative characters.[5,13,14]

Elnabtity and Ibrahim studied the effect of IP 1 $\mu g.kg^{-1}$ dexmedetomidine combined with 2 $mg.kg^{-1}$ bupivacaine 0.25% versus 2 $mg.kg^{-1}$ bupivacaine 0.25% alone at the end of the surgery, in children undergoing laparoscopic appendectomy. They reported reduced pain, opioid consumption, and hospital stay with no significant adverse events and with better overall parent satisfaction in the dexmedetomidine group.[6]

Dexmedetomidine induces analgesia by stimulation of 2A and 2C subtypes of α2-adrenoceptors leading to the stimulation of descending medullispinal noradrenergic pathways or inhibition of the spinal sympathetic outflow at presynaptic ganglionic sites, reducing the release of C-fiber transmitters, and finally augmenting hyperpolarization of postsynaptic dorsal horn neurons.[15]

Magnesium sulfate ($MgSO_4$) has been used through several routes to provide analgesia[7,10] following laparoscopic surgeries.[16-18] It has been administered intraperitoneally combined with local anesthetics to reduce pain after laparoscopic cholecystectomy.[19] Actually, magnesium decreases calcium influx to cells, through non-competitive inhibition of the N-methyl-D-Aspartate (NMDA) receptors, which is vital in the neuronal signaling and pain processing in the central nervous system leading to inhibition of both somatic and visceral pain fibers.[20,21]

Further mechanisms of analgesia produced from IP instillation of local anesthetics and analgesics might be referred as blocking of peritoneal free afferent nerve endings plus the systemic absorption through the large peritoneal surface, as they could be detected in blood after 2 minutes from IP instillation.[6,9]

Nevertheless, the time of IP administration of the analgesic drug is still controversial. In our trial, we chose early IP administration although this analgesic technique was not used commonly in children[3] as some studies[22] reported that early IP administration of local anesthetics and analgesics at the beginning of laparoscopic surgery acts as preemptive analgesia, depressing central neural sensitization before the nociceptive stimulus triggers pain pathways allowing better postoperative analgesia compared with IP administration at the end of the surgery. However, those results were not corroborated by other studies.[23]

In the present study, children who had received preemptive IP dexmedetomidine and magnesium sulfate added to bupivacaine experienced prolonged pain free time with no need for rescue analgesics, without an increase in the incidence of adverse effects or delayed recovery from general anesthesia compared to those who received IP bupivacaine alone. We tried to keep the concentration of the IP administered local anesthetic the same in all patients by preparing it in a separate syringe and instilling it first in the peritoneal cavity before the tested drugs.

Table 2 Postoperative emetic episodes and bowel function recovery time in the three studied groups.

	Group D (n = 32)	Group M (n = 34)	Group C (n = 31)	*p*-value
Children with emetic episodes	6 (18.8)	7 (20.6)	5 (16.1)	0.898
Time to first flatus (h)	15.1 (1.3)	15 (1)	14.8 (1.3)	0.715
Time to first stool (h)	20.3 (1.6)	20.7 (1.7)	20 (1.9)	0.230

Data are presented as mean (SD) and number of patients (%). A *p*-value < 0.05 was considered statistically significant. Group D, dexmedetomidine group; Group M, magnesium sulfate group; and Group C, control group.

Table 3 Functional activity scores of children and parent satisfaction.

	Group D (n = 32)	Group M (n = 34)	Group C (n = 31)	*p*-value
Functional activity score at 6 h				0.084
No limitation	27 (84.4)	30 (88.2)	31 (100)	
Mild limitation	5 (15.6)	4 (11.8)	0 (0)	
Severe limitation	0 (0)	0 (0)	0 (0)	
Functional activity score at 12 h				–
No limitation	32 (100)	34 (100)	31 (100)	
Mild limitation	0 (0)	0 (0)	0 (0)	
Severe limitation	0 (0)	0 (0)	0 (0)	
Functional activity score at 18 h				–
No limitation	32 (100)	34 (100)	31 (100)	
Mild limitation	0 (0)	0 (0)	0 (0)	
Severe limitation	0 (0)	0 (0)	0 (0)	
Functional activity score at 24 h				–
No limitation	32(100)	34 (100)	31 (100)	
Mild limitation	0 (0)	0 (0)	0 (0)	
Severe limitation	0 (0)	0 (0)	0 (0)	
Functional activity score at 48 h				–
No limitation	32 (100)	34 (100)	31 (100)	
Mild limitation	0 (0)	0 (0)	0 (0)	
Severe limitation	0 (0)	0 (0)	0 (0)	
Parent satisfaction				0.026
Excellent	27 (84.4)	26 (76.5)	17(54.8)	
Good	5 (15.6)	8 (23.5)	14 (45.2)	
Fair	0 (0)	0 (0)	0 (0)	
Poor	0 (0)	0 (0)	0 (0)	

Data are expressed as number (%). A p-value < 0.05 was considered statistically significant. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group.

As a rule, effective postoperative analgesia is essential for good recovery after surgery.[24] Tian et al. found that IP ropivacaine could hasten bowel function recovery and reduce postoperative vomiting in toddlers in the same way as that intra and postoperative administration of epidural local anesthesia improves bowel function.[9] In the current study, children in three studied groups had comparable postoperative bowel recovery, emetic episodes, and usual activity recovery.

Wound cosmoses and time to return to full activity are additional parent and/or caregiver concerns. Gause et al. reported 2.5 days as the period until children return to full activity after unilateral laparoscopic inguinal hernia repair.[25] In our trial, the return to normal full activity was similar in all studied children. We believed that good effective analgesia in Group D and M with faster return to activity augments parent satisfaction with the used analgesic drugs.

This study was limited by the lack of sufficient data about the ideal effective dose of IP dexmedetomidine, and magnesium sulfate required for augmenting analgesia in children. Further studies are recommended to investigate different doses of both drugs whether given separately or combined to evaluate their optimal analgesic efficacy.

In conclusion, we have found that IP dexmedetomidine or magnesium sulfate added to bupivacaine before peritoneal insufflation could be an ideal safe effective way for pain control in children after laparoscopic inguinal herniorrhaphy with significant reduction of analgesic consumption, good recovery of gastrointestinal function, and with a faster return to normal usual activity. We suggest that dexmedetomidine given together with magnesium sulfate as an adjuvant to IP bupivacaine could be beneficial.

Trial registration

ClinicalTrials.gov (NCT02820610).

Institutional review board registration

IRB no: 17300153.

Conflicts of interest

The authors declare no conflicts of interest. There were no fundings.

CRediT authorship contribution statement

Seham Mohamed Moeen: Conceptualization, Methodology, Writing – original draft. **Ola Mahmoud Wahba:** Visualization, Formal analysis. **Ahmed Mohamed Mandour:**

Investigation, Data curation. **Noha Abdel Ghany:** Investigation, Data curation. **Mohamed AbdelKader Osman:** Conceptualization, Methodology, Investigation, Supervision. **Tarek Abdelazeem Sabra:** Methodology, Investigation. **Mohammed Hamada Takrouney:** Investigation, Data curation. **Ahmed Mohamed Moeen:** Conceptualization, Methodology, Supervision, Writing — original draft.

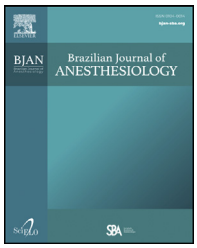
Acknowledgments

We thank all children who participated in the study, and all the research staff.

References

1. Gupta R, Singh S. Challenges in paediatric laparoscopic surgeries. Indian JAnaesth. 2009;53:560—6.
2. Pretorius M, Rasmussen GE, Holcomb GW. Hemodynamic and catecholamine responses to a laparoscopic adrenalectomy for pheochromocytoma in a pediatric patient. Anesth Analg. 1998;87:1268—70.
3. El Basha S, Hanna MG, Soaida SM, Refaee HH. Intraperitoneal instillation of l-bupivacaine in laparoscopic pediatric procedures: a randomized-controlled study. Ain-Shams J Anaesthesiol. 2015;8:247—51.
4. Ahmed A. Laparoscopic surgery in children-anaesthetic considerations. J Pak Med Assoc. 2006;56:5—9.
5. Raof RA, El Metainy SA, Alia DA, Wahab MA. Dexmedetomidine decreases the required amount of bupivacaine for ultrasound-guided transversus abdominis plane block in pediatrics patients: a randomized study. J Clin Anesth. 2017;37:55—60.
6. Elnabtity AM, Ibrahim M. Intraperitoneal dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management in children undergoing laparoscopic appendectomy: A prospective randomized trial. Saudi J Anaesth. 2018;12:399—405.
7. Ali RM, Rabie AH, Elshalakany NA, El Gindy TM. Effect of intraperitoneal magnesium sulfate on hemodynamic changes and its analgesic and antiemetic effect in laparoscopic cholecystectomy. Ain-Shams J Anaesthesiol. 2015;8:153—9.
8. Willis MH, Merkel SI, Voepel-Lewis T. FLACC Behavioral Pain Assessment Scale: a comparison with the child's self-report. Pediatr Nurs. 2003;29:195—8.
9. Tian X, Yang P, Su T, et al. Intraperitoneal ropivacaine and early postoperative pain and postsurgical outcomes after laparoscopic herniorrhaphy in toddlers: a randomized clinical trial. Paediatr Anaesth. 2016;26:891—8.
10. Kim EM, Kim MS, Han SJ, et al. Magnesium as an adjuvant for caudal analgesia in children. Paediatr Anaesth. 2014;24:1231—8.
11. Freilich DA, Houck CS, Meier PM, Passerotti CC, Retik AB, Nguyen HT. The effectiveness of aerosolized intraperitoneal bupivacaine in reducing postoperative pain in children undergoing robotic-assisted laparoscopic pyeloplasty. J Pediatr Urol. 2008;4:337—40.
12. Zanetta VC, Meier-Haran P, Houck CS. The use of intraperitoneal nebulization of bupivacaine reduces the need for postoperative opioids in young children undergoing robotic-assisted laparoscopic reconstructive surgery. J Urol. 2012;187:e298.
13. Ahmed B, Ashraf AE, Doaa R. Antinociceptive effect of adrenoceptor agonist dexmedetomidine vs meperidine, topically, after laparoscpic gynecologic surgery. J Med Sci. 2008;8:400—4.
14. Fares KM, Mohamed SA, Abd El-Rahman AM, Mohamed AA, Amin AT. Efficacy and safety of intraperitoneal dexmedetomidine with bupivacaine in laparoscopic colorectal cancer surgery, a randomized trial. Pain Med. 2015;16:1186—94.
15. She Y-J, Zhang Z-Y, Song X-R. Caudal dexmedetomidine decreases the required concentration of levobupivacaine for caudal block in paediatric patients: a randomized trial. Paediatr Anesth. 2013;23:1205—12.
16. Mentes O, Harlak A, Yigit T, et al. Effect of intraoperative magnesium sulphate infusion on pain relief after laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2008;52:1353—9.
17. Saadawy IM, Kaki AM, Abd El Latif AA, Abd-Elmaksoud AM, Tolba OM. Lidocaine vs. magnesium: effect on analgesia after a laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2010;54:549—56.
18. Kesavan S. Approapriate timing of administration of magnesium sulphate during spinal anesthesia to enhance postoperative analgesia. Br J Anaesth. 2010;104:89—93.
19. Maharjan SK, Shrestha S. Intraperitoneal magnesium sulphate plus bupivacaine for pain relief after laparoscopic cholecystectomy. J Kathmandu Med Coll. 2012;1:21—5.
20. Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anesthetic requirements and postoperative analgesia in gynecology patients receiving total intravenous anesthesia. Br J Anaesth. 2007;1(00):397—403.
21. Jee D, Lee D, Yun S, Lee C. Magnesium sulphate attenuates arterial pressure increase during laparoscopic cholecystectomy. Br J Anaesth. 2009;103:484—9.
22. Pasqualucci A, de Angelis V, Contardo R, et al. Preemptive analgesia: Intraperitoneal local anesthetic in laparoscopic cholecystectomy. A randomized, double-blind, placebo-controlled study. Anesthesiology. 1996;85:11—20.
23. Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesth Analg. 2006;103:682—8.
24. Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesth Analg. 2007;104:689—702.
25. Gause CD, Casamassima MG, Yang J, Hsiung G, Rhee D. Laparoscopic versus open inguinal hernia repair in children ≤ 3: a randomized controlled trial. Pediatr Surg Int. 2017;33:367—76.

Brazilian Journal of Anesthesiology 2024;74(5):744178



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Comparison of the lateral sagittal and costoclavicular approaches for ultrasound-guided infraclavicular block in pediatric patients: a prospective randomized study



Ahmet Murat Yayik [a,b,*], **Sevim Cesur** [c], **Figen Ozturk** [d], **Erkan Cem Celik** [a,b], **Muhammet Emin Naldan** [d], **Ali Ahiskalioglu** [a,b]

[a] *Ataturk University School of Medicine, Department of Anesthesiology and Reanimation, Erzurum, Turkey*
[b] *Clinical Research, Development and Design Application and Research Center, Ataturk University School of Medicine, Erzurum, Turkey*
[c] *Kocaeli University School of Medicine, Department of Anesthesiology and Reanimation, Kocaeli, Turkey*
[d] *Erzurum Regional Training and Research Hospital, Department of Anesthesiology and Reanimation, Erzurum, Turkey*

Received 22 July 2020; accepted 8 May 2021
Available online 6 June 2021

KEYWORDS
Lateral sagittal brachial plexus block;
Costoclavicular brachial plexus block;
Pediatric ultrasound-guided regional anesthesia;
Postoperative analgesia;
Upper extremity surgery

Abstract
Background: The lateral sagittal brachial plexus block is the most used method for pediatric upper extremity surgery, whereas the applications of costoclavicular brachial plexus block are limited. This study aimed to compare the lateral sagittal and costoclavicular approaches for the ultrasound-guided infraclavicular block in pediatric patients.
Methods: Sixty pediatric patients aged 5–15 years undergoing hand or forearm surgery were randomly assigned to two groups. Group LS (n = 30) received ultrasound-guided lateral sagittal block, and Group CC (n = 30) received ultrasound-guided costoclavicular block. The block performing time, needling time, imaging time, needle visibility, number of passes, sensorial/motor block time, and postoperative pain scores were evaluated.
Results: The needling time (82.90 ± 28.17 seconds vs. 64.77 ± 28.11 seconds respectively, $p = 0.004$) and total block performance time (109.53 ± 29.75 seconds vs. 89.70 ± 29.98 seconds respectively, $p = 0.005$) were significantly longer in Group LS than in Group CC. However, there was no significant difference between the groups in imaging time, needle visibility, number of passes, sensorial/motor block time, and postoperative pain scores ($p > 0.05$).
Conclusions: Costoclavicular and lateral sagittal brachial plexus blocks resulted in similar anesthetics effects. Moreover, the costoclavicular method can be a better alternative to lateral sagittal as it has a shorter block performance time.
© 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-mails: m_yayik@hotmail.com, murat.yayik@atauni.edu.tr (A.M. Yayik).

https://doi.org/10.1016/j.bjane.2021.05.005
© 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

Brachial plexus block is frequently used as postoperative analgesia, or as the main anesthetic method in upper extremity surgery.[1,2] Brachial plexus is adjacent to large vessels and vital structures such as the pleura extending from the interscalene region to the axillary region. Since this adjacency is narrower in pediatric patients, ultrasonography becomes much more critical in pediatric regional anesthesia interventions.[3,4] Additionally, ultrasound (US) allows the practitioners to avoid potential complications such as vascular puncture and pneumothorax since it reveals the anatomic structures, needle, and local anesthetic spreading in real time.

Lateral sagittal technique for infraclavicular brachial plexus block is often preferred for hand and forearm surgeries in adults and children. The local anesthetic agent is administered around the axillary artery, which is located deep in the pectoral muscles. However, at this level, the brachial plexus cords are located deeply and are separated from each other.[5] In the costoclavicular fossa, the cords are located more on the surface and are clustered with each other in the immediate lateral side of the axillary artery.[6] This positioning offers many advantages, including short onset time of blockade in single-injection technique and effective distribution of the drug to all the cords in block catheter applications.[7,8] Although studies comparing both methods in adult patients are present in the literature, none are available for pediatric patients.

Our main objective was to analyze whether block performance time is better in costoclavicular block compared to lateral sagittal for pediatric patients.

Methods

Ethical approval was obtained for this prospective randomized study from the Ethical Committee of Ataturk University. The study was registered with a clinical trial registry (ClinicalTrials.gov, identifier NCT04215614). Sixty American Society of Anesthesiologists (ASA) physical status I–II patients aged 5–15 years who underwent hand or forearm surgery were included in the study. Patients with respiratory disease, infection in the injection area, coagulopathy, allergy to any of the drugs to be used, and previously known neurological damage were excluded from the study.

A sealed envelope randomization method was used to randomize consented study participants on a 1:1 ratio to receive the study technique. Patient groups were written into 60 opaque envelopes and sealed, afterward the envelopes shuffled like a deck of cards and numbered. The patient who accepted to participate in the study was taken to the operating room. The envelope with the patient number was opened and the patient was administered the allocated treatment regimen.

Group LS was the lateral sagittal block group and Group CC was the costoclavicular block group. All patients were administered the same anesthetic protocol.

The patients were administered 0.1 $mg.kg^{-1}$ of midazolam intravenously in the premedication room. Routine electrocardiogram (ECG), noninvasive blood pressure, and SpO_2 were monitored, and O_2 (2–4 $L.min^{-1}$) was given via a nasal cannula. During the block procedure and operation, 1 $mg.kg^{-1}$ bolus and 25–50 $mcg.kg^{-1}.min^{-1}$ propofol infusion were started by spontaneous breathing.

All blocks were performed by anesthesiologists who had at least 2 years of experience in USG regional anesthesia. Furthermore, the same USG device, high frequency linear probe, and block needle (22G 50-mm block needle Stimuplex® Ultra, Braun, Germany) were used. The same block mixture (2% lidocaine and 0.5% bupivacaine with a volume of 0.3 $mL.kg^{-1}$ and a ratio of 1:1) was administered to all the patients.

Group LS: The intervention site and the US probe were sterilized. The head of the patient was rotated to the opposite direction of the side to be operated. The sterile USG probe was inserted into the lateral infraclavicular fossa, thereby monitoring the axillary artery and the brachial plexus cords located around it. After skin infiltration with local anesthetics, injection was made from the cranial to the caudal using in-plane technique. The area between the posterior cord and the axillary artery was accessed, which was followed by the administration of the entire local anesthetic solution to this area after ensuring negative aspiration of blood or air (Fig. 1A-B and Fig. 2A).

Group CC: After the sterilization procedure, the head of the patient was rotated to the opposite direction of the side to be operated, and the arm was abducted at an angle of 90°. The sterile USG probe was placed on the lower border of the clavicle in the middle line parallel to it. The axillary artery and the subclavius muscle were displayed in the costoclavicular fossa. Subsequently, three cords of the brachial plexus were displayed in the lateral side of the axillary artery. An in-plane technique at the center of the three brachial plexus cords after negative aspiration of blood or air was employed for administering the injection (Fig. 1C–D and Fig. 2B).

The blocks were checked using the pinprick test for ulnar radial and median nerves (no movement response to a cutaneous pinprick) 20 minutes after the injection of local anesthetic, and the surgery was commenced. Movement response after surgical incision, a 10% increase in heart rate, and a 20% increase in respiratory rate were defined as an insufficient block. Two $mcg.kg^{-1}$ fentanyl was administered to these patients with incremental boluses. Transition to general anesthesia protocol was planned in patients who felt pain and could not tolerate the surgery despite the bolus of fentanyl.

Imaging time was defined as the time interval from the contact of the US probe with the patient until obtaining a satisfactory image of the axillary artery and the brachial plexus cords. The needling time was defined as the time from the needle insertion until the entire administration of the local anesthetic solution. The block performance time was defined as the sum of the imaging time and needling time. The number of needle passes was also recorded. Needle visibility was evaluated using a 5-point Likert scale (1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = very good).

Motor blockade duration was defined as the interval between the brachial plexus puncture time and the movement of the forearm or one of the fingers. Sensory blockade duration was defined as the interval between the brachial plexus puncture time and the first dose of rescue analgesia.

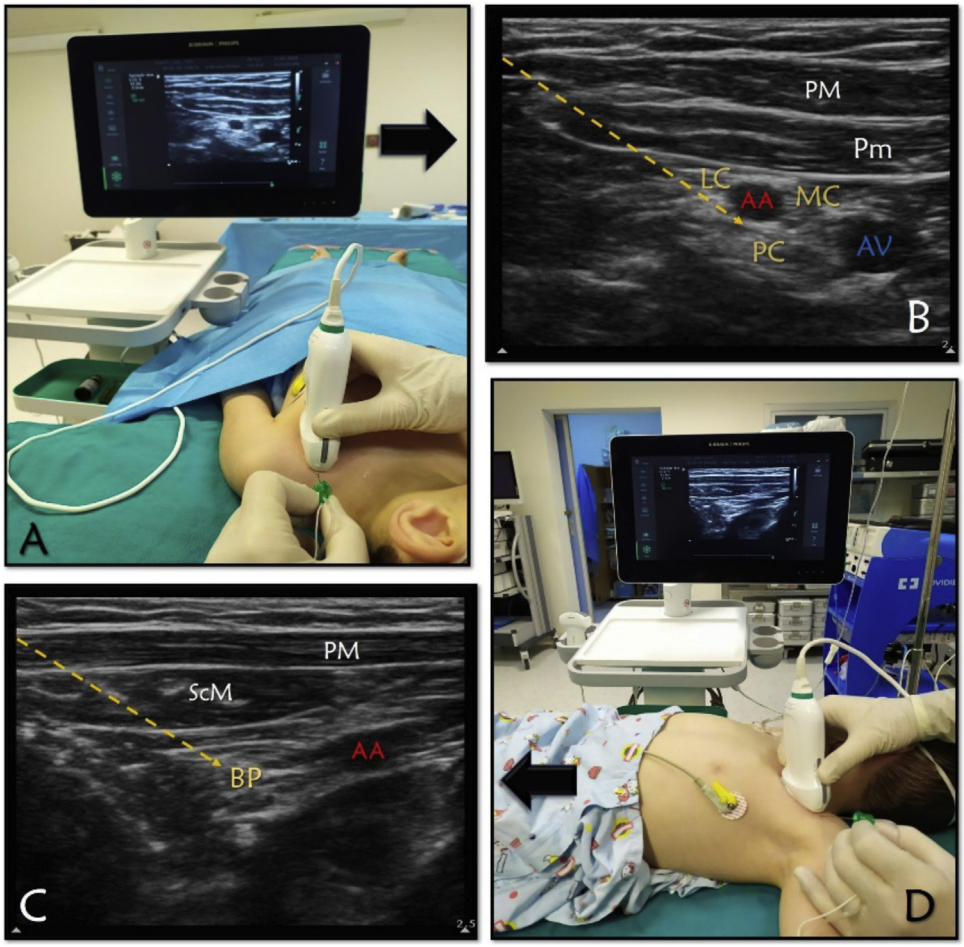


Figure 1 A, Patient, ultrasound set up and needle orientation for lateral sagittal block (LSB); B, Sonographic anatomy of LSB; C, Sonographic anatomy of costoclavicular block (CCB); D, Patient, ultrasound set up and needle orientation for CCB. PM, Pectoralis Major; Pm, Pectoralis minor; LC, Lateral cord; PC, Posterior cord; MC, Medial cord; AA, Axillary artery; AV, Axillary vein; ScM, Subclavius Muscle; BP, Brachial Plexus.

Block complications such as pneumothorax, vascular puncture, Local anesthetic systemic toxicity, hematoma, and Horner's syndrome were recorded.

The same protocol was applied for all the groups for postoperative analgesia. Patients with an Aldrete score of $\geq$ 9 were referred to the ward. Postoperative follow-up and evaluation of the cases were done by a researcher who had no knowledge of the study group. Postsurgical pain assessment was performed using the Wong–Baker FACES Pain Scale at 1, 2, 4, 8, 12, and 24 hours. In patients with a pain score of $\geq$ 4, 10 mg.kg^{-1} paracetamol was administered as a rescue analgesic, and this period was recorded as sensory blockade duration.

Sample size estimation and statistical analyses

G*Power (version 3.1.9.2) was used to estimate the sample size (a priori). The primary aim was to evaluate the block performance time. In our pilot study, we found that the block performance time for Group LS (n = 10) was 110 $\pm$ 34 seconds and that for Group CC (n = 10) was 86 $\pm$ 13 seconds. When a block performance time difference between the two groups of 24 seconds was regarded as significant, it was estimated that a sample size of 26 patients per study group (totally 52 patients) would provide 95% power with an α error of 0.05. To account for an estimated dropout, the required sample size was adjusted to 30 patients for each group.

The SPSS 22.0 (SPSS Inc, Chicago, IL) software was used for statistical analyses. The Chi-squared test was employed to compare the categorical variables between the groups. Normal distribution of numerical parameters was investigated using the Kolmogorov–Smirnov and histogram tests. Student's *t*-test was utilized to compare the normally distributed parameters, and the Mann–Whitney test was used for the non-normally distributed parameters. *p*-values < 0.05 were regarded as statistically significant.

Results

The eligible patients were analyzed for the primary outcomes and were presented in a flow diagram of Consolidated Standards of Reporting Trials (Fig. 3).

The demographic data of the patients are shown in Table 1. There was no difference between the two groups

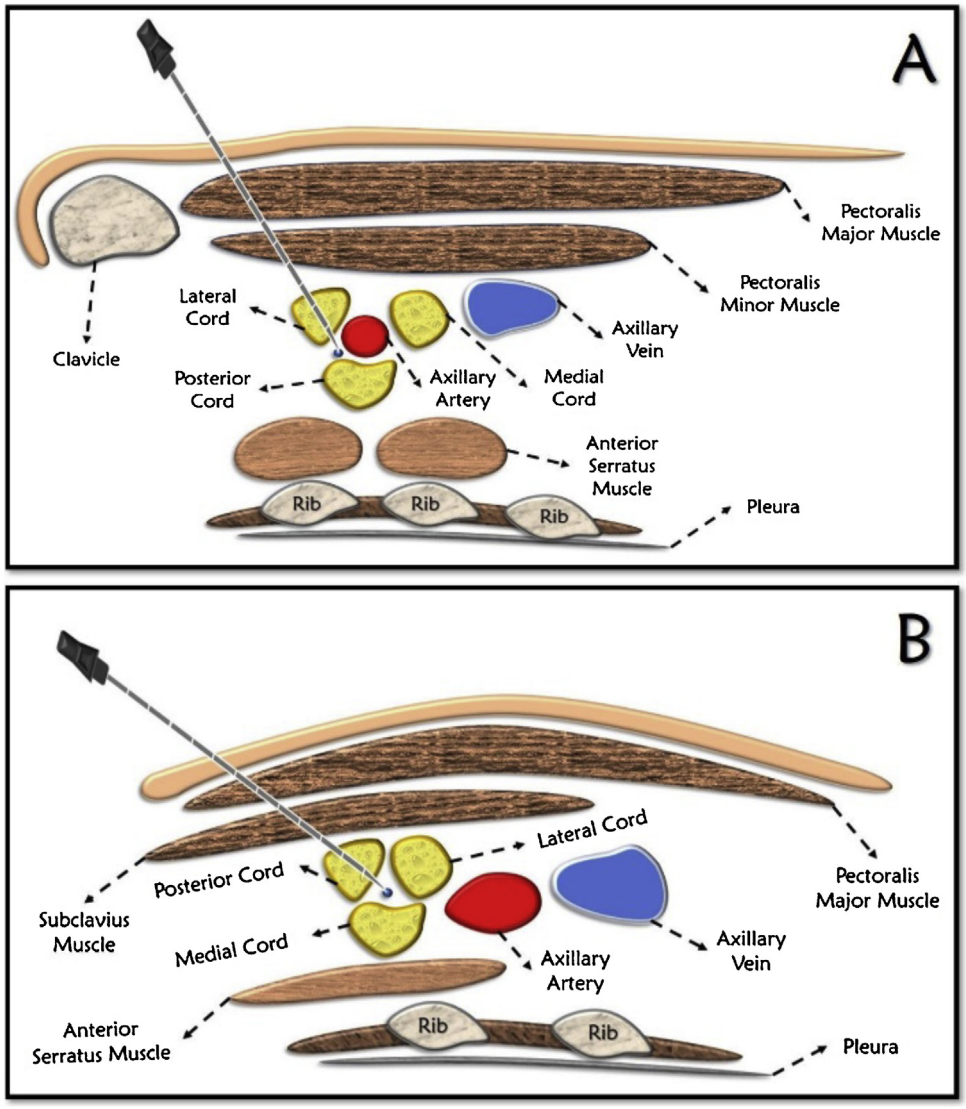


Figure 2 Basic illustration of lateral sagittal block (A) and costoclavicular block (B).

Table 1 Demographic characteristic of study patients.

	Group LS (n = 30)	Group CC (n = 30)	*p*
Age (y)	8.67 ± 2.51	9.53 ± 2.93	0.224[a]
Weight (kg)	26.47 ± 5.14	28.67 ± 5.76	0.124[a]
Gender (F/M)	9/21	13/17	0.284[b]
Duration of surgery (min)	39.17 ± 27.01	40.67 ± 22.00	0.814[a]
Duration of anesthesia (min)	66.67 ± 27.99	64.33 ± 22.73	0.724[a]
Operation region (hand/forearm)	9/21	4/26	0.117[b]
Types of surgery (emergency/elective)	23/7	20/10	0.390[b]

Values are presented as number or mean ± standard deviation.
[a] Independent sample t-test.
[b] Chi-square test.

in terms of age, weight, gender, duration of anesthesia-surgery, type of surgery, and operation area ($p > 0.05$).

The imaging time was similar between Group LS and Group CC, and there was no statistically significant difference between the groups (26.53 ± 8.09 seconds vs 24.40 ± 6.74 seconds, respectively; $p = 0.272$). However, the needling time was statistically significantly longer in Group LS than in Group CC (82.90 ± 28.17 seconds vs 64.77 ± 28.11 seconds respectively; $p = 0.004$), and the block performance time was statistically significantly longer in Group LS than in

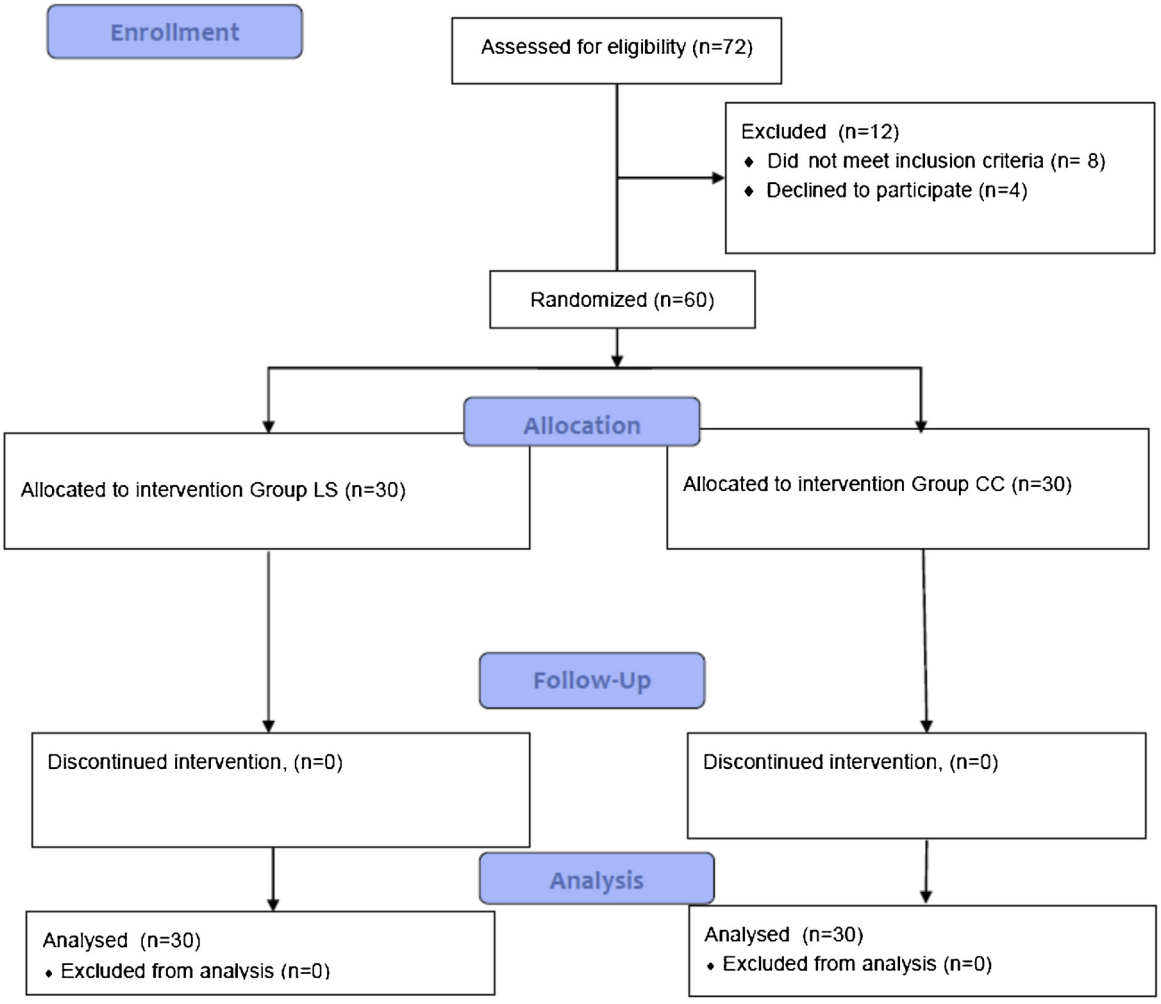


Figure 3 Consolidated standards of reporting trials.

Table 2 Block performance data.

	Group LS (n = 30)	Group CC (n = 30)	*p*
Imaging time (s)	26.53 ± 8.09	24.40 ± 6.74	0.272[a]
Needling time (s)	82.90 ± 28.17	64.77 ± 28.11	0.004[b]
Block performance time (s)	109.53 ± 29.75	89.70 ± 29.98	0.005[b]
Needle visibilty (very poor /poor /fair /good /very good)	0/0/3/10/17	0/0/0/9/21	0.176[c]
Number of passes	1.30 ± 0.53	1.20 ± 0.41	0.418[a]

Values are presented as number or mean ± standard deviation.
[a] Independent sample t-test.
[b] Mann-Whitney U test.
[c] Chi-square test.

Group CC (109.53 ± 29.75 seconds vs 89.70 ± 29.98 seconds respectively; $p = 0.005$). There was no significant difference between the groups in terms of the number of passes and needle visibility ($p > 0.05$) (Table 2).

The block was successful in all patients during the sensory examination at the 20th minute after the block performance, and no patients needed additional fentanyl or transition to general anesthesia after the onset of the surgery.

The postoperative motor blockade duration was 291.50 ± 169.98 minutes in Group LS and 261.50 ± 136.12 minutes in Group CC. The sensory blockade duration was 539.33 ± 258.34 minutes in Group LS and 487.00 ± 212.96 minutes in Group CC. These values did not reveal any statistically significant difference ($p > 0.05$).

Postoperative pain assessment was performed within the first 24-h period using the Wong–Baker FACES Scale.

Table 3 Postoperative Wong-Baker FACES scale.

	Group LS (n = 30)	Group CC (n = 30)	*p*
Postoperative 1 h	0.27 ± 0.69	0.53 ± 0.90	0.200
Postoperative 2 h	0.40 ± 1.10	0.67 ± 1.09	0.161
Postoperative 4 h	0.47 ± 1.01	0.80 ± 1.35	0.333
Postoperative 8 h	2.13 ± 2.16	2.53 ± 2.22	0.472
Postoperative 12 h	2.40 ± 2.54	2.73 ± 2.49	0.570
Postoperative 24 h	1.73 ± 1.82	1.60 ± 1.77	0.765

Values are presented as mean ± standard deviation.
Mann-Whitney U test.

There was no statistically significant difference between the groups during all the time intervals assessed ($p > 0.05$) (Table 3).

No vascular puncture, hematoma, pneumothorax, Horner's syndrome, or neurological complications occurred in any of the patients.

Discussion

The present study shows that the needling time and block performance time were shorter in the costoclavicular approach than in the LS approach of the infraclavicular brachial plexus block in pediatric patients. However, there was no difference between the two approaches in terms of the number of needle passes, needle visibility, pain scores, and sensory and motor block duration.

In recent years, the use of US is increasingly preferred in pediatric regional anesthetic procedures.[9] The visualization of anatomical landmarks and nerves increases block success while simultaneously avoiding possible complications related to critical structures. Since critical structures in children are located closer to the target tissues than in adults, US guidance is even more important in peripheral nerve block procedures.[4] In pediatric patients, US-guided brachial plexus block is often administered from the interscalene, supraclavicular, and infraclavicular regions for postoperative analgesia or anesthesia.[3,10–12]

The most common approach for infraclavicular brachial plexus block in adults and children is the LS method. The brachial plexus is located three cords under the pectoral major and minor muscles, apart from each other around the axillary artery. Although all three cords disperse around the axillary artery in the direction of 3-to-9 o'clock, serious anatomical differences can be present.[13] In the single-injection technique of the lateral sagittal brachial plexus block (LSB), the needle is directed between the axillary artery and the posterior cord. The local anesthetic is expected to reach all three cords with a U-shaped spreading around the axillary artery. However, block onset time may be affected by some aspects of the lateral infraclavicular fossa anatomy, such as the depth of the cords, the distance between them, and individual anatomical variations.[14]

Costoclavicular brachial plexus block (CCB) has been used in adult patients in recent years and has been successfully applied in hand, forearm, and shoulder.[14–16] In the literature, the use of CCB has been reported only in a few pediatric patients, and it was first reported by us in a case series for postoperative analgesia in 2019.[17]

The costoclavicular space is bordered by the clavicle in the superior region, subclavius, and pectoral major muscles in the anterior region, and by the anterior chest wall in the posterior region. The cords of the axillary artery, vein, and brachial plexus pass through this cavity to the lateral infraclavicular fossa. This area is more superficial than the lateral infraclavicular fossa.[18] Moreover, the cords of the brachial plexus are located adjacent to each other immediately in the lateral side of the axillary artery. This anatomical layout offers many advantages both in US imaging and in block procedures. All three cords are located in a single sonographic image in the transverse section, and local anesthetic distribution can be achieved in all three cords with a single injection. The costoclavicular space is also an area suitable for catheter applications; the block catheter applied from this area is located close to all three cords, as well as to the distal end of the catheter, and has a low risk of dislocation since it passes through an intramuscular tunnel.

Few studies have compared LSB and CCB in adults in the literature. In these studies, no difference was found between both groups in terms of block performance time.[14,19] However, there were differences between the two groups in terms of block onset time. In the study by Leurcharusmee et al. conducted using 35 mL of local anesthetics, similar block onset times were obtained in both groups.[19] However, Songthamwat et al. who used a lower volume of local anesthetics (25 mL) in their study, reported significantly shorter sensory and motor block onset times in the CCB group.[14] In the present study, while there was no difference between both groups of pediatric patients in terms of number of needle passes and needle visibility, the block performance time was shorter in Group CC. In the single-injection technique of LSB, the target point lies between the axillary artery and the posterior cord. In interventions targeting this region, vascular puncture should be avoided as the target point in CCB is further away from the axillary artery when compared with LSB. In the present study, although no patient had vascular puncture in either of the two groups, we believe that this anatomical location was advantageous for Group CC and resulted in shorter block performance time. Although the difference in the block application times between the groups was clinically negligible, it was statistically significant. It shows the ease of application of the costoclavicular block. Furthermore, in CCB, the use of USG minimized the risk although the close adjacency of the pleura was a disadvantage.

In CCB, the USG probe was placed parallel to the clavicle to display the anatomical landmarks and cords at the

lower border of the clavicle. Needle entry was performed starting at the lateral side and progressing to the medial side using in-plane technique. In pediatric patients, especially in children under 5 years of age, coracoid process can prevent needle entry and orientation at the right angle. In this case, the mediolateral approach can be considered as an alternative method.[20]

There are some limitations in this study. First, children aged 5–15 years were included in the study. The coracoid process may prevent the block procedure, especially in children under the age of five, which might also affect block performance data and complication rates. A further study is required to investigate block performance time in children under the age of five. Second, block onset time could not be evaluated because children were under sedation. Moreover, the issues such as pain and paresthesia that the patients might have experienced during the block could not be assessed because they were in a state of sedation. Finally, the sample size of the study was determined based on the block performance time, which is the primary purpose of the study. Side effects of the block procedure are not fully identifiable with a small sample size, and hence, further studies involving larger sample sizes may be needed.

In conclusion, costoclavicular and lateral sagittal brachial plexus blocks resulted in similar anesthetics effects. Moreover, the costoclavicular method can be a better alternative to lateral sagittal as it has a shorter block performance time.

Conflicts of interest

The authors declare no conflicts of interest.

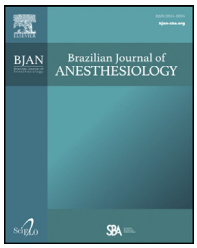
Acknowledgements

Special thanks to Dr. Muhammed Enes Aydin and Dr. Elif Oral Ahiskalioglu for support to manuscript.

References

1. Albrecht E, Mermoud J, Fournier N, et al. A systematic review of ultrasound-guided methods for brachial plexus blockade. Anaesthesia. 2016;71:213–27.
2. Chin KJ, Singh M, Velayutham V, et al. Infraclavicular brachial plexus block for regional anaesthesia of the lower arm. Anesth Analg. 2010;111:1072.
3. Yanal H, Gurkan Y, Kus A, et al. Awake hand surgery under ultrasound-guided infraclavicular block is possible for cooperative children. Agri. 2016;28:190–3.
4. Boretsky KR. Pediatric Regional Anesthesia Advances. Curr Anesthesiol Rep. 2019;9:100–9.
5. De Jose Maria B, Banus E, Navarro Egea M, et al. Ultrasound-guided supraclavicular vs infraclavicular brachial plexus blocks in children. Paediatr Anaesth. 2008;18:838–44.
6. Karmakar MK, Sala-Blanch X, Songthamwat B, et al. Benefits of the costoclavicular space for ultrasound-guided infraclavicular brachial plexus block: description of a costoclavicular approach. Reg Anesth Pain Med. 2015;40:287–8.
7. Li JW, Songthamwat B, Samy W, et al. Ultrasound-Guided Costoclavicular Brachial Plexus Block: Sonoanatomy, Technique, and Block Dynamics. Reg Anesth Pain Med. 2017;42:233–40.
8. Regufe R, Artilheiro V, Dias Mb, et al. Continuous costoclavicular brachial plexus block in a pediatric patient for post-fracture rehabilitation. Paediatr Anaesth. 2020;30:720–1.
9. Walker BJ, Long JB, Sathyamoorthy M, et al. Complications in Pediatric Regional Anesthesia: An Analysis of More than 100,000 Blocks from the Pediatric Regional Anesthesia Network. Anesthesiology. 2018;129:721–32.
10. Xu C, Wang B, Yang A, et al. The efficacy of pediatric ultrasound guided brachial plexus block anesthesia and determination of optimal anesthetic drug dosage. Minerva Pediatr. 2016. Epub ahead of print. PMID: 27827526.
11. Ergonenc T, Can H, Gokhan Beyaz S. Ultrasound-guided interscalene brachial plexus block in a child with acute upper respiratory infection: A case report. Anaesthesist. 2017;66:782–5.
12. Marhofer P, Willschke H, Kettner SC. Ultrasound-guided upper extremity blocks - tips and tricks to improve the clinical practice. Paediatr Anaesth. 2012;22:65–71.
13. Sauter AR, Smith HJ, Stubhaug A, et al. Use of magnetic resonance imaging to define the anatomical location closest to all three cords of the infraclavicular brachial plexus. Anesth Analg. 2006;103:1574–6.
14. Songthamwat B, Karmakar MK, Li JW, et al. Ultrasound-guided infraclavicular brachial plexus block: prospective randomized comparison of the lateral sagittal and costoclavicular approach. Reg Anesth Pain Med. 2018;43:825–31.
15. Aliste J, Bravo D, Layera S, et al. Randomized comparison between interscalene and costoclavicular blocks for arthroscopic shoulder surgery. Reg Anesth Pain Med. 2019, http://dx.doi.org/10.1136/rapm-2018-100055. Online ahead of print.
16. Tulgar S, Ugutmen E. A modified technique for the application of ultrasound-guided costoclavicular brachial plexus block for elbow surgery leading to differential block. J Clin Anesth. 2018;47:65–6.
17. Yayik AM, Cesur S, Ozturk F, et al. Ultrasound guided costoclavicular approach to brachial plexus: First pediatric report. J Clin Anesth. 2019;55:136–7.
18. Sala-Blanch X, Reina MA, Pangthipampai P, et al. Anatomic basis for brachial plexus block at the costoclavicular space: a cadaver anatomic study. Reg Anesth Pain Med. 2016;41:387–91.
19. Leurcharusmee P, Elgueta MF, Tiyaprasertkul W, et al. A randomized comparison between costoclavicular and paracoracoid ultrasound-guided infraclavicular block for upper limb surgery. Can J Anaesth. 2017;64:617–25.
20. Nieuwveld D, Mojica V, Herrera AE, et al. Medial approach of ultrasound-guided costoclavicular plexus block and its effects on regional perfussion. Rev Esp Anestesiol Reanim. 2017;64:198–205.

Brazilian Journal of Anesthesiology 2024;74(5):744114



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Pediatric emergence delirium is linked to increased early postoperative negative behavior within two weeks after adenoidectomy: an observational study

Anne Houben[a], **Shahab Ghamari**[b], **Andreas Fischer**[c], **Claudia Neumann**[b], **Torsten Baehner**[d], **Richard K. Ellerkmann**[a,b,*]

[a] *Klinikum Dortmund, Department of Anesthesiology and Operative Intensive Care Medicine, Dortmund, Germany*
[b] *University Hospital Bonn, Department of Anesthesiology and Operative Intensive Care Medicine, Bonn, Germany*
[c] *ASG GbR Anesthesia and Pain Therapy, Moenchengladbach, Germany*
[d] *St. Nikolaus-Stifts Hospital, Department of Anesthesiology and Operative Intensive Care Medicine, Andernach, Germany*

Received 31 August 2020; accepted 13 March 2021
Available online 19 April 2021

KEYWORDS
Adenoidectomy;
Behavior;
Emergence delirium;
Anesthesia;
Child;
Preschool

Abstract
Background: The aim of this prospective multicenter observational study was to measure the incidence of postoperative pediatric emergence delirium and to investigate the occurrence of early postoperative negative behavior within two weeks after outpatient adenoidectomy in preschool children.
Methods: The study comprised 222 patients (1–7 years of age). All children received a multimodal anesthesia based on total intravenous anesthesia with propofol and remifentanil in combination with piritramid (0.1 $mg.kg^{-1}$), ibuprofen (10 $mg.kg^{-1}$), dexamethason (0.15 $mg.kg^{-1}$), and ketanest S (0.1 $mg.kg^{-1}$). We evaluated emergence delirium using the Pediatric Anesthesia Emergence Delirium Scale (PAED) at different predefined time points during the recovery period. Emergence delirium was defined as a PAED score $\geq$ 9 for the first three criteria. Additionally, we defined early postoperative negative behavior to be present when at least 5 of 27 criteria of the post hospitalization behavior questionnaire were positive.
Results: The incidence of emergence delirium following our anesthetic regime was 23%. The incidence of early postoperative negative behavior was significantly higher among patients with emergence delirium (24% vs. 11%, p = 0.04). The two categories, ''sleep disturbance'' and ''separation anxiety'', tested within the questionnaire for early postoperative negative behavior, were identified as the most common postoperative negative behavioral changes.

* Corresponding author.
E-mail: richard.ellerkmann@klinikumdo.de (R.K. Ellerkmann).

https://doi.org/10.1016/j.bjane.2021.03.008
© 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/).

Conclusion: Emergence delirium not only plays a role immediately after surgery but is also linked to early postoperative negative behavior within two weeks after outpatient adenoidectomy. Parents should be informed that early postoperative negative behavior may occur in 1 out of 4 patients if emergence delirium was present postoperatively.
Trial Registration: DRKS – German Clinical Trial Register ID: DRKS00013121
© 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

Emergence Delirium (ED) following anesthesia remains an unsolved problem.[1,2] Affected children are unaware of their surrounding and show unpurposeful movements. They are unable to focus or get in touch with their trusted caregivers. Crying and weeping increases to a point where neither caregivers nor trained professionals are able to calm them down. These children are prone to injure themselves by dislocating catheters, undo bandages, and thereby compromise surgical outcome. Several risk factors have been identified, for example pain,[3] surgical procedures such as ear, nose and throat surgery,[4,5] and preschool age versus school age.[5,6] In addition to certain anesthetic regimes, such as desflurane-N20-anesthesia, the incidence of ED is described as high as 80%.[7] Nevertheless, several clinical studies have shown that opioids,[8,9] total intravenous anesthesia,[10] ketamine,[9] and dexamethason[11] can reduce the risk of ED. Risk reduction for sevoflurane-anesthesia was measured as 37% for opioids (in particular fentanyl), 35% for propofol, and 30% for ketamine.

However, to the best of our knowledge, no study has yet investigated the incidence of ED following an anesthetic concept combining propofol, ketamine, dexamethasone, and opioids after outpatient adenoidectomy for 1- to 7-year-old children.

Several scales and scores have been published previously to measure ED objectively. The Pediatric Anaesthesia Emergence Delirium Score (PAED score), being the ''gold standard''[12] in the past, has been recently adjusted by Locatelli et al.[13] He modified the scale by focusing only on the first three criteria thus increasing the specificity of this scale. The PAED score originally has 5 criteria, being: the child keeps eye contact, shows purposeful movements, is aware of surrounding, is restless, and is inconsolable (Table 1). Locatelli disregarded criteria 4 and 5 for defining ED as they – more or less – describe agitation. In our present study, we defined ED as proposed by Locatelli with $\geq$ 9 points out of 12 defining ED.

As ED is an acute disorder that occurs immediately after recovery from anesthesia, it is unknown whether long term changes may also occur postoperatively. Kain et al. described the incidence of early Postoperative Negative Behavior (ePONB) after outpatient surgical interventions being as high as 50%.[14] Risk factors for ePONB were identified as increased anxiety of the child in the preoperative holding area,[14–16] the child's age, number of siblings, and baseline temperament.[14]

The aim of this study was to investigate the incidence of emergence delirium and early postoperative negative behavior in patients following a multimodal anesthetic regime.

Methods

Following Ethics Committee approval (University Hospital Bonn, Germany) and parental written informed consent, we consecutively enrolled 222 (166 patients in Bonn, 56 patients in Moenchengladbach) children – from June 2015 till March 2016 – between 1 and 7 years of age scheduled for elective outpatient adenoidectomy with or without myringotomy in a prospective multicenter observational study.

Exclusion criteria were American Society of Anesthesiologists (ASA) physical status $\geq$ 3, critical illness with hemodynamic instability, active bleeding, or intellectual disability.

Premedication was performed orally with Midazolam (0.3–0.5 mg.kg^{-1}) 30 to 60 minutes prior to induction of anesthesia. Induction quality was monitored and documented by a 4-point scale ranging from ''sleeping'' over ''calm and awake'' to ''anxious and cooperative'' and ''crying and uncooperative''. We subsumed the first two states as being ''calm'' whereas the last two states were subsumed as being ''restless''. Anesthesia was preferably induced intravenously with propofol (2–4 mg.kg^{-1}) or alternatively via face mask with 4–8% Sevoflurane and 100% oxygen. Thereafter the anesthesia regime was switched to a total intravenous anesthesia and the airway was secured by a laryngeal mask.

Standard monitoring included ECG, $EtCO_2$, pulse oximetry and noninvasive blood pressure. After surgery was completed and spontaneous breathing restored, the laryngeal mask was removed, and patients were subsequently transferred to the PACU to reunite with their parents. All children received a multimodal anesthesia based on total intravenous anesthesia (propofol and remifentanil), piritramid (0.1 mg.kg^{-1}), ibuprofen (10 mg.kg^{-1}), dexamethason (0.15 mg.kg^{-1}) and ketanest S (0.1 mg.kg^{-1}). Applying intravenous Clonidine (2 μg.kg^{-1}) intraoperatively was left to the discretion of the anesthesiologist.

After recovery from anesthesia sleep, duration in the PACU and the occurrence of ED was monitored applying the PAED score (Table 1). ED was monitored and defined according to Locatelli et al.[13] as a so called ED I score of $\geq$ 9 (0 to 12 possible points) for the first 3 criteria of the PAED score (eye contact, purposeful movement,

Table 1 PAED (Pediatric Anesthesia Emergence Delirium) scale based on Delir-criteria (ED I) and Agitation-criteria (ED II) according to Locatelli et al.[13]

	Criteria	The child	Not at all	Just a little	Quite a bit	Very much	Extremely
Delir- criteria (ED I Score)	1	... keeps eye contact	4	3	2	1	0
	2	... shows purposeful movements	4	3	2	1	0
	3	... is aware of surrounding	4	3	2	1	0
Agitation- criteria (ED II Score)	4	... is restless	0	1	2	3	4
	5	... is inconsolable	0	1	2	3	4

Table 2 German version of the Post-Hospitalization Behavioral Questionnaire (PHBQ) by Buehrer et al.[17]

Number	Questions	Answers		
		Less then before	Same as before	More than before
1.	Does your child make a fuss about going to bed at night?			
2.	Does your child make a fuss about eating?			
3.	Does your child spend time just sitting or lying and doing nothing?			
4.	Does your child need a pacifer?			
5.	Does your child seem to be afraid of leaving the house with you?			
6.	Is your child uninterested in what goes on around him (or her)?			
7.	Does your child wet the bed at night?			
8.	Does your child bite his (or her) fingernails?			
9.	Does your child get upset when you leave him (or her) alone for a few minutes?			
10.	Does your child need a lot of help doing things?			
11.	Is it difficult to get your child interested in doing things (like playing games with toys)?			
12.	Does your child seem to be avoid or be afraid of new things?			
13.	Does your child have difficulty making up his (or her) mind?			
14.	Does your child have temper tantrums?			
15.	Is it difficult to get your child to talk to you?			
16.	Does your child seem to get upset when someone mentions doctors or hospitals?			
17.	Does your child follow you everywhere around the house?			
18.	Does your child spend time trying to get or hold your attention?			
19.	Is your child afraid of the dark?			
20.	Does your child have bad dreams at night or wake up and cry?			
21.	Does your child have irregular bowel movements?			
22.	Does your child have trouble getting to sleep at night?			
23.	Does your child seem to be shy around strangers?			
24.	Does your child have a poor appetite?			
25.	Does your child tend to disobey you?			
26.	Does your child break toys or other objects?			
27.	Does your child suck his (or her) fingers or thumbs?			

aware of surrounding). We additionally evaluated pain in the PACU applying the Face-Legs-Activity-Cry-Consolability-Score (FLACC-Score) to differentiate between pain related agitation and postoperative delirium. Pain was defined as a FLACC score of $\geq$ 4. Score guided assessment started right after awakening (Time 1) and was reevaluated after 20 minutes (Time 2) and prior to discharge from the PACU (Time 3). In addition, reevaluation was performed in case of obvious strange behavior, reawakening, or after an intervention by the anesthesiologist following a previously diagnosed ED.

Patients' parents were interviewed (via phone call) 14 days following the operation using a questionnaire for possible postoperative negative behavior (Table 2) that was handed out to the parents before discharged home. The interviewer was blinded to the occurrence of ED of the interviewed parent's child. We defined ePONB to be present when at least $\geq$ 5 of 27 questions of this questionnaire were answered positively. The questionnaire was validated in a German speaking pediatric population published by Buehrer et al.[17] using a German translation of the PHBQ (Post-Hospitalization

Table 3 Clinical data for male and female patients, data are given as mean ± standard deviation.

	Male	Female	*p*-value
Age	3 ± 1.21	4 ± 1.62	< 0.001
ASA (I:II)	96:21	74:11	0.436
Anesthesia duration (min)	37 ± 14	35 ± 14	0.36
Sleep duration (min)	50 ± 32	47 ± 28	0.43
ED I ≥ 9 (Y:N) (%)	29:71	15:85	0.024
Time 1 ED I	4 ± 4.27	2 ± 3.70	0.04
Time 2 ED I	2 ± 3.70	1 ± 2.86	0.2
Time 3 ED I	1 ± 2.20	0 ± 1.06	0.27
Time 1 FLACC	2 ± 2.60	1 ± 2.36	0.5
Time 2 FLACC	1 ± 2.53	1 ± 2.07	0.12
Time 3 FLACC	0 ± 1.37	0 ± 0.71	0.25
FLACC total	1 ± 2.30	1 ± 1.90	0.17
Induction quality (Calm:Restless) (%)	71:29	76:24	0.44

Behavioral Questionnaire) from Vernon et al.[18] published in 1966.

Statistics

Statistical analysis was performed using Microsoft Excel 2016. Further analysis was performed using Gnu Regression (gretl), Econometrics and Time-series Library 2016 (Allin Cottrell and Riccardo Lucchetti). Power analyses were undertaken by using G*Power (Heinrich-Heine University, Düsseldorf, Germany).

Descriptive statistics and demographic data between male and female patients are presented as mean ± standard deviation. Differences between groups as described in Table 3 were examined using Fisher's exact Test for categorial variables and Student's *t*-test for continuous variables. Repeated analyses of Fisher's exact test were used to compare variables such as sleep duration and ED. Comparisons were considered statistically significant for $p < 0.05$.

The sample size of the study was calculated to investigate the dependency of early postoperative negative behavior following emergence delirium in children. Assuming an α-error of 0.05, an effect size of 0.3 and a power of 95%, a sample size of 145 was calculated for our investigation. To allow for a considerable amount of dropouts of around 30% due to protocol deviations, language barriers, false phone numbers, or unavailability despite several phone call attempts we calculated a sample size of 200 patients.

Results

Written informed consent was given by 234 caregivers. Of these 234 patients 12 had to be discarded from further analysis due to the following reasons: 8 patients only received a myringotomy and 4 patients additionally received a tonsillectomy, resulting in 222 children being included in the study and completing final statistical analysis. Screening for ePONB two weeks after surgery was successful in 178 patients (80.2%). Due to a false phone number (n = 9), unavailability despite several phone call attempts (n = 23), and language barrier (n = 12) 44 patients in total (19.8%) could not be interviewed two weeks after surgery.

Table 4 Correlation of ED (Emergence Delirium defined as ED I ≥ 9) and ePONB (early Postoperative Negative Behavior defined as ≥5 of 27 criteria of the questionnaire being positive).

	ePONB	No ePONB	Total
ED	10	32	42
no ED	15	121	136
total	25	153	178

Fisher's exact test: *p*-value: 0,044867.

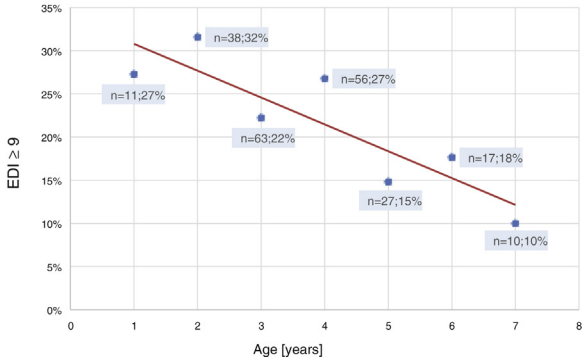


Figure 1 Prevalence of ED according to the patient's age.

Demographic data between the two sites (Bonn and Moenchengladbach) were comparable. The incidence of ED in this observational study was 23% (n = 52 of 222 patients). The occurrence of ePONB within the observed period of time (2 weeks) was 14% (n = 25 of 178 patients). ED was positively correlated with the occurrence of ePONB with an incidence of 24% in patients developing ED versus an incidence of only 11% for patients without ED, $p = 0.04$ (Table 4).

An increase of postoperative sleep duration (defined as sleep in the PACU immediately after surgery) of 15 minutes resulted in a reduction of ED of approximately 50%, $p = 0.0002$. We detected a significant difference in sleep duration between children with or without intraoperative clonidine (55 ± 32 min vs. 42 ± 29 min, $p = 0.002$). Age correlated with the incidence of ED (Fig. 1). Older children had a lower risk for ED than younger children. Unexpectedly,

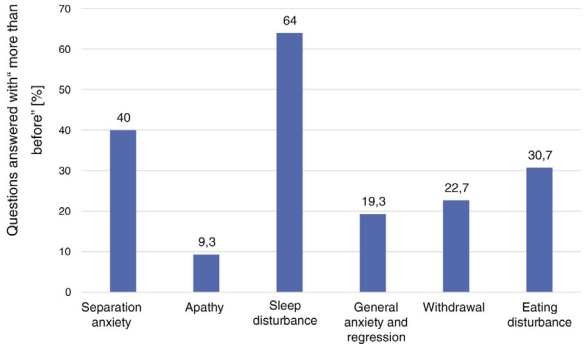


Figure 2 Questions answered with ''more than before'' in % within particular categories; separation anxiety = Category 1; apathy = Category 2; sleep disturbance = Category 3; general anxiety and regression = Category 4; withdrawal = Category 5; eating disturbance = Category 6.

the incidence of ED was significantly higher in male patients compared to female patients (29% vs. 15%, $p = 0.02$). However, boys were significantly younger at the time point of surgery (3 ± 1.2 years) compared to girls (4 ± 1.6 years) ($p < 0.001$) (Table 3).

Further analysis of ePONB revealed that postoperative negative behavioral changes mostly arose in the categories ''sleep disturbance'' and ''separation anxiety'' (Fig. 2). When investigating the 27 items of the PHBQ questionnaire in all patients tested positive for ePONB we could reveal certain questions to be of a higher relevance than others. Out of all patients with ePONB 84% answered positively on either of the two questions: ''Did you detect a higher incidence of nightmares in your child?'' or ''Did you detect more sleeping disturbances?''. From all positively tested patients 76% answered that their child ''became anxious when it was left alone for a few minutes''.

