BJAN

Vol. 75, N. 5 | Sep-Oct 2025 | ISSN 0104-0014

bjan-sba.org

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BJAN
Brazilian Journal of Anesthesiology

Brazilian Journal of ANESTHESIOLOGY

Standardizing the view, refining the approach: towards a universal language in videolaryngoscopy airway visualization

Brazilian Journal of Anesthesiology

Vol. 75 N. 5 | September/October 2025

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SBA Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

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Sociedade Brasileira de Anestesiologia (SBA)
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Telefone: +55 21 3528-1050
E-mail: contato@sbahq.org
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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

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

ISSN 0104-0014 • Volume 75 • Number 5 • September—October 2025

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.

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Imaging classification in videolaryngoscopy: are we on the right track?

The perfect classification of the videolaryngoscopy (VL) image is the Holy Grail of modern intubation. It is important to classify and then stratify the risks of difficulty or failed intubation. Since the introduction of the Macintosh[1] and Miller[2] laryngoscope blades, airway management has evolved, especially in the last two decades.

Jack Pacey (a surgeon) developed in 2001 the first VL which achieved an indirect view of the glottis, permitting tracheal intubation independent of a direct line of sight.[3] Levitan described the percentage of glottic opening (POGO) score using direct laryngoscopy, in 1999, with static images of the glottic opening. The method was proposed to replace the Cormack & Lehane (C&L) grades 1 and 2 with the POGO score.[4]

Prof. Cook described in 2000 a new classification of the original C&L adding a separation of the grades 2 and 3 in grade 2A, 2B, 3A and 3B. Nevertheless, introduced the concept of easy (grade 1 and 2A), restricted (grade 2B and 3A) and difficult (grade 3B and 4). Using this new classification, an easy view predicted easy intubation in 95% of the cases and difficult view was associated with difficult intubation in three-quarters of cases.[5]

Different anesthesia societies recommend the use of videolaryngoscopy for airway management and it is clear now that larynx view is enhanced with the device.[6-8]

The study entitled "VCI Spain: protocol for a prospective multicenter observational study to validate a standardized classification tool for tracheal intubation using videolaryngoscopy" from our Spain colleagues is well designed and aims to address the gap between C&L and POGO classifications. The score has three parts: Blade type (Macintosh (Mac) or Hyperangulated (HA)), POGO (0-25%, 50-75% and > 75%) and Intubation (Easy, Difficult and Failed).[9]

Several considerations should addressed when proposing a new classification. The first important decision is to define the best tool for a specific patient. How should be the initial approach to choose the blade based on phenotypes or clinical conditions?

This is fundamental to offer a better chance for the patient to be successfully intubated on the first attempt without complications. Is it time to abandon the options and suggest which blade should be used for the first attempt (Mac or HA)?

When the option is available, the decision-making process is more difficult and relies on user's experience related to cognitive ease (system 1) or cognitive strain (system 2).[10]

Depending on which blade is chosen for the patient, an intubation can shift from difficult to easy, or vice versa. Also, the size of the blade (3 vs 4) can influence the POGO score and, consequently, the result of a successful intubation.[11]

The POGO classification is valuable, but it's crucial to understand that the visualization proposed is at the exact moment, immediately before advancing the endotracheal tube through the glottis and not the initial or best view. The use of percentage is very good when analyzing a steady picture.

It is more complicated to be sure of the percentage of glottic opening when you are doing the intubation in real time. Relying on anatomical parameters seems to be more objective. Another point is that the POGO classification does not differentiate the C&L grade 3A (restricted) from the grades 3B and 4 (difficult). Are them clinically equivalent or, as proposed by Cook, they are different and the resolution tools to achieve tracheal intubation are not the same?

The authors propose a good categorization regarding the intubation: easy, difficult or failed. Once again, the possibility of intubating a patient depends on various factors and the success is a result of a good strategy, technical and non-technical skills and situational awareness. Consequently, if the initial strategy is to use an adjunct as the first option and the operator obtains success, is this patient going to be labeled as difficult intubation?

It is understandable that different models of videolaryngoscopes are the reality of the hospitals, and the experience of the users varies among preferences and availability. On the other hand, it becomes harder to compare channeled

https://doi.org/10.1016/j.bjane.2025.844671

and non-channeled devices in the case of difficult or failed intubation. Each device has some advantages and also disadvantages, and it should be determined by a direct comparison to understand the incidence of difficulty or failure. Experience with one type of videolaryngoscope does not equate to skill with all videolaryngoscopes.[12]

Finaly, it is essential to refine the classification of the videolaryngoscopic images and translate it into clinical practice to augment the assertiveness of the intubation process and security for the patients. Nonetheless, it is also important to understand the difficulty to standardize a procedure involved with different perspectives and devices.