Discussion

Our investigation revealed a high incidence of ED of 23% following adenoidectomy in preschool children despite a multimodal anesthetic concept. Interestingly, ED seems to be linked to the incidence of ePONB within two weeks after outpatient adenoidectomy. Basically, it seems advisable to explain ED to parents ahead of surgery and inform on ePONB that may occur after discharge.

Incidences of ED published in the literature alter significantly depending on risk factors such as age and type of surgery as well as the applied anesthetic concept. Pieters et al. described an incidence of ED of 53%.[19] Comparing their results with our study is difficult due to different definitions of ED (≥16 points in all criteria of the PAED score vs. ≥ 9 points for criteria 1–3 of the PAED score), different pain-Scores applied (CHEOPS vs. FLACC-Score) and different surgical interventions investigated (tonsillectomy vs. adenoidectomy). Despite these limitations that become apparent when comparing incidences of different studies, we believe that the ''low'' incidence of ED in our study may be attributed to the multimodal anesthetic concept. The highest incidence of ED published by Grundmann et al. after Desflurane anesthesia and ''ENT'' (e.g., adenoidectomy with bilateral myringotomy and insertion of tubes and/or tonsillectomy) surgery was 80%.[7] Chandler et al. could show that the mere change from a volatile anesthetic to a Propofol based anesthesia reduced ED by nearly 50% from an incidence of 38.3% to 14.9% after ''strabismus surgery''.[20] The reported incidence of ED in our study is in line with the published data of Chandler et al. despite the discrepancy in defining ED as a PAED score of ≥ 10 out of 20 in their study.

Aono and colleagues have previously shown that preschool children reveal a higher incidence of ED after sevoflurane anesthesia compared to school children.[6] However, a difference in the incidence of ED between boys and girls has not been reported previously.[21]. The higher incidence of ED in male patients in our study could not be explained by ''higher excitement'' levels during induction of anesthesia or higher FLACC scores after adenoidectomy (Table 3). On the other hand, we detected a significant difference in age between male and female patients. This difference in lower age may have contributed to the detected increased incidence of ED in boys.

Early Postoperative Negative Behavior (ePONB) was diagnosed applying the German version of the PHBQ questionnaire.[17] The questions were grouped in six categories: ''separation anxiety'', ''apathy'', ''sleep disturbance'', ''general anxiety and regression'', ''withdrawal'', and ''eating disturbance''.[17] Incidences of ePONB differ considerably within the published literature.[14,15,21] Comparing these incidences is difficult due to different definitions of ePONB. Kain et al. defined ePONB as at least one positive answered question of the PHBQ,[14] while Faulk et al.[21] defined that at least seven questions must be answered positively. This might explain why the incidence reported by Faulk (8.8%) was lower compared to Kain's investigations (54% and 78.4%). In contrast to Kain et al.'s reported incidences of ePONB within two weeks after outpatient surgery,[14,15] the incidence of ePONB for our patients was comparatively low with 14% (Table 4). It is tempting to speculate that this ''lower'' incidence of ePONB in our study may be attributed to the performed multimodal anesthetic regime resulting in a lower incidence of ED of 23%. In fact, Kain et al. previously described that the incidence of ED is correlated with the incidence of ePONB.[15] Our results of ED being positively correlated with ePONB (24% vs. 11%, $p = 0.04$) are in line with Kain's finding. On the other hand, Faulk's published incidence of ePONB of 8.8%[21] is lower compared to our measured incidence of 14%. An explanation might be seen in the different definition of ePONB (7 positive idems, Faulk et al.[21]) of the PHBQ questionnaire vs. 5-items applied in our investigation). We believe that type of surgery (dental procedure vs. adenoidectomy) and age (1- to 12-years vs. 1- to 7-years) also have an impact on the incidence of ePONB.

It becomes evident that out of the six defined categories within the PHBQ, ''sleep disturbance'' and ''separation anxiety'' (Fig. 2) were found to be the most frequent postoperative changes in our investigated patients. Kain et al. also described a higher prevalence of ''separation anxiety'', while ''sleep disturbance'' was not found to be one of the most common behavioral changes.[14] The difference may be explained by the fact, that the children in our study were younger. Kain et al. used the PHBQ in the version of

Vernon[18] while we used the German Version of the PHBQ from Buehrer et al.[17] An essential difference between these two questionnaires is the different assignment of specific questions to the 6 mentioned categories. While Vernon's version assigns ''having bad dreams or waking up at night crying'' and ''get upset when you leave him (or her) alone for a few minutes'' to the category ''separation anxiety'', Buehrer's version assigns these questions to the category ''sleep disturbance''. When breaking down our results to single questions, our study was in line with Kains[14] results showing that the questions ''having bad dreams or waking up at night crying'' and ''getting upset when left alone for a few minutes'' were the most frequently positively answered questions.

There are limitations of our study that have to be taken into account. The PAED and FLACC scores always leave room for subjective interpretation and scoring known as inter-rater variability. The same limitation is true for the PHBQ where answers were dependent on the objectivity of the parents being interviewed as well as the objectivity of the interviewer. Since all parents were interviewed by the same interviewer being blinded to the occurrence of postoperative ED of all investigated patients, we believe that a possible bias of the interviewer was made impossible at this point.

Despite a multimodal anesthetic regime, the incidence of ED after outpatient adenoidectomy remained as high as 23% in our investigation. ED not only plays a role immediately after surgery but was linked to ePONB within two weeks after adenoidectomy.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. Cochrane Database Syst Rev. 2014:CD007084.
2. Mason KP. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. Br J Anaesth. 2017;118:335–43.
3. Bortone L, Bertolizio G, Engelhardt T, Frawley G, Somaini M, Ingelmo PM. The effect of fentanyl and clonidine on early postoperative negative behavior in children: a double-blind placebo-controlled trial. Paediatr Anaesth. 2014;24:614–9.
4. Swart ED, Rajah C, Rodseth RN. Induction behavior and race and its association with postoperative agitation in paediatric elektive surgery. South African J Anaesth Analg. 2017;23:36–9.
5. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg. 2003;96:1625–30.
6. Aono J, Ueda W, Mamiya K, Manabe M, Takimoto E. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology. 1997;87:1298–300.
7. Grundmann U, Uth M, Eichner A, Wilhelm W, Larsen R. Total intravenous anaesthesia with propofol and remifentanil in paediatric patients: a comparison with a desflurane-nitrous oxide inhalation anaesthesia. Acta Anaesthesiol Scand. 1998;42:845–50.
8. Tan Y, Shi Y, Ding H, Kong X, Zhou H, Tian J. μ-Opioid agonists for preventing emergence agitation under sevoflurane anesthesia in children: a meta-analysis of randomized controlled trials. Paediatr Anaesth. 2016;26:139–50.
9. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth. 2010;104:216–23.
10. Kanaya A, Kuratani N, Satoh D, Kurosawa S. Lower incidence of emergence agitation in children after propofol anesthesia compared with sevoflurane: a meta-analysis of randomized controlled trials. J Anesth. 2014;28:4–11.
11. Sajedi P, Baghery K, Hagibabie E, Mehr AM. Prophylactic use of oral acetaminophen or iv dexamethasone and combination of them on prevention emergence agitation in pediatric after adenotonsillectomy. Int J Prev Med. 2014;5:721–7.
12. Sikitch N, Lerman J. Development, and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138–45.
13. Locatelli BG, Ingelmo PM, Emre S, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Paediatric Anesthesia Emergence Delirium scale. Paediatr Anaesth. 2013;23:301–8.
14. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150:1238–45.
15. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004;99:1648–54.
16. Kain ZN, Caldwell-Andrews AA, Mayes LC, et al. Family-centered preparation for surgery improves perioperative outcomes in children: a randomized controlled trial. Anesthesiology. 2007;106:65–74.
17. Buehrer S, Klaghofer R, Weiss M, Schmitz A. Verhaltensauffälligkeiten von Kindern und Jugendlichen nach Narkose: Entwicklung einer deutschsprachigen Version des Post Hospitalization Behavior Questionnaire (Negative behavioral changes in children and adolescents after anesthesia: Development of a German language version of the Post Hospitalization Behavior Questionnaire). Anaesthesist. 2015;64:115–21.
18. Vennon DT, Schulman JL, Foley JM. Changes in children's behavior after hospitalization. Some dimensions of response and their correlates. Am J Dis Child. 1966;111:581–93.
19. Pieters BJ, Penn E, Nicklaus P, Bruegger D, Mehta B, Weatherly R. Emergence delirium and postoperative pain in children undergoing adenotonsillectomy: a comparison of propofol vs sevoflurane anesthesia. Paediatr Anaesth. 2010;20:944–50.
20. Chandler JR, Myers D, Mehta D, et al. Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanil to inhalational sevoflurane anesthesia. Paediatr Anaesth. 2013;23:309–15.
21. Faulk DJ, Twite MD, Zuk J, Pan Z, Wallen B, Friesen RH. Hypnotic depth and the incidence of emergence agitation and negative postoperative behavioral changes. Paediatr Anaesth. 2010;20:72–81.

Brazilian Journal of Anesthesiology 2024;74(5): 844541



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Preoperative gastric volume assessment using ultrasound in cerebral palsy pediatric patients: a prospective observational study



Jiwon Han [a], Hyo-Seok Na [b,c], Seihee Min [a], Hyun-Jung Shin [b,c,*]

[a] *Chung-Ang University College of Medicine, Department of Anesthesiology and Pain Medicine, Seoul, Republic of Korea*
[b] *Seoul National University Bundang Hospital, Department of Anesthesiology and Pain Medicine, Seoul, Republic of Korea*
[c] *Seoul National University College of Medicine, Department of Anesthesiology and Pain Medicine, Seoul, Republic of Korea*

Received 9 November 2023; accepted 8 July 2024
Available online 16 July 2024

KEYWORDS
Cerebral palsy;
Child;
Fasting;
Stomach;
Ultrasonography

Abstract
Background: Although cerebral palsy is a risk factor for aspiration, there is insufficient research on residual gastric volume after preoperative fasting in children with cerebral palsy. We evaluated the incidence of a full stomach by ultrasound assessment of the gastric volume in children with cerebral palsy who underwent orthopedic surgery after preoperative fasting.
Methods: The patients fasted for 8 h for solid foods and 2 h for clear liquids. We obtained the gastric antral cross-sectional area using ultrasound in the semi-recumbent and right lateral decubitus positions. A calculated stomach volume > 1.5 mL.kg^{-1} was considered as full, which poses a high aspiration risk. The primary outcome was the incidence of full stomach, and the secondary outcomes were the qualitative gastric volume, correlation of disease severity categorized according to the Gross Motor Function Classification System with the residual gastric volume, gastric volume per body weight, and qualitative gastric volume.
Results: Thirty-seven pediatric patients with cerebral palsy, scheduled for elective orthopedic surgery, were included for analysis. Full-stomach status was observed in none, and the gastric volume per body weight was 0.5 (0.4–0.7) mL.kg^{-1}. No significant differences were observed in the residual gastric volume (p = 0.114), gastric volume per body weight (p = 0.117), or qualitative grade of gastric volume (p = 0.642) in relation to disease severities.
Conclusion: Children with cerebral palsy who fasted preoperatively had empty or nearly empty stomachs. Further studies are required to determine the optimal fasting duration for such children.
© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

* Corresponding author.
E-mail: hjshin.anesth@gmail.com (H.-J. Shin).

https://doi.org/10.1016/j.bjane.2024.844541
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

The European Society of Anaesthesiology and Intensive Care[1] introduced preoperative fasting guidelines for healthy children that encourage the consumption of clear fluids for up to 1 hour and allow solid food intake until 6 hours before anesthesia induction. However, their generalization for children with comorbidities requires caution because of limited data.

Cerebral Palsy (CP) is a neurological disease accompanied by motor dysfunction caused by damage to the central nervous system. Depending on the degree of damage, CP is characterized by sensory, perceptual, hearing, visual, language, and cognitive impairments, which are accompanied by various clinical features ranging from mild coordination disorders to bed-ridden status.[2] In addition, most patients (92%) present with gastrointestinal motility dysfunctions such as regurgitation, vomiting, abdominal pain, constipation, delayed gastric emptying, and abnormal esophageal motility, which increase the risk of pulmonary aspiration.[3] Particularly, 41% of pediatric patients with CP experience chronic pulmonary aspiration.[3]

Adequate preoperative fasting is required to prevent pulmonary aspiration of gastric contents.[4] However, excessive fasting may also lead to hypoglycemia and dehydration.[4] Children are particularly more vulnerable to these problems than adults. Furthermore, only a few studies have reported on the residual gastric volume after fasting in children with CP. To improve their perioperative care, clinicians should determine the appropriate fasting time.

We hypothesized that preoperative residual gastric volume, classified as a high-risk factor for pulmonary aspiration, may be larger in children with CP than that in the general population. Thus, we aimed to evaluate the incidence of a full stomach by assessing the gastric volume using ultrasound in children with CP who underwent orthopedic surgery after fasting.

Methods

Study design, ethics, and participants

This prospective observational study was conducted between June 2021 and February 2022. It was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number: B-2104-681-301), and the study protocol was registered at ClinicalTrials.gov (NCT05185336). Written consent was obtained from the parents of all included patients. Consent was also obtained from patients if they could write and understand the study protocol.

Pediatric patients with CP (5—18 years) scheduled for elective orthopedic surgery under general anesthesia were eligible for inclusion. Patients with gastroesophageal reflux disease, a history of esophageal or stomach surgery, or a nasogastric or gastrostomy tube for feeding were excluded. We retrieved information on patient demographics, comorbidities, and medications.

Preoperative fasting guidelines

At our institution, preoperative fasting time for pediatric patients is 8 hours for solid foods and 2 hours for clear liquids.

Ultrasound scanning for gastric volume evaluation

In the preoperative holding area, the Cross-Sectional Area (CSA) of the gastric antrum was measured in the semi-recumbent and Right Lateral Decubitus (RLD) positions[5] using a low-frequency convex array transducer (rC60xi, 2–5 Hz) connected to an ultrasound system (SonoSite Edge II; FUSIFILM Sonosite Inc., Bothell, Washington, United States). Ultrasonographic measurement of CSA was performed by an experienced anesthesiologist according to the standard scanning protocol.[6] The gastric antrum was identified at the epigastric level in the sagittal or parasagittal view between the left lobe of the liver and aorta or inferior vena cava.

The CSA was calculated using the Perpendicular Anteroposterior (AP) and Craniocaudal (CC) diameters of the gastric antrum as follows: $CSA\ (cm^2) = \pi \times AP \times CC/4$. The following formula was used to estimate the gastric volume with antral CSA in the RLD position in pediatric patients: $gastric\ volume = -7.8 + (3.5 \times RLD\ CSA) + 0.127 \times age\ (months)$.[7] A full stomach was defined as a measured gastric volume $> 1.5\ mL.kg^{-1}$ or the presence of solid content in the stomach.[8] A calculated value < 1 mL was considered 0 mL.

In addition, we performed a qualitative assessment that determined the risk of pulmonary aspiration based on the gastric contents according to change in position as follows:[9] Grade 0, no gastric contents are visible in the antrum in both the semi-recumbent and RLD positions; Grade 1, gastric contents are visible only in the RLD position and not in the semi-recumbent position; and Grade 2, gastric contents are visible in both positions.

Outcome measurements

The primary outcome was the incidence of full stomach. The secondary outcomes included the qualitative grade of gastric volume and the correlation between CP severity and the residual gastric volume, gastric volume per body weight, and qualitative grade of gastric volume. CP severity was determined using a Gross Motor Function Classification System (GMFCS) as follows:[10] Level 1, walks without restriction, limitations in more advanced gross motor skills; Level 2, walks without restrictions, limitations in walking outdoors and in the community; Level 3, walks with assistive mobility devices, limitations in walking outdoors and in the community; Level 4, self-mobility with limitations, children are transported or use power mobility outdoors and in the community; and Level 5, severely limited self-mobility even with the use of assistive technology. Additionally, we evaluated the adverse effects of fasting such as signs of dehydration and hypoglycemia (tachycardia, hypotension, dry mouth, and sweating).

Sample size

We calculated the sample size using a web-based system (https://clincalc.com/stats/samplesize.aspx). In a previous study,[8] the incidence of full stomach was 6.2% in the general population after preoperative fasting, and another study[11] reported that the normogastria incidence of pediatric patients with CP was 80%. Assuming the incidence of a full stomach in pediatric patients with CP to be 20%, we

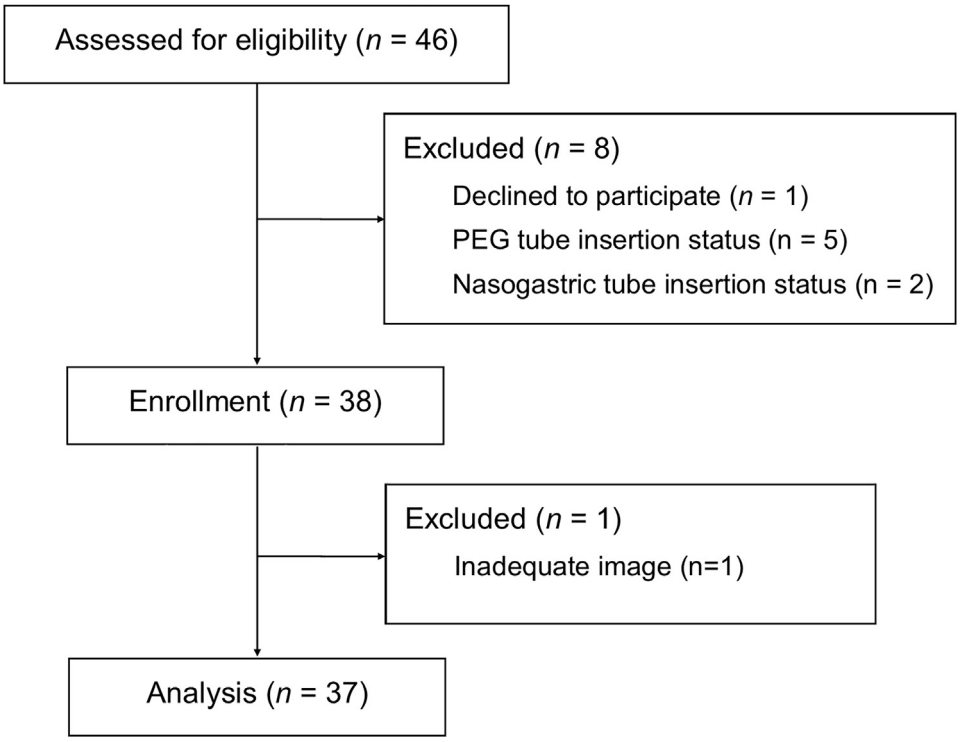


Figure 1 Flow diagram for patient selection. PEG, Percutaneous Endoscopic Gastrostomy.

determined 34 participants with an alpha level of 0.05 and power of 80% to obtain a statistically significant difference. Considering a dropout rate of 10%, 38 participants were required for this study.

Statistical analysis

The Shapiro-Wilk test was performed to determine the normality of continuous variables. Normally distributed data are expressed as mean (standard deviation). For skewed data, the results are presented as medians (interquartile ranges). The Kruskal-Wallis test was performed to analyze continuous data (CSA, gastric volume, and gastric volume per weight). Categorical data (qualitative grade) were analyzed using Fisher's exact test, and the results are expressed as numbers (proportions). We calculated Spearman's rank correlation coefficients to examine the severity of CP, residual gastric volume, residual gastric volume per body weight, and qualitative grade of gastric volume. Statistical Package for Social Sciences (SPSS; ver. 27; IBM Corp., Armonk, NY, USA) software was used for data analysis, and all *p*-values < 0.05 were considered significant.

Results

Forty-six patients were evaluated for eligibility. Eight of them were excluded for the following reasons: one refused to participate, and seven were supplied with nutrition through nasogastric or gastrostomy tubes. One patient was excluded from the final analysis due to unsuitable ultrasound images. Finally, thirty-seven patients were included for analysis (Fig. 1). Table 1 summarizes the baseline patient characteristics.

Full-stomach status was not observed in any patient. The median gastric volume was 20.9 (13.4–25.4) mL and the median gastric volume per body weight was 0.5 (0.4–0.7) $mL.kg^{-1}$ (Table 2). Table 2 also shows the gastric volume according to the CP level. We observed no significant differences in the residual gastric volume ($p = 0.114$), gastric volume per body weight ($p = 0.117$), or qualitative grade of

Table 1 Patient characteristics.

Variables	n = 37
Age (years)	11 (3.4)
Height (cm)	138 (18)
Weight (kg)	38.2 (14.7)
ASA physical status	
II	33 (89.2%)
III	4 (10.8%)
Comorbidities	
Cardiac abnormality	3 (8.1%)
Epilepsy	4 (10.8%)
Medications	
Anticonvulsants	9 (24.3%)
Laxatives	4 (10.8%)
Prokinetic agents	2 (5.4%)
Respiratory medications	2 (5.4%)
Others	2 (5.4%)

Data are expressed as mean (standard deviation) or number (proportion).
ASA, American Society of Anesthesiologists.

Table 2 Gastric volume according to the severity of cerebral palsy categorized by GMFCS.

	Total	GMFCS level					*p*-value
		1	2	3	4	5	
	(n = 37)	(n = 3)	(n = 11)	(n = 6)	(n = 17)	(n = 0)	
Quantitative analysis							
Gastric volume (mL)	20.9 (13.4–25.5)	18.5 (15.3–20.4)	16.9 (11.6–20.9)	25.9 (14.8–141.1)	22.1 (15.4–26.0)	NA	0.114
Gastric volume (mL.kg^{-1})	0.5 (0.4–0.7)	0.6 (0.5–0.6)	0.4 (0.3–0.6)	0.6 (0.5–0.9)	0.5 (0.4–0.8)	NA	0.117
CSA (RLD, cm^2)	2.7 (1.8–4.0)	2.8 (2.6–3.5)	2.2 (1.7–3.3)	3.3 (2.1–6.6)	3.0 (1.7–4.0)	NA	0.527
Qualitative assessment							
Grade 0, n (%)	29 (78.4%)	3 (100%)	8 (72.7%)	4 (66.7%)	14 (82.4%)	NA	0.642
Grade 1, n (%)	8 (21.6%)	0 (0%)	3 (27.3%)	2 (33.3%)	3 (17.6%)	NA	
Grade 2, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	

Data are expressed as median (interquartile range) or number (proportion).
CSA, Cross-Sectional Area; GMFCS, Gross Motor Function Classification System; RLD, Right Lateral Decubitus; NA, Not Applicable.

Table 3 Spearman's rank correlation coefficients between the severity of cerebral palsy according to GMFCS and residual gastric volume (n = 37).

	GMFCS	*p*-value
Residual gastric volume	0.305	0.066
Residual gastric volume per body weight	0.266	0.111
Qualitative grades of gastric contents	−0.020	0.908

GMFCS, Gross Motor Function Classification System.

gastric volume (p = 0.642) among the GMFCS grades. None of the patients were classified as Level 5.

No significant correlations were observed between CP severity and residual gastric volume, residual gastric volume per body weight, or qualitative grade of gastric volume (Table 3). Additionally, there were no cases of adverse events attributed to fasting.

Discussion

In this study, we evaluated the preoperative residual gastric volume in children with CP and observed no patients with full-stomach status after preoperative fasting. In addition, we observed no correlation between CP severity and residual gastric volume. These findings provide evidence for the safety of fasting and warrant further studies to determine an optimal fasting time for children with CP to avoid metabolic deterioration caused by excessive fasting.

Homeostasis of gastrointestinal functions is maintained not only by the autonomic nervous system but also by the central nervous system. Predominantly, it exerts inhibitory effects on gastrointestinal motility and mucosal secretion and regulates gastrointestinal blood flow via vasoconstriction.[12] The upper gastrointestinal tract (esophagus and stomach) is particularly more dependent on extrinsic neural input from the central nervous system than the lower gastrointestinal tract.[13] Consequently, patients with CP experience vomiting, regurgitation, feeding difficulties, malnutrition, and aspiration.[14] Of these symptoms, aspiration causes pneumonitis and pneumonia, which are the major causes of longer hospitalization and mortality in patients with CP.[15,16]

Patients were fasted preoperatively to prevent aspiration. Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the lower respiratory tract, leading to conditions such as bronchospasm, hypoxia, pneumonitis, pneumonia, and acute respiratory distress syndrome.[17,18] Aspiration pneumonia occurs when the aspirated material causes an infectious process; it affects approximately 1% of adult surgical patients and is associated with increased rates of intensive care unit admission, hospitalization duration, medical costs, and in-hospital mortality.[17] Furthermore, aspiration pneumonia accounts for 9% of anesthesia-related mortality.[19] In children, the risk of aspiration is higher because of anatomical vulnerabilities, such as a small oral cavity, short laryngeal and vocal fold lengths, higher-located epiglottis tip, immature airway protective reflexes, and oropharyngeal discoordination. Patients with anatomical

deformities, such as cleft palate or esophageal atresia, as well as those with neuromuscular diseases such as CP or myotonic dystrophy, are at a higher risk.[18,20]

The preoperative fasting guidelines for children report on the usefulness of preoperative ultrasound gastric assessment for the residual gastric volume evaluation.[1] Gastric ultrasound is a noninvasive, real-time, inexpensive, and effective tool for evaluating stomach contents; therefore, it is central to determine the timing of the procedure and induction technique (rapid sequence vs. routine inhalation or intravenous) in non-elective surgery or aspiration in high-risk patients (hypertrophic pyloric stenosis).[21,22] In healthy pediatric patients, ultrasound gastric examination indicated a full stomach in < 1% of the patients following the 2017 American Society of Anesthesiologists (ASA) fasting guidelines (2 h of clear fluid fasting; 6 h of solid fasting).[4] However, it is unclear whether these fasting guidelines are safe for high-risk patients. In these cases, clinicians can use gastric ultrasound to evaluate the stomach volume and reduce the risk of aspiration. Further research is required on the safety of applying the fasting guidelines to patients with CP and for determining the optimal fasting time.

This observational study had some limitations. First, prolonged fasting durations (> 6 h) may have had an impact on stomach emptying. Well-designed research is required to determine the optimal fasting duration for patients with CP. Second, the effect of clear fluid ingestion before 1–2 h on gastric volume is unknown because all patients underwent fasting for at least 8 h for solid foods and for at least 2 h for clear liquids. This warrants additional studies that apply the current preoperative fasting guidelines. Third, the risk of aspiration increases with CP severity.[23] However, we did not observe this correlation because of the relatively small sample size, and the patients in GMFCS 5 level were excluded because they were on nasogastric or gastrostomy feeding. Fourth, the age of the participants in this study ranged between 5 and 18 years, and the rapid physiological changes that occur in growing children may have influenced the results. Despite these limitations, this study adds to our knowledge on the safety of 8 h solid food, 2 h clear liquid fasting in children with CP.

Conclusions

In conclusion, children with CP who fasted for 8 h for solid foods and 2 h for clear liquids had empty or nearly empty stomachs. Further studies are required to determine the optimal fasting duration for such children.

Conflicts of interest

The authors declare no conflicts of interest.

Patient consent statement

Written informed consent was obtained from the guardians of all the patients, and informed consent forms were obtained from the patients if they could write and understand the contents of the study.

Data availability statement

Datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval statement

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital on May 3, 2021 (B-2104-681-301; Chairperson, Hak Chul Jang), and the study protocol was registered at ClinicalTrials.gov (NCT05185336).

This study was approved by the appropriate review committee, and the study protocol was registered at ClinicalTrials.gov.

Funding

This research was supported by the Chung-Ang University Research Grant in 2022.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844541.

References

1. Frykholm P, Disma N, Andersson H, et al. Pre-operative fasting in children. Eur J Anaesth. 2022;39:4–25.
2. Johnston MV, Hoon Jr AH. Cerebral palsy. Neuromolecular Med. 2006;8:435–50.
3. Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. Brain Dev. 1999;21:307–11.
4. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures. Anesthesiology. 2017;126:376–93.
5. Perlas A, Chan VW, Lupu CM, Mitsakakis N, Hanbidge A. Ultrasound assessment of gastric content and volume. Anesthesiology. 2009;111:82–9.
6. Cubillos J, Tse C, Chan VW, Perlas A. Bedside ultrasound assessment of gastric content: an observational study. Can J Anaesth. 2012;59:416–23.
7. Spencer AO, Walker AM, Yeung AK, et al. Ultrasound assessment of gastric volume in the fasted pediatric patient undergoing upper gastrointestinal endoscopy: development of a predictive model using endoscopically suctioned volumes. Paediatr Anaesth. 2015;25:301–8.
8. Van de Putte P, Vernieuwe L, Jerjir A, Verschueren L, Tacken M, Perlas A. When fasted is not empty: a retrospective cohort study of gastric content in fasted surgical patient's dagger. Br J Anaesth. 2017;118:363–71.
9. Perlas A, Davis L, Khan M, Mitsakakis N, Chan VW. Gastric sonography in the fasted surgical patient: a prospective descriptive study. Anesth Analg. 2011;113:93–7.

10. Himpens E, Van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Child Neurol. 2008;50:334—40.
11. Brun AC, Olafsdottir EJ, Bentsen BS, Stordal KS, Johannesdottir GB, Medhus AW. Electrogastrography in children with cerebral palsy: Abnormal postprandial response to both fast- and slow-emptying meals. Clin Nutr ESPEN. 2014;9:215—9.
12. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr Physiol. 2014;4:1339—68.
13. Altaf MA, Sood MR. The nervous system and gastrointestinal function. Dev Disabil Res Rev. 2008;14:87—95.
14. Spiroglou K, Xinias I, Karatzas N, Karatza E, Arsos G, Panteliadis C. Gastric emptying in children with cerebral palsy and gastroesophageal reflux. Pediatr Neurol. 2004;31:177—82.
15. Nolan J, Chalkiadis GA, Low J, Olesch CA, Brown TCK. Anaesthesia and pain management in cerebral palsy. Anaesthesia. 2000;55:32—41.
16. Reddihough DS, Baikie G, Walstab JE. Cerebral palsy in Victoria, Australia: Mortality and causes of death. J Paediatr Child Health. 2001;37:183—6.
17. Kozlow JH, Berenholtz SM, Garrett E, Dorman T, Pronovost PJ. Epidemiology and impact of aspiration pneumonia in patients undergoing surgery in Maryland, 1999—2000. Crit Care Med. 2003;31:1930—7.
18. Pavithran J, Puthiyottil IV, Narayan M, Vidhyadharan S, Menon JR, Iyer S. Observations from a pediatric dysphagia clinic: Characteristics of children at risk of aspiration pneumonia. Laryngoscope. 2018;129:2614—8.
19. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology. 2006;105:1087—97.
20. Tutor JD, Gosa MM. Dysphagia and aspiration in children. Pediatr Pulmonol. 2012;47:321—37.
21. Gagey AC, de Queiroz Siqueira M, Monard C, et al. The effect of pre-operative gastric ultrasound examination on the choice of general anaesthetic induction technique for non-elective paediatric surgery. A prospective cohort study. Anaesthesia. 2018;73:304—12.
22. Gagey AC, de Queiroz Siqueira M, Desgranges FP, Combet S, Naulin C, Chassard D, et al. Ultrasound assessment of the gastric contents for the guidance of the anaesthetic strategy in infants with hypertrophic pyloric stenosis: a prospective cohort study. Brit J Anaesth. 2016;116:649—54.
23. Hafifah CN, Setyanto DB, Putra ST, Mangunatmadja I, Sari TT, Wulandari HF. Gross motor dysfunction as a risk factor for aspiration pneumonia in children with cerebral palsy. Paediatr Indones. 2018;57(5).

Brazilian Journal of Anesthesiology 2024;74(5): 844540



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Pediatric Early Warning Score (PEWS) in predicting prognosis of critical pediatric trauma patients: a retrospective study



Abdulrahman Özel [a,*], **Ulkem Kocoglu Barlas** [b], **Servet Yüce** [c], **Cansu Günerhan** [d], **Meltem Erol** [d]

[a] *Health Sciences University Turkey, Bağcılar Training and Research Hospital, Department of Pediatrics, Pediatric Intensive Care Unit, Istanbul, Türkiye*
[b] *Istanbul Medeniyet University, Goztepe Prof Dr Süleyman Yalcin City Hospital, Department of Pediatrics, Pediatric Intensive Care Unit, Istanbul, Türkiye*
[c] *Department of Public Health, Istanbul Faculty of Medicine, Istanbul University, İstanbul, Türkiye*
[d] *Health Sciences University Turkey, Bağcılar Training and Research Hospital, Department of Pediatrics, Istanbul, Türkiye*

Received 5 February 2024; accepted 8 July 2024
Available online 16 July 2024

KEYWORDS
Child mortality;
Critical care;
Glasgow coma scale;
Multiple trauma

Abstract
Background: This study aimed to compare the predictive value of Pediatric Early Warning Score (PEWS) to Pediatric Risk of Mortality-3 (PRISM-3), Pediatric Trauma Score (PTS), and Pediatric Glasgow Coma Score (pGCS) in determining clinical severity and mortality among critical pediatric trauma patients.
Method: A total of 122 patients monitored due to trauma in the pediatric intensive care unit between 2020 and 2023 were included in the study. Physical examination findings, vital parameters, laboratory values, and all scoring calculations for patients during emergency room admissions and on the first day of intensive care follow-up were recorded. Comparisons were made between two groups identified as survivors and non-survivors.
Results: The study included 85 (69.7%) male and 37 (30.3%) female patients, with an average age of 75 ± 59 months for all patients. Forty-one patients (33.6%) required Invasive Mechanical Ventilation (IMV) and 11 patients (9%) required inotropic therapy. Logistic regression analysis revealed a significant association between mortality and PEWS ($p < 0.001$), PRISM-3 ($p < 0.001$), PTS ($p < 0.001$), and pGCS ($p < 0.001$). Receiver operating characteristics curve analysis demonstrated that the PEWS score (cutoff > 6.5, AUC = 0.953, 95% CI 0.912–0.994) was highly predictive of mortality, showing similar performance to the PRISM-3 score (cutoff > 21, AUC = 0.999, 95% CI 0.995–1). Additionally, the PEWS score was found to be highly predictive in forecasting the need for IMV and inotropic therapy.

* Corresponding author.
E-mail: dr.abdulrahman.ozel@gmail.com (A. Özel).

https://doi.org/10.1016/j.bjane.2024.844540
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Conclusion: The Pediatric Early Warning Score serves as a robust determinant of mortality in critical pediatric trauma patients. Simultaneously, it demonstrates strong predictability in anticipating the need for IMV and inotropic therapy.
© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Trauma is one of the primary reasons for emergency room admissions and intensive care unit stays in the pediatric age group.[1] According to the World Health Organization (WHO) and the United Nations Children's Fund in the "World Report on Child Injury Prevention", childhood trauma is highlighted as a significant health problem requiring urgent attention, with an annual report of approximately 950,000 children succumbing to trauma-related deaths.[2] Scoring systems based on the initial emergency room admissions or the first signs of intensive care unit stays are employed to reduce mortality and morbidity in trauma patients. However, the evaluation of each system's feasibility and the consideration of ease of application are essential factors when using them.[3]

Currently employed scoring systems are generally complex, incorporating multiple variables and often modified versions of scoring systems designed for adults.[4] Among these, the Pediatric Early Warning Score (PEWS) has gained increasing popularity in recent years as a scoring system for predicting early clinical deterioration in critical pediatric patients.[5,6]

The Brighton PEWS, developed in 2005 at the Brighton Children's Hospital in the UK by Monaghan et al,[5] utilizes a scoring system based on assessing changes in the overall appearance, cardiovascular, and respiratory systems to identify clinically deteriorating patients early and initiate prompt treatment. Unlike many scoring systems, Brighton PEWS is easy and quick to apply.[7] Its strength lies not only in predicting mortality but also in frequently being used to identify clinical severity due to its utilization of clinical findings without requiring laboratory investigations.[8]

The primary objective of this study was to compare the predictive abilities of the Brighton PEWS, Pediatric Risk of Mortality-3 (PRISM-3), Pediatric Trauma Score (PTS), and Pediatric Glasgow Coma Score (pGCS) in determining mortality in critical pediatric trauma patients monitored in the Pediatric Intensive Care Unit (PICU). The secondary objective was to compare the abilities of these scores in indicating the need for Invasive Mechanical Ventilation (IMV) and inotropic therapy in patients.

Methods

This study was conducted retrospectively in an eight-bed PICU over a three-year period, and ethical approval for the study was obtained from the hospital's ethics committee, and the principles of the Helsinki Declaration were adhered to (Approval number: 2024/01/06/006).

Inclusion criteria for the study were: 1) Age between one month and 18 years; 2) Follow-up in the PICU due to motor vehicle accidents, falls from height, penetrating injuries, and drowning. Patients aged under one month and over 18 years, trauma patients followed in services outside the PICU, patients with underlying chronic diseases, patients intubated before arriving at the emergency department and sedated at the first encounter, and patients with data limitations were excluded from the study.

Demographic characteristics of the patients (age, sex), need for IMV, use of inotropic therapy, laboratory values (blood base parameters, glucose, potassium, urea, creatinine, white blood cell count, coagulation parameters), type of trauma, anatomical region affected by trauma (head, thorax, abdomen, and extremity), PICU and hospital length of stay, discharge-mortality status were obtained from hospital records. Brighton PEWS was calculated based on the first physical examination findings at the time of emergency room admission (Table 1); PRISM-3[9] (Supplemental Table 1), within the first 24 hours of intensive care monitoring, with the worst laboratory values during monitoring; PTS[10] (Supplemental Table 2) and pGCS (Supplemental Table 3) were calculated based on the vital parameters at the time of the initial emergency room admission and neurological examination findings. Patients were divided into survivors and non-survivors, and comparisons were made between the two groups.

Statistical analysis

IBM SPSS Statistics version 28.0 (IBM SPSS, Armonk, NY, USA) was used for statistical analyses. The data collected for the study were initially entered into the Microsoft Excel® database and then transferred to SPSS. Descriptive statistics were presented as mean ± standard deviation, median, frequency, percentage, minimum, and maximum values. The normal distribution of the data was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Student's *t*-test was used for the comparison of continuous variables showing a normal distribution between two groups, and one-way analysis of variance (ANOVA) was used for comparisons between more than two groups. The Mann-Whitney *U* test was employed for the analysis of continuous variables not showing a normal distribution between two groups, and the Kruskal-Wallis test was used for comparisons involving more than two groups. For the comparison of categorical variables, the Pearson chi-square test and Fisher's exact test were employed. Receiver Operating Characteristic (ROC) curves and the Area Under the Curves (AUCs) were plotted to determine specificity and sensitivity based on threshold values for the predictive powers of the scoring systems in predicting mortality, the need for IMV, and the need for inotropic therapy. All analyses conducted were two-sided, and a p-value < 0.05 was considered significant.

The sample size calculation was conducted using the OpenEpi open-source program. Based on this analysis, the minimum required sample size for a 95% Confidence Interval was determined to be 104 patients. Considering potential

Table 1 Brighton Pediatric Early Warning Score (PEWS).

	0	1	2	3
Appearance/ Behavior	Responsive, appropriate behaviors	Drowsy, agitated but consolable	Irritable or agitated and not consolable	Lethargic/confused **or** reduced response to painful stimuli
Cardiovascular system	Pink **or** Capillary refill time 1–2 seconds	Pale **or** Capillary refill time 3 seconds	Grayish **or** Cyanotic **or** Capillary refill time 4 seconds **or** Heart rate > 20 above normal	Grayish **and** mottled appearance **or** Capillary refill time ≥ 5 seconds **or** Heart rate > 30 above normal **or** Bradycardia
Respiratory system	Respiratory rate within normal limits, no retractions, no oxygen requirement	Respiratory rate > 10 above normal **or** Mild retractions **or** > 30% FiO_2 **or** > 3 liters/minute	Respiratory rate > 20 above normal **or** Retractions **or** > 40% FiO_2 **or** > 6 liters/minute	Respiratory rate < 5 below normal with retractions **or** Grunting **or** > 50% FiO_2 **or** > 8 liters/minute

* Scoring begins with the most severe parameter.
* An additional 2 points are added in case of persistent vomiting after surgery or every 20 minutes of nebulization (including continuous nebulization).
* Use "liters/minute" for regular nasal cannula.
* Use FiO_2 for high-flow nasal cannula.

missing data, we aimed to include an additional 15%, resulting in a target sample size of 120 patients. The study was completed with 122 participants.

Results

Our study included 122 pediatric trauma patients monitored in a third-level PICU between January 2020 and 2023. Figure 1 presents the selection process of study participants.

The mean age of all patients was 75 ± 59 months, 85 (69.7%) of them were male and 37 (30.3%) female. Of the patients, 55% presented to the emergency department due to falls from height, and cranial trauma was the most common type among all patients (61.5%). The demographic characteristics of all patients, the need for IMV and inotropic therapy, initial laboratory values, trauma type and region, PICU and hospital length of stay, all scoring systems, discharge-mortality status, and comparisons between survivors and non-survivors are shown in Table 2. Accordingly, there was no statistically significant relationship between the type of trauma and mortality ($p > 0.05$). The need for inotropic therapy was significantly higher in patients resulting in mortality ($p < 0.05$). PEWS and PRISM-3 scores were significantly higher in patients resulting in mortality ($p < 0.001$, $p < 0.001$, respectively), while PTS and pGCS were significantly lower ($p < 0.001$, $p < 0.001$, respectively).

The predictive powers of the scoring systems for mortality were evaluated through ROC curve analyses in the study. Accordingly, for PEWS, with a cutoff point of 6.5, sensitivity was 92.3%, and specificity was 93.6%; for PRISM-3, with a cutoff point of 21, sensitivity was 100%, and specificity was 99.1 (Fig. 2, 2A and 2B).

The predictive powers of the scoring systems in forecasting the need for inotropic therapy were evaluated through ROC curve analyses in our study. Accordingly, PEWS and PRISM-3 scores were found to have the best predictive abilities (Fig. 3, 3A and 3B).

The predictive powers of the scoring systems in forecasting the need for IMV were evaluated through ROC curve analyses. PEWS and pGCS scores were found to be the most accurate predictive systems (Fig. 4, 4A and 4B).

Discussion

In this study, we compared the predictive abilities of PEWS, PRISM-3, PTS, and pGCS in assessing clinical severity and mortality in critical pediatric trauma patients. The results revealed that, as expected, PRISM-3 was the most sensitive score for predicting mortality, while PEWS emerged as the second most sensitive predictor, showcasing its noteworthy significance. Furthermore, PEWS demonstrated significant value in determining clinical severity.

The rapid changes in clinical findings in critically ill children have increased the importance of easily applicable and accurate scoring systems.[11] Among these, the literature includes various studies on the PEWS, whose results have been corroborated by many researchers. For instance, Cheng et al, in their study on 4717 pediatric patients presenting to the emergency department, found the PEWS to be highly reliable in identifying patients at risk of clinical deterioration.[12] In a study by Lillitos et al, where 273 patients were pediatric trauma patients, PEWS exhibited a specificity of 100% and sensitivity of 10% when a cutoff of three was chosen to predict severe illness.[13] Despite our study focusing on a specific group of patients, the PEWS demonstrated excellent

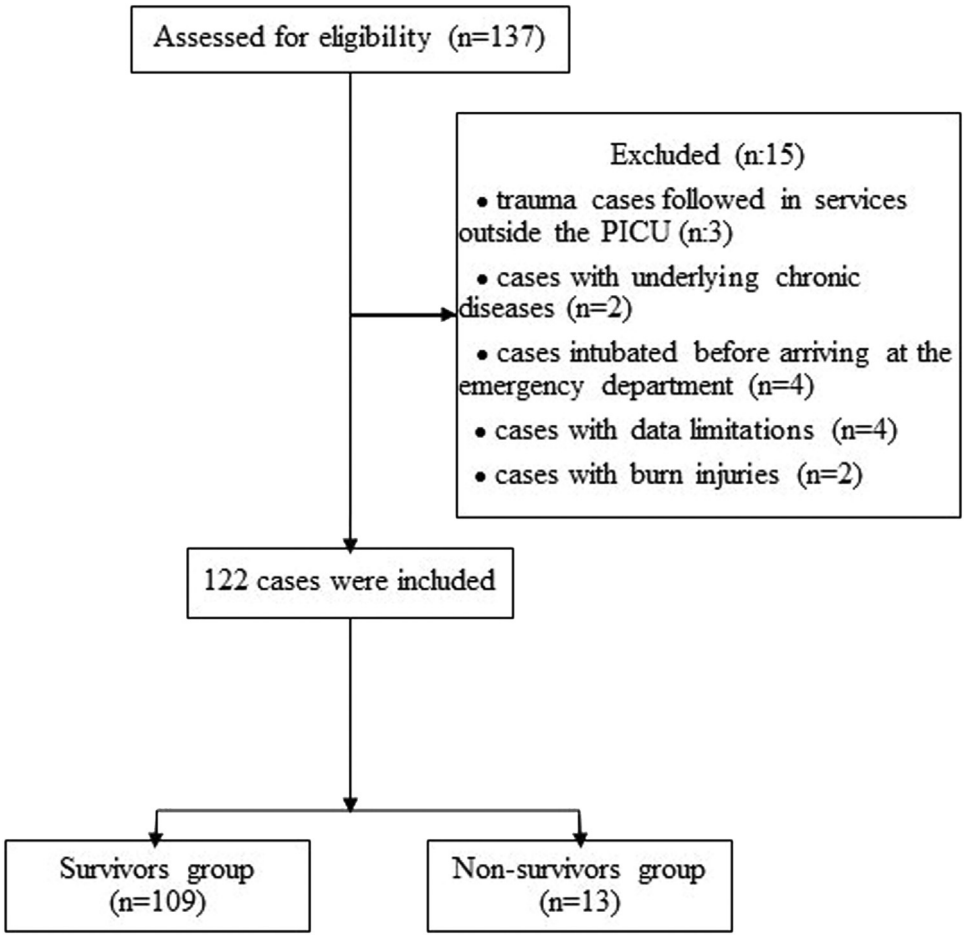


Figure 1 Flow chart of the selection process of study participants.

predictive value for mortality, akin to the PRISM-3 score (AUC: 0.953, 0.999, respectively).

The PRISM-3 score is a scoring system used in PICUs to assist clinicians in predicting mortality. Its disadvantage lies in requiring a plethora of laboratory findings and waiting for the initial 24-hour follow-up. Examining the parameters of the PEWS, it includes general appearance, cardiovascular system findings, and respiratory system findings. Post-traumatic immune system activation leads to the emergence of Systemic Inflammatory Response Syndrome (SIRS), which includes cardiovascular and respiratory system findings in its criteria.[14] Therefore, it can be argued that PEWS is specialized in capturing early-stage SIRS patients. We believe that its superiority in predicting mortality in our study is related to this aspect. In comparison to PRISM-3, the advantage lies in being calculable at the initial presentation to the emergency department without requiring a 24-hour waiting period. This feature is particularly advantageous for critical pediatric trauma patients. It can provide insights into recognizing SIRS early, determining the treatment needs of these patients, and predicting the onset of Multiple Organ Dysfunction Syndrome (MODS). Moreover, the International Liaison Committee on Resuscitation (ILCOR) consensus, "2022 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations", recommends using PEWS in emergency departments to monitor hospitalized children and identify those at risk of deterioration.[15]

In our study, similar to the literature, PTS was found to be a sensitive scoring system for predicting mortality (AUC = 0.951, specificity: 87.2%, sensitivity: 92.3%). The pediatric trauma score, introduced by Tepas et al in 1987, is an easily calculable scoring system that assesses the severity of injury and indicates the risk of sudden death.[10] Patients with a score above 8 in this scoring system have a very low probability of mortality.[16] In the study conducted by Chabok et al[17] on pediatric patients admitted to the intensive care unit due to trauma, the threshold for predicting mortality was $\leq$ 0.5 points with 100% sensitivity and 31% specificity. Similarly, in the study by Kıhtır et al on 155 pediatric patients exposed to high-energy trauma, the threshold for predicting mortality was $\leq$3 points with 100% sensitivity and 90% specificity.[18]

To compare the performance of scoring systems in predicting clinical severity, the need for IMV support and inotropic therapy was used. There are limited studies in the literature investigating the predictive power of the PEWS for IMV need, and these studies have mainly explored the relationship with clinical decompensation in children with respiratory diseases.[13] In the study by Fenix et al, PEWS was found to be a valuable method in predicting clinical deterioration, and a threshold of $\geq$ 3 showed the best

Table 2 Evaluation of demographic characteristics, clinical findings, pediatric scores, and treatment of survivors and non-survivors.

	Survivors (n = 109)	Non-survivors (n = 13)	All patients (n = 122)	*p*
Age, months, mean ± SD	74.8 ± 58.25	77 ± 67.7	75 ± 59	0.891[a]
Sex, n (%)				0.500[b]
Male	77 (70.6%)	8 (61.5%)	85 (69.7%)	
Female	32 (29.4%)	5 (38.5%)	37 (30.3%)	
Need for Invasive Mechanical Ventilation (IMV), n (%)	28 (25.7%)	13 (100%)	41 (33.6%)	**<0.001**[b,c]
Need for inotropic support, n (%)	1 (0.9%)	10 (76.9%)	11 (9%)	**<0.001**[b,c]
Etiology of trauma, n (%)				
Fall from height	60 (54.1%)	8 (61.5%)	68 (55.7%)	0.891[2]
Motor vehicle accident	40 (33.9%)	4 (30.8%)	44 (36.1%)	
Penetrating injury	5 (3.7%)	1 (7.7%)	6 (4.9%)	
Drowning	4 (3.7%)	–	4 (3.3%)	
Pathology, n (%)				
Brain edema	12 (11.0%)	6 (46.2%)	18 (14.8%)	**<0.001**[b,c]
Intracranial hemorrhage	44 (40.4%)	11 (84.6%)	55 (45.1%)	**0.002**[b,c]
Pneumothorax	39 (35.8%)	4 (30.8%)	43 (35.2%)	0.721[b]
Pulmonary contusion	52 (47.7%)	10 (76.9%)	62 (50.8%)	**0.046**[b,c]
Hemothorax	12 (11.0%)	2 (15.4%)	14 (11.5%)	0.64[2]
Liver laceration	23 (21.1%)	1 (7.7%)	24 (19.7%)	0.25[b]
Spleen laceration	13 (11.9%)	6 (46.2%)	19 (15.6%)	**0.001**[b,c]
Intensive Care Unit (ICU) Length of stay, days, mean ± SD	7.51 ± 8.19	4.46 ± 4.79	7.19 ± 7.94	**0.048**[a]
Ward length of stay, days, mean ± SD	4.48 ± 7.97	–	4 ± 7.65	–
pGCS, mean ± SD	12.37 ± 3.45	4.23 ± 1.96	11.5 ± 4.17	**<0.001**[b,c]
PEWS, mean ± SD	2.02 ± 2.26	8.08 ± 1.71	2.66 ± 2.9	**<0.001**[b,c]
PTS, mean ± SD	7.17 ± 3.02	-1.08 ± 3.35	6.3 ± 3.98	**<0.001**[b,c]
PRISM-3, mean ± SD	3.53 ± 5.1	40.77 ± 16	7.5 ± 13.5	**<0.001**[b,c]

pGCS, Pediatric Glasgow Coma Scale; PEWS, Pediatric Early Warning Score; PTS, Pediatric Trauma Score; PRISM, Pediatric Risk of Mortality; SD, Standard Deviation; n, Number of patients; *p*, Statistical significance.
[a] *t*-test,
[b] Pearson Chi-Square test, significant p-values are highlighted in bold and indicated with the
[c] Symbol.

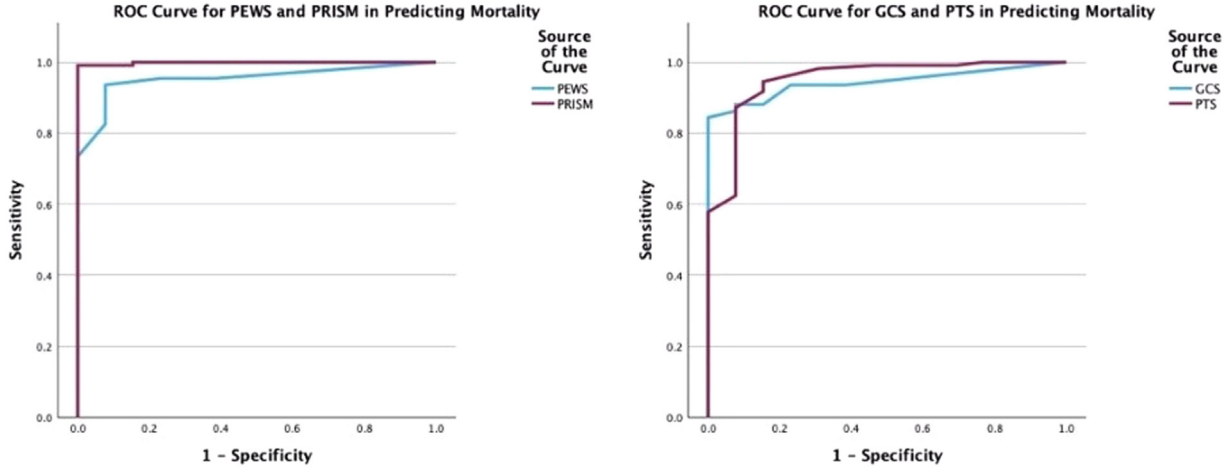


Figure 2 **ROC curves plotted for the Predictive Power of Scoring Systems in mortality.** (A) For the performance of pGCS in predicting mortality, the AUC was calculated as 0.943, sensitivity was 100%, and specificity was 84.4% at the cutoff of 10 ($p < 0.001$). For the performance of PTS in predicting mortality, the AUC was calculated as 0.951, sensitivity was 92.3%, and specificity was 87.2% at the cutoff of 3.5 ($p < 0.001$). (B) For the performance of PEWS in predicting mortality, the AUC was calculated as 0.953, sensitivity was 92.3%, and specificity was 93.6% at the cutoff of 6.5 ($p < 0.001$). For the performance of PRISM-3 in predicting mortality, the AUC was calculated as 0.999, sensitivity was 100%, and specificity was 99.1% at the cutoff of 21 ($p < 0.001$).

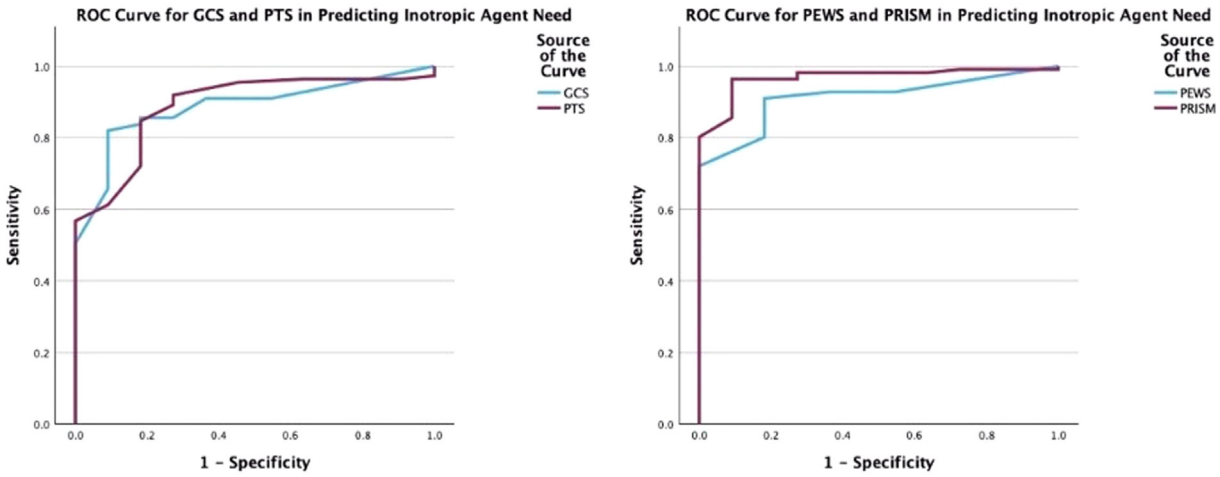


Figure 3 **ROC curves plotted for the Predictive Power of Scoring Systems in inotropic agent need.** (A) For the performance of pGCS in predicting inotropic agent need, the AUC for pGCS was determined to be 0.886, with a sensitivity of 90.9% and specificity of 82.0% at the cutoff value of 10 ($p < 0.001$). For predicting inotropic agent need, PTS demonstrated an AUC of 0.889, with a sensitivity of 81.8% and specificity of 84.7% at the cutoff value of 3.5 ($p < 0.001$). (B) For the performance of PEWS in predicting inotropic agent need, the AUC for PEWS was determined to be 0.912, with a sensitivity of 81.8% and specificity of 91.0% at the cutoff value of 6.5 ($p < 0.001$). For predicting inotropic agent need, PRISM-3 demonstrated an AUC of 0.968, with a sensitivity of 90.9% and specificity of 96.4% at the cutoff value of 21 ($p < 0.001$).

performance.[19] In our study, in terms of predicting the need for IMV, PEWS was found to be the scoring system with the highest performance among the four scoring systems (cutoff value of 2.5, specificity: 91.4%, sensitivity: 85.4%, AUC = 0.951). We believe that, due to the majority of our patients having head trauma, the need for IMV was more related to the neurological condition than to respiratory sources. The parameters of general appearance and consciousness, included in the calculation of PEWS, provided information about the neurological condition of the patients and confirmed the need for IMV.

In predicting the need for inotropic support used to define clinical severity, PRISM-3 (AUC: 0.968, sensitivity: 90.9%, specificity: 96.4%) and PEWS (AUC: 0.912, sensitivity: 81.8%, specificity: 91%) stood out similarly regarding their performance in predicting mortality. The similar performances of scoring systems in predicting the need for inotropic support and mortality can be explained by the aggressive fluid treatment, blood product transfusion, and inotropic therapy used in the management of hypotension resulting from clinical decompensation in patients ending in mortality.

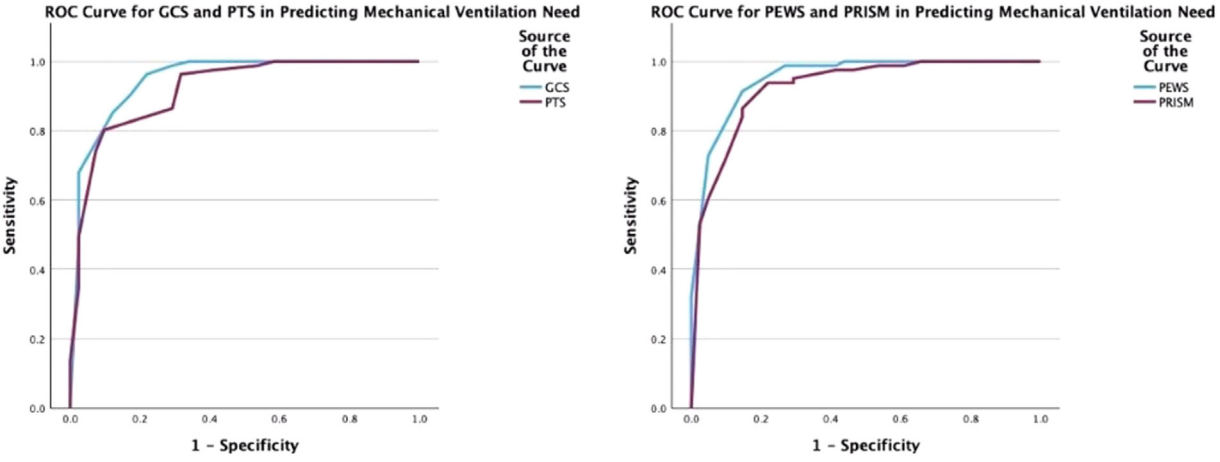


Figure 4 **ROC curves plotted for the Predictive Power of Scoring Systems in mechanical ventilation need.** (A) For the performance of pGCS in predicting Invasive Mechanical Ventilation (IMV) need, the AUC for pGCS was determined to be 0.947, with a sensitivity of 78.0% and specificity of 96.3% at the cutoff value of 11($p < 0.001$). For predicting Invasive Mechanical Ventilation (IMV) need, PTS demonstrated an AUC of 0.917, with a sensitivity of 90.2% and specificity of 80.2% at the cutoff value of 6.5 ($p < 0.001$). (B) For the performance of PEWS in predicting Invasive Mechanical Ventilation (IMV) need, the AUC for PEWS was determined to be 0.951, with a sensitivity of 85.4% and specificity of 91.4% at the cutoff value of 2.5 ($p < 0.001$). For predicting Invasive Mechanical Ventilation (IMV) need, PRISM-3 demonstrated an AUC of 0.924, with a sensitivity of 78.0% and specificity of 93.8% at the cutoff value of 5.5 ($p < 0.001$).

The main limitations of this study are its retrospective nature and the small number of patients. The small number of patients is attributed to being conducted in a single center and in a specific patient population. The Brighton PEWS was only evaluated based on admission findings, and repeated assessments were not performed during the intensive care follow-ups of the patients. We consider the strongest point of our study to be the first evaluation of the Brighton PEWS in critical pediatric trauma patients.

Conclusion

In our study, the Brighton PEWS was found to be as significant as the PRISM-3 score in predicting mortality in critical pediatric trauma patients. Additionally, the Brighton PEWS was equally significant in determining the need for invasive IMV and inotropic therapy, comparable to pGCS and PRISM-3 scores, respectively. Deciding on crucial treatment options in critically ill children requires timely decision-making. The advantage of the Brighton PEWS lies in preventing the loss of time associated with waiting for laboratory results and its calculation based solely on clinical findings. To enhance these features, further studies with a larger patient population and prospective design are essential.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics clearance

This study was evaluated and approved by the University of Health Sciences Turkey, Bagcilar Training and Researh Hospital's Clinical Research Ethics Committee in January 2024, with decision number 2024/01/06/006.

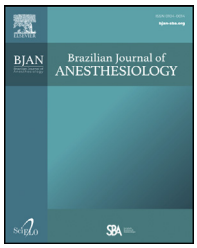
Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844540.