The VCISpain study[9] will be a lighthouse to guide the next steps for new research in the field of image classification and standardization with videolaryngoscopes.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 11 August 2025; accepted 11 August 2025
Available online 13 August 2025

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Thoracic wall blocks in cardiac and thoracic procedures: expanding frontiers for perioperative regional analgesia

Regional anesthesia techniques have gained increasing relevance in cardiac and thoracic surgeries, driven by the pursuit of more effective analgesic strategies, reduced opioid use, and improved postoperative recovery. Traditionally, pain management in surgeries involving thoracotomy or sternotomy relied on intravenous opioids and, in some cases, neuraxial techniques such as thoracic epidural blocks. Although cardiothoracic procedures have advanced significantly toward minimally invasive techniques, such as video-assisted and robotic surgeries and despite the smaller incisions compared to sternotomy and thoracotomy, these approaches are still associated with significant postoperative acute pain and a portion of patients may develop persistent chronic pain that lasts for months or even years after the procedure.[1–3]

The Enhanced Recovery After Cardiac Surgery (ERACS) protocols recommend the use of multimodal strategies for pain management, highlighting the role of myofascial blocks in reducing opioid requirements in the perioperative period. This has led to the growing use of thoracic wall fascial plane blocks, such as the erector spinae plane (ESP) block, transversus thoracic muscle plane (TTMP) block, and pectointercostal fascial (PIF) block.[1–2] While observational studies and case series suggest their effectiveness, significant gaps remain regarding the superiority of specific techniques, their safety profiles in specific populations, long-term clinical outcomes, and cost-effectiveness.[1–3]

In the setting of adult cardiac surgery, regional techniques are increasingly valued as part of multimodal strategies for enhanced recovery. Recent studies demonstrate that fascial plane blocks can significantly reduce opioid consumption, shorten the duration of mechanical ventilation, and facilitate early discharge from the intensive care unit (ICU), even in patients undergoing median sternotomy.[1–2] Kelava et al. highlighted the applicability of ESP, PIF, and TTMP blocks,[1] while Rubio et al. advocated for their routine adoption to support fast-track cardiac anesthesia programs.[2] Conversely, Jia et al. raised concerns about methodological limitations in the current literature, implementation costs, and logistical barriers, calling for caution before generalizing these techniques to all adult cardiac procedures.[3]

Within this debate, Damião et al., published in the Brazilian Journal of Anesthesiology (BJAN), reinforce the benefit of ultrasound-guided ESP block by demonstrating reduced pain scores and morphine consumption after sternotomy.[4] In congenital cardiac surgeries, thoracic wall blocks have also gained attention. A recent meta-analysis published in this BJAN issue evaluated the impact of ESP block in children undergoing cardiac surgery, demonstrating consistent reductions in postoperative pain and opioid requirements within the first 24 hours.[4] Notably, a Bayesian network meta-analysis by Ren et al. compared multiple pediatric regional techniques and found ESP to be the most effective overall, despite moderate-quality evidence.[5] Interestingly, another Bayesian Network meta-analysis identified TTMP as a consistently top-performing technique across outcomes.[6] This scenario is particularly promising in pediatrics due to the favorable safety profile of fascial plane blocks and the known vulnerability of pediatric patients to the adverse effects of opioids. Damião et al. contributed original clinical data on bilateral ESP blocks in pediatric cardiac surgeries, reinforcing their safety and analgesic efficacy.[4] Complementing these findings, Ali Gado et al. conducted a randomized controlled trial specifically examining bilateral ESP blocks in children undergoing cardiac surgery via median sternotomy.[7] Their results confirmed the analgesic efficacy and safety of the technique, highlighting reduced pain scores at rest and during coughing, and supporting the use of ESP as a key component of multimodal analgesia protocols in this population.