References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204–22.
2. Peden M, Oyegbite K, Ozanne-Smith J, Hyder AA, Branche C, Rahman AF, et al. Child injuries in context. World report on child injury prevention: World Health Organization; 2008.
3. De los Ríos-Pérez A, García A, Cuello L, Rebolledo S, Fandiño-Losada A. Performance of the Paediatric Trauma Score on survival prediction of injured children at a major trauma centre: A retrospective Colombian cohort, 2011–2019. Lancet Reg Health Am. 2022;13:100312.
4. Marcin JP, Pollack MM. Triage scoring systems, severity of illness measures, and mortality prediction models in pediatric trauma. Crit Care Med. 2002;30(11 Suppl). S457-S67.
5. Monaghan A. Detecting and managing deterioration in children. Paediatr Nurs. 2005;17:32.
6. Duncan H. Survey of early identification systems to identify inpatient children at risk of physiological deterioration. Arch Dis Child. 2007;92:828.
7. Solevåg AL, Eggen EH, Schröder J, Nakstad B. Use of a modified pediatric early warning score in a department of pediatric and adolescent medicine. PloS One. 2013;8:e72534.
8. Chong S-L, Goh MSL, Ong GY-K, et al. Do paediatric early warning systems reduce mortality and critical deterioration events among children? A systematic review and meta-analysis. Resuscitation Plus. 2022;11:100262.
9. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996;24:743–52.
10. Tepas III JJ, Mollitt DL, Talbert JL, Bryant M. The pediatric trauma score as a predictor of injury severity in the injured child. J Pediatr Surg. 1987;22:14–8.
11. Trubey R, Huang C, Lugg-Widger FV, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. BMJ Open. 2019;9:e022105.
12. Cheng Y, Zhang X, Zhang J, Lu G. The application of pediatric early warning score (PEWS) in emergency observation room. J Pediatr Nurs. 2022;66:1–5.
13. Lillitos PJ, Hadley G, Maconochie I. Can paediatric early warning scores (PEWS) be used to guide the need for hospital admission and predict significant illness in children presenting to the emergency department? An assessment of PEWS diagnostic accuracy using sensitivity and specificity. Emerg Med J. 2016;33:329–37.
14. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury. 2007;38:1336–45.
15. Wyckoff MH, Greif R, Morley PT, et al. 2022 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations: Summary from the basic life support; advanced life support; pediatric life support; neonatal life support; education, implementation, and teams; and first aid task forces. Pediatrics. 2023;151:e2022060463.
16. Kaufmann CR, Maier RV, Rivara FP, Carrico CJ. Evaluation of the pediatric trauma score. Jama. 1990;263:69–72.
17. Yousefzadeh-Chabok S, Kazemnejad-Leili E, Kouchakinejad-Eramsadati L, et al. Comparing Pediatric Trauma, Glasgow Coma Scale and Injury Severity scores for mortality prediction in traumatic children. Turkish Journal of Trauma and Emergency Surgery. 2016;22(4):328–32. Ulus Travma Acil Cerrahi Derg.
18. K¿ht¿r HS, Ongun EA. BIG score is a strong predictor of mortality and morbidity for high-energy traumas in pediatric intensive care unit. Turkish Journal of Trauma & Emergency Surgery. 2022;28:1297.. Ulus Travma Acil Cerrahi Derg.
19. Fenix J, Gillespie CW, Levin A, Dean N. Comparison of pediatric early warning score to physician opinion for deteriorating patients. Hosp Pediatr. 2015;5:474–9.

Brazilian Journal of Anesthesiology 2024;74(5):744169



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Using the Perfusion Index to predict changes in the depth of anesthesia in children compared with the A-line Autoregression Index: an observational study☆

Hala Saad Abdel-Ghaffar *, Amani Hassan Abdel-Wahab, Mohammed Mahmoud Roushdy

Assiut University, Faculty of Medicine, Anesthesia and Intensive Care Department, Assiut, Egypt

Received 14 June 2020; accepted 25 April 2021
Available online 12 May 2021

KEYWORDS
Children;
Sevoflurane;
Consciousness;
Pulse oximetry;
Perfusion index;
Auditory evoked potentials

Abstract
Background: We investigated the performance of the Perfusion Index (PI) derived from pulse oximetry waveform as a tool for assessment of anesthetic depth in comparison with A-line Autoregression Index (AAI) derived from analysis of Middle-Latency Auditory Evoked Potentials (MLAEP) waveform integrated by aepEXplus monitor in children receiving sevoflurane anesthesia for tonsillectomy.
Methods: Forty-one patients (4–12 years old) were included in this study. The PI and AAI were recorded simultaneously every minute during different stages of anesthesia delivery. The statistical tests included descriptive analysis, significance tests, correlation tests, and Receiver Operating Characteristic (ROC) curve. The AAI served as a reference.
Results: The PI significantly decreased during light anesthesia and recovery, and significantly increased during deeper planes of anesthesia, with an inverse mirror-image relationship with the AAI. A negative correlation of low to moderate degree was detected between PI and AAI during the study ($p > 0.05$), that reached a statistical significance at the 5th minute during sevoflurane mask induction ($r = -0.457$, $p = 0.008$). ROC analysis at an AAI < 25 extracted the best cut-off value for PI before intubation as 1.48 (AUC = 0.698 [0.537–0.859], 94.4% sensitivity, 44.5% specificity) and at 10-minute intraoperatively as 2.4 (AUC = 0.537 [0.354–0.721], 91.7% sensitivity, 31% specificity). During recovery, at an AAI $\geq$ 50, the best cutoff was 1.82 (AUC = 0.661 [0.46–0.863], 100% sensitivity and 50% specificity) 2 minutes before spontaneous eye opening.
Conclusions: Compared with the AAI, the PI can track changes in depth of anesthesia in pediatric patients undergoing tonsillectomy under sevoflurane anesthesia.
Trial registration: Clinical Trials. Gov. Identifier: NCT03412214.
© 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/).

☆ Reprints: Hala S. Abdel-Ghaffar, Anesthesia and intensive care department, Assiut university hospital, Assiut, Egypt. Study Affliation: Assiut university main hospital, Assiut University, Assiut, Egypt. Setting: Assiut university main hospital.

* Corresponding author.
E-mails: hala_abdelghaffar@med.aun.edu.eg, hallasaad@yahoo.com (H.S. Abdel-Ghaffar).

https://doi.org/10.1016/j.bjane.2021.04.030
© 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

Can the perfusion index (PI) derived from the pulse oximetry wave form reported to track the depth of anesthesia in children under sevoflurane anesthesia? Using the receiver operating characteristic curve (ROC), we determined the best cutoff values of PI during different stages of anesthesia delivery taking the AAI as a reference monitor. The PI can consistently differentiate between different planes of anesthesia in pediatric patients receiving sevoflurane anesthesia.

Monitoring the depth of anesthesia in anesthetized children is important. It enables the anesthesiologists to adjust the doses of anesthetic agents, helps avoiding intraoperative awareness, and facilitates a faster recovery.[1–3] The depth of anesthesia correlates with the changes in the partial pressure of administered anesthetic drugs in the brain.[1] Monitoring the depth of anesthesia using raw Electroencephalograph (EEG) − based monitoring devices such as the Bispectral Index (BIS) has been linked to improved patient outcomes after anesthesia.[4] Mid-Latency Auditory Evoked Potentials (MLAEP) have also been utilized to monitor the depth of anesthesia. The developmental time of MLAEP extends through the first decade of life, while the raw EEG is not mature before early adulthood.[5,6] Therefore, MLAEP is a potentially more useful parameter to assess the depth of anesthesia than EEG in children.[7] The A-line Autoregression Index (AAI) is calculated from the fast extracted MLAEP waveform analysis.[8]

However, monitors of the depth of anesthesia are expensive and not available in every operating room.[9] Instead, physicians utilize clinical variables denoting sympathetic stimulation such as blood pressure, heart rate, and respiratory rate to assess the depth of anesthesia.[10] The sympathetic nervous system output is increased with lighter planes of anesthesia and surgical stimulation and is depressed by anesthetic drugs. Increased sympathetic tone leads to peripheral vasoconstriction, while its decrease is associated with peripheral vasodilatation.[10]

The Perfusion Index (PI) is the ratio of the pulsatile to the non-pulsatile signal obtained from the pulse oximetry waveform that is incorporated in several modern pulse oximeter monitors available in operating theatres.[11] It decreases with vasoconstriction and increases with vasodilatation, and several studies have suggested that the PI may be a sensitive estimate of the level of sympathetic activity.[12–14] Though working by different principles, both the AAI and the PI can be used to monitor the depth of anesthesia.[13–18]

We conducted this study to investigate the use of PI to predict changes in the depth of anesthesia and recovery in children anesthetized with sevoflurane in direct association with the AAI.

Methods

Ethics

This prospective observational cohort was carried out at the main teaching hospital of the Faculty of Medicine, Assiut University, Assiut, Egypt, after approval from its medical ethics committee (protocol ID: 17300155, date: 14-12-2017, head of ethical committee: Prof. Hamdy N. EL-Talawy). This approval was followed by registration in Clinical Trials (gov. identifier: NCT03412214) before patient enrollment. The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. Written informed consent was taken from the parents or legal guardians of the children.

Study population

Forty-one children aged 4 to 12 years, American Society of Anesthesiologists (ASA) physical status I and II and scheduled for elective tonsillectomy with and without adenoidectomy were enrolled in this study. Patients with significant neurological, cardiac, respiratory, renal, and neuromuscular diseases or hearing impairment were excluded from the study.

Conduct of anesthesia

No sedative premedication was administered to any of our patients. Standard monitoring included electrocardiography, noninvasive blood pressure, end-tidal capnography, and a pulse oximeter (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., China). The pulse oximeter was placed on the index finger of the child, shielded to prevent outside light from interfering with the signal, and kept in place for the whole procedure. In the meantime, the noninvasive blood pressure cuff was put on the other arm. The pulse oximeter continuously displayed the peripheral arterial oxygen saturation and the PI. The skin of the forehead was prepared according to the manufacturer's guidelines. Then the electrodes of the AEP Monitor/2 (Danmeter A/S, Odense, Denmark) were placed on the child's forehead to continuously display the AAI throughout the procedure. The anesthetic protocol was standardized. Anesthesia induction started with sevoflurane inhalation followed by venous cannulation and the administration of 1 $\mu g.kg^{-1}$ fentanyl, 1−1.5 $mg.kg^{-1}$ lidocaine, and 0.5 $mg.kg^{-1}$ atracurium for muscle relaxation. Older children also received 2−3 $mg.kg^{-1}$ intravenous (IV) propofol during the induction of anesthesia, if needed. The size of the cuffed endotracheal tube was selected according to the patient's age. Anesthesia and muscle relaxation were maintained with sevoflurane in a 50% oxygen/air mixture and 0.15 $mg.kg^{-1}$ atracurium at fixed intervals. All the patients received 15 $mg.kg^{-1}$ IV paracetamol and 0.2 $mg.kg^{-1}$ dexamethasone. At the end of the surgery, sevoflurane was turned off, and the patients were extubated awake after the reversal of muscle relaxation with neostigmine and atropine. The monitoring of the children continued in the OR until extubation so as not to interrupt the AAI recordings. After extubation, the patients were transferred to the Postanesthesia Care Unit (PACU) to be discharged to the ward afterward.

Study protocol

To certify an equal condition when comparing the performance of the two investigated indices, the AAI and the PI were recorded simultaneously in the same patient during the

whole procedure of anesthesia delivery and during recovery from anesthesia. The AAI recordings range from 0–100 and are interpreted as follows: 0–15 = deep anesthesia; 15–25 = surgical anesthesia with a peak at 20; 25–40 = light anesthesia, denoting intraoperative awareness; and above 50 = awake level.[3] The clinical stages of anesthesia and recovery were classified into four stations:

Stage I: From mask induction to endotracheal intubation. The pre-induction values of the AAI and the PI were recorded (baseline). Then the two indices were recorded simultaneously for every minute from the start of mask induction of the anesthesia until endotracheal intubation.

Stage II: From endotracheal intubation to surgical incision. Both the AAI and the PI were recorded 1, 2, 3, 4, and 5-minutes after intubation.

Stage III: During the surgical procedure. Both the indices were recorded 1, 2, 3, 4, 5, 10, 20, and 30 minutes intraoperatively.

Stage IV: During recovery from anesthesia. The AAI and the PI were recorded every minute from the discontinuation of sevoflurane until spontaneous eye opening.

Statistics

Power of the study

Changes in the PI during different stages of anesthesia delivery and recovery in direct association with the AAI served as the primary outcome parameter in this study. The secondary outcomes were descriptive analysis, significance tests, correlation testing between the PI and the AAI at different stages of anesthesia delivery, and Receiver Operating Characteristic (ROC) analysis, with the determination of the best cut-off value of the PI at an AAI < 25 and ≥ 50. Based on a previous study,[13] using the G-Power calculator 3.1.9.7 for sample size determination, a minimum of 34 patients for this cohort would be sufficient for our statistical testing based on a priori analysis with the *t*-test family: the difference between two dependent means (matched pairs) for one sample at a two-tailed type I error of 0.05 and a power of 0.8 and effect size of 0.5. Forty-two patients were enrolled to compensate for the dropouts.

Statistical tests

Statistical analysis was done via the Statistical Package for the Social Sciences (SPSS), software version 20, for Microsoft Windows (SPSS Inc., Chicago, IL, USA). The data was checked for normality using the Shapiro-Wilk test. The continuous data was presented as the mean (±SD) with a 95% Confidence Interval for normally distributed data and as the median (range) for not normally distributed data. The categorical data was expressed as numbers and frequencies (%). Data analysis was performed using paired *t*-tests for normally distributed data and the Wilcoxon rank test for abnormally distributed data. A *p*-value of < 0.05 was considered statistically significant.

The correlation between the variables was carried out by applying the Pearson correlation equation for linear relations and the Spearman correlation equation for nonlinear correlation. The degree of correlation was determined based on the coefficient correlation (r) into perfect positive (r = +1), perfect negative (r = -1), no correlation (r = 0), high-degree positive (r = +0.75 to +1), high-degree negative (r = -0.75 to -1), moderate-degree positive (r = +0.25 to +0.75), moderate-degree negative (r = -0.25 to -0.75), low-degree positive (r = 0 to +0.25), and low-degree negative (r = 0 to -0.25).

The ROC curve and its corresponding Area Under the Curve (AUC) was constructed to evaluate the ability of the PI to detect the depth of anesthesia and to distinguish between consciousness and unconsciousness compared with the AAI. The best cut-off value for the PI was the value at which both the specificity and the sensitivity were the highest. For analysis, we defined consciousness as an AAI ≥ 50 and unconsciousness (adequate hypnosis) as an AAI < 25. ROC analysis was conducted using MedCalc for Windows, version 5.6.1 (MedCalc Software, Mariakerke, Belgium).

Table 1 Patients' demographic and clinical characteristics.

Study cohort (n = 41)	
Age (years)	6 (4–12)
Weight (Kg)	23.7 ± 6.5 (21.6–25.7)
Sex: Male/Female	31/10
Induction agent	
Sevoflurane/Sevoflurane and propofol	29/12
Anesthesia time (min)	46.4 ± 13.3 (42.2–50.6)
Induction time (min)	6.2 ± 1.72 (5.7–6.7)
Surgery time (min)	36.1 ± 13.3 (31.9–40.3)
Time to spontaneous eye opening (min)	11.95 ± 2.6 (range: 7–17 min)

Data presented as median (range), mean (±SD) with 95% Confidence Interval, range, and number.

Results

Forty-two patients were enrolled in this study. One patient was dropped because of incomplete data, and 41 patients successfully completed the statistical analysis. Their clinical variables such as the heart rate, blood pressure, temperature, and peripheral arterial oxygen saturation were within the normal limits throughout the procedure. The patients' demographic and baseline characteristics are listed in Table 1.

The trend of PI and AAI through the anesthetic procedure

The baseline median PI was 0.7 (range: 0.2–2.7), which gradually increased during the induction of general anesthesia ($p < 0.0001$). The baseline mean AAI was 62.1±9.1 (95% CI: 59.2–64.9), which gradually decreased during the induction of anesthesia until endotracheal intubation ($p < 0.001$) (Fig. 1A). After endotracheal intubation, a small increase in the PI ($p < 0.021$) was recorded, with no change in the AAI ($p = 0.341$) (Fig. 1B). Intraoperatively, the PI increased further ($p < 0.0001$), and the AAI decreased further ($p < 0.0001$) throughout the anesthetic procedure (Fig. 1C). During recovery from anesthesia, the PI gradu-

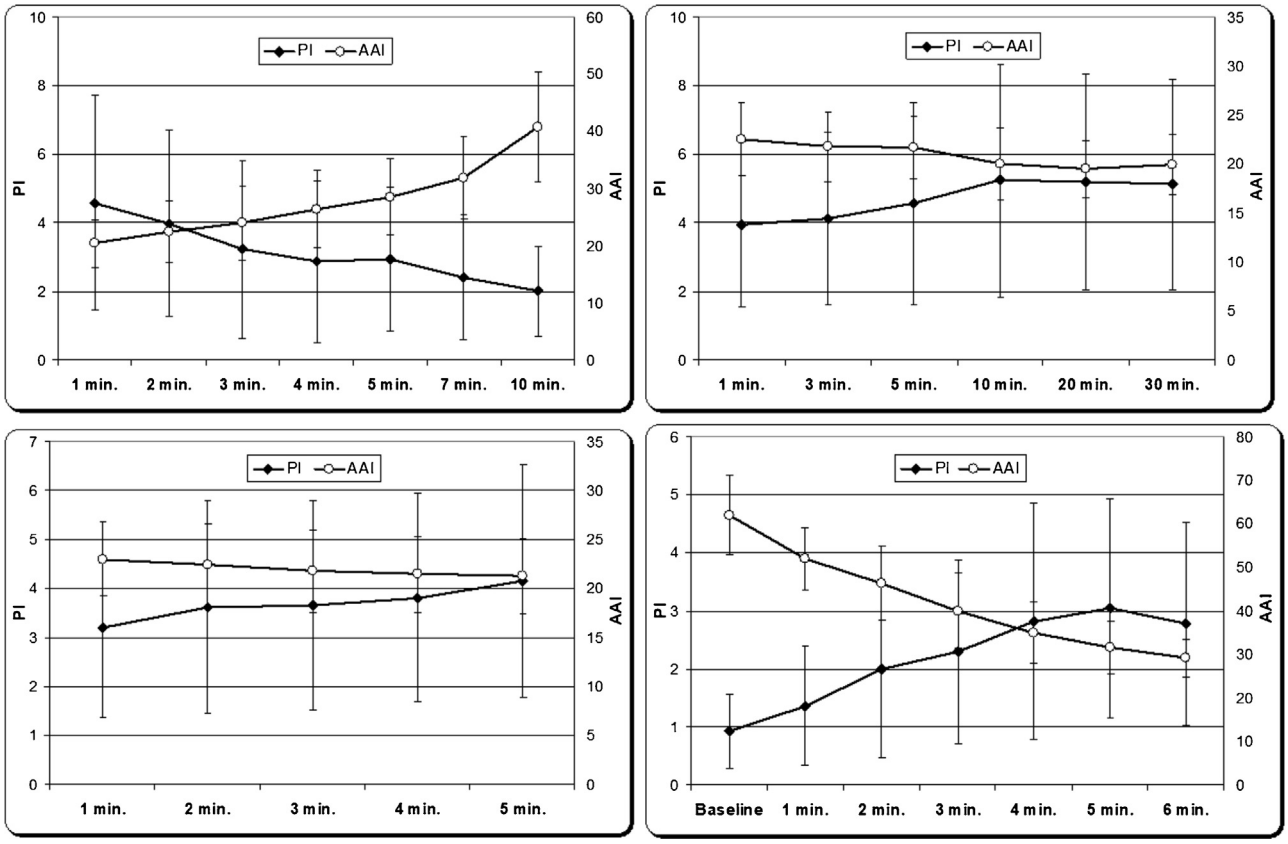


Figure 1 (A) Trend of AAI and PI from induction of anesthesia to endotracheal intubation. (B) Trend of AAI and PI from endotracheal intubation till start of surgery. (C) Trend of AAI and PI during the surgical procedure. (D) Trend of AAI and PI from discontinuation of sevoflurane till spontaneous eye opening. PI, Perfusion Index; AAI, A-line Autoregression Index. Values are presented as mean ± SD.

ally decreased ($p < 0.0001$), and the AAI gradually increased ($p < 0.0001$) (Fig. 1D). At spontaneous eye opening, the median PI, 1.5 (range: 0.5–5.2), was higher ($p < 0.0001$) and the mean AAI (53.2 ± 6.1, 95% CI: 51.2–55.3) was lower ($p < 0.0001$) than their respective baseline values before the delivery of anesthesia. The inverse relationship between the AAI and the PI through the anesthetic procedure is presented as a trend Figure (1A–D) in which the PI and AAI were presented as mean ± SD.

Correlation between the PI and the AAI

Correlation analysis showed a negative correlation between the PI and the AAI of a low to moderate degree at the studied time points, with the p-value > 0.05 (data not represented) except at the 5thminute during the mask induction of sevoflurane, which showed a moderate significant negative correlation (r = -0.457, p = 0.008) (Fig. 2).

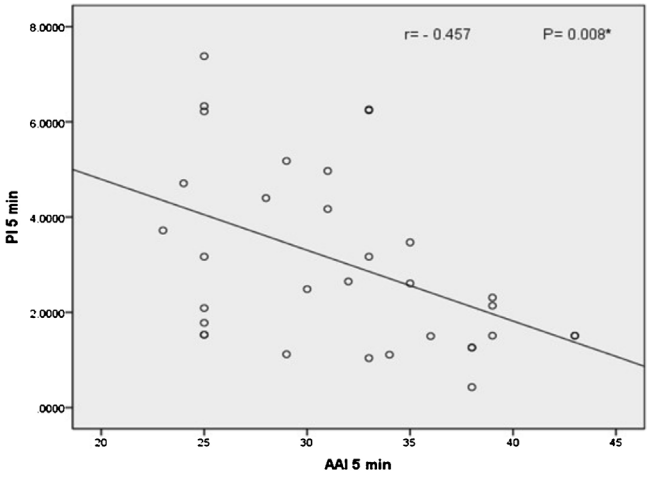


Figure 2 Correlation between PI and AAI at 5th minute before intubation. PI, Perfusion Index; AAI, A-line Autoregression Index.

Receiver operator characteristics analysis of the PI and the AAI

During anesthesia delivery (At an AAI < 25 denoting hypnosis), the best cut off value for the PI before intubation was 1.48, (AUC = 0.698 [95% CI: 0.537–0.859], 94.4% sensitivity and 44.5% specificity), and the best cut off value for the PI at 10 minutes intraoperatively was 2.4, (AUC = 0.537 [0.354–0.721], 91.7% sensitivity and 31% specificity] (Fig. 3A and B).

During recovery from anesthesia (at an AAI ≥ 50 denoting consciousness), the best cut off value for the PI was 1.82, (AUC = 0.661 [0.46–0.863], 100% sensitivity and 50% specificity) 2 -minutes before spontaneous eye opening, 0.78

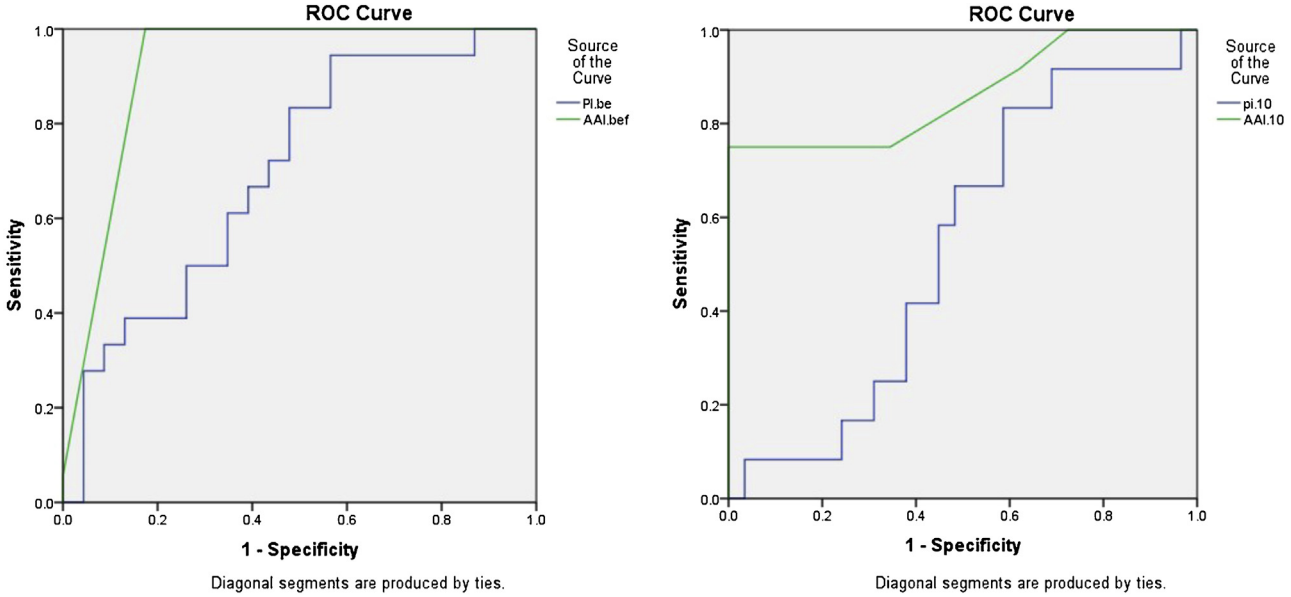


Figure 3 (A) Receiver Operator Characteristics (ROC) analysis of the PI and AAI before intubation. At an AAI < 25, The AUC for PI was 0.698 (0.537–0.859), 94.4% sensitivity and 44.5% specificity. The AUC for AAI was 0.918 (0.826–1.0), 100% sensitivity and 83.6% specificity. (B) Receiver Operator Characteristics (ROC) analysis of the PI and AAI at 10thmin. intraoperative. At an AAI < 25, The AUC for PI was 0.537 (0.354–0.721), 91.7% sensitivity and 31% specificity. The AUC for AAI was 0.918 (0.826–1.0), 75% sensitivity and 100% specificity.

(AUC = 0.545 [0.282–0.803], 100% sensitivity and 15% specificity) 1 minute before spontaneous eye opening, and 1.12 (AUC = 0.543 [0.356–0.730], 73.7% sensitivity and 40.9% specificity) at the event of spontaneous eye opening (Fig. 4 A–C).

Discussion

In this study, we investigated the performance of the PI as a tool to assess the depth of anesthesia during different stages of anesthesia delivery in direct comparison with the AAI. Our results demonstrated that the PI significantly decreased during light anesthesia and recovery and significantly increased during deeper planes of anesthesia, with an inverse relationship with AAI. At whatever time the AAI decreases, the PI increases and vice versa. While the correlation testing between these two indices was insignificant in most of the time points investigated, the ROC analysis was informative, showing clear cut off values with their corresponding sensitivity and specificity.

The physical principles of the PI and the AAI are completely different. Auditory-Evoked Potentials (AEPs) measure time-locked EEG responses to repetitive auditory clicks, testing the neural pathways carrying information from the periphery to the cerebral cortex reflecting the changes in the cortical area.[19] Meanwhile, the PI acts as an indicator of the plethysmographic pulse wave amplitude, reflecting changes in the peripheral vasomotor tone in response to changes in the sympathetic output (i.e., ''subcortical zone'').[12–14] The PI increases with peripheral vasodilatation in response to decreased sympathetic output and decreases with peripheral vasoconstriction in response to increased sympathetic output.[12–14,17]

Light anesthesia and inadequate analgesia both stimulate the sympathetic nervous system and decrease the PI.[12] Ezri et al., in their study on adult females undergoing D&C procedures, reported that the PI decreased with cervical dilatation and during light anesthesia.[10] Korhonen and Yli-Hankala, in their study, also confirmed the relationship between nociception and the PI. They concluded that the quality of analgesia delivered, the type of surgery, and its perceived level of nociception would all affect the PI.[12] This could have confounded the results when we investigated the PI as a tool to assess the depth of anesthesia. However, many clinicians found that these observations make the PI a useful, non-expensive, available continuous tool forecasting the patients' needs for additional analgesia and for deeper planes of anesthesia in busy operating rooms with rapid turnover, thus increasing the patients' safety and reducing perioperative risks.[17] Also, this will financially reserve the specific depth of anesthesia monitors to special patients' categories and types of operations that are commonly associated with intraoperative awareness.[19]

Correlation analysis showed a negative correlation between the PI and the AAI of a low to moderate degree at the studied time points, with the *p*-value > 0.05 except at the 5thminute during the mask induction of sevoflurane, which showed a moderate significant negative correlation (r = -0.489, *p* = 0.004). Indeed, this is the mean time needed to induce deep anesthesia through sevoflurane inhalational mask induction, and this observation is consistent with those of other studies on such a topic.[1,13]

In this study, we conducted an ROC analysis as an approach to quantify the PI performance in comparison to that of the AAI (as a specific monitor for the depth of anesthesia) for analysis at two different states: an adequate level of anesthesia (AAI < 25) and at recovery (AAI ≥ 50),

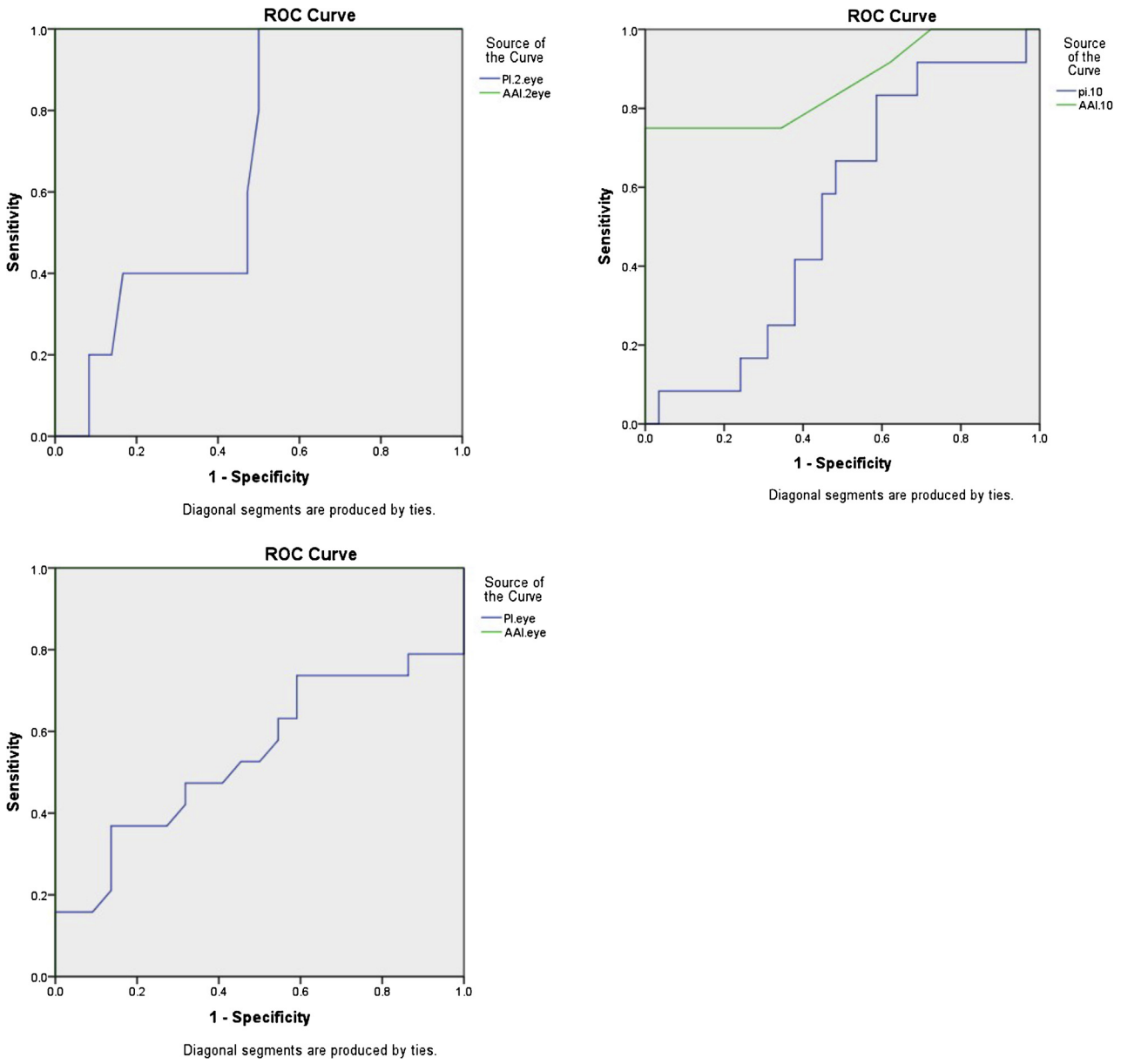


Figure 4 (A) Receiver Operator Characteristics (ROC) analysis of the PI and AAI two minutes before spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.661 (0.46–0.863), 100% sensitivity and 50% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 100% specificity. (B) Receiver Operator Characteristics (ROC) analysis of the PI and AAI one minutes before spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.545 (0.282–0.803), 100% sensitivity and 15% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 94.3% specificity. (C) Receiver Operator Characteristics (ROC) analysis of the PI and AAI at spontaneous eye opening. At an AAI $\geq$ 50, The AUC for PI was 0.543 (0.356–0.730), 73.7% sensitivity and 40.9% specificity. The AUC for AAI was 1.0 (1.0–1.0), 100% sensitivity and 100% specificity.

extracting a clear cut-off value with its corresponding sensitivity and specificity. In this study, the baseline preoperative median PI was 0.7 (range: 0.2–2.7). At an AAI < 25, the best cut-off value for the PI before intubation was 1.48 (94.4% sensitivity and 44.5% specificity), and the best cut-off value for the PI at 10 minutes was 2.4 (91.7% sensitivity and 31% specificity). During recovery from anesthesia at an AAI $\geq$ 50, the best cut off value for the PI was 0.78 (100% sensitivity and 15% specificity) 1 minute before spontaneous eye opening. Despite it not being specific, we found that the PI was sensitive in detecting the depth of anesthesia. Compared with its preoperative value, it doubled before intubation, tripled intraoperatively during adequate anesthesia and analgesia, and returned nearly to its baseline value at recovery. These results are in accordance with those of studies that confirmed the sensitivity of PI for detecting changes in the depth of anesthesia.[10,13,15,17] An added advantage of this study was that we defined clear cut off values for the PI at different stages of anesthesia delivery and during recovery. Considering that the AUC was < 0.7 at all the studied time points, the accuracy of the PI to differentiate the depth of anesthesia might be

defined as low. Further studies are needed to support these findings.

At spontaneous eye opening, the AAI was 53.2 ± 6.1 compared with 62.1 ± 9.1 ($p < 0.001$) before anesthesia induction. This finding is in accordance with those of previous studies that concluded that cortical activity does not fully recover during emergence from anesthesia.[17,18]

In this study, we reported large inter-individual variations in the PI, ranging from 0.18 preoperatively and up to 14.1 at 10 minutes intraoperatively. Similarly, Granelli and Ostman-Smith found a large inter-individual variation of the PI that ranged from 0.02 to 20 in 10,000 healthy newborns recruited in their case-control study.[20] Despite these large inter-individual variations, we think that the PI is a useful tool when comparing the trend of changes in the value of PI in comparison to its baseline value. We conclude that the surges and drops in the PI compared with its respective baseline are highly informative regardless of whatever this value was.

A limitation of this study was that changes in the PI reflect both anesthetic and analgesic needs. In this study, we assumed that the changes in the PI are mainly due to changes in the depth of anesthesia because our patients received an adequate analgesic protocol that is suitable for such operations. In addition, we studied a homogenous sample as regards operative procedure and patient category. So, we can assume that this bias has been controlled. Possible effects of iv propofol on AAI should be considered and a second limitation to this study is that we used IV propofol as a supplementation to sevoflurane inhalational induction in older children in this study. Twelve patients of this cohort (n = 41) received iv propofol supplementation to sevoflurane mask induction. Indeed, this is a common practice in pediatric anesthesia protocols. The minimum propofol dose required for loss of consciousness was used and we did not use any anesthetic adjuvants afterward. We assume that this technique did not affect our results.

In conclusion, compared with the AAI, the PI can track changes in the depth of anesthesia in pediatric patients undergoing tonsillectomy under sevoflurane anesthesia.

Author contribution

Hala S. Abdel-Ghaffar: This author helped study design, data analysis, writing and editing the manuscript.

Amani H. Abdel-Wahab: This author helped conduct of study, data collection and data entry.

Mohammed M Roushdy: This author helped conduct of study.

Funding

Departmental resources were used for the conduct of this study.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors thank the staff of the Departments of Anesthesiology and ENT at the Faculty of Medicine, Assiut University, for their warm encouragement regarding the conduct of this study.

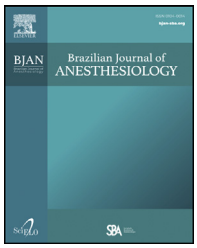
References

1. Davidson AJ. Monitoring the anaesthetic depth in children: an update. Curr Opin Anaesthesiol. 2007;20:236–43.
2. Weber F, Pohl F, Hollnberger H, et al. Impact of the Narcotrend Index on propofol consumption and emergence times during total intravenous anaesthesia with propofol and remifentanil in children: a clinical utility study. Eur J Anaesthesiol. 2005;22:741–7.
3. Weber F, Seidl M, Bein T. Impact of the AEP-Monitor/2-derived composite auditory-evoked potential index on propofol consumption and emergence times during total intravenous anaesthesia with propofol and remifentanil in children. Acta Anaesthesiol Scand. 2005;49:277–83.
4. Fletcher JE, Hinn AR, Heard CM, et al. The effects of isoflurane and desflurane titrated to a bispectral index of 60 on the cortical somatosensory evoked potential during pediatric scoliosis surgery. Anesth Analg. 2005;100:1797–803.
5. Davies FW, Mantzaridis H, Kenny GN, et al. Middle latency auditory evoked potentials during repeated transitions from consciousness to unconsciousness. Anaesthesia. 1996;51:107–13.
6. Daunderer M, Feuerecker MS, Scheller B, et al. Midlatency auditory evoked potentials in children: effect of age and general anaesthesia. Br J Anaesth. 2007;99:837–44.
7. McGee T, Kraus N. Auditory development reflected by middle latency response. Ear Hear. 1996;17:419–29.
8. Struys MM, Vereecke H, Moerman A, et al. Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. Anesthesiology. 2003;99:802–12.
9. Rinehardt EK, Sivarajan M. Costs and wastes in anesthesia care. Curr Opin Anaesthesiol. 2012;25:221–5.
10. Ezri T, Steinmetz A, Geva D, et al. Skin vasomotor reflex as a measure of depth of anesthesia. Anesthesiology. 1998;89:1281–2.
11. Allen J. Photoplethysmography and its application in clinical physiological measurement. Physiol Meas. 2007;28:R1–39.
12. Korhonen I, Yli-Hankala A. Photoplethysmography and nociception. Acta Anesthesiol Scand. 2009;53:975–85.
13. Krishnamohan A, Siriwardana V, Skowno JJ. Using a pulse oximeter to determine clinical depth of anesthesia-investigation of the utility of the perfusion index. Pediatr Anesth. 2016;26:1106–11.
14. Seitsonen ERJ, Korhonen IKJ, van Gils MJ, et al. EEG spectral entropy, heart rate, photoplethysmography and motor responses to skin incision during sevoflurane anaesthesia. Acta Anesthesiol Scand. 2005;49:284–92.
15. Enekvist B, Johansson A. Pulse perfusion value predicts eye opening after sevoflurane anaesthesia: an explorative study. J Clin Monit Comput Springer Netherlands. 2015;29:461–5.

16. Skowno JJ. Perfusion index changes during emergence from anaesthesia in children. Anaesth Intensive Care. 2013;41:556–7.
17. Liu P-P, Wu C, Wu J-Z, et al. The prediction probabilities for emergence from sevoflurane anesthesia in children: A comparison of the perfusion index and the bispectral index. Pediatr Anesth. 2018;28:281–6.
18. Cheung YM, Scoones GP, Stolker RJ, et al. Monitoring depth of hypnosis: mid-latency auditory evoked potentials derived aepex in children receiving desflurane-remifentanil anesthesia. Anesth Analg. 2020;130:194–200.
19. Fahy BG, Chau DF. The technology of processed electroencephalogram monitoring devices for assessment of depth of anesthesia. Anesth Analg. 2018;126:111–7.
20. Granelli DW, Ostman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr. 2007;96:1455–9.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

End-tidal carbon dioxide measurements as a surrogate to arterial carbon dioxide during pediatric laparoscopic surgeries: a prospective observational cohort study

Hala Saad Abdel-Ghaffar [a,*], **Mohammed Abdel-Moneim Bakr** [a], **Mohamed Abdel-Kadr Osman** [b], **Sarah George Labib Hanna** [a], **Wesam Nashat Ali** [a]

[a] *Assiut University, Faculty of Medicine, Anesthesia and Intensive Care Department, Assiut, Egypt*
[b] *Assiut University, Faculty of Medicine, Pediatric Surgery Department, Assiut, Egypt*

Received 31 August 2020; accepted 28 July 2021
Available online 16 August 2021

KEYWORDS
Children;
Anesthesia;
Laparoscopy;
Mechanical ventilation;
Arterial carbon dioxide;
End tidal carbon dioxide

Abstract

Background: Maintaining normocapnia during mechanical ventilation in anesthetized children during laparoscopic surgeries is highly recommended. There is a debate regarding the use of capnography ($ETCO_2$) as a trend monitor for evaluation of arterial carbon dioxide levels ($PaCO_2$). We analyzed the relationship between $ETCO_2$ and $PaCO_2$ with time in elective pediatric laparoscopic surgeries.

Methods: This study was a prospective observational cohort analysis of 116 paired comparisons between $PaCO_2$ and $ETCO_2$ computed from 29 children (ASA I, 12–72 months). Arterial blood samples were withdrawn before, at 15 minutes and 30 minutes during pneumoperitoneum and 1 minute after deflation. $ETCO_2$ value was recorded simultaneously, while arterial blood was withdrawn. $PaCO_2$–$ETCO_2$ relationship was evaluated by Pearson's correlation coefficients and Bland Altman Method of agreement.

Results: Out of the 116 comparisons analyzed, a $PaCO_2$–$ETCO_2$ difference beyond 0 to $\leq$ 5 mmHg was recorded in 71 comparisons (61.2%) with negative difference in 34 comparisons (29.3%). A positive significant correlation between $PaCO_2$ and $ETCO_2$ was recorded before ($r = 0.617$, $p = 0.000$) and at 15 minutes ($r = 0.582$, $p = 0.001$), with no significant correlation at 30 minutes ($r = 0.142$, $p = 0.461$), either after deflation ($r = 0.108$, $p = 0.577$). Bland-Altman plots showed agreement between $ETCO_2$ and $PaCO_2$ before inflation with mean $PaCO_2$-$ETCO_2$ difference 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84–11.2, simple linear regression testing p-value 0.971), with no agreement at 15 minutes (0.51 ± 7.15, -13.5–14.5, $p = 0.000$), 30 minutes. (2.62 ± 7.83, -12.73–17.97, $p = 0.000$), or after deflation (1.81 ± 6.56, -10.93–14.55, $p = 0.015$).

* Corresponding author.
E-mail: hallasaad@yahoo.com (H.S. Abdel-Ghaffar).

https://doi.org/10.1016/j.bjane.2021.07.036
© 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/).

Conclusion: Usage of capnography as a trend monitor in pediatric laparoscopic surgeries may not be a reliable surrogate for $PaCO_2$ levels.
Trial registration: Clinical Trials. gov (Identifier: NCT03361657)
© 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

In 2008 the World Federation of Societies of Anesthesiologists (WFSA) produced international standards for the safe practice in anesthesia which contained pulse oximetry and capnography.[1] Capnography provides a non-invasive estimation of arterial CO_2 levels. It permits physicians to titrate their protocols for mechanical ventilation to maintain normocapnia in operative theatres and in the intensive care.[2] To avoid perioperative central nervous system derangements, clinicians recommend the maintenance of normocapnia during intraoperative mechanical ventilation in pediatric patients specially in younger individuals, hemodynamic instability and in certain operative techniques such as carbon dioxide pneumoperitoneum in laparoscopic surgeries.[3–5]

Clinicians commonly evaluate the arterial carbon dioxide partial pressure by intermittent arterial blood gas analysis coupled with continuous recording of the end-tidal carbon dioxide by capnography.[6,7] Moreover, some clinicians aspirate a single arterial blood gas at the beginning of managing a case intraoperatively to calculate $PaCO_2$–$ETCO_2$ difference then employ capnography as a trend monitor to evaluate and control changes in arterial carbon dioxide partial pressure value, afterwards.[8]

Normally, in healthy individuals there is a positive gap between arterial CO_2 and $ETCO_2$ ($ETCO_2 < PaCO_2$) of approximately 0.5 kPa (3.75 mmHg).[6] Negative gaps ($ETCO_2 > PaCO_2$) were recorded in 34% of patients in pediatric critical care and during general anesthesia.[7,9,10] They occur most frequently in children aged 4–8 years,[9] with decreasing $PaCO_2$ values,[7,9] and with a dead space/tidal volume ratio of less than 0.4.[10] Certain procedures such as pediatric laparoscopic capnoperitoneum are associated with rapidly changing levels of both $PaCO_2$ and $ETCO_2$.[11] This in turn can further affect the $PaCO_2$–$ETCO_2$ difference.

In this study, our aim was to investigate the correlation and agreement between $ETCO_2$ measured by capnography and arterial $PaCO_2$ measured by arterial blood gas analysis and to calculate the $PaCO_2$–$ETCO_2$ difference during pediatric laparoscopic surgeries.

Patients and methods

Ethical considerations

This Prospective observational Cohort was conducted in the Pediatric hospital, faculty of medicine, Assiut University, Assiut, Egypt after obtaining an IRB approval from its Medical Ethics committee (Protocol ID: 17300081, date; 13-7-2017). Registration in Clinical Trials. gov (NCT03361657) was accomplished before patient enrollment. This study follows the ''STROBE'' guidelines for observational studies (STrengthening the Reporting of OBservational studies in Epidemiology). A written informed consent was taken from the legal guardians of children.

Study population

Twenty-nine children of both sexes, aged from 12 to 76 months, ASA I and II and scheduled for elective laparoscopic abdominal or urologic surgery (e.g undescended testis, repair for inguinal hernia, cholecystectomy), were enrolled in this study. Excluded from the study were patients with significant cardiac or respiratory disease.

Study protocol

No sedative premedication was administered. Monitoring included electrocardiography, non-invasive blood pressure, end-tidal capnography, and pulse oximeter (Shenzhen Mindray Bio-Medical Electronics Co, Ltd., China). Anesthesia induction started with sevoflurane inhalation followed with venous cannulation, and the administration of 1 $\mu g.kg^{-1}$ fentanyl, 1–1. 5 $mg.kg^{-1}$ lidocaine and atracurium 0.5 $mg.kg^{-1}$ for muscle relaxation. Older children also received iv propofol 2–3 $mg.kg^{-1}$ during induction of anesthesia, if needed. An appropriately sized cuffed endotracheal tube was inserted. A cannula in the radial artery was inserted to be used for withdrawal of arterial blood samples. Patients were mechanically ventilated in volume-control mode using standard pediatric breathing circuits with tidal volume 8–10 $mL.kg^{-1}$, and at respiratory rates of 15–25 breaths per minute depending on the patient's age which finally adjusted to achieve an end-tidal CO_2 ($ETCO_2$) of 35–45 mm.Hg, and a target $SaO_2\% \geq 97\%$. Any unnecessary connections that may increase the dead space were removed.

Laparoscopic surgeries were performed according to the standard protocols. Pneumoperitoneum was achieved using non-heated non-humidified CO_2 with the intra-abdominal pressure maintained at 10–12 mmHg. Sevoflurane in a 50% oxygen/air mixture and 0.15 $mg.kg^{-1}$ atracurium at fixed intervals were used for maintenance of anesthesia and muscle relaxation, respectively. All patients received 15 $mg.kg^{-1}$ intravenous paracetamol and 0.2 $mg.kg^{-1}$ dexamethasone.

Patients' hemodynamics, arterial blood gas analysis and $ETCO_2$ values were recorded at four predetermined time points: T1; after stabilization of the mechanical ventilation before inflation of pneumoperitoneum, T2; 15 min. after pneumoperitoneum, T3; 30 min. after pneumoperitoneum and T4; 1 min. after deflation of pneumoperitoneum before reversal of muscle paralysis and extubation.

$ETCO_2$ concentrations were measured using an adequately calibrated infrared mainstream capnometer (Datex Instrument Corp., Helsinki, Finland) with the Port connected between the proximal end of the endotracheal tube and the breathing circuit. Arterial blood samples were obtained coated with heparin. At each selected timepoint, the $ETCO_2$ value was recorded simultaneously while the arterial blood was withdrawn.

At the end of the surgery, sevoflurane was turned off and patients were extubated awake after reversal of muscle relaxation with neostigmine and atropine. After extubation, patients were transferred to the Post Anesthesia Care Unit (PACU) to be discharged to the ward, afterwards.

Statistics

The primary aim in this study was to investigate the relationship between $ETCO_2$ and $PaCO_2$ with time in pediatric laparoscopic surgery by computation of Pearson's correlation coefficient analysis and the agreement between the two monitors by the Bland Altman method. Secondary outcomes were the correlations and relationships between the $PaCO_2$–$ETCO_2$ difference and $PaCO_2$, $ETCO_2$, age, weight, and duration of the operative procedure. Using the G-Power calculator 3.1.9.7 for sample size determination, a minimum of 26 patients for this cohort would be sufficient for our statistical testing based on a priori analysis with t tests family: correlation biserial model for one sample at a two tailed type I error of 0.05, and a power of 0.8 and effect size of 0.5. Thirty-two patients were enrolled to compensate for the dropouts.

Statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS) software version 20 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Data was checked for normality by visual inspection of histograms and by the Shapiro–Wilk test. Continuous data was presented as mean ± SD with 95% confidence interval if normally distributed, and as median (Interquartile range and range) if not normally distributed. Categorical data was expressed as number and frequencies (%). Paired comparisons were analyzed using paired-t tests for normally distributed data and Wilcoxon signed rank test for abnormally distributed data. $PaCO_2$–$ETCO_2$ difference of 0 to $\leq$ 5 mmHg was considered as a clinically acceptable range. Correlation between variables was carried out by applying the Pearson correlation equation for linear relations and spearman correlation equation for non-linear correlation. The degree of correlation was determined based on the coefficient correlation (r) into perfect positive (r = +1), perfect negative (r = -1), no correlation (r = 0), high degree positive (r ranges from +0.75 to +1), high degree negative (r: -0.75 to -1), moderate degree positive (r: +0.25 to +0.75), moderate degree negative (r: -0.25 to -0.75), low degree positive (r: 0 to +0.25) and low degree negative (r: 0 to -0.25).

Bland-Altman plots at each studied time-point were used to investigate the agreement between $ETCO_2$ and $PaCO_2$ and this was furtherly confirmed by simple linear regression analysis.[12] A p-value of <0.05 was the cutoff value for statistical significance.

Table 1 Patients' demographic and clinical characteristics.

Item	Study cohort (n = 29)
Age (months)	36 (12–72)
Weight (Kg)	15 (8–35)
Sex: Male/female	24/5
ASA Class: I/II	29/0
Insufflation pressure (cm.H_2O)	12 (10–12)
Operation time (min.)	39.7 ± 14.1 (34.3–45.1)
Pathological diagnosis:	
Chronic cholecystitis	4
Congenital Inguinal hernia	4
Congenital adrenal hyperplasia	2
Gastric volvulus	1
Undescended testis	18

Data presented as median (range), mean (±SD) with 95% confidence interval, range, and number.

Results

Thirty-two patients were enrolled in this study. Three patients were dropped because of protocol violation (diagnostic laparoscopy of short duration). Twenty-nine patients successfully completed the statistical analysis that yielded 116 paired comparisons between the $PaCO_2$ and the $ETCO_2$ at different timepoints. The patients' demographic and baseline characteristics are listed in Table 1.

Compared to the baseline value (T1), both the arterial carbon dioxide partial pressure ($PaCO_2$) and the end-tidal carbon dioxide ($ETCO_2$) significantly increased at 15 min. after inflation of the pneumoperitoneum and continued to increase at 30 min. after inflation ($p < 0.001$). After deflation of the pneumoperitoneum, both variables remained significantly higher than their respective base line values ($p < 0.001$), (Table 2). The median $PaCO_2$–$ETCO_2$ difference increased at 30 min. after inflation of the pneumoperitoneum and after deflation of the pneumoperitoneum ($p > 0.05$) (Table 2).

Out of the 116 paired comparisons of $PaCO_2$ and $ETCO_2$ analyzed in this cohort study, $PaCO_2$–$ETCO_2$ difference beyond 0 to $\leq$ 5 mmHg was recorded in 71 (61.2%) comparisons and negative $PaCO_2$–$ETCO_2$ difference was recorded in 34 comparisons (29.3%). One child showed a negative $PaCO_2$–$ETCO_2$ difference at the four timepoints studied. Negative $PaCO_2$–$ETCO_2$ difference was recorded at three timepoints in 4 children, at two timepoints in 4 children and at 1 timepoint in 10 children.

A moderate degree positive correlation between the $PaCO_2$ and $ETCO_2$ was recorded before inflation of the pneumoperitoneum ($r = 0.617$, $p = 0.000$) and at 15 min. after inflation of the pneumoperitoneum ($r = 0.582$, $p = 0.001$), (Fig. 1 A and B). No significant correlation was recorded between $PaCO_2$ and $ETCO_2$ at 30 min. after inflation of the pneumoperitoneum ($r = 0.142$, $p = 0.461$), either after deflation of the pneumoperitoneum ($r = 0.108$, $p = 0.577$). The $PaCO_2$, $ETCO_2$ and $PaCO_2$-$ETCO_2$ at the selected timepoints did not show significant correlation with age, weight, operative time, or Insufflation pressure (data not represented).

Table 2 Paired sample statistics of Arterial Carbon Dioxide Partial pressure ($PaCO_2$) and the End-Tidal Carbon Dioxide ($ETCO_2$) (mmHg).

Study cohort (n = 29) Time	Arterial carbon dioxide partial pressure ($PaCO_2$)	End-tidal carbon dioxide ($ETCO_2$)	Arterial-end-tidal carbon dioxide difference ($PaCO_2$–$ETCO_2$)
T1: Before inflation	37.6 ± 6.3 (35.2–40.0)	37.5 ± 6.4 (35.04–39.9)	2.7 (6.9) (-13.0–7.0)
T2: 15 min. after inflation	42.0 ± 8.8[b] (38.6–45.2)	41.4 ± 4.8[c] (39.6–43.2)	3.0 (11.6 t) (-13–12.0)
T3: 30 min. after inflation	45.2 ± 7.5[c] (42.4–48.1)	42.6 ± 3.6[c] (41.2–43.9)	5.1 (6.5) (-22.9–12.4)
T4: After deflation	42.3 ± 5.9[b] (40.1–44.6)	40.5 ± 3.6[c] (39.1–41.9)	4.0 (6.9) (-19.0–11.0)

Data presented as mean ± SD with 95% confidence interval and median (Interquartile Range [IQR] and range). $p < 0.05$ denotes significant difference compared to baseline value (T1).
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

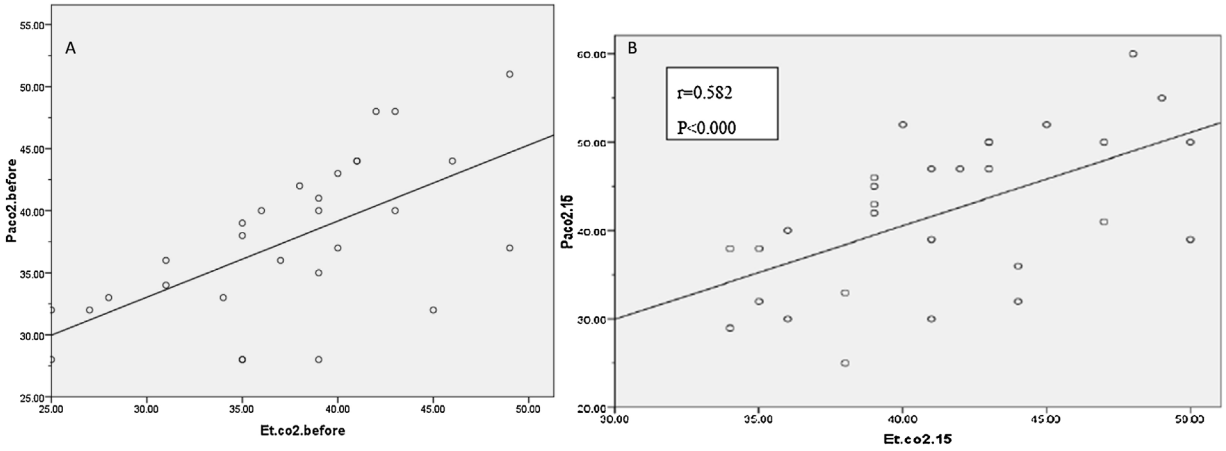


Figure 1 A, Relationship between the End-Tidal Carbon Dioxide ($ETCO_2$) and Arterial Carbon Dioxide ($PaCO_2$) before inflation of the pneumoperitoneum processed by Pearson correlation coefficient. Correlation is significant at the 0.01 level (2-tailed). B, Relationship between the End-Tidal Carbon Dioxide ($ETCO_2$) and Arterial Carbon Dioxide ($PaCO_2$) at 15 min. after inflation of the pneumoperitoneum processed by Pearson correlation coefficient. Correlation is significant at the 0.01 level (2-tailed).

Bland-Altman plots showed an agreement between $ETCO_2$ and $PaCO_2$ before inflation of the pneumoperitoneum with mean of the $PaCO_2$–$ETCO_2$ difference as 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84–11.2 with simple linear regression testing *p*-value as 0.971). No agreement between $ETCO_2$ and $PaCO_2$was found at the other time points namely at 15 min. (mean difference 0.51 ± 7.15, -13.5–14.5, $p = 0.000$), 30 min. (mean difference 2.62±7.83, -12.73–17.97, $p = 0.000$) either after deflation of the pneumoperitoneum (mean difference 1.81±6.56, -10.93–14.55, $p = 0.015$), (Fig. 2 A–D).

Discussion

Arterial blood gas analysis in this study revealed that $PaCO_2$ significantly increased after inflation of the pneumoperitoneum and remained high throughout the operation compared with baseline values. These findings are consistent with the findings recorded in similar studies.[11,13,14]

In a study on thirty adult patients (aged 42.87 ± 7.26 years) undergoing laparoscopic nephrectomy under general anesthesia a significant positive correlation between $ETCO_2$ and $PaCO_2$ was detected at baseline ($r = 0.772$, $p < 0.001$) and at 1h ($r = 0.880$, $p < 0.001$) and 2h ($r = 0.896$, $p < 0.001$) after pneumoperitoneum. The authors concluded that continuous $ETCO_2$ monitoring is a reliable indicator of the trend in arterial carbon dioxide fluctuations in ASA I–II patients undergoing laparoscopic nephrectomy under general anesthesia.[11] In contrast, we found a positive correlation between $PaCO_2$ and $ETCO_2$ before inflation of the pneumoperitoneum ($r = 0.617$, $p = 0.000$) and at 15 min. after inflation of the pneumoperitoneum ($r = 0.582$, $p = 0.001$) with no correlation afterwards.

Ickx et al., investigated a cohort of 129 ASA I–II children (aged 1 day to 15 years old) intubated and mechanically ventilated undergoing different surgical procedures. Based on a single comparison between $PaCO_2$ and $ETCO_2$ performed prior to surgery, they reported a significant correlation between $PaCO_2$ and $ETCO_2$ ($r = 0.66$ and $p < 0.0001$). They also found a significant negative correlation between $PaCO_2$-$ETCO_2$ difference with age ($r = -0.42$, $p < 0.0001$) and weight ($r = -0.44$, $p < 0.0001$). They concluded that $ETCO_2$ remains a key tool as a trend monitor for arterial carbon dioxide, but $PaCO_2$ cannot be extrapolated accurately in children < 4 months or < 5 kg body weight.[9] In this study, age and weight

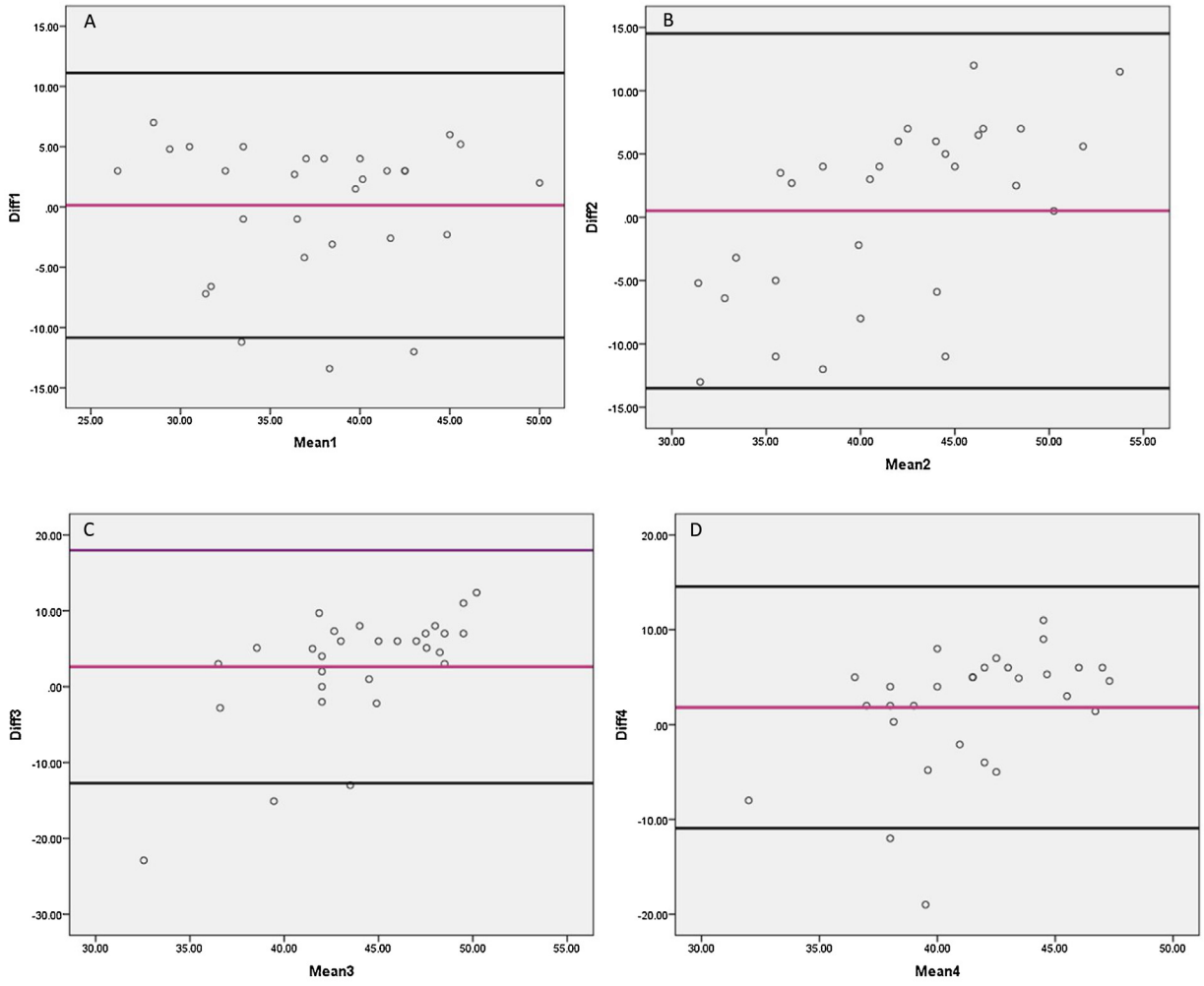


Figure 2 A, Bland-Altman plots comparing $PaCO_2$ and $ETCO_2$ before inflation of the pneumoperitoneum. Mean difference is 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84–11.2 mmHg). Mean1; Each $PaCO_2$–$ETCO_2$ Pair Mean (mmHg) before inflation of the pneumoperitoneum. Diff1; Difference in $PaCO_2$–$ETCO_2$ Pair (mmHg) before inflation of the pneumoperitoneum, (n = 29). B, Bland-Altman plots comparing $PaCO_2$ and $ETCO_2$ at 15 min. after inflation of the pneumoperitoneum. Mean difference 0.51 ± 7.15 (limits of 95% agreement -13.5–14.5). Mean2; Each $PaCO_2$–$ETCO_2$ Pair, Mean (mmHg) at 15 min. after inflation of the pneumoperitoneum. Diff2; Difference in $PaCO_2$–$ETCO_2$ Pair (mmHg) at 15 min. after inflation of the pneumoperitoneum, (n = 29). C, Bland-Altman plots comparing $PaCO_2$ and $ETCO_2$ at 30 min. after inflation of the pneumoperitoneum. Mean difference 2.62 ± 7.83 (limits of 95% agreement -12.73–17.97) Mean3; Each $PaCO_2$–$ETCO_2$ Pair, Mean (mmHg) at 30 min. after inflation of the pneumoperitoneum. Diff3; Difference in $PaCO_2$–$ETCO_2$ Pair (mmHg) at 30 min. after inflation of the pneumoperitoneum, (n = 29). D, Bland-Altman plots comparing $PaCO_2$ and $ETCO_2$ after deflation of the pneumoperitoneum. Mean difference 1.81 ± 6.56 (limits of 95% agreement -10.93–14.55) Mean4; Each $PaCO_2$–$ETCO_2$ Pair, Mean (mmHg) after deflation of the pneumoperitoneum. Diff4; Difference in $PaCO_2$–$ETCO_2$ Pair (mmHg) after deflation of the pneumoperitoneum, (n = 29).

did not show correlation with changes in the $PaCO_2$, $ETCO_2$ either with the $PaCO_2$–$ETCO_2$ difference. An explanation to our findings is that we investigated a homogenous sample with narrow age range (12–72 months) compared with the Ickx's study.[9]

Onodi et al. conducted a retrospective analysis on 799 pediatric patients scheduled for different surgical operations who were and intubated and mechanically ventilated (median age 6.8 [range: 0–18.1] years old). Data sets from 2452 blood gas analysis samples were coupled with vital signs monitoring, anesthesia gas analysis and spirometry data. They found that the bias in mean arterial to end-tidal carbon dioxide difference was -0.18 kPa (limits of 95% agreement -1.10 to 0.74) and 71.2% of samples demonstrated negative values. They concluded that $ETCO_2$ monitoring can be considerably misleading particularly in healthy patients undergoing surgery.[15] In accordance, Yang et al. in their prospective cohort study that included 445 paired comparisons of $PaCO_2$ and $ETCO_2$ from 137 pediatric patients with traumatic brain injury who were intubated and mechanically ventilated in PICU, they also found a weak agreement between $PaCO_2$ and $ETCO_2$. They concluded that $ETCO_2$ values are not a reliable substitute for $PaCO_2$ values during the first 24 hours after pediatric traumatic brain injury.[16] In accordance, in this study, agreement between the two monitors was recorded only before inflation of the pneu-

moperitoneum, with no agreement either during or after deflation of the pneumoperitoneum. These findings suggest that $ETCO_2$ monitoring during laparoscopic surgery may not be accurate specially in prolonged cases.[17,18]

Nunn and Hill recommended that the arterial to end-tidal CO_2 difference ($PaCO_2$–$ETCO_2$) during anesthesia in healthy individuals is relatively constant assuming that the gap between $PaCO_2$ and $ETCO_2$ is positive ($PaCO_2 > ETCO_2$) and of approximately 0.5 kPa that increases with age.[6] In contrast, in this study the $PaCO_2$–$ETCO_2$ difference showed variations between patients and in the same patient at different timepoints. These results also suggest that $ETCO_2$ monitoring can be misleading in the patient group we investigated.

Anatomic and physiologic dead space results in $PaCO_2$ values that are higher than $ETCO_2$ values when paired comparisons are done simultaneously.[16] The alveolar CO_2 concentrations are a little higher than the arterial CO_2 concentrations in blood. This positive gap is attributed to the mixture between alveolar gas that contains CO_2 and the exhalation gas deprived from CO_2 coming from the anatomic dead space.[16,19] However, in this study 29.3% of our $PaCO_2$–$ETCO_2$ paired comparisons showed negative gaps with $ETCO_2 > PaCO_2$. Similar studies also reported this negative gap in healthy anesthetized children of 71.3%[15] and 34%,[9] and in pediatric intensive care (22.7%).[7]

A negative $PaCO_2$-$ETCO_2$ difference has been reported in children aged 4–8 years,[9] with decreasing $PaCO_2$ values[7,9] and with a dead space/tidal volume ratio of less than 0.4.[10] The normal physiologic dead space to tidal volume ratio (Vd/Vt) is 0.20–0.35.[10,19,20] Physiologic dead space ventilation is the sum of anatomical dead space from the conducting airways and alveolar dead space due to disease processes and/or ventilatory techniques. Increase in physiologic dead space increases the $PaCO_2$–$ETCO_2$ difference.[10,19,20]

Pneumoperitoneum with carbon dioxide as an insufflating gas is associated with CO_2 absorption and increased CO_2 concentration in the bloodstream, increasing both $ETCO_2$ and $PaCO_2$ values.[21] Ventilatory techniques commonly used to overcome such problem (higher respiratory rates and low tidal volumes) can iatrogenic ally increase the physiologic dead space with inadequate ventilation of dependent well perfused alveoli.[7] This results in the accumulation of CO_2 in the lower airway thus the exhaled CO_2 in the terminal part of phase-3 capnography may exceed the mean $PaCO_2$, resulting in a negative $PaCO_2$–$ETCO_2$ difference.[7,9] Onodi et al. in their study found that hypocapnia is a strong predictor for lower or more negative $PaCO_2$–$ETCO_2$ difference.[15] So, as a trial to control elevations of $PaCO_2$ in pediatric laparoscopy, iatrogenic hypocapnia can pass unnoticed with its deleterious effects on the cerebral circulation in this vulnerable age group.

Non-invasive transcutaneous carbon dioxide ($PtcCO_2$) monitoring is another modality that can continuously predict $PaCO_2$ particularly in prolonged laparoscopic procedures and the agreement between $PtcCO_2$ and $PaCO_2$ has been confirmed in many studies.[18,22–24] Future studies are needed to prove its' agreement with the $PaCO_2$ in children and to investigate how to overcome its technical drawbacks such as slow response time, long warm-up time and difficulties with patients' skin contact.

In this study, arterial blood gas samples were withdrawn through an arterial cannula inserted in the radial artery to avoid repeated arterial punctures. The overall incidence of complications of arterial cannulation in infants and children is less than 0.2%. We selected the radial artery for cannulation because, it carries less risk of complications compared to other routes such as the femoral route.[25]

Limitations to this cohort were that we investigated patients with healthy lungs anesthetized in the supine position and the small sample size. Further studies of larger sample size investigating diverse pediatric populations undergoing laparoscopic surgeries under different positions are needed.

In conclusion, we recommend that the use of capnography as a trend monitor during pediatric laparoscopic surgeries may not be a reliable surrogate for arterial $PaCO_2$ levels.

Financial support

This work was supported from our departmental resources.

Question

Is the relationship between capnography ($ETCO_2$) and arterial carbon dioxide levels ($PaCO_2$) is constant so that we can rely on $ETCO_2$ as a reliable surrogate to $PaCO_2$ in pediatric laparoscopy?

Meaning

The use of capnography in pediatric laparoscopic surgeries may not be a reliable surrogate for arterial $PaCO_2$ levels.

Findings

Out of the 116 paired comparisons of $PaCO_2$ and $ETCO_2$ analyzed in this cohort study a $PaCO_2$–$ETCO_2$ difference beyond the recommended range of 0 to $\leq$ 5 mmHg was recorded in 71 (61.2%) comparisons with Negative difference ($ETCO_2 > PaCO_2$) in 34 comparisons (29.3%). A positive correlation between $PaCO_2$ and $ETCO_2$ was recorded before and at 15 min. after inflation of pneumoperitoneum with no correlation afterwards. Bland Altman method showed agreement between $ETCO_2$ and $PaCO_2$ before inflation of the pneumoperitoneum, with no agreement during or after deflation of the pneumoperitoneum.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Merry AF, Cooper JB, Soyannwo O, Wilson IH, Eichhorn JH. International standards for a safe practice of anesthesia 2010. Canad J Anesth. 2010;57:1027–34.
2. Whitaker DK. Time for capnography – everywhere. Anaesthesia. 2011;66:544–9.

3. McCann ME, Soriano SG. Perioperative central nervous system injury in neonates. Br J Anaesth. 2012;109 Suppl.1:i60–7.
4. Ringer SK, Ohlerth S, Carrera I, et al. Effects of hypotension and/or hypocapnia during sevoflurane anesthesia on perfusion and metabolites in the developing brain of piglets – a blinded randomized study. Pediatr Anesth. 2016;26:909–18.
5. McCann ME, Schouten AN, Dobija N, et al. Infantile postoperative encephalopathy: perioperative factors as a cause for concern. Pediatrics. 2014;133:e751–7.
6. Nunn JF, Hill DW. Respiratory dead space and arterial to endtidal carbon dioxide tension difference in anesthetized man. J Applied Physiol. 1960;15:383–9.
7. Goonasekera C, Goodwin A, Wang Y, Goodman J, Deep A. Arterial and end-tidal carbon dioxide difference in pediatric intensive care. Indian J Crit Care Med. 2014;18:711–5.
8. Woodham V, Railton KL. End-tidal carbon dioxide monitoring during paediatric general anaesthesia. Anaesthesia. 2018;73:646–7.
9. Ickx B, Dolomie JO, Benalouch M, Melot C, Lingier P. Arterial to end-tidal carbon dioxide tension differences in infants and children. Anaesth Clin Res. 2015;6:2155–6148.
10. McSwain SD, Hamel DS, Smith PB, et al. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respiratory Care. 2010;55:288–93.
11. Jayan N, Jacob JS, Mathew M. Anaesthesia for laparoscopic nephrectomy: Does end-tidal carbon dioxide measurement correlate with arterial carbon dioxide measurement? Indian J Anaesth. 2018;62:298–302.
12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1:307–10.
13. Tanaka T, Satoh K, Torii Y, Suzuki M, Furutani H, Harioka T. Arterial to end-tidal carbon dioxide tension difference during laparoscopic colorectal surgery. Masui. 2006;55:988–91.
14. Seed RF, Shakespeare TF, Muldoon MJ. Carbon dioxide homeostasis during anaesthesia for laparoscopy. Anaesthesia. 1970;25:223–31.
15. Onodi C, Bühler PK, Thomas J, Schmitz A, Weiss M. Arterial to end-tidal carbon dioxide difference in children undergoing mechanical ventilation of the lungs during general anaesthesia. Anaesthesia. 2017;72:1357–64.
16. Yang JT, Erickson SL, Killien EY, Mills B, Lele AV, Vavilala MS. Agreement between arterial carbon dioxide levels with end-tidal carbon dioxide levels and associated factors in children hospitalized with traumatic brain injury. JAMA Netw Open. 2019;2:e199448.
17. Klopfenstein CE, Schiffer E, Pastor CM, Beaussier M, Francis K, Soravia C, et al. Laparoscopic colon surgery: unreliability of end-tidal CO2 monitoring. Acta Anaesthiol Scand. 2008;52:700–7.
18. Xue Q, Wu X, Jin J, Yu B, Zheng M. Transcutaneous carbon dioxide monitoring accurately predicts arterial carbon dioxide partial pressure in patients undergoing prolonged laparoscopic surgery. Anesth Analg. 2010;111:417–20.
19. Yamanaka MK, Sue DY. Comparison of arterial-end tidal PCO_2 difference and dead space/tidal volume ratio in respiratory failure. Chest. 1987;92:832–5.
20. Burrows FA. Physiologic dead space, venous admixture, and the arterial to end-tidal carbon dioxide difference in infants and children undergoing cardiac surgery. Anesthesiology. 1989;70:219–25.
21. Liem MS, Kallewaard JW. de Smet AM, van Vroonhoven TJ. Does hypercarbia develop faster during laparoscopic herniorrhaphy than during laparoscopic cholecystectomy? Assessment with continuous blood gas monitoring. Anesth Analg. 1995;81:1243–9.
22. Nosovitch MA, Johnson JO, Tobias JD. Noninvasive intraoperative monitoring of carbon dioxide in children: end tidal versus transcutaneous techniques. Paediatr Anaesth. 2002;12:48–52.
23. May A, Humston C, Rice J, Nemastil CJ, Salvator A, Tobias J. Non-invasive carbon dioxide monitoring in patients with cystic fibrosis during general anesthesia: end-tidal versus transcutaneous techniques. J Anesth. 2020;34:66–71.
24. Lermuzeaux M, Meric H, Sauneuf B, et al. Superiority of transcutaneous CO_2 over end-tidal CO_2 measurement for monitoring respiratory failure in nonintubated patients: A pilot study. J Crit Care. 2016;31:150–6.
25. Gleich SJ, Wong AV, Handlogten KS, Thum DE, Nemergut ME. Major short-term complications of arterial cannulation for monitoring in children. Anesthesiology. 2021;134:26–34.

Brazilian Journal of Anesthesiology 2024;74(5): 744443



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Posterior transversus abdominis plane block versus lateral quadratus lumborum block in children undergoing open orchiopexy: a randomized clinical trial☆

Özgecan P. Zanbak Mutlu [a,*], Ayşe Ç. Tütüncü [a], Pınar Kendigelen [a], Beril Kara Esen[b]

[a] Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Anesthesiology and Reanimation, Istanbul, Turkey
[b] Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Public Health, Istanbul, Turkey

Received 26 November 2022; accepted 27 June 2023
Available online 8 July 2023

KEYWORDS
Orchiopexy;
Acute pain;
Pediatrics;
Regional anesthesia;
Nerve block

Abstract

Background: Due to the complex innervation of the testicle and spermatic cord, analgesic management can be challenging in orchiopexy. We aimed to compare the effects of posterior Transversus Abdominis Plane (TAP) and lateral Quadratus Lumborum Block (QLB) on analgesic use, pain, and parent satisfaction in unilateral orchiopexy.

Methods: ASA I—III, aged 6 months —to 12 years children undergoing unilateral orchiopexy were included to this double-blinded randomized trial. Patients were randomized into two groups with the closed envelope method before the surgery. Lateral QLB or posterior TAP block was applied under ultrasonography with 0.4 $ml.kg^{-1}$ 0.25% bupivacaine for both groups. The primary outcome was the assessment of additional analgesic usage in the peri-postoperative period. Evaluation of postoperative pain until 24 hours after surgery and parental satisfaction were also assessed as secondary outcomes.

Results: A total of 90 patients were included in the analysis (45 patients in each group). The number of patients needing remifentanil was significantly higher in the TAP group ($p < 0.001$). The average FLACC (TAP: 2.74 ± 1.8, QLB: 0.7 ± 0.84) and Wong-Baker scores (TAP: 3.13 ± 2.42, QLB: 0.53 ± 1.12) were significantly higher for TAP ($p < 0.001$). Additional analgesic consumption at the 10th, 20th minutes, 6th, 16th, and 24th hours, especially after the 6th hour, were significantly higher for TAP. Parent satisfaction was significantly higher in the QLB group ($p < 0.001$).

☆Congresses: Preliminary data for this study were presented as a poster in European Society of Regional Anesthesia Congress that was held as a virtual congress on 2021.

* Corresponding author.
E-mail: pirilz@hotmail.com (Ö.P. Mutlu).

https://doi.org/10.1016/j.bjane.2023.06.004
0104-0014/© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: Lateral QLB provided more effective analgesia than posterior TAP block in children undergoing elective open unilateral orchiopexy.
Clinical Trials Registry: NCT03969316.
© 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Cryptorchidism is a common genitourinary pathology defined as the failure of the testicles to descend into the scrotum during development and seen in 30% of preterm and 3% of term infants, respectively. It should be surgically corrected to avoid significant consequences such as testicular atrophy, torsion, hernia, or malignancy. Orchiopexy is usually performed under general anesthesia, and due to the complex innervation of the testicle and spermatic cord, analgesic management can be challenging.[1]

Pain is crucial in children due to difficulty in assessment and inadequate treatment risk. Inadequate treatment may cause chronic pain and impaired mental motor development.[2] Intraoperative pain can increase morbidity and mortality by inducing risk of laryngospasm.[3] Therefore, current guidelines recommend surgical site-specific regional anesthesia techniques as an essential part of the multimodal treatment.[4] Thanks to the widespread use of ultrasonography (USG) in anesthetic practice, there has been a recently growing interest in abdominal trunk blocks; the technical difficulties and potential complications of neuraxial blocks have been avoided.[5] These methods are preferred over the conventional methods of analgesia, especially in outpatient urological interventions.[6]

The Transversus Abdominis Plane Block (TAPB) is a commonly used abdominal trunk block method in lower abdominal surgeries.[7] Previous research has shown that it is more efficacious, long-lasting, and reliable than the caudal block.[5,6,8] The TAPB method was first defined with the landmark technique through application in the Petit triangle.[7] Later, it was applied to the midaxillary line with USG guidance, giving rise to lateral and posterior concepts.[7,9] Most of the studies with US-guided TAPB were reported with the lateral approach, with US-guided TAPB were reported with the lateral approach, which was controversial due to its limited effect area.[7]

Posterior TAPB is hypothesized as closest to the landmark-guided technique regarding the analgesic spread area and effect.[9] However, the action mechanism and injection site of the posterior approach was not only reminiscent of the landmark technique but also similar to the originally described lateral (type 1) Quadratus Lumborum Block (QLB) by Blanco.[79-11] QLB is a comparatively recent technique that is proven to be effective in lower abdominal surgeries.[12] Several studies have reported that it is more effective and long-lasting than the caudal block.[13,14]

QLB and TAPB studies were usually conducted using a lateral TAPB technique, and QLB subtypes have varied.[12,15] It is still debated whether posterior TAPB and lateral QLB are fundamentally distinct techniques of regional anesthesia.[7] We hypothesized that the lateral QLB would depict better clinical efficacy by providing a wider somatic, visceral analgesic effect and more craniocaudal spread, compared to posterior TAPB.[10,11] In this study, we aimed to compare the analgesic effects of US-guided posterior TAPB and lateral QLB in pediatric patients undergoing orchiopexy. Our primary outcome was the assessment of analgesic usage in the peri-postoperative periods. Evaluation of postoperative pain until 24 hours after surgery and parental satisfaction were also assessed as secondary outcomes.

Methods

This randomized, double-blinded, prospective study was approved by Istanbul University's Institutional Review Board (IRB 71381), and written informed consent was obtained from the parents of all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03969316). This manuscript adheres to the CONSORT guideline and a flow diagram was used for patient enrollment and allocation (Fig. 1).

All pediatric patients with an American Society of Anesthesiologists (ASA) physical status I—III score and aged between 6 months and 12 years undergoing elective unilateral orchiopexy were included in the study. The patients who had contraindications for regional anesthesia, those who refused to consent, laparoscopic approach, ASA physical status IV, and those who needed postoperative intensive care unit admissions were excluded from the study.

After, patients were premedicated with intravenous 0.05 mg.kg-^{1} midazolam and 0.5 mg.kg^{-1} ketamine. The preoperative Ramsay Sedation Scale was recorded for each patient. After standard monitorization, induction was applied with 5 mg.kg^{-1} thiopental, 1 μg.kg^{-1} fentanyl, 0.6 mg.kg^{-1} rocuronium, and orotracheal intubation was performed. Sevoflurane was used for maintenance. The duration of the operations was recorded.

After intubation, patients were randomized with the closed envelope method before the surgery and separated into QLB and TAPB groups. Each patient received a random study number, and these numbers were used in the data assessment. Two experienced anesthesiologists (ACT and PK), blinded to data collecting and analysis until study completion, executed all block procedures. A third anesthesiologist and nurses, who were blinded, performed follow-ups, and handled the registration in the surgery, post anesthesia care unit, and afterward. Patients and parents were also blinded to group assignments. All analyses were performed by an independent statistician (BKE).

QLB was performed at the supine or semi-lateral position, whereas the supine position was used for the TAPB. Both techniques were executed in sterile condition and by using 18|G, 20G, 22G intravenous cannula (Bicakcilar Cooperation, Istanbul, Turkey) based on patient's age. The needle

was navigated by using the linear probe of the USG (GE Logiq-E Ultrasound System with 9L Linear Transducer, Illinois, USA) and employing an "in-plane" technique. After negative blood aspiration with a 2 ml injector and confirmation of the correct position with 0.9% saline, both blocks were induced with 0.4 ml.kg^{-1} 0.25% bupivacaine.

Lateral QLB

After the USG probe was positioned at the umbilicus level, the needle was advanced until visualizing the terminal part of the Transversus Abdominis Muscle (TAM) and Quadratus Lumborum Muscle (QLM). Then, the needle was directed antero-posteriorly, and the local anesthetic was applied between the posterior aponeurosis of the TAM and transversalis fascia, which is located at the anterolateral of the QLM (Fig. 2A).

Posterior TAPB

After, the USG probe was positioned at the mid-axillary line on the anterior superior iliac crest, and was advanced posteriorly until visualizing the thoracolumbar fascia, which is the conjunction of the aponeurosis of the Internal Oblique Muscle (IOM) and TAM. Local anesthetic was applied to the TAP, which is located anterior to the thoracolumbar fascia (Fig. 2B).

After the block was applied, Blood Pressure (BP) and Heart Rate (HR) were recorded before the incision, as well as 5, 10, 20, 30, 45, and 60 min after the incision. The surgery commenced at least 10 min after the application of the block. In case of a 20% increase in HR and BP from baseline, remifentanil infusion was started according to recent guideline recommendations.[4] Remifentanil dose was adjusted based on HR and BP measurements (±20% from the baseline), and the infusion was terminated as soon as possible.

In the postoperative period, patients were followed up primarily in the pediatric postanesthesia care unit for 2 hours, and then in the pediatric surgery in-patient service. Pain at 10th, 20th, 30th minutes, 1st, 2nd, 6th hours were evaluated with the FLACC (Face, Legs, Activity, Cry, Consolability) score. If the FLACC score ≥ 4 and additional analgesia was thought to be required clinically, 1 mg.kg^{-1} tramadol and when the need continued, 15 mg.kg^{-1} paracetamol were administered. Parents were informed and given a copy of the Wong-Baker Pain Scale before discharge of the patients. Moreover, when the patients defined pain with a score of 4 or above, parents were told that they should give 10 mg.kg^{-1} ibuprofen. Pain scores and additional analgesic requirements were asked by phone call at the postoperative 16th and 24th hours. Parent satisfaction was noted as not satisfied (1), partially satisfied (2), and very satisfied (3), depending on the patient's painlessness status.

Sample size

The sample size was calculated using the G*Power program, version 3.1 (Heinrich-Heine University, Duesseldorf, Germany) for Chi-Squared test α = 0.05, power (1-β) = 0.80, df = 1 and effect size of 0.319. The effect size was calculated based on previous data in the literature according to patient requirements for postoperative analgesics.[16] It was determined that at least 78 patients were required to test the hypothesis.

Statistical analysis

SPSS v.21 (IBM, Illinois, USA) was used for statistical analysis. Continuous variables were presented as mean ± SD, median

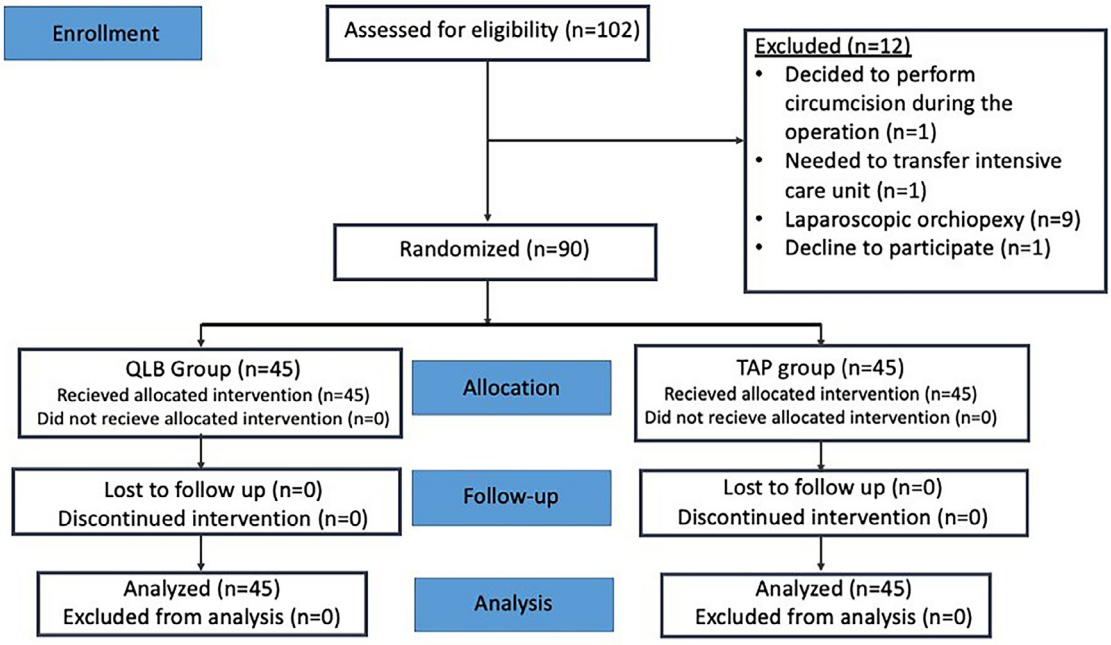


Figure 1 CONSORT diagram.

(25th–75th percentiles), and categorical variables were presented with frequency and percentage. The variables were investigated using visual (histograms, Q-Q plots) and analytical methods (Shapiro-Wilk test) to determine if they were normally distributed. Comparisons of the groups for continuous variables were carried out by Independent Sample's *t*-test or Mann-Whitney U test for two groups according to the data's normality. Chi-Squared or Fisher's Exact test was used to analyze categorical variables when appropriate. Odds ratios were given according to contingency tables run by SPSS. The Wilcoxon test was used to compare the change in two continuous variables. The Friedman test was used to compare the change in two or more continuous variables. The Cohran Q test was used to determine the percentage of patients requiring perioperative remifentanil during each regional anesthesia procedure. Following the Friedman or Cohran Q test, the post-hoc Dunn test was employed to make multiple comparisons and evaluate the significant groups. Differences in groups were determined based on their adjusted *p*-values, provided automatically by SPSS. The time spent without additional analgesia was evaluated between the two groups with Kaplan-Meier analysis and log-rank test. All tests are two-sided, and the significance level was accepted as $p < 0.05$.

Results

Fig. 1 illustrates the CONSORT diagram of study enrollment. Analyses were performed with 90 patients (45 patients in each group). There was no difference between their demographic data, pre-operative Ramsay Sedation Scores, and duration of surgery (Table 1).

Regarding intraoperative hemodynamic parameters, there was no difference between the two groups before and after the incision (Supplementary Table 1, Supplementary Figs. 1–3). Intraoperative remifentanil was used in 28 patients in the TAPB group (62.2%) and 11 patients in the QLB group (24.4%) ($p < 0.001$) (Supplementary Table 2).

The number of patients requiring postoperative analgesics was higher at the 10th and 20th minutes, and 6th, 16th, 24th hours in the TAP group, more prominently after the 6th postoperative hour ($p < 0.001$) (Table 2, Supplementary Fig. 4). Clinically adequate analgesia (FLACC score < 4, Wong-Baker score < 4) could be achieved in both groups, but pain scores were significantly lower for QLB (Total FLACC score: TAP [mean ± SD: 2.74 ± 1.8] vs. QLB [mean ± SD: 0.7 ± 0.84], Total Wong-Baker score: TAP [mean ± SD: 3.13 ± 2.42] vs. QLB [mean ± SD: 0.53 ± 1.12], $p < 0.001$) (Fig. 3 A and B; Supplementary Table 3). The mean time spent without analgesics in the QLB was statistically significantly longer than in the TAPB group ($p = 0.000002$) (Fig. 4, Supplementary Table 4). Patients in the TAPB group had higher pain scores compared with QLB except for the postoperative first hour time point FLACC score (Fig. 3 A and B; Supplementary Table 3). A comparison of parental postoperative satisfaction showed a statistically significant difference between the groups and parent satisfaction was higher in the QLB group ($p < 0.001$). (Fig. 3C, Supplementary Table 5).

There were no hemodynamic abnormalities in either group, and no complications were noted except for postoperative nausea in two patients, and nausea and vomiting in one patient in the first hour in the QLB group.

Discussion

Our findings have shown that lateral QLB significantly reduced analgesic consumption, postoperative pain, and it improved parental satisfaction compared to the posterior TAPB in unilateral elective orchiopexy.

The TAPB was first described by Rafi in 2001.[17] It was applied to the Petit triangle, delineated anteriorly by the external oblique, posteriorly by the latissimus dorsi, and inferiorly by the crista iliaca.[17] It was intended to reach the plane between the IOM and the TAM with a single pop sensation.[17] Subsequently, a double-pop approach was developed with a modification, and it was demonstrated that local anesthetics could reach the intercostal nerves of T7 to T11, subcostal nerves, and ilioinguinal-iliohypogastric nerves,

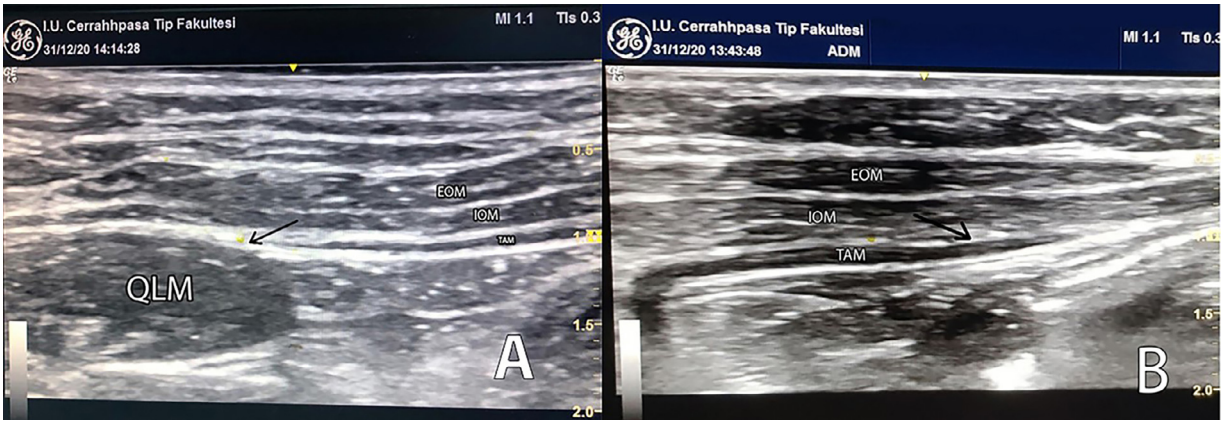


Figure 2 (A) QLM and anterolateral abdominal muscles, sonographic view of the lateral QLB application site. Arrow: The target site of the lateral QLB. (B) Sonographic view of the anterolateral abdominal muscles. Arrow: The target site of the posterior TAP block. QLM, Quadratus Lumborum Muscle; TAM, Transversus Abdominis Muscle; IOM, Internal Oblique Muscle; EOM, External Oblique Muscle.

Table 1 Demographic and clinical data.

	QLB (n = 45)	TAP (n = 45)	*p*
Age (month)*	48 (23–84)	42 (24–84)	0.815[a]
Weight (kg)*	18 (12.75–25)	16 (12.25–30)	0.913[a]
Height (cm)**	103.27 ± 18.35	108.11 ± 21.63	0.255[b]
Surgery***			0.506[c]
Right orchiopexy	31 (68.9%)	28 (62.2%)	
Left orchiopexy	14 (31.1%)	17 (37.8%)	
Preoperative RAMSAY Sedation Scale*	2 (2–3)	2 (2–3)	0.671[a]
Surgery Duration	91.33 ± 19.09	91.07 ± 18.31	0,946[b]

Data are presented as
* median (25 percentile–75 percentile).
** mean (SD).
*** n (%).
[a] Mann-Whitney U Test.
[b] Independent Sample's *t*-test.
[c] Chi-Square test.

providing a sensory block of the lateral and anterior abdominal walls.[7,18]

Based on the difficulty in finding the Petit triangle, and complication risks of the blind technique, US-guided TAPB was defined by Hebbard in 2007.[7] However, US-guided TAPB, unlike the landmark technique, was applied to the midaxillary line instead of the Petit triangle. It was shown that the block applied to this region was limited to T10-L1 dermatomes.[7] Therefore, a new US-guided block technique was constructed compatible with the Petit triangle, called posterior TAPB; and the first defined block, which applied to the midaxillary line, was named the lateral TAPB. Posterior TAPB is applied to TAP at the intersection of quadratus lumborum and lateral abdominal muscles.[7] Carney et al. showed that both the landmark-guided TAPB and the US-guided posterior TAPB caused spread to the paravertebral area, creating a similar effect.[9] Therefore, the posterior TAPB has been stated as the best alternative technique for landmark-guided TAPB is.[9]

QLB was first defined by Blanco in 2007.[11] Soon after, QLB variants were defined via performing injections on different sides of the QLM.[11] Although the mechanism of action has not been fully elucidated, it is hypothesized that the effect is created by local anesthetic spreading to the paravertebral area over various fascial planes in cadaver studies.[10] For the lateral QLB, the local anesthetic is injected to the QLM's anterolateral aspect, between the posterior aponeurosis of the TAM and transversalis fascia.[11] The mechanism of effect is thought to be by spreading to TAP, and through the Anterior Thoracolumbar Fascia (ATF) into the paravertebral area.[11] However, considering its similarity to the posterior TAPB in terms of the injection site and mechanism of action, further studies are needed to evaluate the effects of the two procedures, as highlighted in current reviews.[7]

Table 2 Comparison of postoperative analgesics.

	QLB Group n = 45 n (%)	TAP Group n = 45 n (%)	*p***
Total Number of patients who needed postop. analgesics	17 (37.8%)	39 (86.7%)	**<0.001****
Number of patients who needed postop. analgesics			
10th min.	6 (13.3%)	15 (33.3%)[a,d]	**0.025****
20th min.	2 (4.4%)	10 (22.2%)[a,c]	**0.013****
30th min.	1 (2.2%)	6 (13.3%)[a,b]	0.110[f]
1st hour	0 (0%)	2 (4.4%)[a]	0.494[f]
2nd hour	2 (4.4%)	5 (11.1%)[a,b]	0.434[f]
6th hour	2 (4.4%)	21 (46.7%)[c,d]	**<0.001****
16th hour	6 (13.3%)	28 (62.2%)[d]	**<0.001****
24th hour	0 (0%)	18 (40%)[b,c,d]	**<0.001****
*p** (In-group)	**0.016**[a]	**<0.001**	

* Cohran Q Test.
** Chi-square Test.
[f] Fisher's Exact Test.
[a] No difference in pairwise comparisons.
In group analysis; Each superscript letter denotes a subset of time categories whose row value do not differ significantly form each other at the 0.05 level.
min, minute; QLB, Quadratus Lumborum Block; TAP, Transversus abdominis plane.

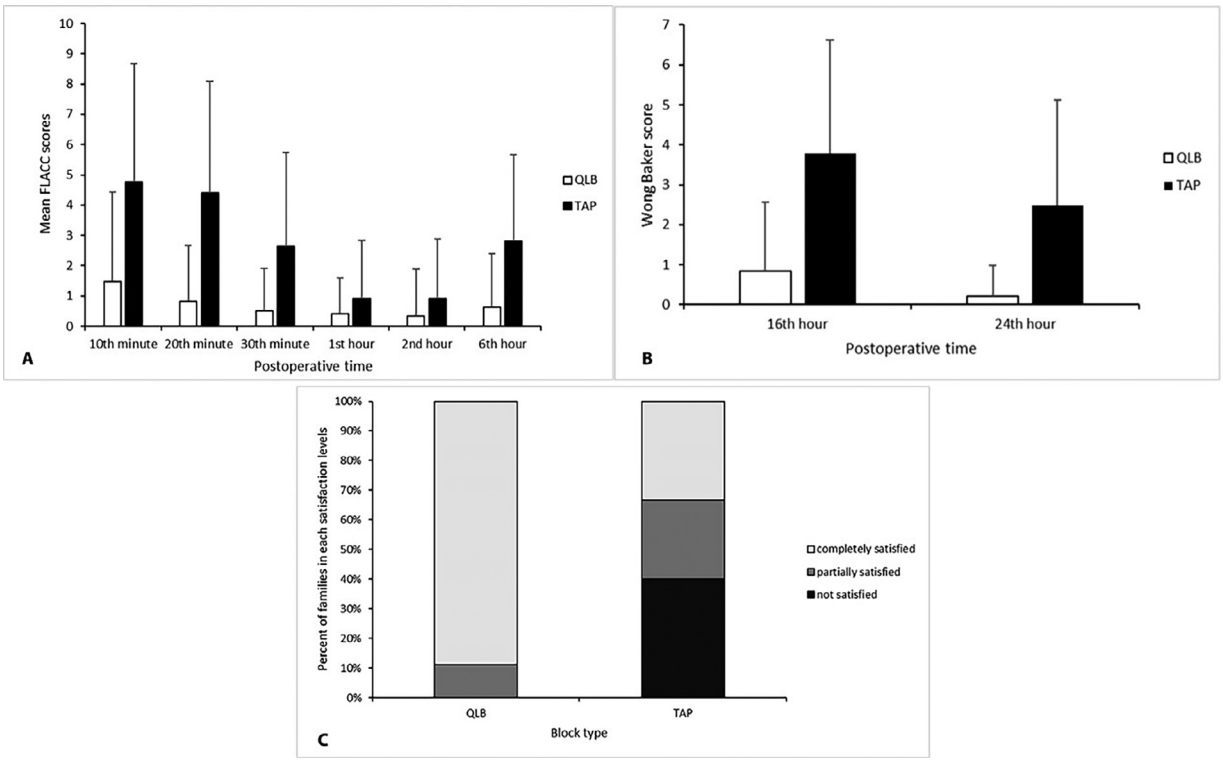


Figure 3 (A) Postoperative FLACC scores of patients. Data were expressed as mean±SD. (B) Postoperative Wong-Baker scores of patients. Data were expressed as mean±SD. (C) Percent of parents in each satisfaction level according to block types. FLACC, Face, Legs, Activity, Cry, Consolability.

Despite the advancements and guidelines emphasizing the significance of pain in children, most children continue to receive insufficient pain treatment.[2] Orchiopexy is a commonly performed surgery in children, and analgesia management is difficult due to the complex innervation of the testis and spermatic cord.[19] In addition, unlike herniorrhaphy, peritoneal dissection is performed to free the testicular vessels and the spermatic cord.[1] Peritoneal stretching and dissection cause severe visceral pain in addition to somatic pain.[1,20] The current study investigated this controversial topic in children who underwent orchiopexy and compared the clinical efficacy of posterior TAPB and lateral QLB.

Our primary outcome was the assessment of additional analgesic usage determined according to pain evaluation. We thought that analgesic administration, the clinical result of pain assessment, was a more accurate option for evaluating block effectiveness. In this respect, the number of patients who required remifentanil during the intraoperative period, and postoperative analgesics in 24 hours were significantly higher in the posterior TAPB than in the lateral

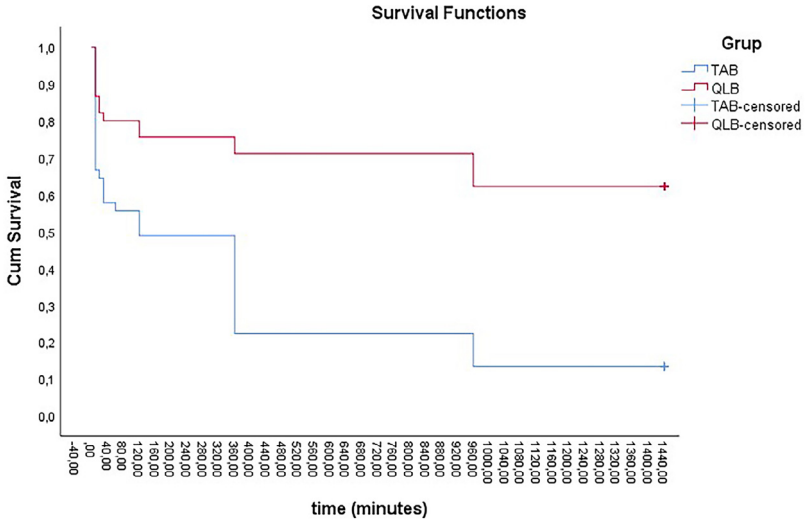


Figure 4 Mean postoperative time without analgesics according to Kaplan-Meier analysis.

QLB group, particularly after the sixth postoperative hour. The mean time spent without analgesics was statistically significantly longer in QLB. Our results were in line with previously conducted studies, which compared the posterior TAPB to QLB. Unlike our study, these studies were conducted in adults and compared posterior TAPB to posterior QLB but not lateral QLB. [21–25] The mechanism of action of the posterior QLB differs from the lateral QLB.[11] Local anesthetic is applied to the Lateral Interfascial Triangle (LIFT), formed by the junction of the middle thoracolumbar fascia and the paraspinal reticular sheath.[11] Although no difference in efficacy can be demonstrated in an RCT comparing posterior QLB with lateral QLB, discrepancies in propagation have been documented in cadaver investigations.[10,26]

To date, several studies comparing TAP with QLB in children have been performed with a lateral TAPB approach, and only somatic analgesia could be achieved with the limited spread.[7,9,12,14,16,27] Öksüz et al. also compared lateral TAPB and posterior QLB in the first study ever reported in children.[16] To our knowledge, there is no RCT with posterior TAPB in children, and data on this subject are limited to case reports and observational studies only.[28]

Both posterior TAPB and lateral QLB can create an effect by spreading to the TAP and the paravertebral area.[9,11,29] However, according to our hypothesis, since the lateral QLB is applied directly to the ATF, with accumulation in the area, it can provide a wider sensory area by spreading to the endothoracic and iliac fascia, the continuation of ATF and thoracolumbar sympathetic nerves.[11] The supposition mentioned above could be the fundamental difference between the two strategies. Furthermore, the thoracolumbar fascia contains two distinct pain mechanoreceptors known as the Ruffini and Vater-Paccini bodies, both of which have autonomic roles.[30] Stimulating these receptors has also been linked to chronic pain, and blockade of these receptors may explain the long duration of action.[11,30]

We postulate that the main rationale for the low analgesic demand in QLB is anatomical variation in local anesthetic dispersion in the thoracolumbar fascia. As a result, an effective visceral block may not be achieved despite the adequate somatic block. Differences in surgical stimuli were assumed to be the secondary reason. The participants in our study had a variety of testicular locations, including inguinal canal, suprascrotal, and high scrotal. This discrepancy may have contributed to the heterogeneity in peri-operative and postoperative analgesic demands.

Limitations to our study include, firstly, the level of sensory block could not be detected in the intraoperative and postoperative periods after applying both techniques. Secondly, patients' parents determined both pain assessment and analgesic administration after the 6th hour due to the outpatient nature of the orchiopexy procedure. Since the FLACC score was unsuitable for parental assessment, the Wong-Baker score was used for post-discharge pain evaluation. Finally, although the FLACC score is more appropriate for children < 7 years of age, it was used in all age groups aimed at uniform pain assessment. However, the mean age of the patients included in our study was 45 months, so we believe it did not affect the results.

In conclusion, this study showed that preoperative lateral QLB reduced analgesic usage and postoperative pain more than the posterior TAPB method. Parent satisfaction was also higher with QLB in pediatric patients undergoing orchiopexy. The clinical efficacy difference of these blocks with analogous mechanisms was presented. Further studies comparing these two blocks are required and need to be supported by cadaver and imaging studies.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors acknowledge Deniz Mutlu, MD, Turgut Bora Cengiz MD and Jean Kim for proofreading activity.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.06.004.

References

1. Echeverría Sepúlveda MP, Yankovic Barceló F, López Egaña PJ. The undescended testis in children and adolescents part 2: evaluation and therapeutic approach. Pediatr Surg Int. 2022;38:789–99.
2. Shah P, Siu A. Considerations for neonatal and pediatric pain management. Am J Health Syst Pharm. 2019;76:1511–20.
3. Birlie Chekol W, Yaregal Melesse D. Incidence and Associated Factors of Laryngospasm among Pediatric Patients Who Underwent Surgery under General Anesthesia, in University of Gondar Compressive Specialized Hospital, Northwest Ethiopia, 2019: A Cross-Sectional Study. Anesthesiol Res Pract. 2020;2020:3706106.
4. Vittinghoff M, Lönnqvist PA, Mossetti V, et al. Postoperative pain management in children: Guidance from the pain committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative). Paediatr Anaesth. 2018;28:493–506.
5. Bryskin RB, Londergan B, Wheatley R, et al. Transversus Abdominis Plane Block Versus Caudal Epidural for Lower Abdominal Surgery in Children: A Double-Blinded Randomized Controlled Trial. Anesth Analg. 2015;121:471–8.
6. Desai N, Chan E, El-Boghdadly K, Albrecht E. Caudal analgesia versus abdominal wall blocks for pediatric genitourinary surgery: systematic review and meta-analysis. Reg Anesth Pain Med. 2020;45:924–33.
7. Tran DQ, Bravo D, Leurcharusmee P, Neal JM. Transversus Abdominis Plane Block: A Narrative Review. Anesthesiology. 2019;131:1166–90.
8. Ganesh B, Swain S, Banerjee S. Comparison of Ultrasound-Guided Transversus Abdominis Plane Block and Caudal Epidural Block for Pain Relief in Children Undergoing Infraumbilical Surgeries. Anesth Essays Res. 2021;15:161–6.

9. Carney J, Finnerty O, Rauf J, Bergin D, Laffey JG, Mc Donnell JG. Studies on the spread of local anaesthetic solution in transversus abdominis plane blocks. Anaesthesia. 2011;66:1023—30.
10. Carline L, McLeod GA, Lamb C. A cadaver study comparing spread of dye and nerve involvement after three different quadratus lumborum blocks. Br J Anaesth. 2016;117:387—94.
11. Elsharkawy H, El-Boghdadly K, Barrington M. Quadratus Lumborum Block Anatomical Concepts, Mechanisms, and Techniques. Anesthesiology. 2019;130:322—35.
12. Zhao WL, Li SD, Wu B, Zhou ZF. Quadratus Lumborum Block is an Effective Postoperative Analgesic Technique in Pediatric Patients Undergoing Lower Abdominal Surgery: A Meta-Analysis. Pain Physician. 2021;24:E555—63.
13. Öksüz G, Arslan M, Urfalloğlu A, et al. Comparison of quadratus lumborum block and caudal block for postoperative analgesia in pediatric patients undergoing inguinal hernia repair and orchiopexy surgeries: A randomized controlled trial. Reg Anesth Pain Med. 2020;45:187—91.
14. İpek CB, Kara D, Yilmaz S, et al. Comparison of ultrasound-guided transversus abdominis plane block, quadratus lumborum block, and caudal epidural block for perioperative analgesia in pediatric lower abdominal surgery. Turk J Med Sci. 2019;49: 1395—402.
15. Kim SH, Kim HJ, Kim N, Lee B, Song J, Choi YS. Effectiveness of quadratus lumborum block for postoperative pain: a systematic review and meta-analysis. Minerva Anestesiol. 2020;86:554—64.
16. Öksüz G, Bilal B, Gürkan Y, et al. Quadratus Lumborum Block Versus Transversus Abdominis Plane Block in Children Undergoing Low Abdominal Surgery: A Randomized Controlled Trial. Reg Anesth Pain Med. 2017;42:674—9.
17. Rafi AN. Abdominal field block: a new approach via the lumbar triangle. Anaesthesia. 2001;56:1024—6.
18. McDonnell JG, O'Donnell BD, Farrell T, et al. Transversus abdominis plane block: a cadaveric and radiological evaluation. Reg Anesth Pain Med. 2007;32:399—404.
19. Patel AP. Anatomy and physiology of chronic scrotal pain. Transl Androl Urol. 2017;6:S51—6. Suppl 1.
20. Boezaart AP, Smith CR, Chembrovich S, et al. Visceral versus somatic pain: an educational review of anatomy and clinical implications. Reg Anesth Pain Med. 2021;46:629—36.
21. Verma K, Malawat A, Jethava D, Jethava D. Comparison of transversus abdominis plane block and quadratus lumborum block for post-caesarean section analgesia: A randomised clinical trial. Indian J Anaesth. 2019;63:820—6.
22. Deng W, Long X, Li M, et al. Quadratus lumborum block versus transversus abdominis plane block for postoperative pain management after laparoscopic colorectal surgery: A randomized controlled trial. Medicine. 2019;98:e18448.
23. Aoyama Y, Sakura S, Abe S, Wada M, Saito Y. Analgesic effects and distribution of cutaneous sensory blockade of quadratus lumborum block type 2 and posterior transversus abdominis plane block: An observational comparative study. Korean J Anesthesiol. 2020;73:326—33.
24. Okur O, Karaduman D, Tekgul ZT, Koroglu N, Yildirim M. Posterior quadratus lumborum versus transversus abdominis plane block for inguinal hernia repair: a prospective randomized controlled study. Braz J Anesthesiol. 2021;71:505—10.
25. Caparlar CO, Altinsoy S, Akelma FK, Ozhan MO, Ergil J. Posterior quadratus lumborum block versus posterior transversus abdominis plane block for unilateral inguinal hernia surgery. Niger J Clin Pract. 2022;25:1457—65.
26. Ökmen K, Ökmen BM, Sayan E. Ultrasound-guided lateral versus posterior Quadratus Lumborum Block for postoperative pain after laparoscopic cholecystectomy: A randomized controlled trial. Turk J Surg. 2019;35:023—9.
27. Priyadarshini K, Behera BK, Tripathy BB, Misra S. Ultrasound-guided transverse abdominis plane block, ilioinguinal/iliohypogastric nerve block, and quadratus lumborum block for elective open inguinal hernia repair in children: a randomized controlled trial. Reg Anesth Pain Med. 2022;47:217.
28. Hernandez MA, Vecchione T, Boretsky K. Dermatomal spread following posterior transversus abdominis plane block in pediatric patients: our initial experience. Pediatric Anesthesia. 2017;27:300—4.
29. Abdallah FW, Laffey JG, Halpern SH, Brull R. Duration of analgesic effectiveness after the posterior and lateral transversus abdominis plane block techniques for transverse lower abdominal incisions: a meta-analysis. Br J Anaesth. 2013;111:721—35.
30. Coote JH, Perez-Gonzalez JF. The response of some sympathetic neurones to volleys in various afferent nerves. J Physiol. 1970;208:261—78.

Brazilian Journal of Anesthesiology 2024;74(5): 844533



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Virtual parental presence with coaching for reducing preoperative anxiety in children: a feasibility and pilot randomized controlled trial

Clyde T. Matava [a,b,*], Martina Bordini [a,b,c], Ben O' Sullivan [a], Gabriela Alcaraz Garcia-Tejedor [a], Nan Gai [a,b], Guy Petroz [a], Conor Mc Donnell [a], Fahad Alam [b,e], Katie Brazel [d], Monica Caldeira-Kulbakas [a]

[a] *The Hospital for Sick Children, Department of Anesthesia, Toronto, Ontario, Canada*
[b] *University of Toronto, Department of Anesthesiology and Pain Medicine, Toronto, Ontario, Canada*
[c] *University of Bologna, Department of Medical and Surgical Sciences (DIMEC), Bologna, Italy*
[d] *Hospital for Sick Children, Child Life Department, Toronto, Ontario, Canada*
[e] *Sunnybrook Health Sciences Centre, Department of Anesthesia, Toronto, Ontario, Canada*

Received 28 November 2023; accepted 8 June 2024
Available online 26 June 2024

KEYWORDS
Anxiety;
Pediatric Anesthesia;
Videoconference;
Parental Presence at Induciton of Anesthesia;
Preoperative anxiety;
MYPAS;
PHBQ

Abstract

Background: Preoperative anxiety in children causes negative postoperative outcomes. Parental presence at induction is a non-pharmacological strategy for relieving anxiety; nevertheless, it is not always possible or effective, namely when parents are overly anxious. Parental presence via video has been demonstrated to be useful in other contexts (divorce, criminal court). This study reports the feasibility of a randomized controlled trial to investigate the effect of video parental presence and parental coaching at induction on preoperative anxiety.

Methods: The study was a randomized, 2 × 2 factorial design trial examining parental presence (virtual vs. physical) and coaching (provided vs. not provided). Feasibility was assessed by enrollment rate, attrition rate, compliance, and staff satisfaction with virtual method with the NASA-Task Load Index (NASA-TLX) and System Usability Scale (SUS). For the children's anxiety and postoperative outcomes, the modified Yale Preoperative Anxiety Scale (mYPAS) and Post-Hospitalization Behavioral Questionnaire (PHBQ) were used. Parental anxiety was evaluated with the State-Trait Anxiety Inventory (STAI) questionnaire.

Abbreviations: Parental Presence at Induction of anesthesia, (PPIA); Virtual Parental Presence with coaching, (vPPIA+); Virtual Parental Presence with no coaching, (vPPIA-); Physical Parental Presence with coaching, (pPPIA+); Physical Parental Presence with no coaching, (pPPIA-); Randomized Controlled Trial, (RCT); modified Yale Preoperative Anxiety Scale, (mYPAS); Induction Compliance Checklist, (ICC); Emotionality Activity Sociability Impulsivity Instrument of Child Temperament, (EASI); Posthospitalization Behavior Questionnaire, (PHBQ); State-Trait Anxiety Inventory, (STAI); NASA Task Load Index, (NASA-TLX); System Usability Scale, (SUS).
Study conducted at the Department of Anesthesia, the Hospital for Sick Children, Toronto, Ontario, Canada.

* Corresponding author.
E-mail: clyde.matava@sickkids.ca (C.T. Matava).

https://doi.org/10.1016/j.bjane.2024.844533
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Results: A total of 41 parent/patient dyads were recruited. The enrollment rate was 32.2%, the attrition rate 25.5%. Compliance was 87.8% for parents and 85% for staff. The SUS was 67.5/100 and 63.5/100 and NASA-TLX was 29.2 (21.5—36.8) and 27.6 (8.2—3.7) for the anesthesiologists and induction nurses, respectively. No statistically significant difference was found in mYPAS, PHBQ and STAI.

Conclusion: A randomized controlled trial to explore virtual parental presence effect on preoperative anxiety is feasible. Further studies are needed to investigate its role and the role of parent coaching in reducing preoperative anxiety.

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

Introduction

Preoperative anxiety in children negatively affects postoperative outcomes and parents' and children's experience of the operating room. However, up to 50% of children develop behavioral stress and anxiety before surgery.[1] Consequences of preoperative anxiety include behavioral changes (separation anxiety, sleep disturbance, and temper tantrums)[2] and more painful postoperative recovery,[3] with correlation between anxiety levels and postoperative pain levels.[4]

Multiple pharmacological and non-pharmacological prevention strategies have been explored.[5] Among non-pharmacological methods, Parental Presence at Induction of Anesthesia (PPIA) has been shown to reduce parent and patient anxiety without impeding operating room efficiency.[6] However, a recent cross-sectional survey reported a rate of PPIA in a tertiary children hospital of 16.9%;[7] among the reasons for not accompanying their child in the operating room, parental anxiety was reported by 14% of parents. It is known that the presence of an overly anxious parent has no obvious benefit for the child during induction.[8] Previous studies[9] failed to demonstrate that preparation of parents before PPIA reduces preoperative anxiety.

Another non-pharmacological intervention is the use of technology as cartoon/video distraction technology. In a Randomized Control Trial (RCT), video distraction showed similar effects on preoperative anxiety compared to PPIA.[10] Technology may be helpful in situations in which PPIA may not be useful, such as for parents anxious in the operating room environment or limited access of family to patient care settings (e.g., as in the COVID-19 pandemic).

To date, there is a paucity of data assessing the role of PPIA via video; however, early work in this area highlighted that infants and toddlers who saw their parents on video during divorce, incarceration, or criminal court proceedings demonstrated the same behavioral and play patterns as though parents were physically present,[11] therefore it may follow that children could also benefit from virtual Parental Presence at Induction of Anesthesia (vPPIA) in healthcare settings. This study aimed to investigate the effects of virtual parental presence and parental coaching on children's level of anxiety at induction of anesthesia, with the hypothesis of a synergistic effect of virtual presence and parental coaching in reducing parental anxiety. As part of the response to the COVID pandemic, our institution among others halted all clinical studies, especially those requiring the use of personal protective equipment.[12-14] We therefore report the study as a pilot and feasibility trial.

Methods

Ethics

The study received approval as an RCT at the Hospital for Sick Children, Toronto (REB# 1000053821). The study was registered on the clinicaltrials.gov platform (ID NCT02950415). Written informed consent was obtained from parents/guardians. Staff consent was implied via completion of the questionnaires.

Study design

The study was a pilot randomized, 2 × 2 factorial design trial examining parental presence (virtual vs. physical) and coaching (provided vs. not provided). Specifically, patient/parent dyads were randomized to one of four groups: virtual Parental Presence with coaching (vPPIA+), virtual Parental Presence without coaching (vPPIA-), physical Parental Presence with coaching (pPPIA+), and Physical Parental presence without coaching (pPPIA-).

Sample size

The primary objective of this report is feasibility. Our available sample size of 41 patient/parent dyads is not powered to detect statistically significant differences among groups. The original RCT was planned to achieve adequate statistical power. Assuming a two-tailed alpha = 0.05, beta = 0.2 (power = 80%), and a dropout rate of 20%, 80 patient/parent dyads in each group should have been recruited, for a total of 320 patient/parent dyads.

Participants

The study was conducted from September 2017 to August 2019 in the operating rooms of The Hospital for Sick Children, Toronto. Children aged from 18 months to 12 years who were undergoing ambulatory day-case surgery, with American Society of Anesthesiologists (ASA) physical status I, II, III were eligible for inclusion. Patient/parent dyads who agreed to participate were randomly allocated to one of the study groups. All patient/parent dyads enrolled received treatment as per group allocation. A complete list of exclusion criteria and changes made to the protocol are provided in the Supplementary material - Appendix A.

Randomization

Group assignments were kept in sealed, opaque, sequentially numbered envelopes and opened the morning of surgery by a designated research assistant who was not involved in data collection. Participants were assigned to a group only after baseline assessments were completed to prevent group selection bias.

Interventions

vPPIA groups

Facetime™ video platform designed by Apple Inc was used on two iPads™. FaceTime is a peer-to-peer videotelephony available on devices that run iOS and Macintosh computers.

Patients in the vPPIA groups were brought to the operating room while parents were accompanied to an anteroom where they could see their child via video. Patients were directed by the research assistant to focus on the video monitor in the operating room while induction took place. The video link remained live until the patient was asleep and the anesthesiologist informed the parent that the child was unaware. A research assistant remained with the parent throughout the induction to help with the technology.

pPPIA groups

Patients were accompanied by the parent into the operating room and remained until patient loss of awareness; the parent was then accompanied back to the waiting room by a research assistant.

Coaching

The coaching sessions occurred with a Child Life Specialist at SickKids. Parents allocated to the coaching groups were shown a brief video that outlined the behaviors they should demonstrate and those less desirable during induction.

Participants were presented a standardized video. For the vPPIA+ group emphasis was placed on the use of words to support their child, for the pPPIA+ group emphasis was placed on both words and actions to support their child.

Parents were also provided with a handout (Supplementary material - Appendix B) summarizing the desired and undesired behavior. Parents in the PPIA- groups (both physical and virtual) did not receive coaching or handouts.

Anesthesia induction

After monitoring, mask induction was conducted using a sevoflurane, nitrous oxide, and oxygen mixture. Patients were encouraged to lie down during induction but could remain sitting up if needed. Anesthesia would proceed with inhalational agents for induction.

Outcomes, instruments and measurements

Primary outcome – Feasibility

To assess feasibility, enrollment (number of enrolled subjects/number of eligible subjects) and attrition rate (number of participants that withdraw/number of participants randomized), compliance among participants in completing study materials and satisfaction were evaluated.

Secondary outcomes

Anxiety in children at induction of anesthesia and induction compliance. The modified Yale Preoperative Anxiety Scale (mYPAS)[15] was used, which was developed specifically to measure anxiety at anesthesia induction. The scale looks at activity, facial expression, alertness and arousal, vocalization, and interaction with adults. It has a good validity against the State-Trait Anxiety Inventory for Children, as well as good intra- and inter-observer reliability.[16] Scores range from 22.5 to 100, with higher scores indicating greater anxiety. The Induction Compliance Checklist (ICC) is an observational scale that describes the compliance of a child during induction.[17] This scale is used routinely at our institution. A higher ICC score corresponds to lower compliance at induction.

Child temperament. The Emotionality Activity Sociability Impulsivity Instrument of Child Temperament (EASI) is a parent-reported instrument that assesses four temperament categories in children. The tool has good validity and test-retest reliability.[18] Scores range from 5 to 25 for each category, with higher scores denoting higher baseline emotionality, activity, sociability, or impulsivity. Higher emotionality has been linked to increased preoperative anxiety, whereas highest activity with reduced anxiety.[19]

Posthospital negative behaviors. The Posthospitalization Behavior Questionnaire (PHBQ) was utilized for child postoperative assessment. This tool is a questionnaire for parents that examines the child's general anxiety, separation anxiety, sleep anxiety, eating disturbance, aggression towards authority, and apathy and withdrawal. Higher scores indicate negative behavior change. Internal consistency is reported to be adequate for subscale scores and excellent for overall scores.[20]

Parental anxiety at induction of anesthesia. At baseline and postoperatively, the State-Trait Anxiety Inventory (STAI) was used for parental anxiety. STAI is the gold standard for assessing anxiety in adults.[21] It comprises 20 questions and has good test-retest reliability. Total scores range from 20 to 80, with higher scores indicating higher levels of anxiety.

Satisfaction. A standard satisfaction questionnaire used routinely at our institution was employed to measure parental satisfaction. Staff satisfaction was measured using the NASA Task Load Index (NASA-TLX) and the System Usability Scale (SUS). The NASA-TLX evaluates the workload of an activity; the workload is considered low for a score of 0–9, medium for 10–29, somewhat high for 30–49, high for 50–79 and very high for 80–100. To evaluate acceptability and usability the System Usability Scale (SUS) was used: a score of > 70 is regarded as acceptable; a score of at least 71.4 suggests good usability, while a score of 85.5 suggests excellent usability. The NASA-TLX is reported to have good validity and reliability.[22] while the SUS is reported to have good validity and excellent reliability.[23]

Study flow

Data collection took place across three timepoints: pre-anesthesia (baseline), during induction of anesthesia, and postoperatively. A flow chart demonstrating the timepoints and data to be collected during each period is provided in the Supplementary material -Appendix C.

Baseline assessments

Following consent, the mYPAS was used to assess the child's baseline anxiety before surgery, at operating room entrance, by two research assistants assigned to the patient. Following each assessment, the research assistants met to reach consensus on the final score. All assessors underwent standardized training to achieve an inter- and intra-rater reliability of at least 95% for the mYPAS. The parent was self-administered STAI and EASI. All parents were provided with verbal anesthesia induction preparatory information focusing on four areas: operating room environment, parent's role during induction, what to expect as the child is induced, and post-induction procedures.

Child anxiety and cooperation assessment during induction of anesthesia

Patient's anxiety level was measured again using the mYPAS at the time of induction by the two research assistants assigned to the patient. Following each assessment, the research assistants met to reach consensus on the final score. The child's cooperation at induction was recorded using the ICC by one of the research assistants assigned to the patient.

Postoperative assessments

Immediately following surgery, the anesthesiologist and the induction nurse were asked by one of the research assistants assigned to the patient to complete the NASA-TLX and the SUS. Two-three days after surgery, parents were contacted by the research assistant assigned to them by phone to complete the PHBQ.

Statistical analysis

Data were summarized as frequencies or percentages for categorical variables and mean for continuous variables, reported with a 95% Confidence Interval (mean, [95% CI]). The Chi-square test was used to compare categorical variables and student's t test was used to compare two continuous variables. Analysis of variance (ANOVA) was also conducted to compare the primary outcome among groups. The two-tailed p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Participants

A total of 41 parent/patient dyads participated in the study. The demographic information of the participants is shown in Table 1. The mean age of patients was 7.5 years (5.2—9.7). Overall, 18 parents (43.9%) had previous experience with anesthesia for their child. No significant differences were observed among the groups in terms of age, sex, parents' previous experience, and number of previous anesthetics; EASI score and STAI preoperatively were not statistically significantly different among groups (Table 2).

Feasibility

Enrollment rate and attrition

In total, 304 parents were approached for eligibility and assessment, 171 being eligible. Fifty-five participants consented to the study (enrollment rate 32.2%). Among the 249 not eligible/excluded, 52.6% of parents were not interested in the study, 30.9% were not eligible, with reasons of exclusion shown in Figure 1. After randomization, 14 participants withdrew from the study. The overall attrition rate was 14/55 (25.5%). The remaining participants were equally distributed among groups (10 vPPIA+, 10 vPPIA-, 11 pPPIA+, 10

Table 1 Participants demographics score.

	Virtual Parental Presence with Coaching (vPPIA+)	Virtual Parental Presence without Coaching (vPPIA-)	Physical Parental Presence with Coaching (pPPIA+)	Physical Parental Presence without Coaching (pPPIA-)
Age: mean [95% CI]	7.5 [5–9.9]	7.7 [5.4—10]	9 [7.2—10.8]	5.6 [4.1—7.1]
Sex: n (%)				
Female	7 (70%)	5 (50%)	3 (27.3%)	2 (20%)
Male	3 (30%)	5 (50%)	8 (72.7%)	8 (80%)
Total	10	10	11	10
Previous experiences — Parent, n (%)				
Yes	4 (40%)	3 (30%)	5 (45.5%)	6 (60%)
No	6 (60%)	7 (70%)	5 (45.5%)	4 (40%)
missing	0	0	1 (9%)	0
Previous experiences — Patient, n (%)				
0	9 (90%)	5 (50%)	9 (82%)	6 (60%)
1	0	1 (10%)	1 (9%)	3 (30%)
2	0	4 (40%)	0	0
> 2	1 (1%)	0	0	1 (10%)
Missing	0	0	1 (9%)	0

Data are expressed as absolute number (n) and percentage (%) and mean and 95% Confidence Interval [95% CI].

Table 2 Baseline assessment for parents (STAI) and children (EASI).

	Virtual Parental Presence with Coaching (vPPIA+)	Virtual Parental Presence without Coaching (vPPIA-)	Physical Parental Presence with Coaching (pPPIA+)	Physical Parental Presence without Coaching (pPPIA-)
STAI pre-op	39.3 [29.9–48.7]	33.6 [26.3–40.9]	35.6 [28.2–42.9]	34.8 [28.4–0.68]
EASI				
Emotionality	13.6 [12–15.2]	14 [11.3–16.7]	12.7 [10.8–14.6]	16 [14.4–17.6]
Activity	17.4 [14.4–28.4]	15.6 [13.4–17.8]	13.5 [10.8–16.2]	18.2 [16.5–19.9]
Sociability	17.3 [14.8–19.8]	16.8 [15.5–18.4]	16.8 [14.7–18.9]	17.5 [16.6–18.4]
Impulsivity	11.8 [9.9–13.7]	10.5 [8.3–12.7]	10.4 [8.7–12.2]	11.6 [9.2–14.4]

Data are expressed as mean (n) and 95% Confidence Interval [95% CI].

pPPIA-) and there were no statistically significant differences on the baseline variables assessed. Figure 1 shows the flow of participants through the study following the CONSORT statement.[24]

Compliance

Among parents, 36/41 completed all the study tasks (compliance of 87.8%); the uncompleted tasks regarded the postoperative assessments (namely, parental satisfaction questionnaire). For the OR staff, compliance for completion of the SUS and NASA-TLX was 18/20 (90%) and 16/20 (80%), for anesthesiologists and induction nurses, respectively.

Satisfaction

Parental satisfaction was rated as "excellent" in more than 50% of parents, overall, but no statistically significant difference was observed among the groups. Parents' outcomes are shown in Table 3.

For anesthesiologists and induction nurses, the SUS-score for video system usability was 67.5 (59.5—77.5) and 63.5 (53.5—73.6) out of 100, respectively. The NASA-TLX Score was 29.2 (21.5—36.8) for the anesthesiologists and 27.6 (8.2—37) for the induction nurses (Supplementary material - Appendix D). The SUS and NASA-TLX scores for the groups vPPIA+ and vPPIA- are provided in Table 4.

Secondary outcomes

Child and parent anxiety

The study was not powered to assess statistical significance, however statistical analysis was employed to look at results. The mean baseline mYPAS score in the vPPIA+, vPPIA-, pPPIA +, and pPPIA- were 27.7 (22.3—33), 26.7 (23—30.3), 25.6 (23.3—27.9), and 23.8 (22.7—25), respectively (p = 0.35). The lowest mYPAS score at induction was observed in the vPPIA+ group. A non-statistically significant difference (p = 0.052) was observed in the mean difference between

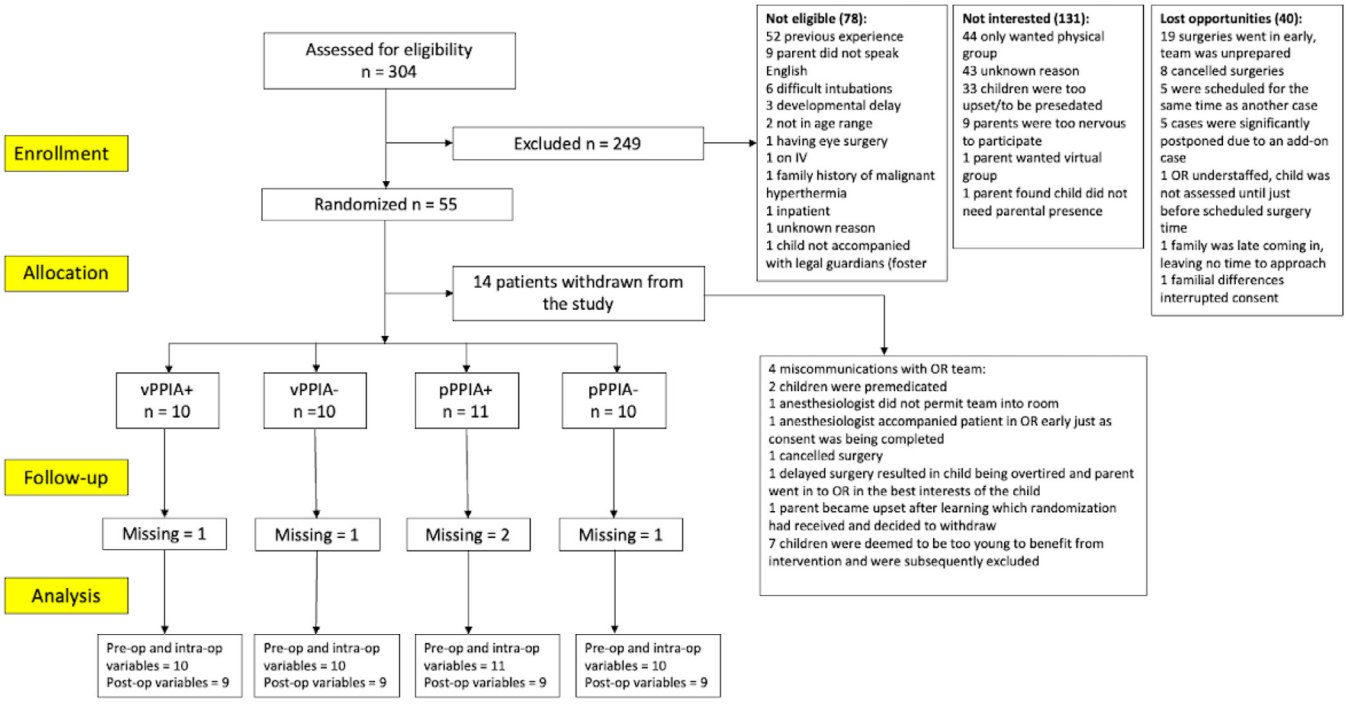


Figure 1 CONSORT 2010 diagram of the study flow and reasons of participants not eligible/excluded.

Table 3 Parental post-operative anxiety and parental satisfaction.

	Virtual Parental Presence with Coaching (vPPIA+)	Virtual Parental Presence without Coaching (vPPIA-)	Physical Parental Presence with Coaching (pPPIA+)	Physical Parental Presence without Coaching (pPPIA-)	*p*-value
STAI post-op	39.7 [32.7–46.7]	41.4 [34.7–48.1]	38 [30.9—45]	36.5 [29.7–43.3]	0.71
Parental satisfaction					0.63
Excellent	7 (77.8%)	6 (66.7%)	6 (66.7%)	5(55.6%)	
Very Good	2 (22.2%)	3 (33.3%)	2 (22.2%)	4(44.4%)	
Good	0	0	1 (11.1%)	0	
Total	9	9	9	9	
Missing	1	1	2	1	

Data are expressed as absolute number (n) and percentage (%) and mean and 95% Confidence Interval [95% CI].

Table 4 Satisfaction of anesthesiologists and induction nurses.

	Virtual Parental Presence with Coaching (vPPIA+)	Virtual Parental Presence without Coaching (vPPIA-)	Virtual Parental Presence (both coaching and without-coaching)
SUS-AN	73.7 [66–81.5]	61.2 (46.6–75.9)	67.5 (59.4–75.6)
SUS-IN	68.5 [53.5–83.5]	58.1 [42.3–74]	63.5 [53.5–73.6]
NASA TX-AN	24.3 [12.1–36.6]	34 [23.5–44.5]	29.2 [21.5–36.8]
NASA TX-IN	16.9 [9.7–24.2]	39.5 [23.4–55.7]	27.6 [18.2–37.1]

Data are expressed as absolute number (n) and percentage (%) and mean and 95% Confidence Interval [95% CI].

Table 5 Assessment of children anxiety at induction (mYPAS and ICC) and PHBQ score.

	Virtual Parental Presence with Coaching (vPPIA+)	Virtual Parental Presence without Coaching (vPPIA-)	Physical Parental Presence with Coaching (pPPIA+)	Physical Parental Presence without Coaching (pPPIA-)	*p*-value
mYPAS (Baseline)	27.7 [22.3—33]	26.7 [23—30.3]	25.6 [23.3—27.9]	23.8 [22.7–25]	0.35
mYPAS (Induction)	25.3 [23.5–27.1]	38.2 [22–54.3]	27.9 [24–31.8]	38.2 [26.2–50.1]	0.1
Mean Differences MYPAS	-2.33 [−6.8–2.2]	11.5 [-4.8–27.8]	2.3 [-3.2–7.7]	14.3 [2.7–26]	0.052
ICC	0.3 [0.2–0.8]	1.5 [0.6–3.6]	0 [0–0]	0.6 [0.3–1.5]	0.19
PHBQ	19.2 [6.4–32]	8.4 [-1.8–18.6]	23.3 [12.5–34.1]	23.7 [12–35.4]	0.14

Data are expressed as mean (n) and 95% Confidence Interval [95% CI].

baseline-mYPAS and induction-mYPAS of the groups. The only intervention that decreased mYPAS score from baseline to induction was the vPPIA+ with a mean difference of -2.3 (-6.8—2.2). There was no statistically significant difference in the mean PHBQ scores (p = 0.14). The highest mean PHBQ score was reported for the pPPIA- group, 23.7 (11.9—35.4); the lowest mean PHBQ score was reported for the vPPIA- group (8.4 [-1.8—18.6]). An additional statistical analysis comparing vPPIA and pPPIA (with or without coaching) was conducted. A lower PHBQ score was observed for the vPPIA group, but not significantly different (p = 0.16). Postoperatively, STAI scores did not differ among groups (p = 0.71). Results are summarized in Table 5.

Discussion

We report the feasibility of a randomized, 2 × 2 factorial design trial, examining parental presence (virtual vs. physical) and coaching (provided vs. not provided). Overall, the study appears feasible, but the results highlight some considerations. First, an enrollment rate of 32.2% was obtained. Participant recruitment is of vital importance for adequately conducting a trial and it is known that often the accrual period is underestimated in the building phase of the trial.[25] The obtained enrollment rate is to be considered in the allocation of sufficient time for participant recruitment. Second, a 25.5% attrition rate was reported. A review by Hewitt et al.[26] suggests that loss to follow-up occurs in many trials — a loss of 20% or greater means that the presence of biases cannot be excluded.[27] However, in our study, loss happened mainly at the randomization period and the subsequent treatment and control groups were evenly distributed. In a future trial, attention should be given to the attrition rate and where losses happen during the study flow. In our study, seven children were excluded after randomization because they were deemed too young to benefit from the intervention; raising the lower age limit for enrollment from 18 months to 24 months could be an effective change to decrease attrition. Most importantly, the trial was designed

in a period when video interactions between parents and caregivers were uncommon. The COVID pandemic changed this and may perhaps have made it easier to recruit participants in the video arm.

The highest SUS score and lowest NASA-TLX score were obtained in the vPPIA+ group. This could be explained by the novelty of the technology at the time of the study. With increased use of videocalls in recent years clinicians and parents may be more adept with these technologies.[28] It is reasonable to expect better SUS and NASA-TLX scores nowadays, due to technology improvement and higher use of videocall technology by people.

Mean mYPAS scores at induction were reduced in the vPPIA+ group. We hypothesized a synergic effect of parental coaching and video presence could improve preoperative anxiety. The theorical framework of this assumption is the modularity concept. Modularity has been defined as the partial representation of a person instead of the whole person, that ends up being accepted, based on activity.[29] In this context, parental presence by video may enable modularity, resulting in reduced anxiety, primarily in children and secondarily in parents. Technology, supporting telepresence interactions through video, may enhance the concept of modularity as children may engage positively with a parent that is partially represented. Similarly, parents may also exhibit more positive and soothing communication with the child due to modularity.

It is known that pPPIA is not effective for parents who are anxious[8] as they can transmit anxiety to the child, and that a consistent proportion of parents feel anxious in accompanying their child to the OR.[7] In contrast, virtual PPIA may reduce parental anxiety, by omitting the parent's physical presence in the operating room, resulting in less or no transmission of anxiety to the child and this may be influenced by the source of the parent's anxiety. At the same time, parents who experience high anxiety while physically present in the OR can still provide comfort to their child via video. Hypothetically, virtual PPIA may also result in less performance anxiety and the subsequent highest satisfaction of OR staff. Other potential benefits of vPPIA may include the reduced need for extra-personnel to accompany and manage parents in the OR during induction and afterwards. An adequately powered study is needed to confirm all these potential advantages.

Coaching is another relatively low-cost intervention that could have an impact on preoperative anxiety. Video or paper tools could be provided to parents/guardian before surgery. In children, a recent RCT by Batuman et al.[30] has shown a reduction in mYPAS and PHBQ scores in children exposed to an informational video before anesthesia and surgery. Additional research is needed to better delineate effects of coaching on parents and indirectly on their child.

Limitations

The pilot results do not provide evidence of any benefits of vPPIA and coaching on preoperative anxiety. Since the feasibility results come from a single-center experience, they may not be applicable to other institutions. Given that the study was carried out before the COVID-19 pandemic, the enrollment rate and satisfaction might differ if the study were conducted today.

Conclusion

The theoretical background of virtual parental presence is promising in reducing preoperative anxiety and a RCT to explore its effect on preoperative anxiety is feasible. Further studies are needed to investigate its role and the role of parental coaching in reducing preoperative anxiety.

Ethical approval

This study received institutional ethics approval. Written informed consent was obtained from parents/guardians of the patients. Anesthesiologist and induction nurse consent was implied via completion of the NASA-TLX and SUS questionnaires.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare no conflicts of interest.

Funding

The authors have no funding disclosures.

Acknowledgements

The authors want to acknowledge the work of Adina Max, Amaan Khawaja, Ivan Lo, Karlena Sathiyascelan, Sally wu, Samantha Mcternan, Valentina Rumeo, Carmina Santos, Kyle Cheung, Lorrie Morley, Allison Alvarez, Kinza Fida-I-Nasir, Julian Andrei, Jaclyn Bedder, Georgiana Forguson, Mehwish Mehwish, Anna Morley as research assistants.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844533.

References

1. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150:1238—45.
2. Sullivan V, Sullivan DH, Weatherspoon D. Parental and Child Anxiety Perioperatively: Relationship, Repercussions, and Recommendations. J Perianesth Nurs. 2021;36:305—9.
3. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics. 2006;118:651—8.
4. Mathias EG, Pai MS. Anxiety and Pain in Children Undergoing Surgery: A Scoping Review. J Perianesth Nurs. 2022;37:545—50.

5. Challa C, Geng-Ramos G, Gray L, Orshan T, Thackeray L, Gupta P. Anxiety in children: A review on how to address it in the perioperative setting post-pandemic. Paediatr Anaesth. 2023;33:422—6.
6. Shih MC, Elvis PR, Nguyen SA, Brennan E, Clemmens CS. Parental Presence at Induction of Anesthesia to Reduce Anxiety: A Systematic Research and Meta-Analysis. J Perianesth Nurs. 2023;38:12—20.
7. Alcaraz Garcia-Tejedor G, Le M, Tackey T, Watkins J, Caldeira-Kulbakas M, Matava C. Experiences of Parental Presence in the Induction of Anesthesia in a Canadian Tertiary Pediatric Hospital: A Cross-Sectional Study. Cureus. 2023;15:e36246.
8. Kain ZN, Caldwell-Andrews AA, Maranets I, Nelson W, Mayes LC. Predicting which child-parent pair will benefit from parental presence during induction of anesthesia: a decision-making approach. Anesth Analg. 2006;102:81—4.
9. Bailey KM, Bird SJ, McGrath PJ, Chorney JE. Preparing Parents to Be Present for Their Child's Anesthesia Induction: A Randomized Controlled Trial. Anesth Analg. 2015;121:1001—10.
10. Kim H, Jung SM, Yu H, Park SJ. Video Distraction and Parental Presence for the Management of Preoperative Anxiety and Postoperative Behavioral Disturbance in Children: A Randomized Controlled Trial. Anesth Analg. 2015;121:778—84.
11. Wolman RN, Pomerance R, editors. Telepresence Technology in Divorce and Separation2012.
12. Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER, et al. Impact of COVID-19 on clinical trials and clinical research: A systematic review. Nepal J Epidemiol. 2020;10:878—87.
13. Iyer RS, Matava C, Alessandro V, et al. A global cross-sectional survey of personal protective equipment practices from 125 institutions in 37 countries during the COVID-19 pandemic. J Clin Anesth. 2022;80:110881.
14. van Dorn A. COVID-19 and readjusting clinical trials. Lancet. 2020;396:523—4.
15. Kain ZN, Mayes LC, Cicchetti DV, Bagnall AL, Finley JD, Hofstadter MB. The Yale Preoperative Anxiety Scale: how does it compare with a "gold standard"? Anesth Analg. 1997;85:783—8.
16. Ahmed MI, Farrell MA, Parrish K, Karla A. Preoperative anxiety in children risk factors and non-pharmacological management. Middle East J Anaesthesiol. 2011;21:153—64.
17. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB. Parental presence during induction of anesthesia versus sedative premedication: which intervention is more effective? Anesthesiology. 1998;89:1147—56. discussion 9A-10A.
18. Ohashi Y, Kitamura T. The EASI: Factor Structure and Measurement and Structural Invariance between the Parent's Gender, the Child's Age, and Two Measurement Time Points. Psychology. 2019;10:2177—89.
19. Chow CHT, Rizwan A, Xu R, Poulin L, Bhardwaj V, Van Lieshout RJ, et al. Association of Temperament With Preoperative Anxiety in Pediatric Patients Undergoing Surgery: A Systematic Review and Meta-analysis. JAMA Network Open. 2019;2:e195614.-e.
20. Vernon DT, Schulman JL, Foley JM. Changes in children's behavior after hospitalization. Some dimensions of response and their correlates. Am J Dis Child. 1966;111:581—93.
21. Spielberger C, Gorsuch R, Lushene R, Vagg PR, Jacobs G. Manual for the State-Trait Anxiety Inventory (Form Y1 — Y2) 1983.
22. Hoonakker P, Carayon P, Gurses A, Brown R, McGuire K, Khunlertkit A, Walker JM. Measuring workload of ICU nurses with a questionnaire survey: the nasa Task Load Index (TLX). IIE Trans Healthc Syst Eng. 2011;1:131—43.
23. Bangor Aaron, Kortum P, T P, Miller T J. The System Usability Scale (SUS): an Empirical evaluation. International Journal of Human-Computer Interaction. 2008;24:574.
24. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, Lancaster GA. Consort 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355:i5239.
25. Carter RE, Sonne SC, Brady KT. Practical considerations for estimating clinical trial accrual periods: application to a multi-center effectiveness study. BMC Med Res Methodol. 2005;5:11.
26. Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. Bmj. 2005;330:1057—8.
27. Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. Bmj. 2006;332:969—71.
28. Ilowite J, Lisker G, Greenberg H. Digital Health Technology and Telemedicine-Based Hospital and Home Programs in Pulmonary Medicine During the COVID-19 Pandemic. Am J Ther. 2021;28:e217—e23.
29. Lee KM. Why Presence Occurs: Evolutionary Psychology, Media Equation, and Presence. Presence: Teleoperators & Virtual Environments. 2004;13:494—505.
30. Batuman A, Gulec E, Turktan M, Gunes Y, Ozcengiz D. Preoperative informational video reduces preoperative anxiety and postoperative negative behavioral changes in children. Minerva Anestesiol. 2016;82:534—42.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



ORIGINAL INVESTIGATION

Effectiveness of intracuff alkalinized lidocaine associated with intravenous dexamethasone in reducing laryngotracheal morbidity in children undergoing general anesthesia for tonsillectomy: a randomized controlled trial

Morenna Ramos e Oliveira [a,*], Norma S.P. Modolo [a], Paulo Nascimento Jr. [a], Rodrigo M. Lima [b], Devin Stirling [c], Glenio B. Mizubuti [c], Leopoldo Muniz da Silva [d], Lais H. Navarro [a,b]

[a] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Anestesiologia, São Paulo, SP, Brazil*
[b] *University of Manitoba, Department of Anesthesiology, Perioperative and Pain Medicine, Winnipeg, MB, Canada*
[c] *Queen's University, Department of Anesthesiology and Perioperative Medicine, Kingston, ON, Canada*
[d] *Hospital São Luiz, Departamento de Anestesiologia, Equipe de Anestesia do CMA, São Paulo, SP, Brazil*

Received 20 August 2021; accepted 27 July 2024
Available online 3 August 2024

KEYWORDS
Endotracheal intubation;
Sore throat;
Tonsillectomy;
Pediatrics;
Lidocaine

Abstract
Background: Postoperative sore throat is one of the main postoperative complaints in patients undergoing tonsillectomy. As the primary outcome, we aimed to determine whether endotracheal tube cuffs filled with alkalinized lidocaine are associated with a lower incidence of postoperative sore throat and anesthesia emergence phenomena in children undergoing tonsillectomy or adenotonsillectomy. We also assessed the potential additional benefits of IV dexamethasone in reducing postoperative laryngotracheal morbidity.
Methods: This is a clinical prospective, randomized, controlled trial. Patients were randomly allocated to one of four groups, as follows: air — endotracheal tube cuff filled with air; air/dex — endotracheal tube cuff filled with air and intravenous dexamethasone; lido — endotracheal tube cuff filled with alkalinized lidocaine; and lido/dex — endotracheal tube cuff filled with alkalinized lidocaine and intravenous dexamethasone. Perioperative hemodynamic parameters and the incidence of postoperative nausea and vomiting, coughing and hoarseness were recorded. Postoperative sore throat was assessed in the postanesthetic care unit and 24 hours post tracheal extubation.
Results: In total, 154 children aged 4—12 years, ASA physical status I or II, undergoing general anesthesia for elective tonsillectomy and adenotonsillectomy, were assessed for postoperative sore throat in this study. The incidence of postoperative sore throat 24 hours after tracheal

* Corresponding author.
E-mail: morenna_ramos@hotmail.com (M.R. Oliveira).

https://doi.org/10.1016/j.bjane.2024.844548
0104-0014/© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

extubation was significantly lower in the lido/dex group compared to groups air and air/dex (p = 0.01). However, no additional reduction in these symptoms was observed from the intravenous administration of dexamethasone when comparing the lido and lido/dex groups. Similarly, there were no differences among groups regarding perioperative hemodynamic variables or postoperative nausea and vomiting, coughing, and hoarseness during the study period.
Conclusion: Intracuff alkalinized lidocaine, associated with intravenous dexamethasone, might be effective in reducing sore throat 24 hours post-tonsillectomy or adenotonsillectomy in children when compared to the use of air as the cuff insufflation media.
© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

One of the main concerns among anesthesiologists is to reduce perioperative morbidity, especially those attributed to anesthesia. Accordingly, the prevention of tracheal intubation-induced sore throat has been the subject of extensive research.

In the past, pediatric intubation was classically performed using uncuffed Endotracheal Tubes (ETT) because of the potential risk of tracheal mucosa injury associated with cuffed ETT. However, in the early 2000s, the safety of ETT with high-compliance and low-pressure cuffs was demonstrated,[1] as long as the tracheal mucosal perfusion pressure is not exceeded.[2] Accordingly, the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) established in 2010 the use of cuffed ETT as a safe alternative in children.[3] Similarly, recent European guidelines for pediatric airway management recommend cuffed ETT for children undergoing tonsillectomy.[4]

Lately, researchers have been trying to find ways to reduce ETT-induced sore throat incidence. Some studies have demonstrated benefits when the ETT cuff is filled with alkalinized lidocaine (rather than air) in reducing adult postoperative laryngotracheal morbidity.[5,6] A 2015 meta-analysis showed that both alkalinized and non-alkalinized lidocaine, when used to fill the ETT cuff, reduce the incidence of Postoperative Sore Throat (POST) and post-intubation emergence phenomena.[7] The post-intubation-related emergence phenomena is a cluster of airway complications associated with tracheal intubation or extubation after general anesthesia.[7] During emergence from general anesthesia, patients may experience vigorous coughing, agitation or restlessness. Other laryngeal complications, such as hoarseness, dysphonia, or dysphagia, may also be noted during postoperative care.[7] Finally, a recent study also showed a reduction in POST (as well as a more favourable hemodynamic response to tracheal extubation) in pediatric patients when ETT cuffs were filled with alkalinized lidocaine.[8] None of these studies, however, included children undergoing tonsillectomy or adenotonsillectomy.

POST is one of the main complaints in patients undergoing throat surgeries. Thus, different strategies have been employed to mitigate postoperative pain, including ntravenous (IV) corticoid administration,[9] local anesthetic infiltration of the surgical site, and various surgical techniques.

Accordingly, as the primary outcome of the present study, we aimed to determine whether ETT cuffs filled with alkalinized lidocaine are associated with a lower incidence of POST and anesthesia emergence phenomena in children undergoing tonsillectomy or adenotonsillectomy. We also assessed the potential additional benefits of IV dexamethasone in reducing postoperative laryngotracheal morbidity.

Methods

Local research ethics approval (protocol number: CAAE 4443-2012) and written informed consent from the patient's parents/legal guardians were obtained. This manuscript adheres to the applicable CONSORT guidelines and was registered at www.ensaiosclinicos.gov.br (RBR-9x4s6y) by one of the investigators (PN Jr) in October 2016.

This prospective, randomized, controlled trial was conducted in a Brazilian teaching hospital from November 2016 to May 2018. Children aged 4—12 years of both sexes, classified as American Society of Anesthesiologists (ASA) physical status I or II, undergoing elective tonsillectomy or adenotonsillectomy under general anesthesia, were eligible for inclusion.

Children with oropharyngeal or neck malformations; patients who presented with stridor or dysphonia before surgery; patients who had previously required tracheal intubation or tracheostomy; those requiring a nasogastric tube or more than two attempts at tracheal intubation; those with signs of upper respiratory tract infection; those whose parents did not sign the informed consent; and patients requiring postoperative Intensive Care Unit (ICU) admission (e.g., children with severe obstructive sleep apnea and hypopnea syndrome) were not included in the study. Moreover, patients who presented with severe intraoperative bleeding, need for reoperation, accidental extubation during surgical procedure, and change in the surgical plan were excluded from the final analysis.

An independent researcher allocated eligible patients to one of four groups: air – ETT cuff filled with air and IV administration of saline 0.1 mL.kg^{-1} at anesthesia induction; air/dex – ETT cuff filled with air and IV administration of dexamethasone 0.2 mg.kg^{-1} at anesthesia induction. Dexamethasone was diluted in order to achieve a volume of 0.1 mL.kg^{-1}; lido – ETT cuff filled with alkalinized lidocaine 1% and IV administration of saline 0.1 mL.kg^{-1} at anesthesia induction; lido/dex – ETT cuff filled with alkalinized lidocaine 1% and IV administration of dexamethasone 0.2 mg.kg^{-1} at anesthesia induction. Dexamethasone was diluted in order to achieve a volume of 0.1 mL.kg^{-1}.

The randomization list was generated using a computer sequence number, and the patient allocation ratio was 1:1:1:1. Written group allocation was sealed in individual opaque envelopes marked externally only with study identification numbers. Envelopes were opened upon the patient's admission to the Operating Room (OR). An anesthetic assistant not participating in the study prepared the drug solution after breaking the codes.

The alkalinized lidocaine solution was prepared by mixing 9.5 mL lidocaine 1% with 0.5 mL 8.4% sodium bicarbonate. The syringe containing dexamethasone or saline was prepared by a nurse, who was not directly involved in the study. The attending anesthesiologist, as well as the research team, were blinded to the type of IV solution administered to each patient. Polyvinyl chloride ETT with high-volume low-pressure cuffs (Well Lead Medical Instruments Co Ltd, Guangzhou, China) were used in all patients. The ETT size was chosen according to Motoyama's table[10] and larger and smaller inner diameter ETT were also available.

Upon admission to the OR, standard monitors (electrocardiography, pulse oximeter, and non-invasive blood pressure) were applied, and anesthesia induction was carried out with 4%–5% sevoflurane in 100% oxygen via a facemask followed by peripheral intravenous line insertion. Fentanyl 3 mcg.kg^{-1} and propofol 3 mg.kg^{-1} were, then, administered, followed by rocuronium 0.5 mg.kg^{-1} to facilitate tracheal intubation. Upon full muscle relaxation (i.e., absence of response to Train-Of-Four [TOF]), direct laryngoscopy was performed and an appropriately-sized cuffed ETT with the cuff fully deflated and the tip lubricated with a water-soluble gel (Johnson & Johnson, New Brunswick, NJ, USA) was orally inserted into the trachea. The cuff was, then, filled with air or alkalinized lidocaine until the seal pressure was achieved during manual positive pressure ventilation with a pressure of 20 cm H_20. Mechanical ventilation was initiated with a tidal volume of 6–8 mL.kg^{-1}. Anesthesia was maintained with sevoflurane (2 vol %) in an O_2/N_2O mixture of 40%–60%. Minute ventilation was adjusted to maintain end-tidal CO_2 (Et_{CO2}) within 35 and 40 mmHg. The cuff pressure was continuously measured with a portable digital manometer (Mallinckrodt; Covidien, Dublin, Ireland) connected to the pilot-balloon valve in the air-filled cuff groups. In the lidocaine-filled cuff groups, the pressure was measured with a pressure transducer (Smith Medical ASD, Inc, Dublin, OH, USA) connected to a Dixtal DX 2023 monitor (Philips Healthcare, São Paulo, Brazil). Cuff pressure was maintained at < 20 cm H_20 throughout the case in all patients.

Hemodynamic (blood pressure and heart rate) and respiratory (pulse oximetry and Et_{CO2}) parameters were recorded five minutes pre- and five minutes post-tracheal intubation, and every 15 minutes thereafter. Nitrous oxide was initiated upon tracheal intubation. ETT cuff pressure was first recorded upon tracheal intubation and then every 15 minutes thereafter.

Senior residents performed surgical procedures under the direct supervision of a board-certified otolaryngologist. The surgical technique (i.e., extracapsular cold dissection) was the same for all patients. Neither local anesthetics (topical or systemic) nor additional opioids were administered throughout the case.

Prior to the end of the surgical procedure, all patients receive IV ondansetron 0.1 mg.kg^{-1}, metamizole 30 mg.kg^{-1} and tramadol hydrochloride 1 mg.kg^{-1}. Antagonism of neuromuscular blockade (with sugammadex 2 mg.kg^{-1}) was left at the discretion of the attending anesthesiologist, followed by careful oropharyngeal suction. Tracheal extubation was carried out once the following parameters were achieved: TOF $\geq$ 0.9; spontaneous ventilation with adequate tidal volumes; and response to verbal commands (eye-opening and movement of the limbs). At this point, the ETT cuff pressure was recorded and the cuff was completely deflated followed by tracheal extubation. Patients were transferred to the Postanesthetic Care Unit (PACU).

Hemodynamic variables were also recorded five minutes pre- and five minutes post-tracheal extubation. Postoperative laryngotracheal morbidity (namely coughing, hoarseness, and sore throat) was serially evaluated by the attending anesthesiologist upon tracheal extubation, and by blinded observers in the PACU and 24h post-tracheal extubation. Hoarseness was assessed subjectively by perceptual analysis of voice by the patient, the parent and the clinician. Nausea is the subjective unpleasant sensation of imminent vomiting. Accordingly, nausea was assessed by observation of gagging reflex or referral of nausea sensation by the child in the PACU and 24 hours after extubation. Vomiting was also assessed at the same time points. In the PACU, pain was self-informed by the patient based on a numeric scale ranging from 0 (absence of pain) to 10 (worst imaginable pain), or evaluated according to the faces pain scale,[11] when the child was too young to fully comprehend the numeric scale. If the child presented with pain $\geq$ 5, IV morphine 25 mcg.kg^{-1} was administered as a rescue drug with a repeat similar dose after 10 min if necessary. Once patients achieved a score $\geq$ 9 on the modified Aldrete-Kroulik scale, they were transferred to the ward, where analgesia consisted of oral metamizole 30 mg.kg^{-1} every 6 hours and tramadol hydrochloride 1 mg.kg^{-1} every 8 hours. All surgeries were performed in the afternoon and all patients were discharged in the morning of the following day.

Our primary outcome was the incidence of POST. Secondary outcomes included perioperative hemodynamic variability, postoperative nausea/vomiting, coughing, and hoarseness. In the PACU, data collection was carried out by an investigator blinded to the group allocation. After 24 hours of tracheal extubation, data collection was carried out by another investigator through telephone contact with the parent/legal guardian, when 4 questions were asked to determine the presence/absence of sore throat: 1) Did the child objectively complain of pain?; 2) Was it necessary to give any analgesic medication to the child?; 3) After hospital discharge, has the child been able to ingest liquids and food?; 4) How is the general status of the child?. Of note, the presence/absence of sore throat was determined based on children's responses and subjective analysis by the parents/legal guardians.

Statistical analysis

As our primary outcome was the incidence of sore throat post-tonsillectomy, the sample size was calculated on the basis of a minimum difference of 12% in the frequency of POST among groups with ETT cuffs filled with saline or lidocaine in adults.[6] Thirty-five patients per group were required to achieve a significance level of 0.05 and a power of 80%.

ANOVA was performed for quantitative variables that were compared between groups, followed by a Tukey's test when significance was detected, in the case of symmetric distribution. Otherwise, the comparisons were made by fitting a gamma distribution followed by a Wald posthoc test. A p-value of < 0.05 was considered statistically significant. Pearson Chi-Squared test was employed for categorical variables, and partitioning Chi-Square when the value of $p < 0.05$. To be able to gauge the significance of the results in view of the multiple statistical comparisons, we included the corrected alpha level according to sequential Bonferroni correction. The significance level was lowered appropriately (Bonferroni method) to reduce the probability of a type I error. Residual analysis was calculated to identify those specific cells making the greatest contribution to the Chi-Square test result. Statistical analysis was performed using the computer software SAS for Windows (V. 9.4).

Results

Figure 1 depicts the study flowchart. Of 160 eligible children, 154 were included in the final analysis. The four randomized groups were similar regarding morphometric and demographic data, as well as ASA physical status (Table 1). Likewise, surgical duration, time to extubation (from the end of surgery), and total time in PACU were similar among groups (Table 1).

The incidence of POST 24h after tracheal extubation was significantly lower in the lido/dex group, compared with groups air and air/dex (Table 2); ($\chi^2 = 5.76$; $p = 0.010$). The largest residual to the chi-square test was observed in the lido/dex group. No significant difference was observed when comparing groups air, air/dex and lido ($\chi^2 = 2.99$; $p = 0.08$). There was also no difference when comparing only groups lido and lido/dex ($\chi^2 = 0.84$; $p = 0.35$). No difference was observed among groups regarding nausea, vomiting and hoarseness during the study period.

Hemodynamic variables recorded pre- and post-tracheal extubation are shown in Table 3. There were no differences among groups regarding hemodynamic variables at anesthesia emergence.

In PACU, low incidence (and no difference among groups) of sore throat, nausea/vomiting, coughing and hoarseness were observed (Table 4).

Mean ETT cuff pressures were kept below 20 cm H_20 throughout the case in all groups. The analyzed patients had no adverse effects or harms related to the ETT.

Discussion

The present study demonstrated a significant reduction in the incidence of POST at 24h post-extubation among children who underwent tonsillectomy and received a combination of IV dexamethasone and cuff insufflation with alkalinized lidocaine. However, such interventions were not able to attenuate the hemodynamic changes during emergence from anesthesia, nor were they effective in reducing

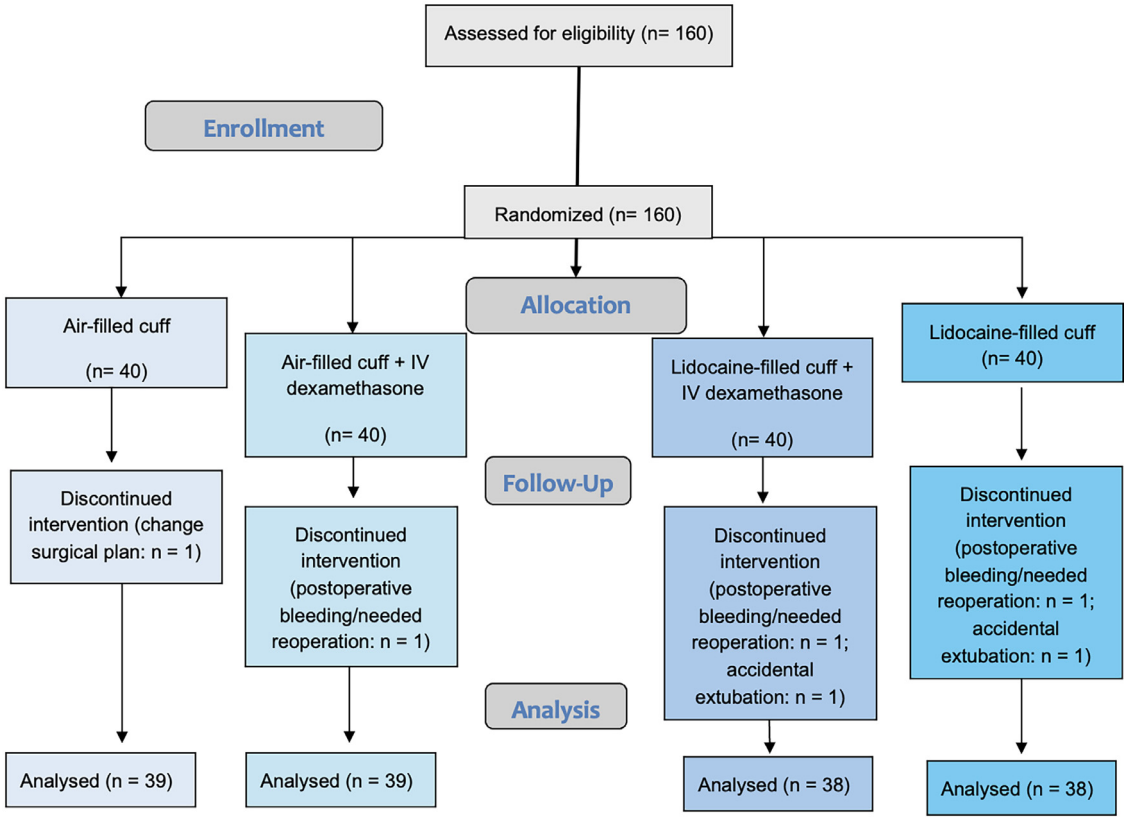


Figure 1 CONSORT flow of the study. CONSORT, Consolidated Standards Of Reporting Trials.

Table 1 Preoperative demographic and morphometric patient characteristics, ASA physical status, surgical duration, time to extubation (from end of surgery), and time in PACU. Results expressed in Mean ± Standard Deviation (SD), or in frequency of occurrence (%).

	Groups				
Variables	Air	Air/Dex	Lido	Lido/Dex	p-value
Age (years)[a]	7.1 ± 2.6	6.8 ± 2.2	7.2 ± 2.4	6.3 ± 2.4	
Weight (kg)[b]	31.1 ± 14.7	30.7 ± 12.4	29.8 ± 12.7	28.7 ± 13.7	
Sex[c]					
Female	44%	59%	34%	37%	
Male	56%	41%	66%	63%	
ASA physical status[c]					
I	82%	87%	74%	82%	
II	18%	13%	26%	18%	
Surgery time (min)[a]	64.2 ±27.9	55.5 ± 20.8	57.7 ± 25.3	61.2 ± 23.1	0.42
Time to extubation (min)[a]	12.3 ± 0.7	15.9 ± 8.4	14.6 ± 6.2	15.1 ± 7.8	0.13
Time in PACU (min)[a]	49.5 ± 27.8	52.3 ± 27.3	46.7 ± 23.2	47.4± 19.3	0.71

[a] ANOVA followed by Tukey multiple comparison test.
[b] Adjust in gamma distribution followed by Wald multiple comparison test.
[c] Chi-Square test.
G, Group; PACU, Post Anesthesia Care Unit.

Table 2 Laryngotracheal morbidity evaluated 24h post tracheal extubation. Results are expressed in frequency of occurrence (%).

	Groups				
Variables	Air	Air/Dex	Lido	Lido/Dex	p
Sorethroat[a]	74%	74%	58%	47%[b]	0.01
(Residual analysis)	−1.61	−1.61	0.84	2.40	
Nausea	5%	20%	16%	5%	0.08
Vomiting	3%	18%	13%	8%	0.13
Hoarseness	21%	13%	11%	16%	0.64

Values expressed as % (n).
[a] Proportion comparison test (Chi-Square) — Partitioning test: Incidence of sore throat: Lido/Dex group < Air, Air/Dex (χ^2 = 5.76; p = 0.010).
[b] Lido group = Air and Air/Dex groups (χ^2 = 2.99; p = 0.08); Lido group = Lido/Dex group (χ^2 = 0.84; p = 0.35). A Bonferroni corrected p-value set statistical significance at p ≤ 0.017.

Table 3 Hemodynamic variables before and after tracheal extubation in the studied groups. Results expressed in Mean ± SD.

	Groups				
Variables	Air	Air/Dex	Lido	Lido/Dex	p-value
Systolic blood pressure					
Before extubation	104.5 ± 12.6	104.4 ± 12.7	103.8 ± 11.8	101.1 ± 10.8	0.56
After extubation	124.3 ± 18.2	120.9 ± 14.0	123.6 ± 14.2	122.6 ± 16.3	0.80
Variation	19.4 ± 14.9	16.1±10.8	19.8 ± 13.9	21.5 ± 15.4	0.38
Diastolic blood pressure					
Before extubation	56.9 ± 10.5	57.0 ± 10.5	56.1 ± 10.8	53.2 ± 10.9	0.37
After extubation	70.5 ± 13.1	65.2± 10.8	70.2 ± 13.2	66.7 ± 14.6	0.20
Variation	13.3 ± 11.8	8.0 ± 7.6	14.1 ± 14.7	13.5 ± 16.4	0.14
Heart rate (beats.min)					
Before extubation	98.2 ± 17.6	99.3 ± 18.1	97.2 ± 19.7	97.9 ± 19.3	0.97
After extubation	124.3 ± 18.2	123.2 ± 21.7	127.1 ± 20.6	124.5 ± 22.6	0.87
Variation	25.5 ± 19.3	23.3 ± 20.4	29.9 ± 24.8	26.6 ± 24.5	0.62

ANOVA followed by Tukey multiple comparison test.

Table 4 Laryngotracheal morbidity evaluated in PACU. Results are expressed in frequency of occurrence (%).

	Groups				
Variables	Air	Air/Dex	Lido	Lido/Dex	p-value
Sore throat	33%	26%	24%	26%	0.79
Nausea	5%	5%	5%	3%	0.93
Vomiting	5%	5%	5%	0%	0.56
Coughing	5%	10%	8%	5%	0.79
Hoarseness	2%	5%	3%	8%	0.64

Proportion comparison test (Chi-Square).
PACU, Post-Anesthesia Care Unit.

the incidence of other laryngotracheal morbidities, such as postoperative coughing and hoarseness.

Laryngotracheal injury has many risk factors, namely ETT cuff hyperinflation (leading to ischemic injury), traumatic/prolonged intubation, multiple attempts at intubation, and surgical manipulation. In our study, cuff pressure < 20 cm H_2O was maintained, which is considered a safe threshold for ischemic airway injury in children.[1]

Lidocaine is a reasonable analgesic strategy to prevent POST as it blocks tracheal nociceptors.[11] Previous studies in adults[5,6] have demonstrated, by analysis of blood samples collected during surgical procedures, that alkalinized lidocaine was detectable in serum as early as 10 minutes after its instillation in the ETT cuff and the median concentration of serum lidocaine ranged from 1.12 to 1.52 mcg.mL^{-1}, similar to the concentration achieved 120 minutes after intracuff lidocaine instillation (1.10 to 1.6 mcg.mL^{-1}). Another study involving pediatric patients[8] encountered a serum concentration of 0.08 mcg.mL^{-1} after 30 minutes following the application of 1% alkalinized lidocaine into the ETT cuff.

After diffusing through the ETT cuff membrane,[12] lidocaine is able to block voltage-gated sodium channels of tracheal nociceptors, suppressing peripheral noxious transmission.[13] This localized effect has been shown to improve tolerance to ETT and reduce the incidence of POST and hemodynamic response to tracheal extubation in adults[5] and children.[8] A Cochrane systematic review and meta-analysis confirmed the effectiveness of intracuff lidocaine for the prevention of POST in adults.[13] In our study, however, the incidence of POST was reduced only at 24h after tracheal extubation, which cannot be explained by the topical/local effect of lidocaine, given its duration of action of < 2 hours in children.[14] Rather, we speculate that systemic absorption of the intracuff lidocaine may have contributed to the better analgesia observed on the first postoperative day. Indeed, systemic lidocaine has analgesic and anti-inflammatory properties by inhibiting potassium and calcium channels and G-protein-coupled receptors[15] which may last for weeks.[16] Also, at serum concentrations of 1–20 mcg.mL^{-1} lidocaine reversibly suppresses the tonic action potential discharge of acutely injured nerves, contributing to pain relief.[16] Notably, our group had previously measured serum lidocaine concentrations in adults[5,6] and children[8] and demonstrated that plasma absorption of effective concentrations of the local anesthetic (> 1 mcg.mL^{-1}) occurs as quickly as 10 min following its application in the ETT cuff.[5,6]

A previous study in children undergoing adenotonsillectomy found a similar incidence of coughing and hemodynamic changes upon anesthesia emergence between IV versus intracuff lidocaine.[17] The authors, however, did not alkalinize the lidocaine solution. In our study, sodium bicarbonate was added to the lidocaine solution, which increases the pH, making it more diffusible through the cuff membrane.[18]

Corticosteroids are well known for their antiemetic and anti-inflammatory properties. Dexamethasone, in particular, is an effective, safe, and inexpensive option to reduce postoperative emesis and pain in children undergoing tonsillectomy.[9] We opted to administer dexamethasone at the induction of anesthesia, given its higher efficacy when compared to later administration.[19] Nevertheless, in our study, we did not observe significant reduction in POST with dexamethasone. This may be due to the fact that the drug's anti-inflammatory effect may take several hours to appear. Some authors,[9] for example, have demonstrated a significant reduction in POST after tonsillectomy not earlier than on the second postoperative day. Perhaps this same difference would have been detected by our group if we had also evaluated POST 48 hours post-surgery.

In the present study, the only group that benefited from a significant reduction in POST 24h post-surgery received a combination of IV dexamethasone and cuff instillation with alkalinized lidocaine. There was, however, no significant decrease in POST when these interventions were instituted in isolation. Hence, our study supports the concept of multimodal analgesia which has been strongly advocated for the pediatric population.[20] The combination of different strategies allows for more effective analgesia with decreased opioid requirements, thereby minimizing the incidence/severity of side effects. The combination of dexamethasone and intracuff lidocaine, therefore, is a cheap and effective alternative with a potential synergistic effect with other analgesics as part of the multimodal management of post-tonsillectomy sore throat.

A 2018 RCT showed that dexamethasone associated or not with lidocaine was effective in reducing the incidence of POST in patients requiring prolonged tracheal intubation.[21] Their patient population (adults undergoing all types of surgery) and route (intravenous) of lidocaine administration, however, differed from our study. Another study suggested that local anesthetic did not reduce the number of supplemental analgesics required post-tonsillectomy, but recommended the routine use of IV dexamethasone.[22]

Currently, IV dexamethasone is a well-established and recommended strategy to prevent POST in children undergoing tonsillectomy. However, the benefits of combining

dexamethasone with lidocaine remain the subject of debate. Some authors advocate for such a combination on the basis of a synergistic effect resulting in more effective and prolonged benefits.[23,24] Others, on the other hand, have shown no difference when these agents are administered either in combination or separately.[21,25]

To our knowledge, the present study is the first to evaluate the combination of IV dexamethasone and intracuff alkalinized lidocaine in comparison to such interventions in isolation. As the benefits were greater when used in combination, we speculate that IV dexamethasone potentialized the systemic effect of lidocaine. Nonetheless, further studies are needed to evaluate the synergistic effect of these two interventions in preventing POST in different surgical settings. Moreover, other studies are necessary to evaluate the incidence of POST 48 h post tracheal extubation.

Finally, we observed a low incidence of sore throat in the PACU. This may be due to the residual effect of anesthetic/analgesic agents administered intraoperatively. There was no difference among groups regarding hemodynamic changes upon anesthesia emergence. This corroborates our hypothesis that the effect of lidocaine was more systemic than local.

Our study has some limitations. First, it was not possible to determine whether the reported throat pain was supraglottic (surgical site) or infraglottic (ETT cuff site). However, the clinical benefit on the first postoperative day was clearly noted, either way. Secondly, as the study was conducted in pediatric patients, some of the information regarding pain was subjectively provided by parents. Without objective pain scales, parents may underestimate their child's pain. Further studies are needed to evaluate the effectiveness of an adapted pain scale for parent observation in children with acute pain. Moreover, we did not measure lidocaine serum concentrations. However, as plasma diffusion of intracuff lidocaine has been previously demonstrated, we opted to spare our pediatric patients from the stress associated with serial blood sampling.

In conclusion, intracuff alkalinized lidocaine, associated with IV dexamethasone, may reduce POST 24h post-tonsillectomy/adenotonsillectomy in children. Considering the lack of similar studies in other settings, the present study warrants further investigation of possible ways to mitigate laryngotracheal morbidity in pediatric patients.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Weiss M, Gerber AC. Cuffed tracheal tubes in children — things have changed. Pediatr Anesth. 2006;16:1005—7.
2. Seegobin RD, Hasselt GL. Endotracheal tube cuff pressure and tracheal mucosal blood flow: endoscopic study of effects of four volume cuffs. BMJ. 1984;288:965—8.
3. Kleinmam ME, de Caen AR, Chameides L, et al. Part 10: Pediatric basic and advanced life support. 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. 2010;122:466—515.
4. Dadure C, Sabourdin N, Veyckemans F, et al. Management of the child's airway under anesthesia: the French guidelines. Anaesth Crit Care Pain Med. 2019;38(19):681—93.
5. Navarro LHC, Braz JRC, Nakamura G, Lima RM, Silva FP, Módolo NSP. Effectiveness and safety of endotracheal tube cuffs filled with air versus filled with alkalinized lidocaine: a randomized clinical trial. Sao Paulo Med J. 2007;125:1390—6.
6. Navarro LH, Lima RM, Aguiar AS, Braz JR, Carness JM, Módolo NS. The effect of intracuff alkalinized 2% lidocaine on emergence coughing, sore throat, and hoarseness in smokers. Rev Assoc Med Bras. 2012;58:248—53.
7. Lam F, Lin YC, Tsai HC, Chen TL, Tam KW, Chen CY. 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.
8. Soares SMF, Arantes VM, Módolo MP, et al. The effects of tracheal tube cuffs filled with air, saline or alkalinised lidocaine on haemodynamic changes and laryngotracheal morbidity in children: a randomised, controlled trial. Anaesthesia. 2016;72:496—503.
9. Hermans V, De Pooter F, De Groote F, De Hert S, Van der Linden P. Effect of dexamethasone on nausea, vomiting, and pain in paediatric tonsillectomy. Brit J Anaesth. 2012;109:427—31.
10. Motoyama EK. Endotracheal intubation. In: Motoyama EK, Davis PJ, eds. Smith's Anesthesia for infants and children, 5th ed., St Louis: Mosby; 1990:269—75.
11. Camporesi EM, Mortola JP, Sant'ambrogio F, Sant'ambrogio G. Topical anesthesia of tracheal receptors. J Appl Physiol Respir Environ Exerc Physiol. 1979;47:1123—6.
12. Sconzo JM, Moscicki JC, DiFazio CA. In vitro diffusion of lidocaine across endotracheal tube cuffs. Reg Anesth. 1990;15:37—40.
13. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015;7:Cd004081.
14. Amitai Y, Zylber-Katz E, Avital A, Zangen D, Noviski N. Serum lidocaine concentrations in children during bronchoscopy with topical anesthesia. Chest. 1990;98:1370—3.
15. Kindler CH, Yost CS. Two-pore domain potassium channels: new sites of local anesthetic action and toxicity. Reg Anesth Pain Med. 2005;30:260—74.
16. McCleane G. Intravenous lidocaine: an outdated or underutilized treatment for pain? J Palliat Med. 2007;10:798—805.
17. Behzadi M, Hajimohamadi F, Alagha AE, Abouzari M, Rashidi A. Endotracheal tube cuff lidocaine is not superior to intravenous lidocaine in short pediatric surgeries. Int J Ped Otorhinolaryngol. 2010;74:486—8.
18. Dollo G, Estebe JP, Le Corre P, Chevanne F, Ecoffey C, Le Verge R. Endotracheal tube cuffs filled with lidocaine as a drug delivery system: in vitro and in vivo investigations. Eur J Pharm Sci. 2001;13:319—23.
19. Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg. 2000;91:136—9.
20. Ferland CE, Veja E, Ingelmo PM. Acute pain manegement in children: challenges and recent improvements. Curr Opin Anaesthesiol. 2018;31:327—32.
21. Subedi A, Tripathi M, Pokharel K, Khatiwada S. Effect of Intravenous Lidocaine, Dexamethasone, and Their Combination on Postoperative Sore Throat: a Randomized Controlled Trial. Anesth Analg. 2019;129:220—5.
22. Carpenter P, Hall D, Meier JD. Postoperative care after tonsillectomy: what's the evidence? Curr Opin Otolaryngol Head Neck Surg. 2017;25(6):498—505.

23. Hassani E, Mahoori A, Aghdashi MM, Pirnejad H. Evaluating the quality of intravenous regional anesthesia following adding dexamethasone to lidocaine. Saudi J Anaesth. 2015;9:418—21.
24. Hermeto LC, Rossi R, Bicudo NA, Assis KT, Escobar LL, Camargo OS. The effect of epidurally administered dexamethasone with lignocaine for post-operative analgesia in dogs undergoing ovariohysterectomy. A dose-response study. Acta Cir Bras. 2017;32:307—18.
25. Moallemy A, Jarineshin H, Fekrat F, et al. Effect of adding dexamethasone to lidocaine on the quality of intravenous regional anesthesia for upper extremity orthopedic operations: A randomized clinical trial. Electron Physician. 2018;25(10):6631—9.

Brazilian Journal of Anesthesiology 2024;74(5): 844519



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

An update on the mechanisms and risk factors for anesthesia-related cardiac arrest in children: a narrative review

Leandro Gobbo Braz *, Jose Reinaldo Cerqueira Braz, Teofilo Augusto Araújo Tiradentes, Daniela de Sa Menezes Porto, Cristiano Martins Beserra, Luiz Antonio Vane, Paulo do Nascimento Junior, Norma Sueli Pinheiro Modolo, Mariana Gobbo Braz

Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Especialidades Cirúrgicas e Anestesiologia, Comissão de Estudos de Parada Cardíaca e Mortalidade em Anestesia, Botucatu, SP, Brazil

Received 27 November 2023; accepted 7 May 2024
Available online 27 May 2024

KEYWORDS
Cardiac arrest;
Children;
Developed countries;
Low-income countries

Abstract The relation between surgery and anesthesia safety in children and a country's Human Development Index (HDI) value has been described previously. The aim of this narrative review was to provide an update on the mechanisms and risk factors of Anesthesia-Related Cardiac Arrest (ARCA) in pediatric surgical patients in countries with different HDI values and over time (pre-2001 vs. 2001–2024). Electronic databases were searched up to March 2024 for studies reporting ARCA events in children. HDI values range from 0 to 1 (very-high-HDI countries: ≥ 0.800, high-HDI countries: 0.700–0.799, medium-HDI countries: 0.550–0.699, and low-HDI countries: < 0.550). Independent of time, the proportion of children who suffered perioperative Cardiac Arrest (CA) attributed to anesthesia-related causes was higher in very-high-HDI countries (50%) than in countries with HDI values less than 0.8 (15–36%), but ARCA rates were higher in countries with HDI values less than 0.8 than in very-high-HDI countries. Regardless of the HDI value, medication-related factors were the most common mechanism causing ARCA before 2001, while cardiovascular-related factors, mainly hypovolemia, and respiratory-related factors, including difficulty maintaining patent airways and adequate ventilation, were the major mechanisms in the present century. Independent of HDI value and time, a higher number of ARCA events occurred in children with heart disease and/or a history of cardiac surgery, those aged younger than one year, those with ASA physical status III–V, and those who underwent emergency surgery. Many ARCA events were determined to be preventable. The implementation of specialized pediatric anesthesiology and training programs is crucial for anesthesia safety in children.
© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

* Corresponding author.
E-mail: leandro.braz@unesp.br (L.G. Braz).

https://doi.org/10.1016/j.bjane.2024.844519
0104-0014/© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Perioperative Cardiac Arrest (CA) remains one of the most catastrophic complications of pediatric anesthesia. The occurrence of perioperative CA in children is related not only to the patient's condition/disease but also to factors such as surgical management and inappropriate anesthesia.[1-3]

The Human Development Index (HDI), which was established by the United Nations Development Programme, is calculated based on rates of enrollment in higher education and literacy, per capita income, and life expectancy.[4] The HDI value ranges from 0 to 1, representing the lowest and highest levels of development, respectively. The relationship between surgery and anesthesia safety and the HDI value has been described in previous studies involving children,[5] older patients[6] and patients of all ages.[7-10]

A recent systematic review of global studies involving children demonstrated that Anesthesia-Related Cardiac Arrest (ARCA) rates were inversely correlated with HDI values and did not change over time in either high-HDI countries (HDI value $\geq$ 0.8) or low-HDI countries (HDI value $<$ 0.8); however, ARCA rates were significantly higher in low-HDI countries than in high-HDI countries and higher in children aged less than one year than in children aged 1 year or older in high-HDI and low-HDI countries.[11]

Investigations into the causes and factors associated with ARCA in children have been conducted for more than 150 years[12,13] but have been limited by the low incidence and lack of consistent definitions of such events.[14]

Owing to considerable advances in safe anesthesia care for children in recent decades, especially in high-HDI countries, and the gap in health care systems between low- and high-HDI countries,[7-10] we verified whether the ARCA mechanisms and risk factors in pediatric surgical patients differ in countries with different HDIs and over time.

Methods

We constructed our narrative review according to the scale for the quality assessment of narrative review articles.[15] Ethical approval was not necessary because we conducted a narrative review.

We searched the literature to identify all studies reporting perioperative CA and/or ARCA in a surgical child population. We searched the PubMed, Embase, and Lilacs databases from inception to March 27, 2024. The search was conducted using index terms (e.g., MeSH) and text words, as well as word variants for "an(a)esthesia", "cardiac arrest", and "mortality", including a list of synonyms. Titles and abstracts were screened, and the full texts of studies deemed potentially relevant were reviewed. No language restrictions were imposed, and translation services were used when necessary. We included only published full-text articles. Stand-alone abstracts and unpublished studies were excluded from the review.

The outcomes of interest were the mechanisms and risk factors for ARCA events in children in countries with different HDIs. ARCA events are subdivided entirely and partially. The entire ARCA subgroup included events exclusively attributed to anesthesia personnel or the anesthetic process (e.g., ventilatory depression with resultant hypoxemic CA after intravenous opioid injection in a stable child patient without comorbidities). The partial ARCA subgroup included events in which anesthesia personnel, or the anesthetic process clearly played a role, but other factors related to the patient's disease/condition or surgical procedure may have also played a role in the sequence of events reported (e.g., CA immediately after the induction of anesthesia in an unstable, hypovolemic child patient). ARCA events were classified by the authors of the studies included in this review. Many of the included studies separated the results into entire and partial ARCA subgroups. For this analysis, we summed both entire and partial ARCA events.

Considering the differences in surgery and anesthesia safety among countries, as demonstrated in studies,[16,17] the country development level was classified according to the HDI established by the United Nations Development Programme as follows: $\geq$ 0.800 for very-high-HDI countries, 0.700–0.799 for high-HDI countries, 0.550–0.699 for medium-HDI countries, and $<$ 0.550 for low-HDI countries.[4] Since the HDI of a country may change over time and studies often report data spanning several years, the HDI of each country was calculated as the mean of the HDIs in the first and last years studied.[10,18]

Considering that the focus of this study was on identifying changes in the mechanisms and causes of ARCA in children in the current century in relation to those in the last century, we divided the study into two periods: pre-2001 (last century) and 2001–2022 (present century).

Our search strategy identified 42,353 citations. After excluding 28,801 duplicates, the titles and abstracts of remaining articles were reviewed, and an additional 13,314 irrelevant studies were excluded. We retrieved 238 potentially relevant full-text articles for detailed evaluation. Overall, 31 studies met the predefined outcomes of interest (Fig. 1). The characteristics of the included studies are reported in Supplementary Table 1.

Perioperative CA attributed to anesthesia-related causes in children

Two studies from a very-high-HDI country (USA) demonstrated high proportions of children with perioperative CA attributed to anesthesia-related causes in different periods: 52% in 1994–1997[19] and 49% in 1998–2004.[20] Two studies in children from a very-high-HDI country (Germany) in the present century reported similar findings, with ARCA events accounting for 50% of the perioperative CA events and non-ARCA events accounting for the remaining 50% of cases in 2008–2016[21] and 2008–2018.[22]

In contrast, studies from a high-HDI country (Brazil) in the last century[23] and the present century[3] demonstrated lower proportions of children with perioperative CA events attributed to anesthesia-related causes (20% in 1996–2004 and 15% in 2005–2010, respectively), while disease/condition-related CA was the most important factor triggering perioperative CA, with proportions of 80% and 73%, respectively. Studies from a medium-HDI country (India)[2] and a low-HDI country (Nigeria)[24] conducted in the present century also demonstrated lower proportions of children with perioperative CA attributed to ARCA events than non-ARCA events (26% and 36%, respectively, versus 74% and 64%,

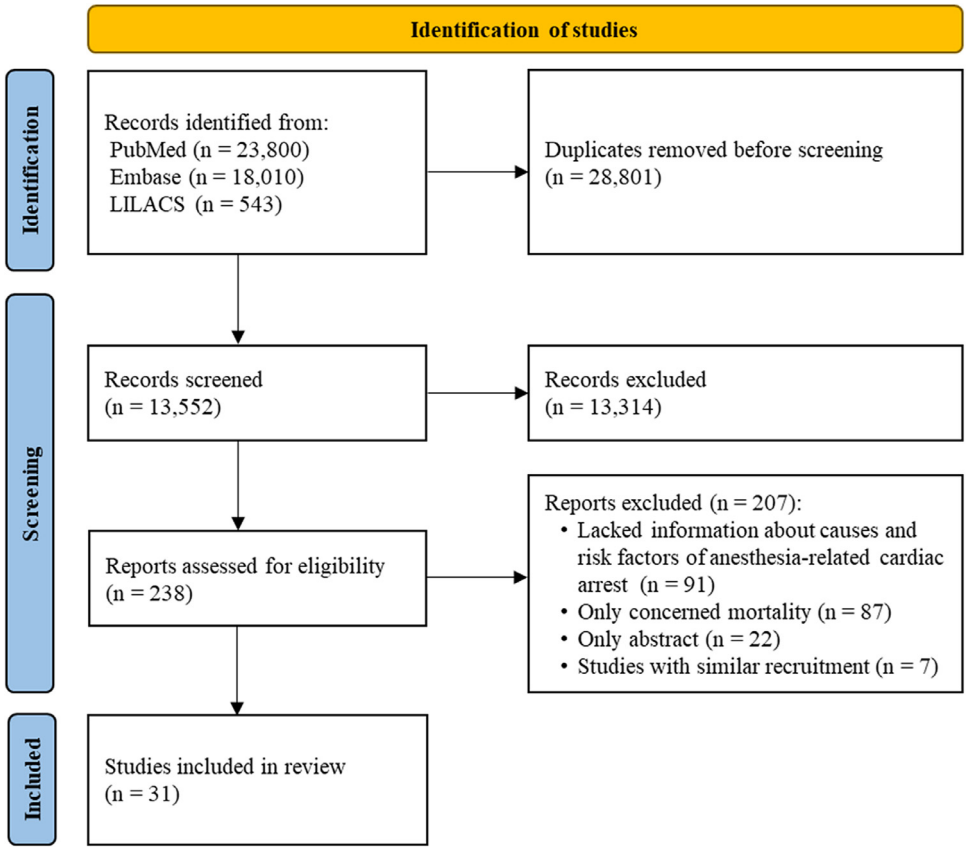


Figure 1 Flowchart of study identification.

respectively). Interestingly, a study from a high-HDI country (Thailand) in the present century reported an increase in the proportion of perioperative CA attributed to anesthesia-related causes in different periods, from 33% in 2003–2004[25] to 54% in 2014–2019.[26]

According to the authors, the different proportions of children with ARCA events attributed to perioperative CA among countries with different HDIs were due to the high proportions of disease/condition-related CA as a factor triggering perioperative CA in countries with an HDI value less than 0.8.[2,3,23-26] Many of these children live outside the centers where they are definitively managed, and considering the reported poor index of suspected health disorders among health care providers in primary and secondary care facilities and the insufficient number of surgical beds and neonatal and/or pediatric intensive care units, there is a delay in initial diagnosis and referral to appropriate centers, resulting in delayed diagnosis and intervention.[27]

Mechanisms of ARCA events in children

Reports prior to 2001 demonstrated that medication-related factors were the most common mechanism of ARCA events in children. Thus, a pioneering study in a very-high-HDI country (USA)[13] demonstrated a high proportion of ARCA events due to cardiovascular depression caused by inhalation anesthetic overdose (ether or chloroform) followed by, to a lesser extent, respiratory events due to hypoxia and even anoxia. The initial findings of the Perioperative Cardiac Arrest (POCA) registry in very-high-HDI countries (USA and Canada) from 1994–1997 showed that medication-related events due to inhalation agents, especially halothane, were the most common mechanism of ARCA (37%), particularly in children with American Society of Anesthesiologists (ASA) physical status I–II and children younger than 1 year of age, followed, to a lesser extent, by cardiovascular (32%), respiratory (20%) and equipment-related (7%) mechanisms.[19] However, in the same study, in children with ASA physical status III–IV, cardiovascular etiologies were the most common mechanism of ARCA. Similarly, other studies from a very-high-HDI country (USA)[28-30] and a study from a low-HDI country (Pakistan)[1] also showed that medication-related factors were the most common mechanism of ARCA pre-2001. Late data from the POCA registry in the 1998–2004 period, compared to the earlier period (1994–1997), demonstrated that the rate of ARCA events due to medication-related mechanisms declined to 18%, while ARCA events due to cardiovascular or respiratory mechanisms were more common (41% and 27%, respectively).[20]

Certainly, the discontinuation of halothane as the primary inhaled anesthetic and the introduction of new anesthetics, such as inhaled halogenated sevoflurane and intravenous propofol, contributed significantly to the decrease in medication-related ARCA events in children.[20] Sevoflurane has been reported to have less potential for causing bradycardia[31] and myocardial depression[32,33] in children than halothane. Halothane also causes a higher number of hypotensive episodes than sevoflurane in children with congenital heart disease.[34]

Studies in the present century from very-high-HDI countries (Spain,[35] South Korea,[36] USA,[37] and Germany[21])

demonstrated that cardiovascular-related factors and respiratory-related factors were the major mechanisms of ARCA in children, followed by medication-related factors to a lesser extent. However, studies in the same period showed that ARCA caused by respiratory-related factors occurred in greater proportion than other mechanisms in a very-high-HDI country (USA),[22,38] a high-HDI country (Brazil),[3] a medium-HDI country (India),[2] and a low-HDI country (Nigeria).[39] However, a study from a low-HDI country in Africa (Nigeria)[24] showed that medication-related factors are still an important contributors to ARCA events due to the use of halothane as an inhaled anesthetic.

Mechanisms of ARCA events according to the phase of anesthesia care

Studies have shown different mechanisms of ARCA events according to the phase of anesthetic care. Thus, independent of time and HDI, most of the ARCA events due to respiratory-related factors occurred in the induction phase followed by the emergence and recovery phases in very-high-HDI countries,[20,21,22,30,36-38,40-42] high-HDI countries,[3,23,25] a medium-HDI country[2] and low-HDI countries,[24,39] while most of the ARCA events due to cardiovascular-related factors occurred during anesthesia maintenance in very-high-HDI countries,[19-21,35-38,43] a medium-HDI country,[2] and a low-HDI country.[44]

Mechanisms of ARCA events according to the surgical procedure

Studies after 2000 demonstrated a significant correlation between the surgical procedure and the mechanism of ARCA events. Thus, a study from a very-high-HDI country (USA) showed that cardiovascular-related factors were the most important mechanism of ARCA events in children undergoing neurosurgery or spine surgery (71%) and cardiovascular procedures (45%), while respiratory-related factors were the most common mechanism of ARCA events in children undergoing airway, ear, nose, and throat surgeries (49%).[20] Another study from a very-high-HDI country (Spain) also demonstrated that cardiovascular-related factors were the most important mechanism (50%) of ARCA events in children undergoing cardiovascular procedures, while respiratory-related factors were the most common mechanism of ARCA events in children undergoing noncardiovascular procedures.[35]

Causes of ARCA events due to cardiovascular-related factors

Studies from very-high-HDI countries in the 2001–2022 period demonstrated that the most common cause of ARCA events was hypovolemia related to blood loss[20,35] due to the following cardiovascular-related factors:[20] the underestimation of blood loss, lack of a central venous catheter, inadequate peripheral venous access, lack or malfunctioning of an arterial catheter, and underestimation of preexisting hypovolemia, among other causes. Other commonly cited cardiovascular causes were arrythmia, electrolyte imbalance and inadequate/inappropriate fluid therapy.[20,37]

Causes of ARCA events due to respiratory-related factors

In the past and present centuries, with no differences in HDI values and periods, the most cited causes of respiratory events responsible for ARCA were airway obstruction mainly due to laryngospasm and bronchospasm, the inability to oxygenate or ventilate, inadvertent or premature tracheal extubation, esophageal or endobronchial intubation, aspiration and pneumothorax in very-high-HDI countries,[19-22,30,36-38,41,42,45,46] high-HDI countries,[3,23,25] a medium-HDI country,[2] and low-HDI countries.[24,39]

Children, especially neonates and infants, are at increased risk of hypoxemia because of their smaller functional residual capacity, increased heart rate, and increased metabolic requirements compared with adults; additionally, the proportionally large head and tongue, restricted submandibular space, high location of the larynx in the neck, and flaccid epiglottis in children present special challenges in airway management.[47] Recent studies have demonstrated two major advances regarding this issue: the use of videolaryngoscopes, which has improved the first-attempt success rate of tracheal intubation and decreased the rate of airway complications,[48] and apneic oxygenation, which has been shown to significantly prolong the safe apnea time until desaturation in neonates and infants and depends on adequate preoxygenation and the implementation of high-flow nasal oxygen during endotracheal intubation, ensuring adequate oxygenation during prolonged airway manipulation or difficult intubation.[49]

Causes of ARCA due to medication-related or equipment-related factors

Studies from the 2001–2022 period in very-high-HDI countries demonstrated that the main causes of ARCA in children were inhaled halogenated anesthetics, intravenous agents, local anesthetics, and allergic reactions, while the main causes of equipment-related CA were central venous catheter complications (arrythmia, pneumothorax, hemothorax, and hemopericardium), kinked or plugged tracheal tubes, and breathing circuit problems.[20,35,37]

ARCA risk factors in children

There are many risk factors for ARCA in children, such as postnatal age, ASA physical status, heart disease, and the nature of surgery (Table 1).

Postnatal age groups

A recent review of global studies involving children demonstrated that the rate of ARCA in children has not declined over the past 60 years and is inversely related to the HDI value.[11] This same review demonstrated that the worldwide rates of ARCA in high-HDI countries (HDI values $\geq$ 0.8) were 3.1-fold higher among children younger than one year old than among those aged one year or older before 2001 (5.54 vs. 1.76 per 10,000 anesthetic procedures) and 8-fold higher in 2001–2022 (10.69 vs. 1.48 per 10,000 anesthetic procedures), while in low-HDI countries (HDI values $<$ 0.8), these rates were 6.6-fold higher among children younger than one year old than among those $\geq$ 1 year of age before 2001 (10.46

Table 1 Risk factors of anesthesia-related cardiac arrest in children.

- Age younger than one year old, especially preterm neonates with low and very low birth weights
- ASA physical status III–V
- Heart disease in cardiac or noncardiac surgery
- Emergency surgery
- Anesthesiologist without subspecialty pediatric training

vs. 1.67 per 10,000 anesthetic procedures) and 7.3-fold higher 2001–2022 (36.02 vs. 2.86 per 10,000 anesthetic procedures).[11] According to the authors of the review, the high ARCA rate in children younger than one year old, even in very-high-HDI countries, may be due to the increase in the number of surgical patients with a poorer ASA physical status (≥ III), as demonstrated in a global systematic review of studies.[7] A study from a high-HDI country reported that the total proportion of children aged less than 1 year and the proportion of children aged less than one year with an ASA physical status of III to V were higher in the period from 2014 to 2016 than in the period from 2008 to 2013, confirming increases in underlying risks and complexity among pediatric surgical patients.[21] In addition, studies have indicated increases in the numbers of preterm neonates with low and very low birth weights who are treated with surgical interventions, which are associated with high morbidity and mortality rates.[22,50]

These findings demonstrate a persistent need to improve the quantity and quality of resource utilization by increasing the number of pediatric anesthesia staff, organizing multidisciplinary discussions of adverse events, and adopting perioperative medical practices with demonstrable effectiveness, particularly in neonates and infants.

ASA physical status

A study from a very-high-HDI country (France)[41] before 2001 reported a greater number of ARCA events in children with ASA physical status I–II than in those with ASA physical status III–V. In contrast, in the present century, studies have identified a higher risk of ARCA events in children with ASA physical status ≥ III than in those with ASA physical status I–II in very-high-HDI countries (USA,[20,37,38] Spain,[35] and Germany[21]), a high-HDI country (Thailand)[26] and a low-HDI country (Pakistan).[44]

A study of the POCA registry revealed fewer children with ASA physical status I who experienced ARCA events (7%) in the 1998–2004 period than in the 1994–1997 period (15%).[20] The authors of this study also verified that 75% of the ARCA events occurred in children with ASA physical status III–V. However, ARCA events still occurred in children with ASA physical status I in the 2001–2022 period, as demonstrated in reports from high- and low-HDI countries[39,51] and very-high-HDI countries.[20,37,52]

Studies from very-high-HDI countries after 2000 have demonstrated that ASA physical status III–V is strongly associated with high ARCA rates in children according to univariable and multivariable analyses.[20,21,37,38]

Heart disease and/or cardiac surgery

In the present century, studies from very-high-HDI countries (USA[38,53] and Spain[35]) demonstrated higher ARCA rates among children undergoing cardiac surgeries than among those undergoing noncardiac surgeries. It has been shown that children with heart disease have an increased frequency of ARCA events when undergoing cardiac surgery[53,54] and noncardiac surgery,[51,53] with a higher risk among neonates and infants; however, ARCA events were not associated with an increase in anesthesia-related mortality.[54] Children with a single ventricle, aortic stenosis, or cardiomyopathy have an increased frequency of ARCA and mortality events.[53]

Emergency surgery

A study from the POCA registry in very-high-HDI countries (USA and Canada) in 1994–1997 demonstrated that emergency surgery was a predictor of ARCA and mortality in children by multivariate analysis, with an odds ratio of 3.88 compared with that of elective surgery.[19]

Univariate analyses of several studies from very-high-HDI countries in the present century revealed a significantly higher rate of ARCA events in children undergoing emergency surgeries than in children undergoing nonemergency surgeries.[21,35,38] However, after adjustment for an ASA physical status ≥ III and an age ≤ 6 months, a study demonstrated no significant correlation between ARCA events and emergency surgery.[38]

Anesthesiologist-related factors and the risk of ARCA events

A study from a very-high-HDI country (USA) in children undergoing surgeries before 2001 verified no ARCA events in the presence of pediatric anesthesiologists (0 per 10,000 anesthetic procedures), while there were four ARCA events (19.7 per 10,000 anesthetic procedures) in the presence of anesthesiologists without subspecialty pediatric training.[29] Similarly, a study[37] from a very-high-HDI country (USA) in 2001–2022 demonstrated via univariate analyses that the risk of ARCA events was significantly higher for anesthesiologists with a lower caseload and/or a lower number of annual days in which anesthetic procedures were performed. In addition, these authors demonstrated that anesthesiologists with the highest academic rank and who had years of experience had higher odds ratios of experiencing ARCA events. However, after adjustment for an ASA physical status ≥ III and an age ≤ 6 months, the authors verified that the association of ARCA events with a lower number of annual days providing anesthetics remained, but the other practitioner-related factors were no longer significant. However, other studies in 2001–2022 from very-high-HDI countries (USA and Germany) demonstrated opposite findings. Christensen and colleagues[38] verified no significant correlation between ARCA events and pediatric anesthesiologist-related risk factors (academic rank, years of experience, annual caseload, annual days providing anesthetics, annual number of child cases, or annual number of patients with ASA physical status ≥ III, even after adjusting for an age ≤ 180 days and ASA physical status > II)

in univariate or adjusted analyses. In contrast, Hohn and colleagues[21] verified that the implementation of a specialized pediatric anesthesia team and training program in 2014 was associated with lower rates of pediatric perioperative CA (43.2% lower) and ARCA events (62.8% lower) in 2014–2016 than in 2008–2013.

Timing of the ARCA events according to the phase of anesthesia care

The timing of the ARCA events varied by phase of anesthesia care regardless of the HDI value in the present century. Between 40% and 50% of the ARCA events occurred during anesthesia maintenance, 30% to 40% occurred in the anesthesia induction or tracheal intubation phases, 10% to 15% occurred during anesthesia emergence, transport, or recovery, and 5% occurred in the postoperative period.[20,25,35,37,38]

ARCA events in children with heart disease according to the anesthetic setting

A report from a very-high-HDI country (USA) in the present century demonstrated a higher ARCA rate (21.88 per 10,000 anesthetic procedures) among children with heart disease in cardiac operating rooms than among those in radiological suites and general operating rooms according to univariate analysis (2.73 and 1.78 per 10,000 anesthetic procedures, respectively).[37] Despite the lower proportion of ARCA events in children, a higher proportion of ARCA events with mortality occurred in nonoperating rooms than in operating rooms.[35] As interventional techniques become more complex, more children are receiving anesthetic care outside traditional operating room settings. Challenges related to patient safety in these locations include a remote location, a limited and ergonomically inefficient anesthesia workspace, poor lighting (because of the need for fluoroscopy), different procedures and equipment, and a lack of regular interactions with personnel in these areas.[55]

Risk of ARCA events according to the time of day and day of the week

Univariate associations between the ARCA rate and time of day (daytime vs. nighttime) and day of week (weekday vs. weekend) among children undergoing surgeries showed no significant correlation in studies from a very-high-HDI country (USA) conducted in the present century.[37,38]

Implications of the available evidence

The use of safety monitors for oxygen, carbon dioxide and anesthetic gas administration, equipment for resuscitation, modern anesthesia equipment, and new anesthetics, as well as neonatal and pediatric intensive care units, is not routine in several high- and medium-HDI countries, especially in low-HDI countries.[17,24,56] In low-HDI countries, the combination of poverty and poor healthcare and the increase in the child population,[2,57] the increasing number of pediatric patients with poorer physical conditions,[17,21] the limited anesthesia and surgical workforce[58] and the limited number of surgical beds[57] in conjunction with poor infection and hemorrhage control have contributed to the high perioperative CA risk in children.[2,3,23] Thus, many ARCA events were considered preventable.[1,21]

Table 2 The 10-Ns of maintenance of physiological homeostasis for the safe conduct of anesthesia in children.[61]

1. No fear
2. Normovolemia
3. Normotension
4. Normal heart rate
5. Normoxemia
6. Normocapnia
7. Normonatremia
8. Normoglycemia
9. Normothermia
10. No pain

The professional responsibility of anesthesiologists to avoid ARCA events in pediatric patients receiving anesthesia is achieved by delivering care to the best of their knowledge and ability in the preoperative, operative and postoperative conditions in conjunction with coordination of care, organizational culture, communication with nursing and surgical teams, and practice guidelines.[59] Pediatric anesthesia in very-high-HDI countries is frequently administered by a trained anesthesiologist.[60] However, in high- and medium-HDI countries, pediatric anesthesiologists are rare, and anesthesiologists with little experience in pediatric anesthesia often provide anesthesia services to children. In low-HDI countries, nonphysicians are often involved in providing pediatric anesthesia services due to the lack of anesthesiologists, especially in African countries.[58]

In 2015, the Safetots.org initiative (www.safetots.org) addressed the well-known perioperative risks in young children and provided a framework for the safe administration of pediatric anesthesia.[61] Thus, the 10-Ns of anesthesia were introduced as criteria for appropriately performed pediatric anesthesia (Table 2).[61]

Limitations of this review

Some limitations of the data in this review may have affected the findings. First, considering the small number of children in many studies, especially in countries with lower HDIs,[1-3,23,24] and because ARCA is an infrequent event, slight fluctuations in the numbers of children might have affected the reporting of these events in different studies, especially retrospective studies. Second, the small number of ARCA events in several studies, mainly from high-, medium- and low-HDI countries, restricted the review and analysis of the mechanisms of and risk factors for ARCA in children to studies from very-high-HDI countries. Third, the selective reporting bias of ARCA events may have varied according to the medico-legal circumstances of each country. Thus, ARCA events may be associated with malpractice issues; underreporting is likely in this situation. To minimize the risk of underreporting of ARCA events, the reporting of these events needs to be mandatory, and summaries need to be prepared without assigning responsibility for the CA event.[43] Each summary was submitted anonymously to an independent study commission for analysis. Commission members from outside the institution could provide a more unbiased

evaluation of these cases than faculty members from the institution of the study.[43] Fourth, the majority of the included studies in our review are representative of experience from university hospitals and may not represent the entire spectrum of surgery and anesthesia care practices in each country. Fifth, considering that the studies included in the current review were not designed to evaluate causality, we can only infer a relationship between differences in HDI levels depending on the country and the mechanisms and risk factors for ARCA events.

Conclusions

There were differences and similarities in the mechanisms and risk factors for ARCA events in pediatric surgical patients according to period and country HDI level. Independent of the period, the proportion of ARCA in patients experiencing perioperative CA was higher in very-high-HDI countries than in countries with lower HDI levels, but the ARCA rate was lower in very-high-HDI countries than in countries with lower HDI levels. Independent of country-HDI level, medication-related factors were the most common mechanism of ARCA before 2001, while cardiovascular-related and respiratory-related factors were the major mechanisms of ARCA in 2001–2022. Independent of the period and country HDI value, most cardiovascular-related ARCA events occurred during anesthesia maintenance in cardiovascular surgeries, mainly due to hypovolemia, while most respiratory-related ARCA events occurred during anesthesia induction followed by the emergence and recovery phases, mainly in noncardiovascular surgeries, due to difficulty in maintaining patent airways and adequate ventilation. ARCA events at all HDI levels were higher in children with heart disease and/or who were undergoing cardiac surgery, who were younger than one year old versus one year old or older, who had an ASA physical status III–V, who underwent emergency surgery. The implementation of specialized pediatric anesthesiologists and training programs is crucial for the safety of anesthesia in children.

Conflicts of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Leandro Gobbo Braz: Conceptualization, Project administration, Investigation, Methodology, Writing — original draft, Writing — review & editing, Funding acquisition, Supervision. **Jose Reinaldo Cerqueira Braz:** Conceptualization, Project administration, Investigation, Methodology, Writing — original draft, Writing — review & editing, Supervision. **Teofilo Augusto Araújo Tiradentes:** Investigation, Methodology, Writing — review & editing. **Daniela de Sa Menezes Porto:** Methodology, Writing — review & editing. **Cristiano Martins Beserra:** Investigation, Writing — review & editing. **Luiz Antonio Vane:** Investigation, Writing — review & editing. **Paulo do Nascimento Junior:** Investigation, Writing — review & editing. **Norma Sueli Pinheiro Modolo:** Investigation, Writing — review & editing. **Mariana Gobbo Braz:** Investigation, Methodology, Writing — original draft, Writing — review & editing.

Funding

Leandro G. Braz received a fellowship from the National Council for Scientific and Technological Development – CNPq (grant number 307966/2021-6). CNPq is a Brazilian governmental agency dedicated to promoting scientific research. No other external funding or other competing interests are declared.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844519.

References

1. Ahmed A, Ali M, Khan M, Khan F. Perioperative cardiac arrests in children at a university teaching hospital of a developing country over 15 years. Paediatr Anaesth. 2009;19:581—6.
2. Bharti N, Batra YK, Kaur H. Paediatric perioperative cardiac arrest and its mortality: database of a 60-month period from a tertiary care paediatric centre. Eur J Anaesthesiol. 2009;26:490—5.
3. Gonzalez LP, Braz JR, Módolo MP, de Carvalho LR, Módolo NS, Braz LG. Pediatric perioperative cardiac arrest and mortality: a study from a tertiary teaching hospital. Pediatr Crit Care Med. 2014;15:878—84.
4. UNDP (United Nations Development Programme). Human Development Report 2023/2024. New York: Breaking the gridlock Reimagining cooperation in a polarized world; 2024. Available from URL: https://hdr.undp.org/system/files/documents/global-report-document/hdr2023-24reporten.pdf [accessed March 27 2024].
5. Lee KS, Park SC, Khoshnood B, Hsieh HL, Mittendorf R. Human development index as a predictor of infant and maternal mortality rates. J Pediatr. 1997;131:430—3.
6. Braghiroli KS, Einav S, Heesen MA, et al. Perioperative mortality in older patients: a systematic review with a meta-regression analysis and meta-analysis of observational studies. J Clin Anesth. 2021;69:110160.
7. Bainbridge D, Martin J, Arango M, Cheng D. Evidence-based Peri-operative Clinical Outcomes Research (EPiCOR) Group. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. Lancet. 2012;380:1075—81.
8. Koga FA, Dib RE, Wakasugui W, et al. Anesthesia-related and perioperative cardiac arrest in low- and high-income countries: A systematic review with meta-regression and proportional meta-analysis. Medicine (Baltimore). 2015;94:e1465.
9. Braz LG, Braz MG, Tiradentes TAA, Braz JRC. A correlation between anaesthesia-related cardiac arrest outcomes and country Human Development Index: A narrative review. J Clin Anesth. 2021;72:110273.
10. Braz LG, Einav S, Heesen MA, et al. Association between intraoperative cardiac arrest and country Human Development Index status: a systematic review with meta-regression analysis and

meta-analysis of observational studies. Anaesthesia. 2021;76:1259–73.
11. Tiradentes TAA, Einav S, Braz JRC, et al. Global anaesthesia-related cardiac arrest rates in children: a systematic review and meta-analysis. Br J Anaesth. 2023;131:901–13.
12. Knight 3rd PR, Bacon DR. An unexplained death: Hannah Greener and chloroform. Anesthesiology. 2002;96:1250–3.
13. Rackow H, Salanitre E, Green LT. Frequency of cardiac arrest associated with anesthesia in infants and children. Pediatrics. 1961;28:697–704.
14. Christensen RE, Lee AC, Gowen MS, Rettiganti MR, Deshpande JK, Morray JP. Pediatric perioperative cardiac arrest, death in the off hours: A report from Wake Up Safe, The Pediatric Quality Improvement Initiative. Anesth Analg. 2018;127:472–7.
15. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5.
16. Hodges SC, Walker IA, Bösenberg AT. Paediatric anaesthesia in developing countries. Anaesthesia. 2007;62:26–31.
17. Bharati SJ, Chowdhury T, Gupta N, Schaller B, Cappellani RB, Maguire D. Anaesthesia in underdeveloped world: Present scenario and future challenges. Niger Med J. 2014;55:1–8.
18. Braghiroli KS, Braz JRC, Rocha B, et al. Perioperative and anesthesia-related cardiac arrests in geriatric patients: a systematic review using meta-regression analysis. Sci Rep. 2017;7:2622.
19. Morray JP, Geiduschek JM, Ramamoorthy C, et al. Anesthesia-related cardiac arrest in children: initial findings of the Pediatric Perioperative Cardiac Arrest (POCA) Registry. Anesthesiology. 2000;93:6–14.
20. Bhananker SM, Ramamoorthy C, Geiduschek JM, et al. Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. Anesth Analg. 2007;105:344–50.
21. Hohn A, Trieschmann U, Franklin J, et al. Incidence of perioperative paediatric cardiac arrest and the influence of a specialised paediatric anaesthesia team: Retrospective cohort study. Eur J Anaesthesio.l. 2019;36:55–63.
22. Jansen G, Borgstedt R, Irmscher L, et al. Incidence, mortality, and characteristics of 18 pediatric perioperative cardiac arrests: an observational trial from 22,650 pediatric anesthesias in a German tertiary care hospital. Anesth Analg. 2021;133:747–54.
23. Braz LG, Braz JR, Módolo NS, do Nascimento P, Brushi BA, Raquel de Carvalho L. Perioperative cardiac arrest and its mortality in children. A 9-year survey in a Brazilian tertiary teaching hospital. Paediatr Anaesth. 2006;16:860–6.
24. Adekola OO, Asiyanbi GK, Desalu I, Olatosi JO, Kushimo OT. The outcome of anaesthesia-related cardiac arrest in a sub-Saharan tertiary hospital. Egypt J Anaesth. 2016;32:315–21.
25. Bunchungmongkol N, Somboonviboon W, Suraseranivongse S, Vasinanukorn M, Chau-in W, Hintong T. Pediatric anesthesia adverse events: the Thai Anesthesia Incidents Study (THAI Study) database of 25,098 cases. J Med Assoc Thai. 2007;90:2072–9.
26. Rattana-Arpa S, Chaikittisilpa N, Srikongrak S, Udomnak S, Aroonpruksakul N, Kiatchai T. Incidences and outcomes of intraoperative vs. postoperative paediatric cardiac arrest: A retrospective cohort study of 42 776 anaesthetics in children who underwent noncardiac surgery in a Thai tertiary care hospital. Eur J Anaesthesiol. 2023;40:483–94.
27. Ekenze SO, Ajuzieogu OV, Nwomeh BC. Challenges of management and outcome of neonatal surgery in Africa: a systematic review. Pediatr Surg Int. 2016;32:291–9.
28. Keenan RL, Boyan CP. Cardiac arrest due to anesthesia. A study of incidence and causes. JAMA. 1985;253:2373–7.
29. Keenan RL, Shapiro JH, Dawson K. Frequency of anesthetic cardiac arrests in infants: effect of pediatric anesthesiologists. J Clin Anesth. 1991;3:433–7.
30. Flick RP, Sprung J, Harrison TE, et al. Perioperative cardiac arrests in children between 1988 and 2005 at a tertiary referral center: a study of 92,881 patients. Anesthesiology. 2007;106:226–37.
31. Sarner JB, Levine M, Davis PJ, Lerman J, Cook DR, Motoyama EK. Clinical characteristics of sevoflurane in children. A comparison with halothane. Anesthesiology. 1995;82:38–46.
32. Holtzman RS, van der Velde ME, Kaus SJ, et al. Sevoflurane depresses myocardial contractility less than halothane during induction of anesthesia in children. Anesthesiology. 1996;85:1260–7.
33. Wodey E, Pladys P, Copin C, et al. Comparative hemodynamic depression of sevoflurane versus halothane in infants: an echocardiographic study. Anesthesiology. 1997;87:795–800.
34. Russell IA, Miller Hance WC, Gregory G, et al. The safety and efficacy of sevoflurane anesthesia in infants and children with congenital heart disease. Anesth Analg. 2001;92:1152–8.
35. Sanabria-Carretero P, Ochoa-Osorio C, Martín-Vega A, et al. Parada cardiaca relacionada con la anestesia en pediatría. Registro en un hospital infantil terciário. Rev Esp Anestesiol Reanim. 2013;60:424–33.
36. Lee JH, Kim EK, Song IK, et al. Critical incidents, including cardiac arrest, associated with pediatric anesthesia at a tertiary teaching children's hospital. Paediatr Anaesth. 2016;26:409–17.
37. Zgleszewski SE, Graham DA, Hickey PR, et al. Anesthesiologist- and system-related risk factors for risk-adjusted pediatric anesthesia-related cardiac arrest. Anesth Analg. 2016;122:482–9.
38. Christensen R, Haydar B, Leis A, Mentz G, Reynolds P. Anesthesiologist-related factors associated with risk-adjusted pediatric anesthesia-related cardiopulmonary arrest: a retrospective two level analysis. Paediatr Anaesth. 2021;31:1282–9.
39. Zoumenou E, Gbenou S, Assouto P, et al. Pediatric anesthesia in developing countries: experience in the two main university hospitals of Benin in West Africa. Paediatr Anaesth. 2010;20:741–7.
40. Olsson GL, Hallén B. Cardiac arrest during anaesthesia. A computer-aided study in 250,543 anaesthetics. Acta Anaesthesiol Scand. 1988;32:653–64.
41. Tiret L, Nivoche Y, Hatton F, Desmonts JM, Vourc'h G. Complications related to anaesthesia in infants and children. A prospective survey of 40240 anaesthetics. Br J Anaesth. 1988;61:263–9.
42. Montobbio G, Pini-Prato A, Guida E, Disma N. Mameli. Provisional unicentric experience with an electronic incident reporting form in pediatric anesthesia. Paediatr Anaesth. 2012;22:1080–6.
43. Newland MC, Ellis SJ, Lydiatt CA, et al. Anesthetic-related cardiac arrest and its mortality: a report covering 72,959 anesthetics over 10 years from a US teaching hospital. Anesthesiology. 2002;97:108–15.
44. Khoso N, Ghaffar WB, Abassi S, Khan FA. Pediatric anesthesia severe adverse events leading to anesthetic morbidity and mortality in a tertiary care center in a low- and middle-income country: A 25-year audit. Anesth Analg. 2021;132:217–22.
45. Fiscella LF, Martínez DF, Graziola ED, et al. Complicaciones graves y fatales de anestesia. Análisis prospectivo en 20.840 intervenciones quirúrgicas. Rev Arg Anestesiol. 1991;49:197–263.
46. Kawashima Y, Seo N, Morita K, et al. Anesthesia-related mortality and morbidity in Japan (1999). J Anesth. 2002;16:319–31.
47. Holm-Knudsen RJ, Rasmussen LS. Paediatric airway management: basic aspects. Acta Anaesthesiol Scand. 2009;53:1–9.
48. Garcia-Marcinkiewicz AG, Kovatsis PG, Hunyady AI, et al. First-attempt success rate of video laryngoscopy in small infants (VISI): a multicentre, randomised controlled trial. Lancet. 2020;396:1905–13.

49. Lyons C, Callaghan M. Apnoeic oxygenation in paediatric anaesthesia: a narrative review. Anaesthesia. 2021;76: 118–27.
50. Ammar S, Sellami S, Sellami I, et al. Risk factors of early mortality after neonatal surgery in Tunisia. J Pediatr Surg. 2020;55: 2233–7.
51. Kan H, Ding Y, Wu S, Zhang Z. Retrospective study of perioperative cardiac arrest from a Chinese tertiary hospital. Medicine (Baltimore). 2021;100:e26890.
52. Murat I, Constant I, Maud'huy H. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth. 2004;14:158–66.
53. Ramamoorthy C, Haberkern CM, Bhananker SM, et al. Anesthesia-related cardiac arrest in children with heart disease: data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. Anesth Analg. 2010;110:1376–82.
54. Odegard KC, DiNardo JA, Kussman BD, et al. The frequency of anesthesia-related cardiac arrests in patients with congenital heart disease undergoing cardiac surgery. Anesth Analg. 2007;105:335–43.
55. Woodward ZG, Urman RD, Domino KB. Safety of non-operating room anesthesia: A closed claims update. Anesthesiol Clin. 2017;35:569–81.
56. Hadler RA, Chawla S, Stewart BT, McCunn MC, Kushner AL. Anesthesia care capacity at health facilities in 22 low- and middle-income countries. World J Surg. 2016;40:1025–33.
57. Mullapudi B, Grabski D, Ameh E, et al. Estimates of number of children and adolescents without access to surgical care. Bull World Health Organ. 2019;97:254–8.
58. Kempthorne P, Morriss WW, Mellin-Olsen J, Gore-Booth J. The WFSA global anesthesia workforce survey. Anesth Analg. 2017;125:981–90.
59. Buck D, Kurth CD, Varughese A. Perspectives on quality and safety in pediatric anesthesia. Anesthesiol Clin. 2014;32:281–94.
60. Coleman ML, Waisel DB. 100 years of pediatric anesthesia with Anesthesia & Analgesia: Growing together. Anesth Analg. 2022;135:S31–6.
61. Weiss M, Vutskits L, Hansen TG, Engelhardt T. Safe Anesthesia For Every Tot - The SAFETOTS initiative. Curr Opin Anaesthesiol. 2015;28:302–7.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



REVIEW ARTICLE

Comparison of intranasal dexmedetomidine versus oral midazolam for premedication in pediatric patients: an updated meta-analysis with trial-sequential analysis

Eduardo Maia Martins Pereira [a], **Tatiana Souza do Nascimento** [b], **Mariana Gaya da Costa** [c,*], **Eric Slawka** [d], **Carlos Galhardo Júnior** [e]

[a] *Universidade Federal de Minas Gerais, Departamento de Medicina, Belo Horizonte, MG, Brazil*
[b] *Hospital Federal Cardoso Fontes, Departamento de Anestesiologia, Rio de Janeiro, RJ, Brazil*
[c] *University Medical Center of Groningen, Department of Anesthesiology, Groningen, The Netherlands*
[d] *Universidade Federal do Rio de Janeiro, Departamento de Medicina, Rio de Janeiro, RJ, Brazil*
[e] *McMaster University & DeGroote Schol of Medicine, Department of Anesthesiology, Hamilton, Canada*

Received 24 January 2024; accepted 7 May 2024
Available online 25 May 2024

KEYWORDS
Dexmedetomidine;
Meta-analysis;
Midazolam;
Pediatrics;
Premedication

Abstract

Background: Midazolam is routinely used as preanesthetic medication in pediatric patients. Recently, dexmedetomidine has emerged as an alternative as a premedicant. We aimed to add more evidence about the efficacy and safety of two common routes of administration for pediatric premedication: oral midazolam versus intranasal dexmedetomidine.

Methods: We systematically searched Randomized Controlled Trials (RCTs) involving patients ≤ 18 years old undergoing preanesthetic medication and comparing intranasal dexmedetomidine with oral midazolam. Risk Ratio (RR) and Mean Difference (MD) with 95% Confidence Intervals (95% CI) were computed using a random effects model. Trial-sequential analyses were performed to assess inconsistency.

Results: Sixteen RCTs (1,239 patients) were included. Mean age was 5.5 years old, and most procedures were elective. There was no difference in satisfactory induction or mask acceptance (RR = 1.15, 95% CI 0.97—1.37; p = 0.11). There was a higher incidence of satisfactory separation from parents in the dexmedetomidine group (RR = 1.40; 95% CI 1.13—1.74; p = 0.002). Dexmedetomidine was also associated with a reduction in the incidence of emergence agitation (RR = 0.35; 95% CI 0.14—0.88; p = 0.02). Heart rate and mean arterial pressure were marginally lower in the dexmedetomidine group but without clinical repercussions.

Conclusion: Compared with oral midazolam, intranasal dexmedetomidine demonstrated better separation from parents and lower incidence of emergence agitation in pediatric premedication, without a difference in satisfactory induction. Intranasal dexmedetomidine may be a safe and effective alternative to oral midazolam for premedication in pediatric patients.

* Corresponding author.
E-mail: m.gaya.da.costa@umcg.nl (M.G. da Costa).

https://doi.org/10.1016/j.bjane.2024.844520
0104-0014/© 2024 Published by Elsevier España, S.L.U. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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

Introduction

The anxiety and stress in pediatric patients undergoing surgical procedures or imaging exams is one of the major challenges for anesthesiologists. Children might be uncooperative or show physical resistance, which may make separation from parents, mask application, and anesthesia induction difficult. In fact, it has been reported that up to 60% of children suffer from fear, stress, or anxiety during the perioperative period or imaging procedures.[1] Different premedicants, doses, and routes of administration have been studied in clinical practice in order to minimize emotional discomfort and therefore improve parental separation and the induction of anesthesia, as well as to decrease the likelihood of developing postoperative negative behavioral changes.[2,3]

Midazolam, a short-acting benzodiazepine, is the most commonly prescribed sedative premedication in children due to its widely demonstrated sedative and anxiolytic efficacy, rapid onset, and high metabolic clearance.[4-6] However, it has undesirable effects on pediatric patients, such as cognitive impairment, negative postoperative behavioral changes, and insufficient prevention of Emergence Agitation (EA), which make this drug far from an ideal premedication for this population.[7,8]

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, is also commonly used as premedication due to its different properties, such as sedation, anxiolysis, analgesia, and minimal respiratory depression.[9] The intranasal administration of dexmedetomidine has emerged as an attempt to increase the compliance of children receiving the premedication.

Previous meta-analyses assessed the efficacy of midazolam and α2-adrenoceptor agonists in pediatric premedication; however, those studies either included multiple routes of administration[10] or were limited by the small number of patients and trials.[11] Herein, we also include recently published trials, perform a Trial-Sequential Analysis (TSA), and provide new evidence to comprehensively assess the efficacy and safety of two common and specific routes of administration: intranasal dexmedetomidine and oral midazolam.

Methods

This systematic review and meta-analysis were conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Intervention guidelines.[12,13] The predefined protocol of the present study was registered in the International Prospective Register of Systematic Reviews (PROSPERO; identifier CRD42023446844).

Eligibility criteria

The inclusion criteria were as follows: 1) Randomized Controlled Trials (RCTs); 2) That included pediatric patients (≤ 18 years-old); 3) Comparing intranasal dexmedetomidine with oral midazolam, and 4) Reporting at least one of the outcomes of interest. Exclusion criteria were any non-randomized studies (observational or retrospective cohorts), trial protocols, abstracts without peer-reviewed manuscript publications, and studies presenting patients older than 18 years old. Endpoints of interest included the efficacy outcomes — satisfactory separation from parents and satisfactory induction or mask acceptance — and safety outcomes: the incidence of EA, Heart Rate (HR), and Mean Arterial Pressure (MAP).

Search strategy

Eligible trials were systematically searched using the MEDLINE, Embase, and Cochrane electronic databases. We also searched Google Scholar for non-indexed relevant publications. The final search had no restrictions on language, publication year, country of origin, or journal. The complete literature search strategy is listed in Table S1.

Study selection

Two independent reviewers (EM and TN) selected eligible studies based on the inclusion and exclusion criteria, and a cross-section was performed using the Rayyan software.[14] After removing duplicates, all results were pooled and selected based on their titles or abstracts. Finally, the remaining articles were read in full to assess eligibility. Any disagreement between the two reviewers was resolved through a discussion with a third reviewer (CG).

Data extraction

After study selection, the final RCTs included underwent data extraction to summarize the following variables: author, publication year, type of surgery or procedure, dose of intranasal dexmedetomidine and oral midazolam, number and age range of participants, the result of outcomes of interest, and the scale used for outcomes measurements. When continuous data were reported as a median and interquartile range, the values were converted to mean and standard deviation using the Wan et al method.[15] The values reported in the graphs were extracted using PlotDigitalizer (https://plotdigitizer.com/app).

Risk of bias assessment

Two reviewers (EM and TN) independently evaluated the risk of bias using the revised Cochrane risk of bias tool for randomized trial 2 (RoB 2),[16] which consists of five categories: 1) Bias arising from the randomization process; 2) Bias due to deviations from intended interventions; 3) Bias caused by missing outcome data; 4) Bias in the measurement of the outcome; and 5) Bias in the selection of the reported result. Risk of bias was classified as “low risk”, “some concerns”, or

"high risk". The Robvis tool was used to create the final figure.[17] Any disagreements were resolved by consensus through discussion among all authors.

Certainty of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[18] system was used to assess the evidence's certainty level. This system comprises five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality was classified as high, moderate, low, or very low. The quality of all outcomes was assessed by two independent reviewers (EM and TN), and any disagreements were resolved through discussion among all authors.

Statistical analysis

Review Manager 5.4[19] was used for data analysis. Risk Ratios (RR) with 95% Confidence Intervals (95% CI) were calculated for dichotomous variables. Mean Differences (MD) with 95% CI were computed for continuous outcomes, such as HR and MAP. A random-effects model was chosen for all outcomes due to anticipated heterogeneity among studies.

Cochran Q test and I^2 statistics were used to assess for heterogeneity. Heterogeneity among studies was categorized as low (I^2 = 0—40%), moderate (I^2 = 30—60%), substantial (I^2 = 50—90%) or considerable (I^2 = 75—100%), according to the Cochrane handbook guidelines.[13] Publication bias was investigated by funnel plot analysis, and Egger's linear regression test[20] was performed to explore publication bias further when at least ten studies were included in the outcome analysis.

Statistical significance was set at $p < 0.05$. We also performed a sensitivity analysis by omitting each study individually under a random-effects model to identify a possible small study effect or publication bias using the R software (https://www.r-project.org). Furthermore, we performed a TSA to minimize the risk of type I and type II errors and estimate the required information size. A type I error of 0.05 and a type II error of 0.20 (80% power) were allowed. The adjustment of thresholds for the *Z* score was set with the O'Brien-Fleming alpha spending function, and all the outcomes were assessed under a random-effects model (DerSimonian-Laird method). The software TSA version 0.9 beta (http://www.ctu.dk/tsa) was used for the analysis.[21]

Results

Study selection and characteristics

A total of 444 articles were initially identified. Of these, 134 were removed owing to duplication, and 279 were excluded after title and abstract screening. The remaining 31 articles were read in full, and 15 studies were excluded based on the inclusion and exclusion criteria. The final analysis included 16 publications in total (Fig. 1).[22-37] The study included 1239 pediatric patients, of whom 643 (51.9%) and 596 (48.1%) were assigned to the intranasal dexmedetomidine and oral midazolam group, respectively.

One study included only children who underwent imaging tests (computed tomography scans),[24] whereas other studies had pediatric patients who underwent elective surgeries. All studies included a midazolam dose of 0.5 mg.kg^{-1}, and the intranasal dexmedetomidine dose ranged from 0.5 to 2 μg.kg^{-1}. The characteristics of the RCTs included, and the scales for the outcome measurements are summarized in Table 1.

Efficacy outcomes

The satisfactory separation from parents was assessed by ten RCTs, with 817 patients. Satisfactory parental separation was achieved in 83.5% of the intranasal dexmedetomidine group and 62.9% of the patients in the oral midazolam group. The pooled effect size significantly increased (RR = 1.40; 95% CI 1.13—1.74; p = 0.002; I^2 = 91%) in satisfactory parental separation favoring intranasal dexmedetomidine (Fig. 2). Of the 16 RCTs, 11 reported satisfactions at the time of anesthesia induction or mask acceptance, with 837 patients. The incidence of satisfactory induction or mask acceptance in the intranasal dexmedetomidine and the oral midazolam group was 70.5% and 62%, respectively. However, there was no statistically significant difference in the pooled effect size (RR = 1.15, 95% CI 0.97—1.37; p = 0.11; I^2 = 77%; Fig. 3A).

Safety outcomes

The incidence of EA was reported in seven studies, with 608 patients included. EA was significantly reduced in the intranasal dexmedetomidine group (10.3%), as compared with the oral midazolam group (29.3%) (RR = 0.35; 95% CI 0.14—0.88; p = 0.02, I^2 = 75%) (Fig. 3B). A total of four RCTs, with 351 patients, reported the MAP. Intranasal dexmedetomidine was associated with a greater reduction in MAP compared to oral midazolam (MD = -3.35 mmHg; 95% CI -5.97 to -0.72 mmHg; p = 0.01, I^2 = 37%) (Fig. 4A). The HR was reported in eight RCTs with 643 patients. The HR was also lower in the group that received intranasal dexmedetomidine (MD = -6.35 bpm; 95% CI -10.12 to -2.58 bpm; p = 0.001, I^2 = 85%) (Fig. 4B).

Heterogeneity and sensitivity analysis

Visual inspection of the funnel plot for the outcome of satisfactory separation from parents (Fig. S1) showed considerable heterogeneity, likely from a small study effect carried out by three studies,[27,28,37] and the sensitivity analysis (Fig. S2) confirmed the heterogeneity attributed to these same studies. Egger's test consistently reached statistical significance, suggesting publication bias ($p < 0.0001$). However, despite the high heterogeneity, the pooled effect size remained significant with the exclusion of any individual study. Similarly, qualitative assessment of the funnel plot for satisfactory induction or mask acceptance (Fig. S3) suggests a small study effect, and Egger's test for publication bias was also significant (p = 0.038). Still, the sensitivity analysis showed that excluding any study would not create the statistical significance of the pooled effect size (Fig. S4).

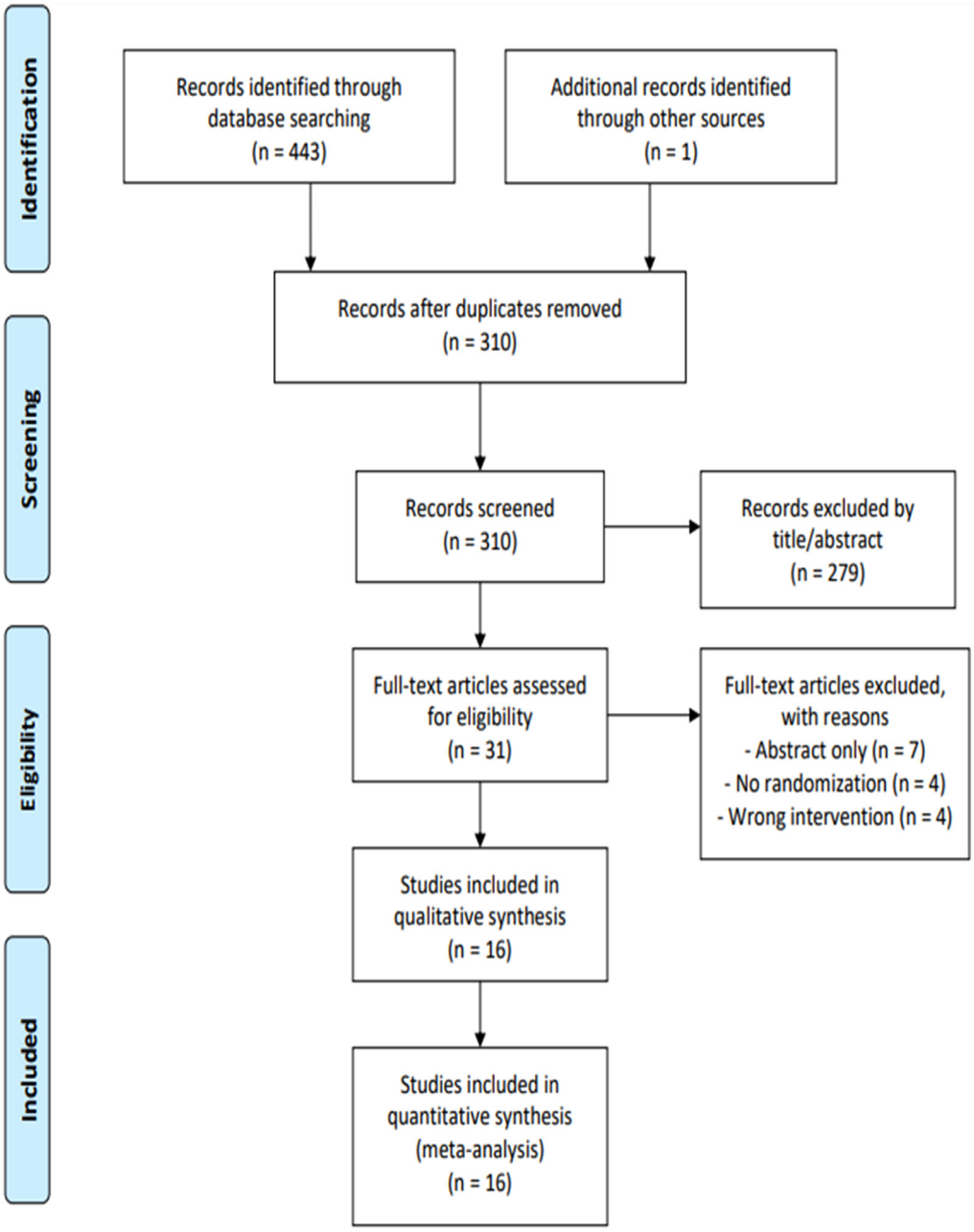


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of study selection. Four hundred forty-four articles were identified through electronic databases and other sources (non-indexed journals). After removing 310 duplicate studies, 279 articles were excluded based on title or abstract. The full texts of the remaining 31 studies were reviewed, and 15 were excluded from the final selection. Finally, 16 randomized clinical trials were included in the final analysis.

Risk of bias

The risk of bias summary and the overall plot of the risk of bias are shown in Figure S5. The risk of bias was classified as "some concerns" in three studies[26,28,32] and low in the remaining 13 studies. All included RCTs randomly assigned the patients to the groups, but in three studies,[26,32,37] the authors did not clearly describe whether the allocation sequence was concealed until all participants were assigned to the intervention. Bias due to deviations from the intended intervention was a concern in two studies[32,33] due to uncertain caregiver blinding, and bias in the measurement of outcomes was also assigned as "some concerns" in one study[32] due to unclear outcome measurement. Bias due to missing outcome data was assessed as low in all studies, and bias in the selection of reported results was classified as "some concerns" in three studies.[26,28,32]

TSA

The TSA for both safety outcomes and EA did not cross the trial sequential monitoring boundaries or reach the required information sample size (Figs. 5A, 5B, and 5C). In the analysis of satisfactory induction or mask acceptance, three

Table 1 Baseline characteristics of included RCTs.

Author, Year	Type of procedure	Patients, n DEX/MID	Age, years (range)	Male, % DEX/MID	DEX dose ($\mu g.kg^{-1}$)	Scale for parental separation satisfaction	Scale for induction satisfaction	Scale for emergence agitation
Bromfalk, 2021[22]	ENT surgery	30/27	2 – 6	57/63	2	Not measured	10-point scale	Not measured
Cai, 2021[23]	Lower abdominal or perineal surgery	46/37	2 – 6	89/92	2	4-point PSAS	4-point MAS	PAED
Ghai, 2016[24]	CT scan	30/29	1 – 6	30/48	2.5	3-point scale	Not measured	Not measured
Ghali, 2011[25]	Elective adenotonsillectomy	60/60	4 – 12	57/47	1	mYPAS	Not measured	Not measured
Jambure, 2016[26]	Cardiac catheterization	31/30	2 – 10	87/63	2	Not measured	Not measured	Not measured
Kumar, 2017[27]	Abdominal surgery	30/30	2 – 12	50/63	1	6-point scale	6-point scale	4-point scale
Rani, 2017[28]	Elective surgery	32/32	4 – 12	94/94	1	MOAA/S	MOAA/S	Not measured
Sathyamoorthy, 2019[29]	Dental surgery	36/37	5 – 18	67/70	2	UMSS	4-point MAS	Not measured
Savla, 2014[30]	Elective surgery	19/15	1 – 6	95/93	2	Not measured	RSS	Not measured
Segovia, 2014[31]	Elective surgery	52/56	2 – 12	46/57	1	Not measured	mYPAS	mYPAS
Singh, 202[32]	Dental surgery	51/51	4 – 7	47/51	2	4-point PSAS	4-point MAS	Not available
Talon, 2009[33]	Reconstructive Surgery	50/50	1 – 18	46/60	2	Ramsey-like 4-point scale	4-point scale	4-point scale
Wang, 2020[34]	Dental surgery	30/30	3 – 6	53/50	2	4-point PSAS	4-point MAS	PAED
Yadav, 2019[35]	Minor surgery	30/30	1 – 8	50/60	0.5	Not measured	Not measured	Not measured
Yao, 2020[36]	Strabismus surgery	52/50	2 – 6	58/66	2	Not measured	Not measured	PAED
Yuen, 2008[37]	Elective minor surgery	64/32	2 – 12	92/94	0.51	MOAA/S	MOAA/S	Not measured

RCTs, Randomized Clinical Trials; DEX, Intranasal Dexmedetomidine group; MID, Oral Midazolam group; ENT, Ear, Nose and Throat; PSAS, Parental Separation Anxiety Scale; MAS, Mask Acceptance Scale; PAED, Pediatric Anesthesia Emergence Delirium scale; mYPAS, Modified Yale Preoperative Anxiety Scale; UMSS, University of Michigan Sedation Scale; RSS, Ramsay Sedation Scale; MOAA/S, Modified Observer's Alertness/Sedation scale; CT, Computerized Tomography.

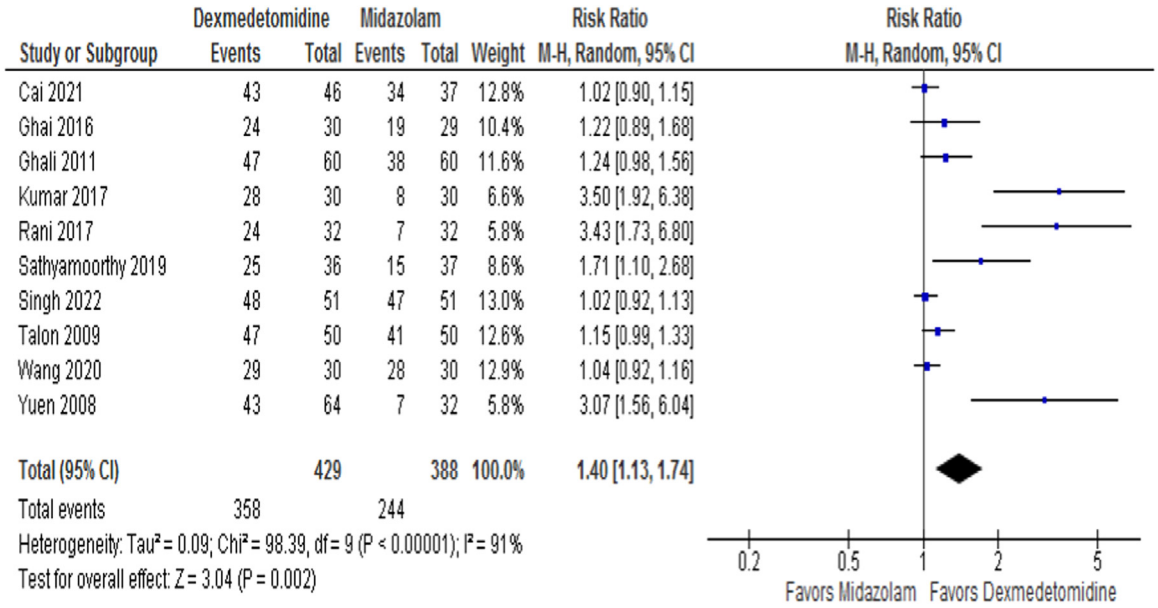


Figure 2 Forest plot for satisfactory separation from parents. Patients in the intranasal dexmedetomidine group showed better parental separation in comparison to patients in the oral midazolam group.

trials[27,30,34] were ignored in the interim due to too little information use (< 1.0%). However, the monitoring boundaries were crossed in the assessment of MAP and HR, and the required information size was achieved in the analysis of HR (Fig. 5D and 5A).

Certainty of evidence

Although the results from the risk of bias assessment partially indicate that the quality of the included RCTs was reasonable, the GRADE assessment demonstrated that the overall level of certainty of the evidence in this meta-analysis was low for the efficacy outcomes and for EA, moderate for HR, and high for MAP. This is primarily due to the high heterogeneity among studies, especially for safety outcomes, and the publication bias suggested by the funnel plot analyses. Table S2 shows the overall GRADE summary of findings for each outcome.

Discussion

In this meta-analysis, intranasal dexmedetomidine as a premedicant in pediatric patients was associated with 1) A higher rate of satisfactory separation from parents, 2) Lower incidence of EA, and 3) A marginally lower HR and MAP in comparison with the use of oral midazolam. There was no difference in satisfactory induction or mask acceptance between groups.

Although preanesthetic medication is often administered in pediatric patients, the optimal drug and ideal route of administration remain controversial. The most commonly used drug for premedication in children is the benzodiazepine midazolam, especially through the oral route. However, oral administration of midazolam may result in low bioavailability, and there may be low acceptability by children due to its poor palatability.[38,39] Intranasal administration of dexmedetomidine, a highly selective α2-adrenoceptor agonist, is a relatively simple and noninvasive method to reduce preoperative anxiety and provide sedation to pediatric patients undergoing invasive procedures or imaging scans. The intranasal route is effective due to the bypass of first-pass metabolism and the abundant blood supply at the nasal mucosa. In addition, the administration of intranasal dexmedetomidine is tasteless and odorless, which increases the rates of acceptability by children and has led to increased popularity in clinical practice over the years.[40]

In a meta-analysis published in 2020 by Lang et al,[10] the authors compared premedication with dexmedetomidine and midazolam through various routes, including intravenous, inhalational, and sublingual. However, no subgroup of the route of administration was performed, and the findings of two of the most commonly used in clinical practice (intranasal dexmedetomidine and oral midazolam) remained unclear, especially concerning the differences in hemodynamic parameters, which were not compared in-depth in their analysis. The authors even attributed the high heterogeneity in all endpoints to the different administration routes. Although their results were similar to ours, the pediatric age group has physiological and pharmacological particularities. It lacks specific research compared to other anesthesia fields,[41] which is illustrated by the "off-label" use of dexmedetomidine in pediatric anesthesia. An analysis of specific administration methods, such as the one presented herein, must be performed to confirm robust findings, considering these differences and the current lack of evidence about the ideal route of premedication.[42]

Our study was written concomitantly with a recent meta-analysis published by Zhang et al,[11] comparing intranasal dexmedetomidine with oral midazolam in pediatric patients. Our results support similar findings regarding successful separation from parents, although with a more in-depth report, such as the TSA and five additional trials (455 new patients).

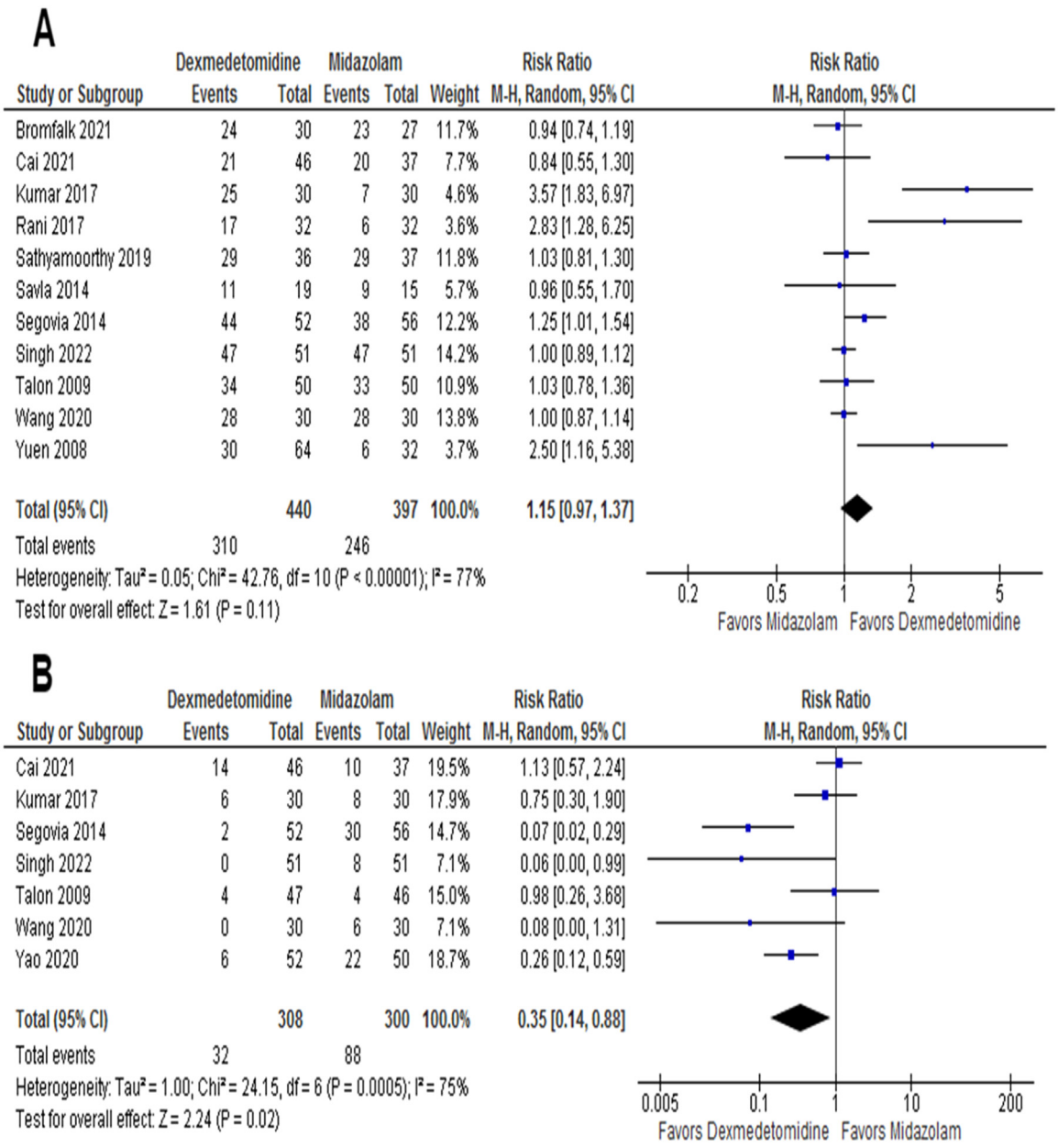


Figure 3 (A) Forest plot for satisfactory induction or mask acceptance. No statistically significant difference was found between both groups. (B) Forest plot for emergence agitation. The intranasal dexmedetomidine group showed less incidence of emergence agitation compared with the oral midazolam group.

In contrast, the prior work did not assess the incidence of EA and the hemodynamic parameters. In addition, in their analysis, anesthesia induction and mask acceptance were assessed separately, resulting in a small sample of trials (3 and 4, respectively). They found better anesthesia induction in the dexmedetomidine group; however, the analysis was under a fixed-effect model, and our study did not support this finding. Furthermore, unlike the authors, we did not include the study by Schmidt et al,[43] since dexmedetomidine was administered by the sublingual route and, therefore, may have resulted in different findings.

The results of the present meta-analysis suggest that intranasal dexmedetomidine, when administered as premedication in pediatric patients, provides more successful separation from parents than oral midazolam. However, the TSA did not confirm enough information to draw a definitive conclusion. Despite the high heterogeneity found for this outcome, the sensitivity analysis in our study did not change the pooled effect size with the exclusion of any particular study, which indicates that the presented results are consistent and robust to sensitivity analysis.

Dexmedetomidine, unlike other sedatives, acts in the locus coeruleus, thus providing an easy shift from sleep to arousal, particularly with external stimulations such as in anesthesia induction and mask placement.[44] Therefore, the absence of difference in the outcomes of satisfactory anesthesia induction and mask acceptance between groups, shown in our study, is reassuring. This indicates no significant

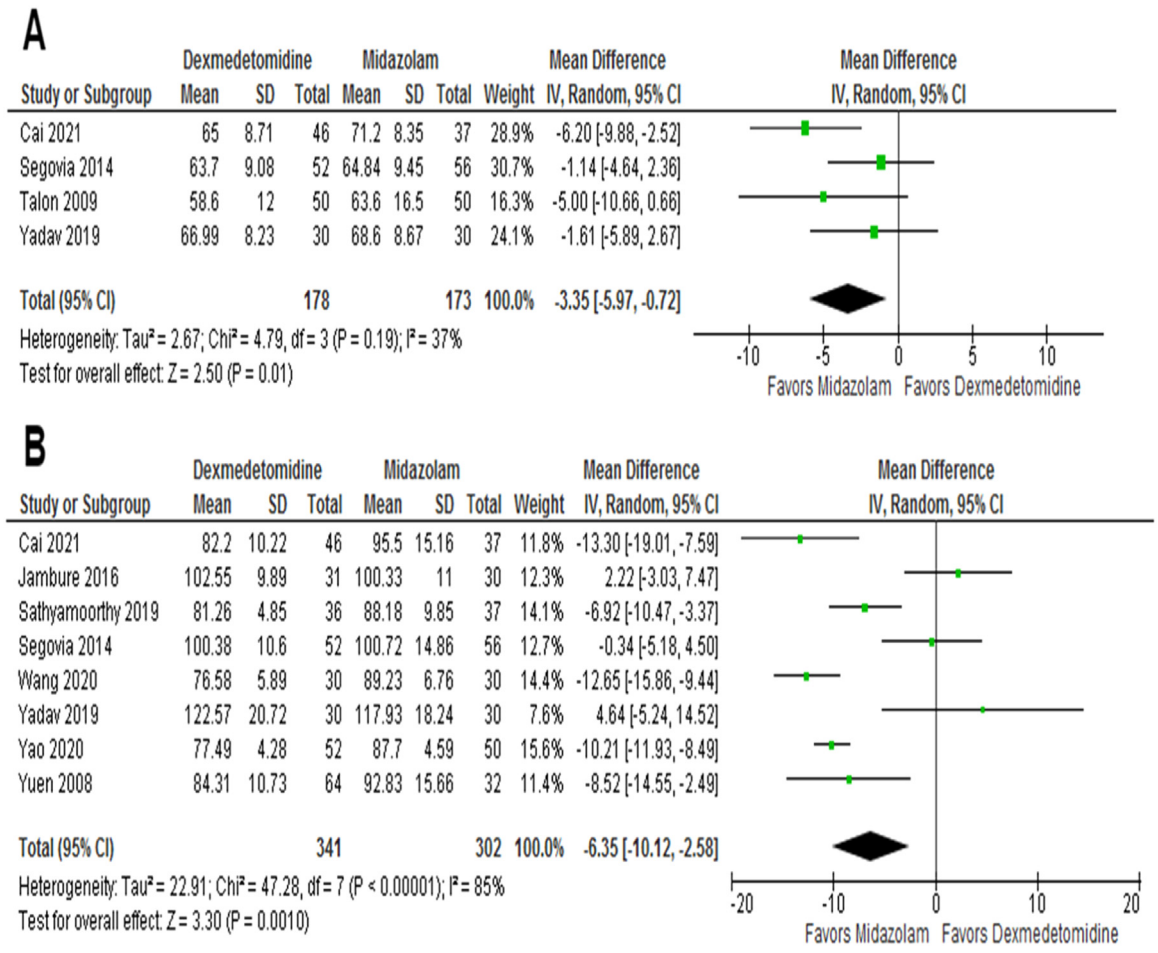


Figure 4 (A) Forest plot for mean arterial pressure. Patients who received intranasal dexmedetomidine showed a greater reduction in MAP compared with the oral midazolam group. (B) Forest plot for heart rate. The intranasal dexmedetomidine group showed a greater reduction in HR in comparison with the patients who received oral midazolam.

loss in the clinical efficacy of premedication with dexmedetomidine despite the easier arousal.

Compared to oral midazolam, intranasal dexmedetomidine reduced the incidence of EA. The high variability observed in our study may have been caused by using different metrics to evaluate the occurrence of EA. However, several etiologies, including the type of operation, age, preoperative anxiety level, timing of pre-medication, and pain management, may contribute to the development of EA.[45] In our study, the premedicants were given before surgery in all the included trials, and most surgeries were minor elective procedures, which may have helped reduce the incidence of EA. Furthermore, as a highly selective α2-adrenoceptor agonist, dexmedetomidine has analgesic effects that might have contributed to the greater reduction in EA found in our meta-analysis since it is well-known that pain plays an important role in the development of EA.[46]

Our study found that intranasal dexmedetomidine premedication showed a greater intraoperative reduction in both HR and MAP compared to oral midazolam, confirmed by TSA. This contrasts with a previous study comparing intranasal dexmedetomidine with intranasal midazolam, which indicates the differences in administration routes of both drugs.[47] Notably, hypotension and bradycardia are the most commonly reported adverse events associated with dexmedetomidine. These hemodynamic changes are due to the post-synaptic activation of alpha-2 receptors at the locus coeruleus, which lowers the sympathetic outflow, thus leading to a decrease in HR and blood pressure. However, reports of hemodynamic collapses or the need for pharmacological resuscitation remain rare.[48] Furthermore, dexmedetomidine has been shown to have minimal effects on respiration, which is an important advantage over other agents.[49] Nonetheless, only one study[26] stated the occurrence of these adverse events: two episodes of bradycardia and one episode of hypotension in the intranasal dexmedetomidine group, and only one episode of bradycardia in the oral midazolam group. No episodes of bradycardia or hypotension occurred in the other studies; thus, a comparison could not be carried out. Therefore, given that the variations in vital signs were identified in our meta-analysis but that intranasal dexmedetomidine did not appear to be connected with adverse events, it is unlikely that the small difference between groups in HR and MAP has any clinical significance, albeit statistically significant.

This meta-analysis has some limitations. Although only three RCTs[26,28,32] showed some concerns about the risk of bias assessment, the low and moderate GRADE assessment must be considered when interpreting the results, mainly due to high heterogeneity. Different variables probably

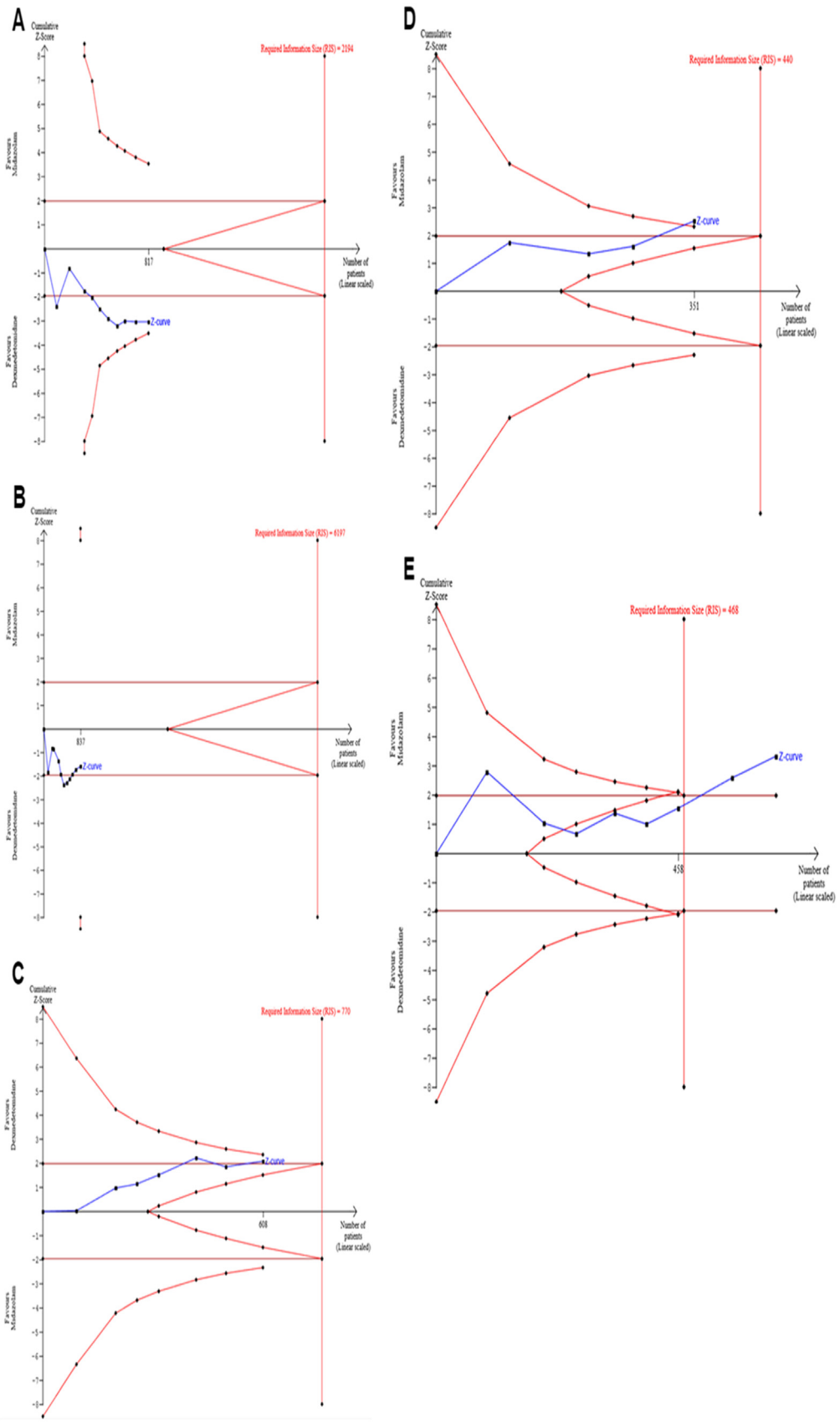


Figure 5 The trial-sequential analysis. for the outcomes analyzed. (A) Satisfactory separation from parents. (B) Satisfactory induction or mask acceptance (three trials[27,30,34] were ignored in the interim due to too low information use [<1.0%]). (C) Incidence of emergence agitation. (D) Mean arterial pressure. (E) Heart rate. None of the graphs about efficacy outcomes and emergence

carried out this heterogeneity. First of all, there has never been a reliable way to quantify EA or to evaluate anxiety and sedation concerning parental separation, induction, or mask acceptance. Thus, the use of different scales must be taken into consideration. Second, including small, single-center trials with different procedures, doses, ages, and anesthesia protocols may also have caused discrepancies in the results. The absence of patient-level data precluded a more granular assessment of characteristics associated with the relative comparison between groups, including age and dose of anesthetic agent. Due to a lack of reported data, we could not assess additional outcomes, such as the emergence time, time to post-operative care unit discharge, analgesia requirement, and postoperative nausea or shivering. Finally, our results may also be subject to (1) Publication bias, as indicated by the funnel plot analysis and confirmed by Egger's test, and (2) Type I and type II errors, since TSA findings indicated insufficient power and sampling to draw a definitive conclusion for the outcomes of satisfactory separation from parents, satisfactory induction and mask acceptance and incidence of EA. Therefore, further research on these two specific routes of administration is needed, specifically to verify the efficacy and the incidence of EA, preferably with standardized scales.

Conclusion

In pediatric patients undergoing sedation, premedication with intranasal dexmedetomidine, compared with oral midazolam, improved parental separation satisfaction, lowered the incidence of EA, and was associated with a marginally lower HR and MAP, without a significant difference in satisfactory induction or mask acceptance. Intranasal dexmedetomidine may be considered a safe and effective alternative to oral midazolam for anesthetic premedication in pediatric patients.

Declaration of competing interest

The authors declare no conflicts of interest.

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

Data availability statement

This study was based on data extracted from previously published trials, and the authors do not have access to patient-level data from individual studies. We encourage you to contact the corresponding author from each study for further requests. The datasets used for this meta-analysis are available from the corresponding author upon reasonable request.

Disclosures

All authors (1) report no relationships that could be construed as a conflict of interest, (2) take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation, and (3) have approved the final article.

Acknowledgements

The authors would like to thank Dr. Rhanderson Cardoso, MD, for his review of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844520.

References

1. Kain Z, Mayes L, O'Connor T, et al. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150:1238–45.
2. Watson A, Visram A. Children's preoperative anxiety and postoperative behaviour. Paediatr Anaesth. 2003;13:188–204.
3. Kain Z, Wang S, Mayes L, et al. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg. 1999;88:1042–7.
4. Lerman J. Preoperative assessment and premedication in paediatrics. Eur J Anaesthesiol. 2013;30:645–50.
5. Kogan A, Katz J, Efrat R, et al. Premedication with midazolam in young children: a comparison of four routes of administration. Paediatr Anaesth. 2002;12:685–9.
6. Marshall J, Rodarte A, Blumer J, et al. Pediatric pharmacodynamics of midazolam oral syrup. Pediatric Pharmacology Research Unit Network. J Clin Pharmacol. 2000;40:578–89.
7. Lönnqvist P, Habre W. Midazolam as premedication: is the emperor naked or just half-dressed? Paediatr Anaesth. 2005;15:263–5.
8. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth. 2010;104:216–23.
9. Shen F, Zhang Q, Xu Y, et al. Effect of intranasal dexmedetomidine or midazolam for premedication on the occurrence of respiratory adverse events in children undergoing tonsillectomy and adenoidectomy: a randomized clinical trial. JAMA Netw Open. 2022;5:e2225473.
10. Lang B, Zhang L, Zhang W, et al. A comparative evaluation of dexmedetomidine and midazolam in pediatric sedation: a meta-analysis of randomized controlled trials with trial sequential analysis. CNS Neurosci Ther. 2020;26:862–75.
11. Zhang G, Xin L, Yin Q. Intranasal dexmedetomidine vs. oral midazolam for premedication in children: a systematic review and meta-analysis. Front Pediatr. 2023;11:1264081.

agitation crossed the trial sequential monitoring boundaries and did not reach the required information size. The monitoring boundaries were crossed in the analysis of mean arterial pressure and heart rate, and the required information size was achieved for heart rate.

12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006—12.
13. Cumpston M, Li T, Page M, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.
14. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2006;5:210.
15. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
16. Sterne J, Savović J, Page M, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
17. McGuinness L, Higgins J. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12:55—61.
18. Atkins D, Best D, Briss P, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
19. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629—34.
21. Thorlund K, Wetterslev J, Brok J, et al. User manual for trial sequential analysis (TSA). In Copenhagen Trial Unit, Centre for Clinical Intervention Research. 2011: 1—115.
22. Bromfalk Å, Myrberg T, Walldén J, et al. Preoperative anxiety in preschool children: a randomized clinical trial comparing midazolam, clonidine, and dexmedetomidine. Paediatr Anaesth. 2021;31:1225—33.
23. Cai Y, Wang C, Li Y, et al. Comparison of the effects of oral midazolam and intranasal dexmedetomidine on preoperative sedation and anesthesia induction in children undergoing surgeries. Front Pharmacol. 2021;12:648699.
24. Ghai B, Jain K, Saxena A, et al. Comparison of oral midazolam with intranasal dexmedetomidine premedication for children undergoing CT imaging: a randomized, double-blind, and controlled study. Paediatr Anaesth. 2017;27:37—44.
25. Ghali A, Mahfouz A, Al-Bahrani M. Preanesthetic medication in children: a comparison of intranasal dexmedetomidine versus oral midazolam. Saudi J Anaesth. 2011;5:387—91.
26. Jambure N, Nagre A. Comparison of Intranasal dexmedetomidine and oral midazolam as premedication for cardiac catheterization procedure in pediatric patients. Anaesth Pain Intensive Care. 2016;20(Suppl 1):S48—52.
27. Kumar L, Kumar A, Panikkaveetil R, et al. Efficacy of intranasal dexmedetomidine versus oral midazolam for paediatric premedication. Indian J Anaesth. 2017;61:125—30.
28. Rani J, Rani S, Unnikrishnan G. Comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anaesthesia – a randomized controlled trial. J Med Sci Clin Res. 2017;05(02):2455. -0450.
29. Sathyamoorthy M, Hamilton T, Wilson G, et al. Pre-medication before dental procedures: a randomized controlled study comparing intranasal dexmedetomidine with oral midazolam. Acta Anaesthesiol Scand. 2019;63:1162—8.
30. Savla J, Ghai B, Bansal D, et al. Effect of intranasal dexmedetomidine or oral midazolam premedication on sevoflurane EC50 for successful laryngeal mask airway placement in children: a randomized, double-blind, placebo-controlled trial. Paediatr Anaesth. 2014;24:433—9.
31. Segovia L, García M, Ramírez I, Guerrero J, et al. Pre-anesthetic medication with intranasal dexmedetomidine and oral midazolam as an anxiolytic: a clinical trial. An Pediatr (Barc). 2014;81:226—31.
32. Singh G, Trivedi S, Singh A, et al. Intranasal dexmedetomidine and oral midazolam in pediatric dental patients as premedication under general anaesthesia. Int J Acad Med Pharm. 2022;4:95—9.
33. Talon M, Woodson L, Sherwood E, et al. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res. 2009;30:599—605.
34. Wang L, Huang L, Zhang T, et al. Comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric dental patients under general anesthesia: a randomised clinical trial. BioMed Res Int. 2020;2020:5142913.
35. Yadav S, Vardhan V, Grupta P, et al. Comparative efficacy and safety of intra-nasal dexmedetomidine and oral midazolam as premedication in children undergoing minor elective surgical procedures: results of a randomized, double-blind trial. MedPulse Int J Anesthesiol. 2019;12:48—54.
36. Yao Y, Sun Y, Lin J, et al. Intranasal dexmedetomidine versus oral midazolam premedication to prevent emergence delirium in children undergoing strabismus surgery: a randomized controlled trial. Eur J Anaesthesiol. 2020;37:1143—9.
37. Yuen V, Hui T, Irwin M, et al. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg. 2008;106:1715—21.
38. Reed M, Rodarte A, Blumer J, et al. The single-dose pharmacokinetics of midazolam and its primary metabolite in pediatric patients after oral and intravenous administration. J Clin Pharmacol. 2001;41:1359—69.
39. Khalil S, Vije H, Kee S, et al. A paediatric trial comparing midazolam/Syrpalta mixture with premixed midazolam syrup (Roche). Paediatr Anaesth. 2003;13:205—9.
40. van Hoorn C, Flint R, Skowno J, et al. Off-label use of dexmedetomidine in paediatric anaesthesiology: an international survey of 791 (paediatric) anaesthesiologists. Eur J Clin Pharmacol. 2021;77:625—35.
41. Quintão V, Carmona M. A call for more pediatric anesthesia research. Braz J Anesthesiol. 2021;71:1—3.
42. Sengupta S, Bhattacharya P, Nag D, Sahay N. Search for the ideal route of premedication in children far from over? Indian J Anaesth. 2022;66(Suppl 4):S188—92.
43. Schmidt A, Valinetti E, Bandeira D, et al. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Paediatr Anaesth. 2007;17:667—74.
44. Lee S. Dexmedetomidine: present and future directions. Korean J Anesthesiol. 2019;72:323—30.
45. Kanaya A. Emergence agitation in children: risk factors, prevention, and treatment. J Anesth. 2016;30:261—7.
46. Lee S, Sung T. Emergence agitation: current knowledge and unresolved questions. Korean J Anesthesiol. 2020;73:471—85.
47. Fu Y, Zhang Q, Jiang Y, et al. A comparative evaluation of intranasal α2-adrenoceptor agonists and intranasal midazolam as premedication in pediatric sedation: a meta-analysis of randomized controlled trials. PloS One. 2023;18:e0281751.
48. Lin R, Ansermino J. Dexmedetomidine in paediatric anaesthesia. BJA Educ. 2020;20:348—53.
49. Weerink M, Struys M, Hannivoort L, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56:893—913.

Brazilian Journal of Anesthesiology 2024;74(5): 844543

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



REVIEW ARTICLE

The effect of nalbuphine on prevention of emergence delirium in children: a systematic review with meta-analysis☆

Ka Ting Ng [a,*], **Wei En Lim** [b], **Wan Yi Teoh** [c], **Mohd Fitry Bin Zainal Abidin** [a]

[a] *University of Malaya, Department of Anesthesiology, Kuala Lumpur, Malaysia*
[b] *University of Glasgow, Department of Anesthesiology, Glasgow, United Kingdom*
[c] *University of Liverpool, Department of Medicine, Liverpool, United Kingdom*

Received 27 December 2023; accepted 11 July 2024
Available online 22 July 2024

KEYWORDS
Nalbuphine;
Emergence delirium;
Child;
Pain, postoperative;
Nausea;
Vomiting

Abstract

Background: Emergence delirium remains a major postoperative concern for children undergoing surgery. Nalbuphine is a synthetic mixed agonist-antagonist opioid, which is believed to reduce the incidence of emergence delirium in children. The primary objective was to examine the effect of nalbuphine on emergence delirium in children undergoing surgery.

Methods: Databases of MEDLINE, EMBASE, and CENTRAL were searched from their starting dates until April 2023. Randomized Clinical Trials (RCT) and observational studies comparing nalbuphine and control in children undergoing surgery were included.

Results: Eight studies (n = 1466 patients) were eligible for inclusion of data analysis. Compared to the control, our pooled data showed that the nalbuphine group was associated with lower incidence of emergence delirium (RR = 0.38, 95% CI [0.30, 0.47], $p < 0.001$) and reduced postoperative pain scores (MD = -0.98, 95% CI [-1.92, -0.04], $p = 0.04$).

Conclusions: This review showed the administration of nalbuphine is associated with significant decrease in the incidence of emergence delirium and postoperative pain scores among children undergoing surgery. However, due to limited sample size, high degree of heterogeneity and low level of evidence, future adequately powered trials are warranted to explore the efficacy of nalbuphine on emergence delirium among the pediatric population.

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

Introduction

Emergence delirium is common in pediatric patients when they recover from anesthesia at the end of surgery, ranging from 10–80% depending on the type of anesthetic agent, criteria of emergence delirium and scoring system.[1] It is

☆ This project was accepted for the oral presentation competition at the Malaysian Society of Anaesthesiologists Conference 2023.

* Corresponding author.
E-mail: katingng1@gmail.com (K.T. Ng).

https://doi.org/10.1016/j.bjane.2024.844543
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

characterized as a brief state of extreme irritability and dissociation with children who do not respond to consoling measures after anesthesia has been discontinued.[2] This can lead to possible self-injury, such as children falling off the bed, removing intravenous/urinary catheters, and damaging surgical dressings.[3] Furthermore, it is also associated with significant anxiety in parents, leading to poor parental satisfaction levels[4] and prolonged hospital stays.[5]

Numerous studies have contributed to our understanding of prevention of emergence delirium via the administration of various drugs such as midazolam or propofol in children.[6,7] However, their use is limited due to various adverse effects, such as bradycardia, hypotension, and slow recovery from anesthesia.[8,9] These limitations warrant future studies of alternative drugs with better efficacy and safety profile.

Nalbuphine is a semi-synthetic opioid that acts as a κ-receptor agonist and μ-receptor antagonist and plays a crucial role in providing analgesic and sedation. Nalbuphine is equianalgesic to morphine with faster onset of action and has minimal adverse effects such as lower incidence of desaturation, nausea and vomiting.[10] It also features a ceiling effect for respiratory depression, making it one of the safer analgesics for children.[11] Current evidence shows that nalbuphine is used as an adjunctive anesthesia agent for pain management among pediatric patients.[12,13] Several Randomized Controlled Trials (RCT) showed promising results on the efficacy of nalbuphine in lowering the incidence of emergence delirium in children as compared to placebo.[14-19] Nalbuphine reduces the incidence of emergence delirium, yet the underlying mechanism remains unclear.[14]

However, most of the established data on the efficacy of nalbuphine was performed on adults undergoing surgery.[20,21] Therefore, a comprehensive systematic review and meta-analysis is warranted to summarize current evidence on the use of nalbuphine in children undergoing surgery.

We hypothesized that nalbuphine would attenuate the incidence of emergence delirium in children undergoing surgery. We also hypothesized that nalbuphine could reduce postoperative pain scores and the incidence of nausea and vomiting in children. The primary objective of this review was to examine the effect of nalbuphine on the incidence of emergence delirium in pediatric patients. Secondary objectives were to investigate the effect of nalbuphine on the postoperative pain score and incidence of nausea and vomiting in children after surgery.

Methods

This review was carried out in accordance with the Cochrane Handbook of Systematic Reviews.[22] Our study protocol was registered on PROSPERO, CRD42023416518 before the beginning of the systematic search for relevant articles. The research questions were formulated using a Population-Intervention-Comparison-Outcome (PICO) approach. The primary outcome was the incidence of emergence delirium among children undergoing surgery. Secondary outcomes included postoperative pain scores, incidence of nausea and vomiting, and incidence of desaturation.

Literature search and study identification

Databases of the MEDLINE, EMBASE, and Cochrane Central Register of Trials were searched from their starting dates until April 2023. ClinicalTrials.gov.my and the WHO International Clinical Trial Registry were searched for any ongoing or unpublished clinical trials. No restrictions were applied based on the publication date or language of publication. The search terms and search strategy are listed in Supplementary Table 1. The inclusion criteria were listed below: 1) All Randomized Controlled Trials (RCTs) or observational studies comparing nalbuphine versus control groups were included; 2) All RCTs or observational studies comparing nalbuphine versus control groups involving children undergoing surgery, regardless of the type of surgery and reported outcomes.

Letters to editors, case reports, case series, and conference abstracts were excluded. Trials comparing nalbuphine and control in adult patients undergoing surgery were excluded. The references to all the included studies were searched for relevant articles that fulfilled our inclusion criteria. The authors of relevant studies were contacted at least three times if no response was received for any uncertainty in their data.

Study selection and data extraction

The review was reported according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses Statement (PRISMA) 2020.[23] Two authors (WT and WL) were briefed by the main author (KN) on the eligibility and exclusion criteria. Titles and abstracts of studies were systematically searched and identified based on the inclusion criteria by both review authors (WT and WL). The final selection of all included studies was discussed and agreed among all the three authors (KN, WT, and WL). Data from relevant studies were independently extracted by the two authors (WT and WL) using a standardized data collection form. Clinical characteristics of the included studies were documented by both authors (WT and WL) separately and cross-checked for any discrepancies, as illustrated in Table 1.

Risk of bias assessment

All the included RCTs were evaluated for the risk of bias using the Cochrane Collaboration Risk of Bias Assessment Tool by two authors (WT and WL) independently.[24] The observational studies were assessed for the risk of bias using the Newcastle-Ottawa Scale.[25] The principles of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system were applied to assess the quality of evidence of the primary and secondary outcomes.[26] The summary of findings and the level of evidence were carried out independently by both authors (WT and WL) using the GRADEpro/GDT software (Guideline Development Tool [Software]). The certainty of evidence was assessed based on the five major criteria (risk of bias, inconsistency, indirectness, imprecision, and publication bias).[24] Any disagreements were solved by the main author (KN).

Table 1 Clinical characteristics of included studies.

Author	Year	References	Type of Surgery	Design	Drug	Dose of Nalbuphine	Control Group Drug	Dose of Control	Timing of Administration	Type of Anesthesia	Dose of Anesthesia	Mean Age (Control)[a]	Mean Age (Nalbuphine)[a]	Mean BMI (Control)[a]	Mean BMI (Nalbuphine)[a]	n[a]
Kim	2008	[18]	Strabismus Surgery	RCT	Nalbuphine	0.1 mg.kg^{-1}	Normal Saline	0.1 mg.kg^{-1}	End of Surgery	Sevoflurane	6 L.min^{-1}	4.7 ± 1.3	4.8 ± 1.2	–	–	90
Chang	2008	[19]	Strabismus Surgery	RCT	Nalbuphine	0.2 mg.kg^{-1}	Normal Saline	0.2 mg.kg^{-1}	During Surgery except for high agitation score then nalbuphine is administered additionally after surgery	Desflurane	4%–6% with N_2O:O_2 is 2:1	7.3 ± 2.3	7.0 ± 3.3	–	–	41
Mohammed	2017	[16]	Tonsillectomy with or without adenoidectomy	RCT	Nalbuphine	0.1 mg.kg^{-1}	Midazolam	0.03 mg.kg^{-1}	5 min before the end of surgery	Sevoflurane	6 L.min^{-1} with increments of 1% at each breath up to 8%.	5.7±1.3	5.6±1.3	–	–	90
Vavrina	2017	[17]	Adenotonsillectomy	Observational Study	Nalbuphine	0.17 ± 0.03 mg.kg^{-1}	Alfentanil	0.012 ± 0.004 mg.kg^{-1}	During surgery	Propofol or 40% Oxygen, 60% Nitrous Oxide and Sevoflurane	–	5.7 ± 3.1	5.1 ± 1.7	–	–	114
Zhao	2017	[14]	Dental Surgery	RCT	Nalbuphine	0.1 mg.kg^{-1}	Normal Saline	0.1 mg.kg^{-1}	Before the end of surgery	Sevoflurane	8% in 100% oxygen	4.4 ± 1.2	4.5 ± 1.3	–	–	84
El-Din	2018	[15]	Adenotonsillectomy	RCT	Nalbuphine	0.1 mg.kg^{-1}	Midazolam	0.03 mg.kg^{-1}	5 min before the end of surgery	Sevoflurane	6 L.min^{-1} with increments of 1% at each breath up to 8%	5.7 ± 1.3	5.6 ± 1.3	–	–	90
Elagamy	2020	[30]	Adenotonsillectomy	RCT	Nalbuphine	0.1 mg.kg^{-1}	Dexmedetomidine	0.5 μg.kg^{-1}	During the surgery	Sevoflurane	8% in 100% of oxygen	4.5 ± 0.8	4.7 ± 1	-	-	160
He	2023	[14]	Adenotonsillectomy	RCT	Nalbuphine	0.1 mg.kg^{-1}	Normal Saline	0.1 mg.kg^{-1}	During surgery	Sevoflurane	6 L.min^{-1}	5.1 ± 1.8	5.0 ± 1.9	15.7 ± 2.5	15.5 ± 2.1	797

[a] Values are in Mean ± Standard Deviation. RCT, Randomized Controlled Trial; BMI, Body Mass Index; n, Total Sample Size.

Summary measures and synthesis of results

Statistical meta-analysis was conducted using Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark).[27] A two-tail p-value < 0.05 was indicated as having statistical significance. Our findings were reported as Risk Ratio (RR) and 95% Confidence Interval for binary outcomes. With regards to the continuous outcomes, the Mean Difference (MD) and 95% Confidence Interval were calculated. Due to the variation in clinical settings, the degree of heterogeneity of the pooled data was evaluated. The I-square (I^2) with values of < 40%, 40% to 60%, and > 60% were classified as low, moderate, and high, respectively. A fixed-effects model was applied to summarize the estimates of outcomes. If significant heterogeneity (I^2 > 60%) was observed, a random-effects model was utilized to analyze the data. When the values were reported as median or interquartile range, these values were converted to mean and standard deviation.[28] Sensitivity analysis was performed on the primary outcome by focusing on the RCT studies only to eliminate the introduction of bias from the inclusion of observational studies. However, funnel plot analysis to test for publication bias could not be conducted due to the limited number of studies (number of studies ≤ 10).

Results

The study selection process is illustrated in the PRISMA diagram (Fig. 1). Our search generated 99 non-duplicated articles for title and abstract screening. Of all, eleven articles were identified and retrieved for full text screening. After applying the inclusion and exclusion criteria, three articles were excluded, as shown in Supplementary Table 2. A total of eight studies (seven RCTs, one observational study; n = 1466) were included in the quantitative analysis of the primary outcome of the review, whereas one of studies was not included owing to its type of data being continuous instead of dichotomous.[29] The search of the main registries identified two ongoing studies (Supplementary Table 3).

The clinical characteristics of all the included studies are depicted in Table 1. Among all the included studies, four were adenotonsillectomy,[14,17,18,29] two were strabismus surgery,[15,30] one was dental surgery[19] and another study was tonsillectomy with or without adenoidectomy.[16] The dose of nalbuphine ranged from 0.1 mg.kg^{-1} to as high as 0.2 mg.kg^{-1}. With regards to the control group, two studies used midazolam,[16,17] one gave alfentanil,[18] one used dexmedetomidine[29] while the remaining four studies used normal saline as a placebo.[14,15,19,30] All the included studies administered sevoflurane for maintenance of anesthesia,[14-16,18,19,29] except for one of the studies that used desflurane[30] in pediatric patients. The average ages of the nalbuphine and control group were 5.3 years old (Standard Deviation [SD = 1.45]) and 5.4 yearsold (SD = 1.63), respectively. The publication year of the included studies ranged from 2008 to 2023. The data analysis of the primary and secondary outcomes is shown in Table 2 whereas the level of evidence is illustrated in Table 3. In the overall risk of bias assessment, two studies were of low risk of bias[14,29] and six studies were evaluated as unclear or high risk of bias.[15-19,30] because of the lack of blinding of participants or personnel, and the lack of blinding of outcome assessors (Supplementary Table

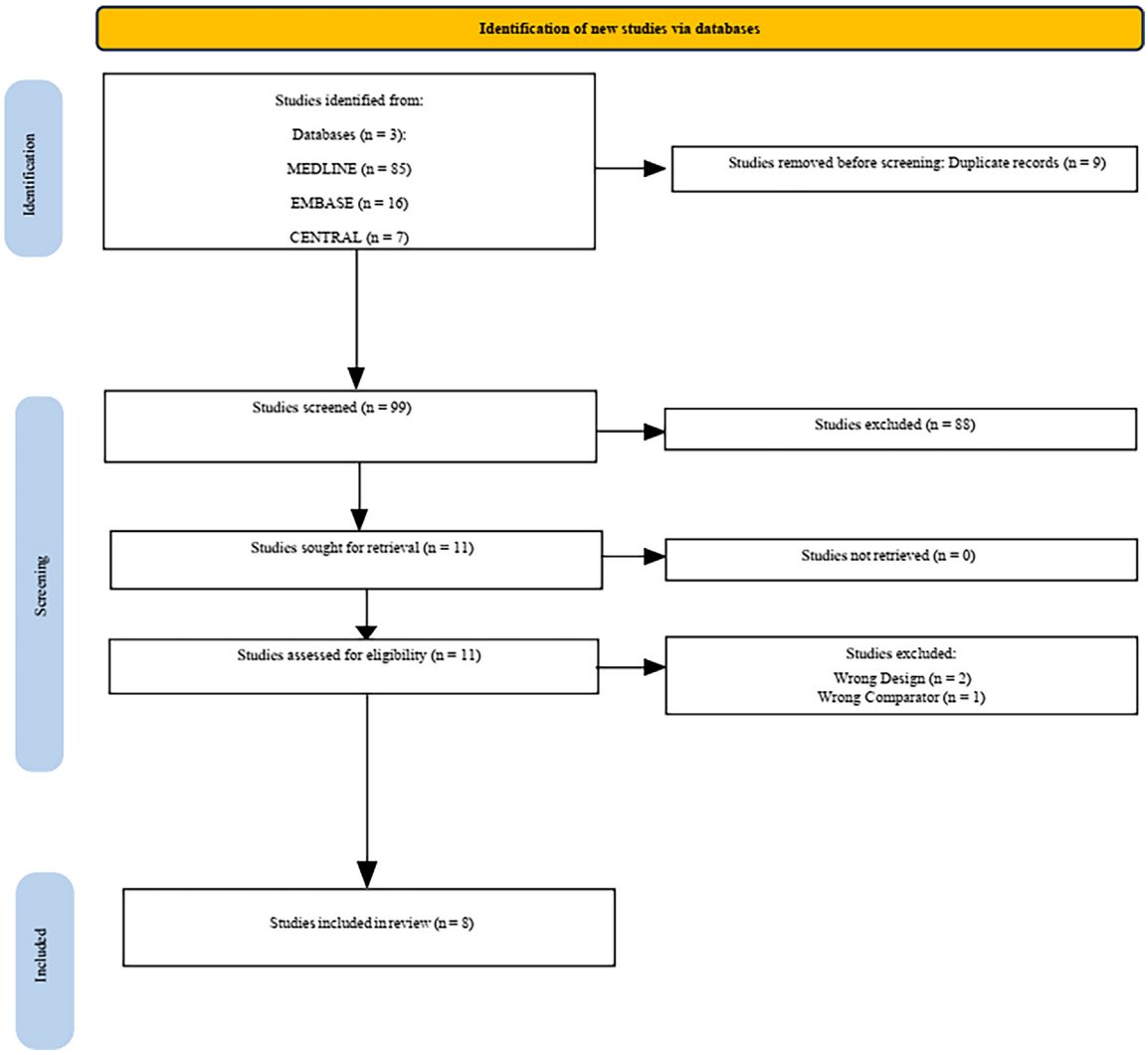


Figure 1 Prisma diagram of systematic review.

Table 2 Summary of findings of primary and secondary outcomes.

N°	Outcomes	Trials	n	I^2(%)	MD/RR (95% CI)	p-value
1	Incidence of Emergence Delirium (Main Analysis)	7	1,319	0	RR: 0.38 [0.30, 0.47]	<0.001
2	Incidence of Emergence Delirium					
	a) Aono's Scale	3	264	0	0.35 [0.22, 0.56]	<0.001
	b) PAED Score	2	881	0	0.37 [0.28, 0.50]	<0.001
	c) Watcha Scale	1	114	N/A	0.50 [0.27, 0.92]	0.03
	d) Cole Agitation Score	1	60	N/A	0.37 [0.18, 0.74]	0.005
	e) Placebo	4	1,025	0	0.37 [0.29, 0.48]	<0.001
	f) Control	3	294	0	0.40 [0.26, 0.63]	<0.001
3	Pain Score (Main Analysis)	3	971	68	MD = −0.98 [−1.92, −0.04]	0.04
4	Pain Score					
	a) CHEOPS	2	174	0	−1.52 [−2.40, −0.63]	<0.001
	b) FLACC	1	797	N/A	−0.40 [−0.60, −0.20]	<0.001
5	Incidence of Nausea and Vomiting	5	1,191	0	RR = 1.45 [0.78, 2.70]	0.24
6	Incidence of Desaturation	3	234	N/A	RR = 5.00 [0.25, 99.95]	0.29

n, Total Sample Size; MD, Mean Difference; RR, Risk Ratio; CI, Confidence Interval; I^2, Heterogeneity; N/A, Not Applicable; CHEOPS, The Children's Hospital of Eastern Ontario Pain Scale; FLACC, The Face, Legs, Activity, Cry, Consolability Scale; PAED, Pediatric Anesthesia Emergence Delirium.

Table 3 Level of Evidence. The level of evidence ranged from very low to low.

Question: Nalbuphine compared to Control for the incidence of emergence delirium.										
Certainty assessment							№ of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nalbuphine	Control	Relative (95% CI)	Absolute (95% CI)	
Incidence of Emergence Delirium											
7	Randomised trials	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[c]	86/659 (13.1%)	228/660 (34.5%)	**RR 0.38** (0.30 to 0.47)	**214 fewer per 1,000** (from 242 fewer to 183 fewer)	⊕◯◯◯ Very low
Pain Scale											
3	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[c]	486	485	-	MD 0.98 **lower** (1.92 lower to 0.04 lower)	⊕⊕◯◯ Low
Incidence of Nausea and Vomiting											
5	Randomised trials	Serious[d]	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[c]	22/617 (3.6%)	15/615 (2.4%)	**RR 1.45** (0.78 to 2.70)	**11 more per 1,000** (from 5 fewer to 41 more)	⊕◯◯◯ Very low
Incidence of Desaturation											
3	Randomised trials	Serious[e]	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[c]	2/117 (1.7%)	0/117 (0.0%)	**RR 5.00** (0.25 to 99.95)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low

CI, Confidence Interval; MD, Mean Difference; RR, Risk Ratio.
Explanations:
[a] One of the included studies is an observational study.
[b] Sample group size < 400.
[c] Small studies with positive results.
[d] Half of the included studies possess high or unclear risk of bias.
[e] All of the studies possess high or unclear risk of bias.

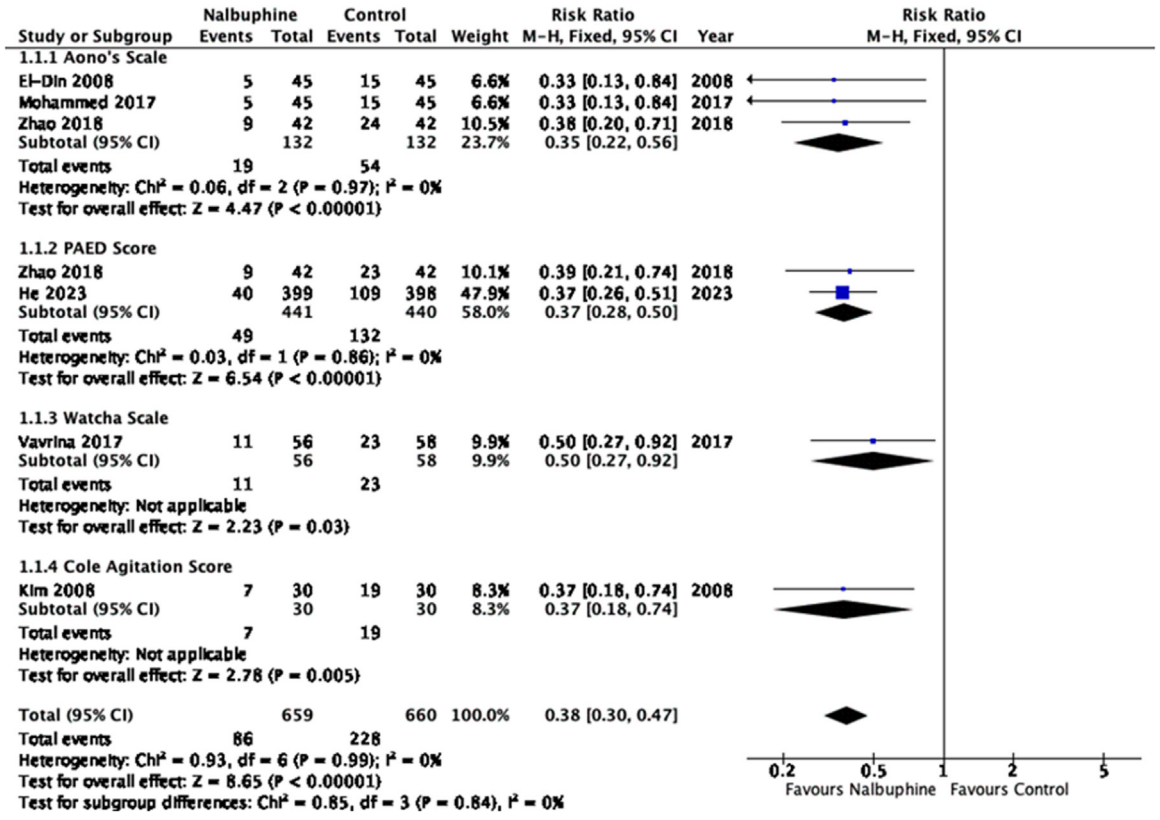


Figure 2 Incidence of Emergence Delirium in pediatric patients receiving nalbuphine or control drugs. Nalbuphine significantly reduced the incidence of emergence delirium in comparison to the control group.

4). The PRISMA Checklist was done according to the PRISMA 2020 guidelines.[23]

Primary outcome: incidence of emergence delirium

In our primary analysis, six individual trials were identified. Within these trials, a total of seven distinct comparison groups were examined. Six trials with seven sets of data (n = 1319 patients; nalbuphine group = 659, control group = 660) investigated the effects of nalbuphine versus control on the incidence of emergence delirium.[14-16,18,19] The incidence of emergence delirium in the nalbuphine and control groups was 13.05% and 34.65% respectively, which was statistically significant (RR = 0.38, 95% CI [0.30, 0.47], $p < 0.001$, level of evidence: very low) (Fig. 2). The statistical heterogeneity across studies was low (I^2 = 0%). Subgroup analysis was performed based on different types of emergence delirium scoring systems, specifically Aono's scale (n = 264, RR = 0.35, 95% CI [0.22, 0.56], $p < 0.001$), Pediatric Anesthesia Emergence Delirium (PAED) Score (n = 881, RR = 0.37, 95% CI [0.28, 0.50], $p < 0.001$, I^2 = 0%), Watcha Scale (n = 114, RR = 0.50, 95% CI [0.27, 0.92], $p = 0.03$) and Cole Agitation Score (n = 60, RR = 0.37, 95% CI [0.18,0.74], $p = 0.005$) (Fig. 2). Another subgroup analysis was performed on the use of nalbuphine versus placebo (n = 1,025, RR = 0.37, 95% CI [0.29, 0.48], p < 0.001) and control (n = 294, RR = 0.40, 95% CI [0.26, 0.63], $p < 0.001$) (Supplementary Fig. 1). Sensitivity analysis of RCTs only showed that the nalbuphine group was associated with a lower incidence of emergence delirium in children undergoing surgery (n = 1,205, RR = 0.37, 95% CI [0.29, 0.46], $p < 0.001$) (Supplementary Fig. 2).

Secondary outcomes: pain scores, incidence of nausea and vomiting

In comparison to the control group, the nalbuphine group was associated with statistically lower postoperative pain scores (nalbuphine group = 486, control group = 485, MD = -0.98, 95% CI [-1.92, -0.04], $p = 0.04$, level of evidence: low) (Supplementary Fig. 3).[14,17,19] However, a high degree of heterogeneity was noted across studies (I^2 = 68%). Subgroup analysis based on different scoring systems such as FLACC (Face, Legs, Activity, Cry, Consolability Scale) (MD = -0.40, 95% CI [-0.60, -0.20], $p < 0.001$) and Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) systems (MD = -1.52, 95% CI [-2.40, -0.63], $p < 0.001$) revealed that postoperative pain scores were statistically lower in the nalbuphine group than in the control group (Supplementary Fig. 3).[14,17,19] In terms of post-operative nausea and vomiting, the pooled data showed no significant differences between the nalbuphine and control groups (n = 1,164, nalbuphine group = 596, control group = 595, RR = 1.45, 95% CI [0.78, 2.70], $p = 0.24$, I^2 = 0%, level of evidence: very low) (Supplementary Fig. 5).[14,15,17,19,29]

Discussion

Our review demonstrated that nalbuphine was associated with decreased incidence of emergence delirium and

reduced postoperative pain scores in children undergoing surgery. However, no significant difference was noted in the incidence of postoperative nausea and vomiting. The level of evidence ranged from very low to low due to risk of bias, imprecision, and strong suspicion of publication bias.

Although the mechanism of action of nalbuphine on emergence delirium remains unclear, our pooled data showed that children undergoing surgery randomized to nalbuphine were associated with a lower incidence of emergence delirium and lower postoperative pain scores. Nalbuphine is a mixed opioid agonist-antagonist that has agonist action on the kappa-receptor found in the brain and spinal cord to produce analgesia and sedative effects[31] which can be reversed by naloxone.[11] Its antagonist action on the μ-opioid receptor produces a capping effect on respiratory depression, and the respiratory depression will not worsen with any further increment of dosage.[32] This ceiling effect is crucial in preventing severe respiratory depression, making nalbuphine a safer drug for treating pediatric patients. However, there are other confounding factors, such as the type of short-acting volatile anesthesia, type of surgery, and patient anxiety, that could influence the occurrence of emergence delirium.[33]

One of the hypotheses by Lewis on the development of emergence delirium asserts that the lack of clearance of volatile anesthetics can disrupt the balance of excitation and inhibition on the central nervous system, leading to different recovery rates of brain function after surgery.[34] In addition, these inhalational agents like desflurane and sevoflurane possess a low blood/gas partition coefficient (0.42 and 0.69 respectively) as compared to isoflurane[35] which may cause rapid awakening from anesthesia, leading to dissociation and altered cognition in children. Most of the included studies applied either sevoflurane or desflurane to maintain anesthesia in pediatric patients whereas one of the studies utilized propofol, implying that the impact of nalbuphine on emergence delirium cannot be fully elucidated in children who received either total intravenous anesthesia or inhalational anesthesia. Recent findings by Voepel-Lewis and colleagues reported that Ear, Nose, and Throat (ENT) surgery (55.4%) is an independent risk factor that can contribute to the incidence of emergence delirium among pediatric patients.[34] Therefore, the inclusion of ENT surgery and other types of surgeries in our review may convey a high degree of variability in our pooled analysis, making the interpretation of the impact of nalbuphine on emergence delirium difficult due to limited data available in the literature.

The incidence of emergence delirium was diagnosed based on different scoring systems (PAED score, Watcha scale) in all the included studies, which could have introduced bias to our primary outcome. For example, the Watcha Scale, Aono's Scale, and Cole Agitation Score are measured based on crying and inconsolability only, which may cause Type II error due to the lower sensitivity of 0.34 and specificity of 0.95.[36] In contrast, the PAED scale incorporates a wider range of behavior such as awareness of surroundings and making eye contact with a higher sensitivity of 0.93 and specificity of 0.94.[36] Another important aspect was the different cut-off value of the PAED scores for emergence delirium in our included studies; for instance, He and colleagues indicated a cut-off $\geq$ 12 on the PAED scale to diagnose the incidence of emergence delirium[14] while Zhao used a threshold value $\geq$10.[19] Therefore, the assessment tool of emergence delirium and the specific cut-off point should be standardized in future RCTs to eliminate this assessment bias.[6,37]

It is believed that nalbuphine reduces the release of pro-inflammatory cytokines and oxidant stress factors, such as IL-6, tumor necrosis factor-alpha and Malondialdehyde (MDA), which exert good analgesia control to patients undergoing surgery.[38] Ruan and colleagues concluded that nalbuphine down-regulates the nuclear factor of kappa-light chain enhancer of the activated B-cells, which helped to reduce the amount of visceral pain in rat models.[39] In addition, nalbuphine is demonstrated to block central sensitization of pain,[40] which is defined as the state of increased neuronal excitability and recruitment of non-nociceptive A-β fibers into the nociceptive pathway.[41] Our finding was consistent with the results of previous experimental studies, demonstrating the beneficial analgesic effect of nalbuphine on postoperative pain relief in children. Similar conclusions were drawn by Kruszynski and colleagues showing that nalbuphine could be a better alternative to morphine in preventing postoperative pain due to its longer duration of action (4—5 hours).[42]

Measurement of pain scores was standardized in most of the included studies using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), which is the one of the most appropriate tools for monitoring postoperative pain among children with high sensitivity of 0.93 and high specificity of 0.67.[43] However, when given the same type of pain stimuli, pain scores can differ among patients depending on the individual's tolerance to pain and the use of other adjuncts analgesic medications.[44] In a study by He,[14] the synergic effect with nalbuphine and sufentanil/remifentanil may have provided better postoperative pain control in children after surgery.[45] In a sensitivity analysis by removing this study, the mean difference of the postoperative pain scale remained statistically significant with a lower degree of heterogeneity. However, our finding might be premature due to the small sample size of included studies.

Nalbuphine exerts antagonist activity on μ receptors, which is theorized to lower the incidence of nausea and vomiting as compared to other opioids that have full agonist activity on the μ receptors.[46] A meta-analysis of 15 trials (820 adult patients) showed a lower incidence of vomiting and nausea in the nalbuphine group as compared to the morphine group.[47] Our review disagreed with the previous meta-analysis as our pooled data of a small sample size revealed no significant difference in the incidence of postoperative nausea and vomiting in children undergoing surgery. The administration of opioids activates μ receptors, leading to centrally mediated decrease in respiratory rate, which could cause desaturation[48] and hypoxic insults to patients after surgery.[49] It is believed that nalbuphine's antagonistic activity on μ receptors can minimize the risk of respiratory depression.[11] Our review revealed no significant differences between the nalbuphine and control groups on the incidence of desaturation. However, given the limited number of studies with small sample size, these findings must be interpreted with caution. Therefore, the effects of nalbuphine on postoperative nausea and vomiting and incidence of desaturation remain to be elucidated in future adequately powered RCTs.

Our systematic review has several limitations. Firstly, one of the limitations is contributed by the lack of a standardized definition of emergence delirium across all the included studies. Besides, most of the included studies were underpowered, with each arm possessing less than 400 patients. In addition, a significant portion of the sample size was contributed by a single study (He et al), which accounted for almost 50% of the meta-analysis's weight, which may have skewed the overall results. Most of the included studies were underpowered to study our primary outcome. To date, there are limited studies on the use of nalbuphine to prevent emergence delirium. This could be due to concerns regarding the safety and efficacy profile of nalbuphine and its potential interactions with other anesthesia drugs, specifically among the pediatric population. Therefore, future adequately powered RCTs are warranted to study the true impact of nalbuphine on emergence delirium among children undergoing surgery.

In conclusion, to the best of our knowledge, this was the first systematic review and meta-analysis exploring the use of nalbuphine in the incidence of emergence delirium in children undergoing surgery. This meta-analysis demonstrated the promising effects of nalbuphine in lowering the incidence of emergence delirium in pediatric patients. However, small sample size and low quality of evidence limit a strong recommendation of the use of nalbuphine on emergence delirium in children.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844543.

References

1. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: An update. Curr Opin Anaesthesiol. 2014;27:309—15.
2. Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. Anesth Analg. 2007;104:84—91.
3. Lerman J. Emergence delirium and agitation in children - UpToDate [Internet]. UpToDate. 2023 [cited 2023 Apr 4]. Available from: https://www.uptodate.com/
4. Urits I, Peck J, Giacomazzi S, et al. Emergence Delirium in Perioperative Pediatric Care: A Review of Current Evidence and New Directions. Adv Ther. 2020;37:1897—909.
5. Lepousé C, Lautner CA, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. BJA. 2006; 96:747—53.
6. Lee SJ, Sung TY. Emergence agitation: Current knowledge and unresolved questions. Korean J Anesthesiol. 2020;73:471—85.
7. Kim HS, Byon HJ, Kim JE, Park YH, Lee JH, Kim JT. Appropriate dose of dexmedetomidine for the prevention of emergence agitation after desflurane anesthesia for tonsillectomy or adenoidectomy in children: Up and down sequential allocation. BMC Anesthesiology. 2015;15:1—6.
8. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth. 1993;5:194—203.
9. Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anaesthesia in children undergoing adenotonsillectomy. Paediatr Anaesth. 2002;12:604—9.
10. Zeng Z, Lu J, Shu C, Chen Y, Guo T, Wu QP, et al. A Comparision of Nalbuphine with Morphine for Analgesic Effects and Safety: Meta-Analysis of Randomized Controlled Trials. Sci Rep. 2015;5:10927.
11. Larsen D, Maani CV. Nalbuphine. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [cited 2023 Apr 09]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534283/.
12. Kubica-Cielińska A, Zielińska M. The use of nalbuphine in paediatric anaesthesia. Anaesthesiol Intensive Ther. 2015;47:252—6.
13. Chen ZM, Gao BH, Wang LS. Effect of two different doses of nalbuphine for postoperative analgesia in children with cleft palate: a randomized controlled trial. BMC Anesthesiol. 2024;24:1—6.
14. He J, Zhang L, Tao T, et al. Nalbuphine reduces the incidence of emergence agitation in children undergoing Adenotonsillectomy: A prospective, randomized, double-blind, multicenter study. J Clin Anesth. 2023: 85.
15. Kim HJ, Kim HS, Kim SD, et al. Effects of propofol and nalbuphine on emergence agitation after sevoflurane anesthesia in children for strabismus surgery. Korean J Anesthesiol. 2008; 55:575—8.
16. Mohammed KSA, Ali KEDH, Ahmed HEA, Ibrahem HA. Comparative study between midazolam versus nalbuphine on prevention of emergence agitation after sevoflurane anesthesia in pediatric patients undergoing tonsillectomy with or without adenoidectomy. Tanta Med Jour. 2017;45:73.
17. Noor El-Din T, Sharaf M, Alkumity A, Mahmoud E, Eman AS. Midazolam Versus Nalbuphine On Prevention Of Emergence Agitation In Pediatric Patients On Sevoflurane Anesthesia. Al-Azhar Med J. 2018;47:537—85.
18. Vavřina M, Žurek J, Fedora M, Dominik P, Forbelská M, Bienertova-Vasku J. Reduction of paediatric emergence agitation after adenotonsillectomy with nalbuphine. Curr Pediatr Res. 2017;21:490—6.
19. Zhao N, Wu Y, Yu C. Effect of intravenous nalbuphine on emergence agitation in children undergoing dental surgery under sevoflurane anesthesia. Int J Clin Exp Med. 2018;11:10215—22.
20. Chang H, Hong H, Lee J, et al. Effect of Nalbuphine on Emergence Agitation and Recovery after Desflurane Anesthesia in Children for Strabismus Surgery. Korean J Anesthesiol. 2008;54.
21. Gao XN, Nie XY, Gao JL, et al. Pharmacokinetic Study of Nalbuphine in Surgical Patients Undergoing General Anesthesia with Varying Degrees of Liver Dysfunction. Drug Des Devel Ther. 2022;16:2383—93.
22. Ji K, Gong X, Luan T, Gao X, Zang B. Pain management of nalbuphine and sufentanil in patients admitted intensive care unit of different ages. BMC Emerg Med. 2022: 22.
23. Higgins JPT, Thomas J, Chandler J, eds. Cochrane handbook for systematic reviews of interventions version 6.4 (updated August 2023), Cochrane; 2023. Available from www.training.cochrane.org/handbook.
24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372372:n71.
25. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

26. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Insititute. 2011.
27. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. Rating Quality of Evidence and Strength of Recommendations: What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336:995.
28. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration; 2020.
29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
30. Elagamy AE, Mahran MG, Mahmoud AZ. Dexmedetomidine versus nalbuphine in prevention of emergence agitation following adenotonsillectomy in pediatrics. Egypt J Anaesth. 2020;36: 24—9.
31. De Souza EB, Schmidt WK, Kuhar MJ. Nalbuphine: an autoradiographic opioid receptor binding profile in the central nervous system of an agonist/antagonist analgesic. J Pharmacol Exp Ther. 1988;244:391—402.
32. Gunion MW, Marchionne AM, Anderson CTM. Use of the mixed agonist—antagonist nalbuphine in opioid based analgesia. Acute Pain. 2004;6:29—39.
33. Moore AD, Anghelescu DL. Emergence Delirium in Pediatric Anesthesia. Pediatr Drugs. 2017;19:11—20.
34. Voepel-Lewis T, Malviya S, Tait A. Prospective Cohort Study of Emergence Agitation in the Pediatric Post Anesthesia Care Unit. Anesth Analg. 2003;96:1625—30.
35. Khan J, Liu M. Desflurane [Internet]. StatPearls: StatPearls Publishing; 2022. p. 1—4https://www.ncbi.nlm.nih.gov/books/NBK537106/.
36. Locatelli BG, Ingelmo PM, Emre S, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Paediatric Anesthesia Emergence Delirium scale. Paediatr Anaesth. 2013;23:301—8.
37. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatr Anaesth. 2010;20:704—11.
38. Xi MY, Li SS, Zhang C, Zhang L, Wang T, Yu C. Nalbuphine for Analgesia After Orthognathic Surgery and Its Effect on Postoperative Inflammatory and Oxidative Stress: A Randomized Double-Blind Controlled Trial. J Oral Maxillofac Surg. 2020;78:528—37.
39. Ruan D, Wang Y, Li S, Zhang C, Zheng W, Yu C. Nalbuphine alleviates inflammation by down-regulating NF-κB in an acute inflammatory visceral pain rat model. BMC Pharmacol Toxicol. 2022; 23:1—10.
40. Rao ZA, Choudhri A, Naqvi S. Ehsan-ul-Haq. Walking epidural with low dose bupivacaine plus tramadol on normal labour in primipara. J Coll Physicians Surg Pak. 2010;20:295—8.
41. Cayrol T, van den Broeke EN. Central sensitisation: causes, therapies, and terminology. Lancet Rheumatol. 2021;3:e548.
42. Kruszyński Z, Jaworska-Grajek M, Wiewiórowski K, Warzybok K. Comparative studies of nalbuphine and morphine in the therapy of postoperative pain in gynecology. Gineko Pol. 1989;60:216—22.
43. Blount RL, Loiselle KA. Behavioural assessment of pediatric pain. Pain Res Manag. 2009;14:47—52.
44. McCormack HM, Horne DJ de L, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18:1007—19.
45. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC Anesthesiol. 2005;5:5.
46. Benzon HA, Shah RD, Benzon HT. Perioperative Nonopioid Infusions for Postoperative Pain Management. Essentials of Pain Medicine. Fourth. Elsevier. 2018. 111-116.e2.
47. Zeng Z, Lu J, Shu C, Chen Y, Guo T, Wu QP, et al. A comparison of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. Sci Rep. 2015; 5:10927.
48. Boland J, Boland E, Brooks D. Importance of the correct diagnosis of opioid-induced respiratory depression in adult cancer patients and titration of naloxone. Clin Med (Lond). 2013; 13:149—51.
49. Shebl E, Mirabile VS, Sankari A, Burns B. Respiratory Failure [Internet]. Treasure Island (FL). StatPearls Publishing. StatPearls Publishing; 2023. [cited 2023 Apr 09]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526127/.

Brazilian Journal of Anesthesiology 2024;74(5): 744368



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Real-time ultrasound-guided epidural catheter placement in infants: a case series



Manoj Kamal [a,*], **Mritunjay Kumar** [b], **Pooja Bihani**[c], **Tanya Mital**[a], **Geeta Singariya** [c], **Pradeep Bhatia** [a]

[a] *All India Institute of Medical Sciences, Anaesthesiology & Critical Care, Jodhpur, India*
[b] *All India Institute of Medical Sciences, Anaesthesiology, Critical Care and Pain Medicine, New Delhi, India*
[c] *Dr S N Medical College, Anaesthesiology & Critical Care, Jodhpur, India*

Received 2 December 2020; accepted 8 March 2022
Available online 18 March 2022

KEYWORDS
Case report;
Epidural;
Pediatrics;
Ultrasound

Abstract Although epidural catheter insertion under ultrasound (US) guidance in the pediatric age group has been reported in the literature, it is yet to be adopted widely in clinical practice. The incomplete fusion of bones in pediatric patients provides an acoustic window for the US. The epidural space in children is at shallow depth, hence a high-frequency probe, which provides better resolution can be used. We present a case series in which real-time US-guided epidural catheter placement was performed in 10 infants in lower thoracic and upper lumbar interspaces. We reiterate that the use of real-time US during epidural catheter placement in patients increases the success rate of epidural catheter placement while decreasing procedural complications.
© 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

Epidural analgesia is the standard and reliable technique of perioperative pain relief in patients undergoing abdominal and thoracic surgeries.[1] But, its use in the infant age group is not that common because of concerns about higher chances of dural puncture and neurological complications as they have thinner and softer ligamentum flavum, narrower interspace, and as most of the epidural catheter in children is performed under general anesthesia[2] The ultrasound (US) improves the success rate and safety margin in epidural catheter placement.[3]

There is a dearth of literature on this. We present a case series of ten American Society of Anesthesiologists (ASA) physical status I/II infants undergoing abdominal surgeries, in which a real-time US-guided epidural catheter was placed. We also used a unique Parasagittal Oblique (PSO) view for performing this procedure.

Case presentation

Institutional ethics committee approval and informed written parental consent were taken. A thorough preoperative checkup was done one day before the scheduled operative day. Exclusion criteria included children with a history of spine deformity or surgery, neurological disorder, coagulopathy, local infection or sepsis, and allergy to local anesthetics.

* Corresponding author.
E-mail: geetamanoj007@yahoo.co.in (M. Kamal).

https://doi.org/10.1016/j.bjane.2022.03.004
0104-0014/© 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/).

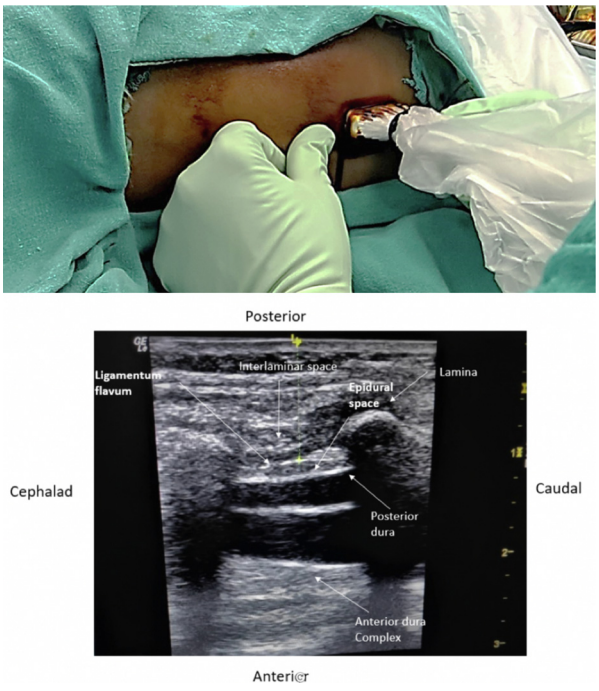


Figure 1 Probe placement and ultrasound image of epidural space.

All epidurals were performed by two anesthesiologists, who had sufficient experience in pediatric regional anaesthesia (MK and PB) under general anesthesia in the left lateral position, congruent epidurals were inserted in lower thoracic and lumbar regions using linear/hockey probe (8 to 13 MHz) (GE LOGIQe 9L, GE Healthcare, Wauwatosa, Wisconsin) after getting an optimal view of ligamentum flavum and anterior and posterior dura complexes by PSO approach (Fig. 1). The posterior epidural space is seen as a hypoechoic area between the hyperechoic ligamentum flavum and the posterior dura. A 19G, 50- mm Tuohy needle (Vygon, Aachen, Germany), marking at every 0.5 cm from 1 cm from the distal tip was inserted in-plane from the caudal end of the probe and advanced under real-time US guidance. Constant visualization of the lamina and the posterior epidural space helped in the depth determination and prevention of dural puncture or damage to the spinal cord. Further confirmation of epidural space was done by the 10- mL plastic syringe with loss of resistance to saline technique and simultaneous visualization of downward displacement of posterior dura complex on the US (Fig. 1). The 22G epidural catheter was threaded through the needle till 2.5–3 cm inside in epidural space. Procedure time (start from skin needle insertion to access of epidural space), number of bone contacts or needle redirections, number of attempts, and procedure-related complications like dural puncture, bloody tap were recorded.

Results

The median age was 10 (8.8–11.25) months and the median weight was 7.25 (6.6–7.6) kg. The real-time US-guided epidural catheter placement was performed with a 100% success rate. The mean procedure time taken was 212 seconds (range 60–480 seconds). Seven out of 10 required single needle insertion attempts, while 2 and 3 attempts were needed in 2 and 1

Table 1 Patient details.

Name of surgery	Sex	Age (months)	Weight (kg)	Level of epidural	Number of attempts	Bone contacts	Redirections	Time (sec)	Complications
Colostomy closure	M	12	7.0	L1–L2	1	1	2	130	None
Colostomy closure	M	10	8.2	T12–L1	2	2	2	180	None
Case of ARM – Colostomy formation	F	9	6.8	T11–T12	1	None	0	60	None
Colostomy closure	F	10	7.5	T11–T12	1	2	2	360	None
Elective kasai procedure	F	2	3.7	T9–T10	1	1	2	70	None
PSARP	M	9	7.5	T12–L1	1	1	1	210	None
Hepatico-enterostomy	F	7	7.0	T8–T9	1	None	0	300	None
Urethroplasy	M	11	7.5	L3–L4	1	1	1	115	None
Gastric pull up	F	12	9	T7–T8	3	2	2	480	None
Colostomy closure	M	11	6	T12–L1	1	2	2	150	None

ARM, Anorectal malformation; PSARP, Posterior Sagittal Anorectoplasty.

patients, respectively. Two patients had no bone contact, while 4 had single bone contact, and 4 had it twice. No needle redirections were required in 2 patients, single redirections in 2 patients, and two redirections in 5 patients (Table 1). Any procedure-related complications were not observed.

Discussion

Ultrasound guidance has advantages, particularly in young children in terms of success rate.

The US helps in visualizing interlaminar space, ligamentum flavum, dural complexes, needle tip, the position of the epidural catheter, and the spread of the local anaesthetic solution. In pediatric patients, due to the lack of ossification of posterior elements of the spinal canal, an acoustic window can be easily obtained. The ultrasound can also be used to locate conus medullaris and dural sac as well as any structural abnormalities that preclude the use of epidural blockade. The US helps in precise localization of targeted interspace and to visualize the spread of caudally administered drugs, hence it will help in achieving better postoperative analgesia. The real-time visualization of the epidural needle under the US offers additional safety and benefits. However, additional studies are required before concluding that ultrasound guidance reduced the rate of bloody puncture.

The Pediatric Regional Anesthesia Network (PRAN) provided highly audited data on practice patterns and complications in infants and children. Almost all (95%) blocks were placed under GA, single-injection caudal blocks were the most frequently performed (40%). Single-injection blocks had fewer adverse events than continuous blocks, although the most frequent events (33% of all events) in the latter group were catheter-related problems.[4]

The longitudinal PSO view is a good view for epidural catheter placement in pediatric patients. It allows needle manipulation along with probe placement in limited space available in children. The complications like dural puncture and injury to the spinal cord encountered during traditional epidural catheter placement in pediatric patients can be minimized by using the US. Commonly practiced caudal route of epidural catheter placement in children also comes with risks of contamination with anal bacteria and chances of coiling and failure.[5]

However, real-time US-guided epidural catheter placement in small children and infants needs some degree of expertise and has a learning curve.

Conclusion

Lumbar or thoracic epidural catheter placement in infants is gaining momentum in pediatric anesthesia practice. US use can increase the success rate and margin of safety while reducing needle redirections and insertion attempts.

Authors' contribution

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form.

Conflicts of interest

The authors declare no conflicts of interest.

Previous presentation in conferences

Euroanaesthesia 2019 conference at Vienna, Austria.

Institutional Ethical Committee

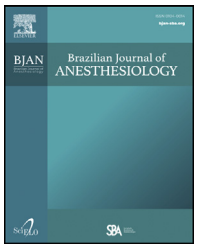
Reference no AIIMS/IEC/2018/1647, dated 31/12/2018.

References

1. Willschke H, Bosenberg A, Marhofer P, Willscheke J, Schwindt J, Weintraud M, et al. Epidural catheter placement in neonates: Sonoanatomy and feasibility of ultrasonographic guidance in term and preterm neonates. Reg Anesth Pain Med. 2007;32:34—40.
2. Willschke H, Marhofer P, Bösenberg A, Johnston A, Wanzel O, Sitzwohl C, et al. Epidural catheter placement in children: comparing a novel approach using ultrasound guidance and a standard loss-of-resistance technique. Br J Anaesth. 2006;97:200—7.
3. Marhofer P, Lönnqvist PA. The use of ultrasound-guided regional anaesthetic techniques in neonates and young infants. Acta Anaesthesiol Scand. 2014;58(9):1049—60.
4. Walker BJ, et al. Complications in Pediatric Regional Anesthesia: An Analysis of More than 100,000 Blocks from the Pediatric Regional Anesthesia Network. Anesthesiology. 2018 Oct;129 (4):721—32.
5. Wiegele M, Marhofer P, Lönnqvist PA. Caudal epidural blocks in paediatric patients: a review and practical considerations. Br J Anaesth. 2019;122(4):509—17.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



CASE REPORT

Ultrasound-guided popliteal sciatic nerve block in a pediatric patient with complex regional pain syndrome: a case report

Patrícia Milena Souza Vinent, Eduardo José Silva Gomes de Oliveira, Caio Márcio Barros de Oliveira, Ed Carlos Rey Moura, Elizabeth Teixeira Noguera Servin, Lyvia Maria Rodrigues de Sousa Gomes, Plinio da Cunha Leal *

Universidade Federal do Maranhão (UFMA), São Luís, MA, Brazil

Received 23 October 2020; accepted 10 July 2021
Available online 26 July 2021

KEYWORDS
Complex regional pain syndrome;
Pain;
Nerve block;
Case report

Abstract In the pediatric population, complex regional pain syndrome (CRPS) is a challenging condition that leads to chronic psychosocial dysfunction. This case is of a 12-year-old male patient, 50 kg, who, after twisting his right ankle, started to present intense pain. Without adequate diagnosis and treatment, his family sought a pain specialist. During the evaluation, a change in sensitivity and temperature was observed, besides hyperalgesia, allodynia, redness, edema, and motor dysfunction, being diagnosed with CRPS. Ultrasound-guided sciatic blocks were performed on the affected limb, increasing the interval between crises, reducing pain intensity, and promoting a return to daily activities.
© 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

In the pediatric population, complex regional pain syndrome (CRPS) is often a challenging disorder that is closely associated with a prolonged course of psychosocial pain and dysfunction. Commonly, in this population, various forms of approaches are needed for the adequate and universal treatment of the patient's symptoms.[1]

The treatment modalities of CRPS focus on the use of opioids, anticonvulsants, corticosteroids, and bisphosphonates, as well as interventional treatment with a sympathetic plexus blockade. There is still no proven superior therapy however an excellent clinical response to plexus blocks is observed.[1]

Popliteal sciatic nerve block (PSNB) promotes a sensory and sympathetic fiber block. It is a difficult technique to

* Corresponding author.
E-mail: pliniocunhaleal@hotmail.com (P.C. Leal).

https://doi.org/10.1016/j.bjane.2021.07.012
© 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/).

perform that became popular with the use of ultrasound to assist in performing the technique.[2] Although there are few studies with this type of intervention in CRPS in the pediatric population, regional blocks are described as an alternative in cases presenting with dysautonomia and sympathetically mediated pain.[3]

This study presents a case report, according to the CARE guidelines,[3] of a pediatric patient with CRPS that received a sequence of PNSB. Due to the lack of reports on the subject, especially in pediatrics, its importance is emphasized, being one of the first studies with this type of approach in a difficult-to-manage pain.

Case report

A 12-year-old male child, 50 kg, with CRPS in the right lower limb was submitted to a series of popliteal sciatic nerve blocks (PSNBs). The patient reported intense pain in the right foot after twisting the ankle during sports practice. The next day, he underwent a computed tomography scan of his right foot, showing slight joint effusion. The joint was immobilized for 11 days due to intense pain. After the removal of the immobilization, the patient presented pain during physical activities.

The child was accompanied by an orthopedist and a rheumatologist due to persistent pain and gradual worsening of the pain. After 3 months, he underwent 3 magnetic resonance images and several laboratory markers, which showed only mild diffuse bone edema without laboratory changes.

The pain worsened and became continuous. After 4 months of the lesion, he continued with limitation, requiring a wheelchair to move. Motor and analgesic physiotherapy were started without improvement.

Given the difficulty in pain control and frequent reports of foot shocks, the patient was referred to the pain specialist. During the physical examination, he reported pain disproportionate to the trigger event and a change in sensitivity and temperature in the right foot was observed, in addition to hyperalgesia, allodynia, redness, edema, pain in limb handling, and motor dysfunction (with decreased strength and tonus) (Fig. 1). A diagnosis of complex regional pain syndrome was made according to the criteria of the International Association for the Study of Pain (IASP), also called Budapest criteria. Through the evaluation, it was possible to classify CRPS in a dystrophic or subacute stage (second stage/grade).

He started treatment with gabapentin 300 mg every 8 hours, methadone 5 mg every 12 hours and amitriptyline 25 mg daily, which was later exchanged for duloxetine 60 mg daily, since with amitriptyline there was a complaint of dry mouth and dizziness that were not tolerated by the patient. Physiotherapy for pain control was also maintained.

After two weeks of treatment, the patient presented his first pain crisis and was hospitalized. He reported intense (10/10), continuous pain. Then, his first popliteal ischial nerve block (PSNB) was performed in June 2019, with significant pain improvement. Using ultrasonography, the ischial nerve was identified in the popliteal fossa, and 20 ml of ropivacaine 0.2% associated with betamethasone dipropionate 5 mg and betamethasone disodium phosphate 2 mg were injected. Another four PSNB procedures were performed monthly with 20 ml of 0.2% ropivacaine, with gradual improvement. The interventions were well tolerated by the



Figure 1 A, Difference in the color of the right lower limb (cyanosis) compared to the left; B and C, Dorsal cyanosis of the right foot and dystrophy on the third finger; D, Plantar cyanosis of the right foot.

patient who once related a gradual and continuous improvement after the procedures.

Despite the important improvement in pain (2/10) and the patient's ability to move without help, the family members reported that the patient had a depressed mood and no motivation to perform the activities he usually liked to perform. One year after the injury, the patient started a psychiatric follow-up, was diagnosed with depression, and started treatment.

Until then, he used gabapentin 300 mg every 8 hours, methadone 5 mg every 12 hours, fluoxetine 20 mg daily and cannabidiol 4.2 mg every 8 hours, with good adherence to the treatment, reporting good pain control. Thus, through the positive results obtained after the combination of intervention and optimized pharmacological treatment, duloxetine and methadone were gradually withdrawn, maintaining fluoxetine 20 mg daily and cannabidiol 4.2 mg every 8 hours in the therapeutic plan.

After almost one year of his last PSNB, the patient presented a new pain crisis, and it was necessary to perform a new PSNB, in addition to reintroducing methadone 5 mg 12 hours daily, which had been gradually withdrawn. Additionally, he returned to his psychiatrist and, during the evaluation, the patient reported dreaming of his parents' death by COVID-19, which may have worsened his pain symptoms. With another PSNB intervention and adjustments to his therapeutic plan, the patient reported good control of symptoms, denying pain (0/10). Currently, the patient has returned to practicing sports and can perform his daily activities without hindrance.

Discussion

CRPS is an autonomic pathology that usually appears after trauma in limb extremities, and it may or may not be associated with nerve injury. In the pediatric population, it is a challenging disorder that is often associated with a prolonged course of pain and psychosocial dysfunction for the patient, such as anxiety and depression. In comparison with adults, in pediatric patients, CRPS tends to affect the lower extremities and is more common in women between 11 and 12 years of age. In this affected population, several forms of approaches are necessary for adequate treatment.[1,3,4]

Randomized clinical trials for the treatment of CRPS are limited. In general, treatment with medications, including anticonvulsants, antidepressants, and anti-inflammatories, in association with physical, occupational, and psychological therapies is initiated. In specific cases, in the absence of improvement, interventional procedures are indicated, as in the case described.

Peripheral nerve blocks, such as sciatic nerve and saphenous nerve blocks can be performed singularly or in continuous infusion and are useful in the treatment of dysautonomia and sympathetically mediated pain in the lower limbs of patients with CRPS.[3,4] They provide unilateral analgesia, promote a restricted and localized sympathetic and sensory block, and have no effect on bladder or bowel function. Analgesia allows and facilitates the performance of physiotherapy, a fundamental component of the gradual rehabilitation of functional capacity in CRPS.[1,4] In the literature review, there was more emphasis on studies with continuous blocks,[1] and this study is one of the first cases in which a series of singular blocks were used for pain management in pediatric CRPS, with beneficial results for the patient.

The beneficial effects and safety of glucocorticoids in analgesia are well established. However, controversy continues regarding whether perineurial glucocorticoids have a similar or better analgesic effect than intravenous glucocorticoids. A recent meta-analysis suggested that perineal glucocorticoids have a lower minimum dose and/or provide more effective analgesia than the same intravenous dose.[5]

Dexamethasone, a hydrophilic and nonparticle corticoid, is most commonly used with the effect of prolonging the blockade of peripheral nerves for 6 to 8 hours.[5] Lipophilic glucocorticoids and particulates, such as betamethasone, exhibit efficacy and safety similar to nonparticulates, but with longer durations.

Particulate glucocorticoids in peripheral nerve blocks have been described only in isolated studies that have a lack of safety data. However, the adverse events reported were mainly related to intrathecal injection or intravascular injection, and no complications were reported for peripheral nerve blocks.[5] Moreover, monthly applications may lead to the effects of chronic corticoid use, such as hypertension, insulin resistance, and adrenal insufficiency. In this way, repeating the blockade with the use of corticoids was avoided.

The approach with pharmacological treatment, associated with specific physiotherapy, did not present a satisfactory response in pain control. Only after a sequence of five PSNB in the right popliteal region was it possible to have a gradual improvement of its clinical scenario, changing the course of the disease and allowing the patient to return to his daily activities.

In summary, with the use of ultrasonography, the quality and safety of peripheral nerve blocks were greatly improved, allowing performance in anatomical areas of difficult access. Taking into consideration the possible adverse effects related to the chronic use of corticoids, the PSNB series with a solution of a local anesthetic and corticoids in association with conventional treatment for CRPS in acute and subacute stages is an alternative to be considered to obtain better pain control and facilitate adherence to conventional treatment. In addition, it is important to remember that psychiatric alterations that can be triggered by the condition[4] are fundamental to multidisciplinary follow-up.

Disclosure

The authors did not receive any specific grants from funding agencies in the public, commercial or non-profit sectors, and did not declare any conflict of interest.

Declaration of Ethical Approval

This study was approved by the Research and Ethics Committee of Hospital São Domingos (CAAE 35222920.8.0000.5085/ Number 4.210.526).

Informed assent and consent

The patient and his/her guardian have provided a written informed consent form and an informed consent form to present the case.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Everett A, Mclean B, Plunkett A, et al. A unique presentation of complex regional pain syndrome type I treated with a continuous sciatic peripheral nerve block and parenteral ketamine infusion: a case report. Pain Med. 2009;10:1136–9.
2. Barbosa FT, Barbosa TR, Cunha RM, et al. Anatomical basis for sciatic nerve block at the knee level. Rev Bras Anestesiol. 2015;65:177–9.
3. Zernikow B, Wager J, Brehmer H, et al. Invasive treatments for complex regional pain syndrome in children and adolescents: a scoping review. Anesthesiology. 2015;122:699–707.
4. Logan DE, Williams SE, Carullo VP, et al. Children and adolescents with complex regional pain syndrome: more psychologically distressed than other children in pain? Pain Res Manag. 2013;18:87–93.
5. Zorrilla-Vaca A, Li J. Dexamethasone injected perineurally is more effective than administered intravenously for peripheral nerve blocks: a meta-analysis of randomized controlled trials. Clin J Pain. 2018;34:276–84.

Brazilian Journal of Anesthesiology 2024;74(5): 744339



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CASE REPORT

Transfusion-related acute lung injury and treatment with high-flow oxygen therapy in a pediatric patient: a case report



Cengiz Sahutoglu *, Cansu Balci , Taner Balcioglu

Ege University School of Medicine, Department of Anesthesiology and Reanimation, Izmir, Turkey

Received 6 March 2021; accepted 5 December 2021
Available online 17 December 2021

KEYWORDS
Transfusion-related acute lung injury;
Blood transfusion;
Pediatrics;
Oxygen inhalation therapy;
Case report

Abstract Transfusion-Related Acute Lung Injury (TRALI) is an immune-inflammatory lung pathology that manifests within the first 6—72 hours after administration of blood products. However, due to reduced awareness of TRALI, it continues to be an underreported and often underdiagnosed complication of transfusion therapy. We report a case of a 6-year-old girl with myelodysplastic syndrome and TRALI developed in the first hour after platelet transfusion. Diagnosis of TRALI is based on the exclusion of etiologic factors such as volume overload and cardiogenic pulmonary edema following transfusion. Symptoms responded to high-flow oxygen therapy, so intubation was not attempted and full recovery was achieved.
© 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

Transfusion-related acute lung injury (TRALI) is an immune-inflammatory lung pathology that manifests with tachycardia, tachypnea, dyspnea, hypoxia, and bilateral pulmonary edema within the first 6—72 hours after administration of blood products. Symptoms such as pinkish secretion, hypotension, fever, and cyanosis are seen in the respiratory tract.[1] It is the main cause of death from transfusion and the mortality rates range between 6—14 percent.[1,2]

Transfusion-related acute lung injury and transfusion-associated circulatory overload (TACO) are acute respiratory distress syndromes that occur within 6 hours after blood transfusion. It is very difficult to distinguish TRALI and TACO from the underlying causes of lung injury, fluid overload, or from each other. TACO is characterized by pulmonary hydrostatic (cardiogenic) edema, while TRALI manifests as non-cardiogenic permeability pulmonary edema.[2-4]

In this case report, a high-flow oxygen therapy (HFOT) treatment of a pediatric patient who developed TRALI after platelet transfusion was discussed.

Abbreviations: TRALI, Transfusion-Related Acute Lung Injury; TACO, Transfusion-Associated Circulatory Overload; HFOT, High-Flow Oxygen Therapy; PEEP, Positive end-Expiratory Pressure; FiO2, Fraction of inspired Oxygen; PACU, Postanesthesia Care Unit; PaO2, Partial pressure of Arterial Oxygen; PaCO2, Partial pressure of Arterial Carbon dioxide; SO2, Arterial Oxygen Saturation.

* Corresponding author.
E-mail: csahutoglu@yahoo.com (C. Sahutoglu).

https://doi.org/10.1016/j.bjane.2021.12.001
0104-0014/© 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/).

Table 1 Postoperative blood gas analyses of the patient.

Postoperative	20th min	2nd h	6th h	10th h	24th h	48th h
PH	7.31	7.34	7.28	7.37	7.43	7.43
$PaCO_2$ (mmHg)	44	41.5	47	41.3	38.2	39.3
PaO_2 (mmHg)	56.8	64.3	89.8	80.9	72.1	124
SO_2 (%)	82.6	88	96.1	95.8	94.5	99
Lactate ($mmoL.L^{-1}$)	1.7	1.7	1.5	1.9	1.7	1.1
PaO_2/FiO_2	113	107	150	162	160	276
Blood pressure (mmHg)	85/40	96/50	95/52	92/45	90/48	94/46
Heart rate (bpm)	145	125	120	118	112	108
Respiratory rate (min^{-1})	45	28	26	24	20	20
Fluid balance (mL)	+520	+170	+10	-150	-200	-250
Temperature (°C)	36.2	36.3	36.6	36.8	36.7	36.6
Therapy	Mask	HFOT	HFOT	HFOT	HFOT	HFOT

Mask, Simple Face Mask (5 $L.min^{-1}$ O_2); HFOT, High-Flow Oxygen Therapy; min, minute; h, hour; PaO_2, Partial pressure of Arterial Oxygen; $PaCO_2$, Partial pressure of Arterial Carbon dioxide; SO_2, Arterial Oxygen Saturation.

Case report

A 6-year-old girl (17 kg, 110 cm) was admitted for splenorenal shunting due to the development of portal hypertension. Her medical history revealed myelodysplastic syndrome and upper gastrointestinal bleeding five times due to esophageal varices. Her hemogram values were as follows: leukocyte: 1.920 mm^{-3}, hematocrit: 25.9%, and platelet: 45.000 mm^{-3}. Since a shunt operation was planned for the patient without active bleeding, preoperatively platelet transfusion was not indicated. The patient was given midazolam (0.5 $mg.kg^{-1}$ oral) for premedication and general anesthesia was performed under standard anesthesia monitoring including electrocardiogram, pulse oximetry, noninvasive blood pressure, and axillary temperature (basal arterial blood pressure: 92/42 mmHg, heart rate: 108 bpm, respiratory rate: 22 min^{-1}, Sat: 96% in-room air, and temperature: 36.6°C). Atropine (20 $\mu g.kg^{-1}$), ketamine (0.5 $mg.kg^{-1}$), and rocuronium (0.6 $mg.kg^{-1}$) were administered to the patient after induction of anesthesia with 8% sevoflurane. Maintenance of anesthesia was provided with sevoflurane (0.5–1 MAC), remifentanil infusion (0.25–0.5 $\mu g.kg^{-1}.min^{-1}$), and rocuronium (0.15 $mg.kg^{-1}$) when necessary. Mechanical ventilation settings after intubation with volume control mode were as follows: 7 $mL.kg^{-1}$ tidal volume (120 mL), 24 min^{-1} respiratory rate, 5 cmH_20 positive end-expiratory pressure (PEEP), 50% Fraction of inspired Oxygen (FiO_2), peak pressure: 15 cmH_20, and plateau pressure: 12 cmH_20 (The Dräger Perseus A500, Dräger Medical, Lubeck, Germany). The fluid treatment was provided with 4/2/1 rule (Holliday and Segar formula) and 0.9% NaCl for the patient who had a preoperative fasting period of 8 hours. Platelet transfusion was performed at 10 $mL.kg^{-1}$ (at an infusion rate of 170 $mL.h^{-1}$), approximately in the middle of the operation due to low platelet count and bleeding in the form of leakage in the tissue. The operation time was 180 minutes and the patient was given 550 mL isotonic and 170 mL platelet solution. The amount of bleeding during the operation was 50 mL and the urine output was 150 mL. The patient, who underwent decurarization with sugammadex (4 $mg.kg^{-1}$), was taken to the postanesthesia care unit (PACU) after being extubated in the operating room (arterial blood pressure: 88/44 mmHg, heart rate: 118 bpm, respiratory rate: 25 min^{-1}, Sat: 95% in-room air, and temperature: 36°C). In PACU at 20 minutes, desaturation (Sat: 80%, in-room air) and respiratory distress developed in the patient (Table 1). The patient did not have a pink frothy airway secretion. Oxygen therapy (5 $L.min^{-1}$) was started with a simple face mask (non-breathing mask,

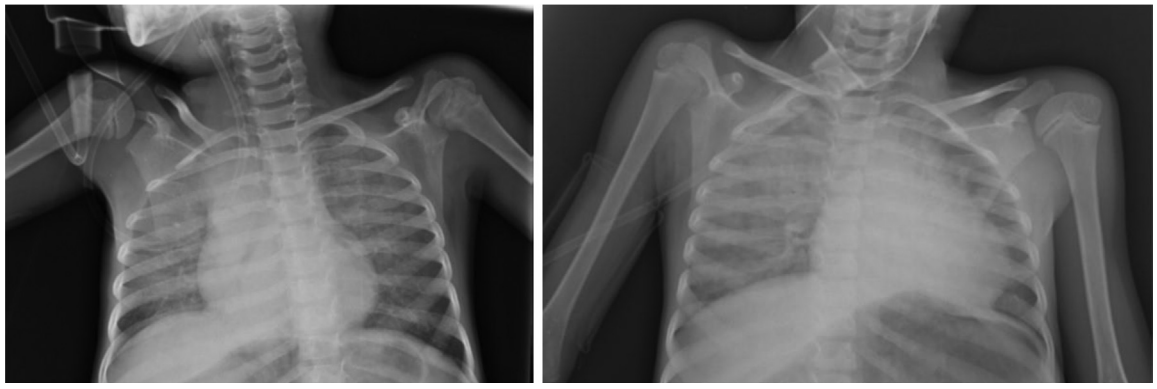


Figure 1 (a) Posterior-anterior chest radiography at the postoperative 20th minute. (b) Posterior-anterior chest radiography at the postoperative 2nd hour (after furosemide treatment was stopped).



Figure 2 Posterior-anterior chest radiography at the postoperative 24th hour (high-flow oxygen therapy was being implemented).

Plastimed, Turkey). On the other hand, widespread crepitant rales were detected during auscultation of the lung. Pulmonary edema was confirmed by a chest X-Ray (Fig. 1a). Furosemide bolus was administered at a dose of 0.5 mg.kg^{-1} with a preliminary diagnosis of pulmonary edema and the dose of the oxygen was increased to 10 L.min^{-1}. Within one hour after bolus injection of furosemide, 350 mL of urine diuresis was provided. Ejection fraction of the patient was 65% in transthoracic echocardiography performed by a pediatric cardiologist at the first hour in PACU, the patient had not demonstrated any evidence of cardiac failure and the diagnosis of TRALI was confirmed (Furosemide treatment was stopped) (Fig. 1b). There was no response to oxygen therapy delivered with the simple face mask (arterial blood pressure: 81/38 mmHg, heart rate: 142 bpm, respiratory rate: 44 min^{-1}, Sat: 85%); for this reason, HFOT (10 L.min^{-1} flow, 60% FiO_2) was administered with a nasal cannula (Optiflow Junior 2 Nasal Interface, Fisher And Paykel Healthcare Limited (F&PH) Airvo2 HFNC High-flow oxygen therapy, Auckland, New Zealand) and the patient was transferred to the ICU. The postoperative fluid therapy was set to 1500 mL.m^{-2} (Isolyte P in 5% Dextrose, Eczacibasi-Baxter, Istanbul, Turkey). Paracetamol (60 mg.kg^{-1}.day^{-1}) and morphine infusion (20 μg.kg^{-1}.h^{-1}) was started for analgesia. In the second hour after surgery, the ABG parametres of the patient were as follows: pH: 7.34, $PaCO_2$: 41.5 mmHg, PaO_2: 64.3 mmHg, SO_2: 88%. After these ABG parametres were obtained, the flow in HFOT was increased to 15 L.min^{-1} and then parametres of blood gas analysis were determined as pH: 7.28, $PaCO_2$: 47 mmHg, PaO_2: 89.8 mmHg (Table 1). High-flow oxygen therapy was continued for three days and the flow rate and FiO_2 were adjusted for ABG results (Fig. 2 and 3, Table 1). The patient did not need an inotrope or a vasoconstrictor during intraoperative and postoperative periods. At the end of the third day, the patient was followed with a simple face mask ventilation (3–5 L.min^{-1} O_2) for two days. The patient who was found to have the functional distal splenorenal shunt by ultrasound examination was discharged after being followed up in the pediatric surgery service for 5 days.



Figure 3 Postoperative 3rd day (after high-flow oxygen therapy).

Discussion

Transfusion-related acute lung injury is a complication of a serious transfusion of blood products and is the most common cause of transfusion-related deaths. Although its etiology and incidence are not fully known, it is estimated to be one in 5,000 blood product transfusions.[2] Patients with diagnosis of malignancy, shock, higher peak airway pressure during mechanical ventilation, positive intravascular fluid balance, low interleukin-10 levels, systemic inflammation, and those undergoing cardiovascular and liver surgery pose a risk for TRALI.[4] Our patient had myelodysplastic syndrome, so she had received transfusions many times within the last 2 years. Due to these factors, our patient was in the risk group for TRALI. However, in the preoperative period, she had not edema or rales and fluid therapy was not administered. High-pressure values were not applied in mechanical ventilation. Nevertheless, the patient's postoperative PaO_2/FiO_2 ratios showed that a moderate TRALI developed. In the intraoperative period, positive-pressure mechanical ventilation applied, and lack of increase in airway pressures may have masked TRALI symptoms.

Transfusion-associated circulatory overload, which develops after excessive blood volume, gives symptoms of dyspnea, tachypnea, hypoxemia, and jugular venous fullness and is the most commonly confused condition with TRALI. Diagnosis of TACO is made with left heart failure, high blood pressure, or tachycardia, and may include evidence of positive fluid balance or cardiogenic involvement. In contrast, TRALI is absolutely non-cardiogenic, there is no arterial hypertension and therefore volume overload should be excluded.[4] There is no specific treatment method for TRALI and transfusion should be terminated as soon as it is diagnosed. Fluid therapy and vasopressor agent support may be required in patients with hypotension. Therefore, it is recommended to avoid diuretics.[2,3]

In our patient, TRALI developed in the first hour after platelet transfusion, and manifested with dyspnea, tachypnea and desaturation. Hemodynamic instability and fever

were not detected. TRALI was confirmed by excluding excessive volume overload or TACO by transthoracic echocardiography. Therefore, diuretic treatment was stopped and fluid therapy was delivered at 1500 mL m^{-2}. Since there was no hypotension, there was no need for a vasoconstrictor. Despite diuretic treatment, the symptoms of the patient did not improve.

In TRALI, all patients need additional oxygen and more than 70% of patients need mechanical ventilation.[1] It has been found that HFOT can reduce the mortality of patients admitted to the intensive care unit due to acute respiratory failure compared to noninvasive ventilation. The beneficial effects of HFOT can be explained by its good tolerance and physiological properties such as high FiO_2, positive PEEP effect, and continuous dead space washout contributing to decreased work of breathing.[5]

Oxygen therapy and fluid restriction were applied primarily to our patient. Since oxygen therapy with the mask was inadequate we switched to HFOT. The patient's compliance to therapy was increased by using HFOT and both intubation and mechanical ventilation were avoided. If our patient had severe TRALI, intubation would have been inevitable. Physiological abnormalities and pulmonary infiltrations of TRALI usually improve in about 80% of patients in 4 days.[1] In our patient, the clinical symptoms and pulmonary infiltration resolved at the end of the 3rd day.

Conclusion

It should be kept in mind that TRALI may develop in patients with a history of transfusion. Because of vital importance in the treatment of hypoxemia while managing the patient, high-flow oxygen therapy, which is a well-tolerated noninvasive method, should be considered as an option in moderate or mild TRALI.

Informed consent

Informed consent from patient's family was received.

Financial disclosure

The authors declared that this study received no financial support.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

This article was presented as an oral presentation at the 22nd International Intensive Care Symposium in Istanbul-Turkey on May 03-04, 2019.

References

1. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA. TRALI Consensus Panel. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev. 2005;19:2—31.
2. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. Hematology Am Soc Hematol Educ Program. 2018;2018:585—94.
3. Murphy EL, Kwaan N, Looney MR, et al. Risk factors and outcomes in transfusion-associated circulatory overload. Am J Med. 2013;126:357. e29-38.
4. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood. 2019;133:1840—3.
5. Frat JP, Coudroy R, Thille AW. Noninvasive ventilation or high-flow oxygen therapy: When to choose one over the other? Respirology. 2019;24:724—31.

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



LETTER TO THE EDITOR

Development and evaluation of an educational comic leaflet for pediatric anesthesia care

Dear Editor,

Preoperative anxiety has been reported in over 60% of children undergoing anesthesia.[1,2] High levels of preoperative anxiety reduce the ability to cooperate during anesthesia and appear to be associated with an increased incidence of emergence delirium,[1] decreased pain threshold leading to increased postoperative pain, and development of postoperative mal-adaptive behavioral changes such as enuresis, apathy, social isolation, sleep and eating disorders.[2] Preoperative anxiety has therefore been addressed in various ways, including pharmacological and non-pharmacological methods.

The use of preanesthetic medications such as midazolam, ketamine, and dexmedetomidine are possible pharmacological strategies and should always be considered and discussed but have specific indications and are not exempt of adverse events. In turn, play therapy, comic strips, and video games are examples of non-pharmacological approaches that may have relatively low negative outcomes.[3,4] The literature regarding this set of approaches is limited, but some interesting results have been shown worldwide. For instance, a cartoon-based anesthesia information leaflet has effectively reduced preoperative anxiety in children aged 6 to 17 years who were candidates for elective surgery and was considered an interesting and cost-effective tool.[2]

Resolution 1.274/2017 of the Brazilian Federal Council of Medicine, regarding the practice of anesthesia, proposes that all patients, including children, must undergo a preoperative anesthesia visit before being submitted to elective procedures. This is an opportunity for the anesthesiologist to introduce the leaflet and interact with children in a way that can have a positive impact on reducing anxiety and its poor outcomes on the day of surgery.

A literature review over leaflets and preoperative care was carried out in the MEDLINE database. This was fundamental for selecting the leaflet's content, as well as determining the formatting used to present it to the pediatric audience in the preoperative setting. A team member wrote the text using the information collected, anesthesia team routines, as well as input from childcare and education experts. This text was presented to children in the targeted age group and some adaptations were adopted based on their insights. To stimulate interest and increase interaction with the contents of the leaflet, a mascot was designed, and pictures were drawn to help introduce the information. A specific space where children could actively participate in the story and draw their desired dream while sleeping under anesthesia was included (Fig. 1). After elaboration, the leaflet was evaluated according to the BALD criteria (Baker Able Leaflet Design) by the research team.[5] The leaflet created achieved 27 points, which is considered sufficient in terms of layout and design.

Approval was obtained from the anesthesia team, as well as pediatric surgeons and pediatric specialists. Subsequently, 87 leaflets were printed and distributed to children during the preoperative anesthesia examination that occurred from one month to at least one day prior to surgery. The patients were between 2 and 8 years old and had no diseases or conditions that led to delays in neuropsychomotor development. All selected children were accompanied by a caregiver who was able to read and understand the contents of the brochure. The caregiver was informed about the study. Within 24 hours of delivery of the brochure, a telephone text message containing a questionnaire was sent by a research assistant to the caregiver who attended the consultation. The questionnaire contained 4 questions, and the average response time was about 3 minutes. In case the questionnaire was not answered within 48 hours, a researcher actively reached out to the family and asked for their engagement.

A total of 52.7% of caregivers answered the questionnaire. The mean age of the addressed children was 4.4 years old, and the most prevalent surgery type was adenoidectomy (64.4%). The introduction of the anesthetic act in an appointment prior to surgery day using a comic strip leaflet was considered useful by 99.98% of participants. The leaflet itself was positively received by caregivers as 91.5% of them declared they enjoyed it. There were no significant concerns declared by caregivers. Suggestions given included the development of a video with the leaflet's content and the comic strip's character physically present on the day of surgery.

Our results show that information prior to surgery regarding the anesthetic act may be well accepted by children and caregivers when presented as a comic strip leaflet. Thus, we

https://doi.org/10.1016/j.bjane.2024.844521
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

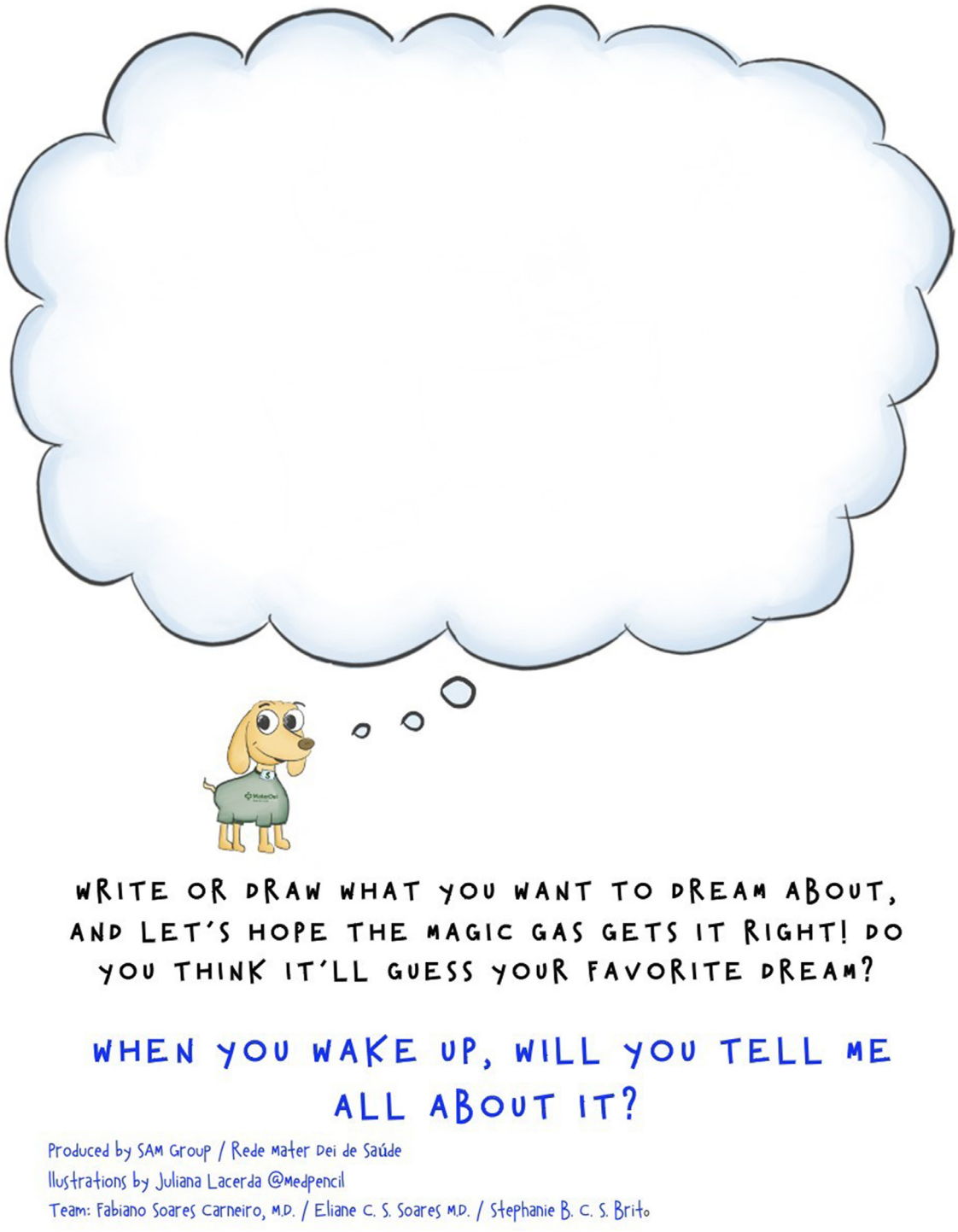


Figure 1 Space in the leaflet for children to participate in the story.

concluded that the leaflet was found to be accessible, informative and useful. Although the reduction in anxiety level was not addressed in the present study, the positive response to this initiative can lead to further investigation regarding this matter.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004;99:1648—54.
2. Kassai B, Rabilloud M, Dantony E, et al. Introduction of a paediatric anaesthesia comic information leaflet reduced preoperative anxiety in children. Br J Anaesth. 2016;117:95—102.
3. Clark EKR, Sanghavi SS, Farrell S, Fritz Z. Development and evaluation of an illustrated paediatric leaflet 'Coming to Hospital: a guide to what goes on'. BMJ Paediatr Open. 2021;5:e000889.

4. Bellew M, Atkinson KR, Dixon G, Yates A. The introduction of a paediatric anaesthesia information leaflet: an audit of its impact on parental anxiety and satisfaction. Paediatr Anaesth. 2002; 12:124—30.
5. Mathew EM, Rajiah K, Sharma KK. Consumer's Perception on Design and Layout of Consumer Medical Information Leaflets on Obesity and Lipid Lowering Drugs. J Clin Diagn Res. 2013; 7:2800—2.

Fabiano Soares Carneiro [a], Juliana Lacerda de Oliveira Campos [b], Stephanie Bruna Camilo Soares de Brito [b], Flávia Marques de Melo [c], Eliane Cristina de Souza Soares [c,*]

[a] *TSA/SBA, Grupo SAM (Serviço de Anestesiologia e Medicina) — Rede Mater Dei de Saúde, Belo Horizonte, MG, Brazil*
[b] *Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*
[c] *Grupo SAM (Serviço de Anestesiologia e Medicina) — Rede Mater Dei de Saúde, Belo Horizonte, MG, Brazil*

[*] Corresponding author.
E-mail: elianecssoares@gmail.com (E.C. Soares).
Received 27 November 2023; accepted 7 May 2024
Available online 29 May 2024

Brazilian Journal of Anesthesiology 2024;74(5): 844546



Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

The effect of gestational age on short- and long-term complications following primary esophageal atresia repair



Dear Editor,

Esophageal Atresia (EA) is a rare congenital anomaly with an incidence of 1.2 to 4.5 per 10,000 live births.[1] It is frequently associated with comorbidities which pose significant challenges in the perioperative period.[2] Although notable progress in treatment options and survival has been made during the past decades, patients with esophageal atresia still encounter long-term complications that severely impact their quality of life. The majority relate to gastrointestinal and respiratory problems which result in multiple hospital admissions as well as diagnostic and therapeutic interventions.[2–4] Prematurity, among other factors, may affect overall long-term outcomes following successful esophageal atresia repair.[5] This current study hence investigated the impact of gestational age on gastroesophageal and respiratory complications during the first 5 years of life.

We conducted a retrospective chart review including all patients who underwent primary surgical repair at Montreal Children's Hospital between 2005 and 2023, using a predefined paper-based Case Report Form (CRF). The study was approved by the hospital research ethics board (MP-CHU-HSJ-08-003). Prematurity was defined as babies born alive before 37 weeks of pregnancy. Outcomes included patient demographics, medical and surgical history, and ongoing clinical care relating to gastrointestinal and respiratory complications (Table 1). All data were transferred into an electronic REDCap database. Differences between preterm and full-term births were examined using independent *t*-tests or Mann-Whitney *U* test for continuous data and Chi-Squared tests or Fischer exact tests for binomial data. We examined the relationship between gestational age and the incidence of gastrointestinal and respiratory complications using the Chi-Square test and logistic regression. Clinically relevant variables were added to the model to adjust for potential confounding.

A total of 137 patients (39.4% females with a mean Gestational Age (GA) of 37.2 ± 3.2 weeks and a mean birth weight of 2679 ± 708 g) underwent esophageal atresia repair and were included in this analysis. The anatomical variations stratified according to the EA Gross classification included Type A = 3%, Type B = 1.6%, Type C = 82.2%, Type D = 4.8% and Type E = 8%.[6] A VACTERL association was observed in 17 patients (27%) and CHARGE syndrome in one patient (1.6%). Congenital anomalies affected vertebral (23%), anorectal (9.5%), cardiac (45.2%), renal (27.9%), skeletal (11.1%), respiratory (8.6%), digestive (54.7%), and other (20.7%) systems. Preterm patients more frequently required gavage feeding (54.5% vs. 14.8%, OR = 6.67 [1.33 to 33.33], $p = 0.019$) and had stenosis (72.7% vs. 37.0%, OR = 4.55 [0.97 to 20], $p = 0.046$), but were prescribed anti-H2 less frequently (18.2% vs. 77.8%, OR = 0.063 [0.011 to 0.38], $p = 0.001$).

The incidence of respiratory complications was higher in the full-term patient population (respiratory deteriorations 57.7% vs. 33.3%, abnormal respiratory symptoms 84.6% vs. 66.7%, and abnormal auscultation 73.1% vs. 46.7%), with the exception of exertional dyspnea which was higher in the preterm population (13.3% vs. 7.7%). None of the results reached statistical significance.

Our demographic study population closely aligns with previous reports. The use of anti-H2 blocker therapy was significantly higher in full-term patients, while the number of cases of gavage feeding, and stenosis was higher in the premature population. These findings suggest that a subgroup of gastrointestinal complications may be related to gestational age. Future prospective studies should explore additional factors and underlying mechanisms. No association between gestational age and respiratory complications during the first 5 years of life was observed. The study has several limitations, including small sample size, missing data, and variability in reporting of outcomes. Study limitations are attributed to the retrospective data collection in a single institution, and potentially to evolution over time in surgical techniques and perioperative approaches. These results and limitations suggest that the establishment of international defined core outcomes and cross boarder collaboration is essential to advance research in rare disease populations such as EA.

Progress in the treatment of esophageal atresia has been made using an ever-increasing collaborative network. While limited surgical outcome databases have been established for some time, successful large anesthesia outcome networks have only been established more recently in pediatric anesthesia — with the APRICOT and NECTARINE leading examples.[7,8] Close collaborations between surgical and pediatric anesthesia networks will permit evaluation of an "esophageal bundle" strategy,[9] including multidisciplinary perioperative outcomes and long-term follow-up.

https://doi.org/10.1016/j.bjane.2024.844546
0104-0014/© 2024 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Table 1 Collected information of all patients who underwent esophageal atresia repair at the Montreal Children's Hospital between 2005 and 2023.

Demographic data	Sex, date and place of birth, gestational age, birth weight, Apgar score, date of admission to hospital, date of surgery
Prenatal data	Intrauterine growth delay Date of diagnosis of esophageal and/or tracheoesophageal fistula Multiple pregnancy In Vitro Fertilization
Additional anomalies	Skeletal, anorectal, cardiac, renal, limb, gastrointestinal, respiratory, other
Type of esophageal atresia	Gross classification
Syndromes	Vacterl, charge, Other
Gastrointestinal outcomes	Medications during first 5 years of life: proton pump inhibitors; cisapride; domperidone; H2 receptor blocking agents; Need for gavage feeding Esophageal pathology (esophagitis, barret's esophagus, Stenosis, Hiatal hernia, esophageal diverticulum); Stomach and duodenal pathology (ectopic pancreas, microgastria) and abnormal histology (peptic esophagitis, eosinophilic esophagitis, dilatation required)
Respiratory outcomes	Medications during first 5 years of life (antibiotics, per so steroids, inhalational steroids, ventolin) Deteriorations; admission to hospital (intensive care unit, emergency, ward); Diagnostics (pneumonia, bronchitis, sinusitis, asthma attack); abnormal respiratory symptoms (coughing, morning cough, night-time cough, grumbling breathing, grumbling (eating), wheezing, respond to ventolin); exertional dyspnea; continuous dosing aerosol (corticosteroids, without long-acting beta agonists, With long-acting beta agonists, other inhaler) and abnormal auscultation (rhonchi, crackles, wheezing)

Declaration of competing interest

The authors declare no conflicts of interest.

References

1. Sfeir R, Bonnard A, Khen-Dunlop N, et al. Esophageal atresia: data from a national cohort. J Pediatr Surg. 2013;48:1664—9.
2. Comella A, Tan Tanny SP, Hutson JM, et al. Esophageal morbidity in patients following repair of esophageal atresia: A systematic review. J Pediatr Surg. 2021;56:1555—63.
3. Mirra V, Maglione M, Di Micco LL, Montella S, Santamaria F. Longitudinal Follow-up of Chronic Pulmonary Manifestations in EsophagealAtresia: A Clinical Algorithm and Review of the Literature. Pediatr Neonatol. 2017;58:8—15.
4. Dellenmark-Blom M, Quitmann J, Dingemann C. Health-Related Quality of Life in Patients after Repair of Esophageal Atresia: A Review of Current Literature. Eur J Pediatr Surg. 2020;30:239—50.
5. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016;21:74—9.
6. The Surgery of Infancy and Childhood: Its Principles and Techniques.Gross RE, Ladd WE. AMA Arch Intern Med. 1954;93(3):478—9.
7. Disma N, Veyckemans F, Virag K, et al. NECTARINE Group of the European Society of Anaesthesiology Clinical Trial Network; Austria; Belgium; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Netherlands; Norway; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Switzerland; Turkey; Ukraine; United Kingdom.Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). Br J Anaesth. 2021;126:1157—72.
8. Habre W, Disma N, Virag K, et al. APRICOT Group of the European Society of Anaesthesiology Clinical Trial Network. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. Lancet Respir Med. 2017;5:412—25.
9. van den Berg MJ, Johansen M, Disma N, et al. Perioperative anesthetic management and short-term outcome of neonatal repair of esophageal atresia with or without tracheoesophageal fistula in Europe. A sub-analysis of the neonate and children audit of anesthesia practice in Europe (NECTARINE) prospective multicenter observational study. Eur J Anaesthesiol. 2023;40:936—45.

Mathias Johansen [a,*], Samuel Wasserman [b], Dan Poenaru[c], Jean Martin Laberge [c], Sam J. Daniel[d], Thomas Engelhardt[b]

[a] *McGill University, Montreal Children's Hospital, Department of Pediatric Anesthesia, Montreal, Quebec, Canada*
[b] *McGill University Health Center, Montreal Children's Hospital, Department of Anesthesia, Montreal, Quebec, Canada*
[c] *McGill University Health Center, Montreal Children's Hospital, Harvey E. Beardmore Division of Pediatric Surgery, Montreal, Quebec, Canada*
[d] *Montreal Children's Hospital, Division of Pediatric Otolaryngology, Montreal, Quebec, Canada*

[*] Corresponding author
E-mail: mathias.johansen.med@ssss.gouv.qc.ca
(M. Johansen).

Received 24 December 2023; accepted 23 July 2024
Available online 3 August 2024

BJAN

Brazilian Journal of Anesthesiology

Contact us

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

BJAN Brazilian Journal of Anesthesiology Vol. 74 N. 5 | September/October 2024