In thoracic surgeries, several studies have demonstrated effective analgesia with blocks such as the ESP block, thoracic paravertebral block, and serratus anterior block.[8,9] The PROSPECT group (Procedure-Specific Postoperative Pain Management) recommends, with level A evidence, thoracic epidural anesthesia or paravertebral block as the techniques of choice for postoperative analgesia.[9,10] However, despite its popularity, the ESP block exhibits erratic spread of local anesthetic, as shown in cadaveric studies and clinical practice, leading to block failures.[8]

https://doi.org/10.1016/j.bjane.2025.844670

In 2023, Tulgar et al. described the superior posterior serratus intercostal plane block (SPSIPB), demonstrating homogeneous spread of local anesthetic toward upper thoracic and cervical fibers in cadaver studies.[11] This technique is applicable to thoracic, breast, and shoulder surgeries. In this BJAN issue, Doğan et al. conducted a prospective randomized clinical trial comparing SPSIPB with thoracic paravertebral block in patients undergoing video-assisted thoracic surgery (VATS).[11] Results showed that SPSIPB was non-inferior to the paravertebral block, offering similar analgesic efficacy, despite the paravertebral block showing lower pain scores only in the first postoperative hour.[11]

In both thoracic and cardiac surgeries, Enhanced Recovery After Surgery (ERAS) protocols have driven transformative changes in perioperative care by emphasizing multimodal analgesia, early extubation, rapid mobilization, and reduced hospital length of stay.[1,2] The integration of fascial plane blocks into ERAS and ERACS pathways is a growing trend, offering promising improvements in patient satisfaction, respiratory outcomes, and health care costs. Nevertheless, the success of these protocols depends on local infrastructure, the availability of trained personnel, team engagement, and appropriate case selection.[1–3] Makkad et al. emphasized that regional techniques should be integrated contextually, tailored to institutional capabilities, and continuously evaluated for clinical impact.[8]

In summary, thoracic wall fascial plane blocks are emerging as valuable tools for postoperative analgesia in cardiac and thoracic surgeries. Their widespread implementation will depend on higher-quality evidence, especially from randomized controlled trials assessing functional outcomes. The articles presented in this BJAN issue contribute significantly to the field by providing data supporting the efficacy and feasibility of myofascial blocks across age groups and surgical settings. Future research priorities include standardizing technique, elucidating the mechanism of action, evaluating long-term outcomes, and incorporating these strategies into value-based perioperative care. We are in a good time to consolidate these techniques with scientific rigor.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 5 August 2025; accepted 8 August 2025

Available online 13 August 2025

Brazilian Journal of Anesthesiology 2025;75(5): 844669

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Beneath the surface: the emerging concern of covert stroke in surgery

The incidence of stroke in patients undergoing non-cardiac, non-neurological surgery ranges from 0.1% to > 1%, with a reported mortality rate of 25%–50%, substantially higher than that associated with non-perioperative strokes.[1,2] These data, largely derived from retrospective studies,[1] reflect variations in patient comorbidities and the nature of the surgical procedures. Perioperative stroke places a burden on healthcare systems, prolonging hospital stays, increasing ICU utilization, and often requiring discharge to chronic care facilities. These outcomes are devastating for patients and their families.[1]

The World Health Organization had defined stroke as a "focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours".[3] According to the consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care (SNACC), perioperative stroke includes ischemic or hemorrhagic cerebrovascular events occurring intraoperatively or within 30 days post-surgery.[4] Overt perioperative strokes, those with clinical manifestations, are well characterized. Their etiology is primarily embolic rather than hypotensive, though intraoperative hypotension may exacerbate embolic injury. Risk factors such as chronic kidney disease, advanced age, previous transient ischemic attack or stroke, and atherosclerosis have been identified, yet many are non-modifiable and serve mainly to guide preoperative risk discussion.[1-3]

Covert Stroke, also known as Silent Brain Infarctions (SBI), are acute ischemic events detected exclusively by imaging, with no clinically apparent deficits.[1,5] In 2013, the American Heart Association (AHA) modified the definition of stroke to include the extensive use of imaging technology: "Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion".[6] Their importance is underscored by their inclusion in the ICD-11 as silent cerebral infarction. However, it is noteworthy that the European Stroke Organization and World Stroke Organization do not endorse a definition of stroke that does not include symptoms.[6]

Population-based cohort studies report a wide prevalence (6%–55%), reflecting variability in sample size, imaging protocols, and lack of standardized definitions.[7] Frequency increases with age and vascular risk factors such as hypertension, carotid and coronary artery disease, hyperhomocysteinemia, oxidative stress, sleep apnea, and hypercoagulable states.[7]

There are numerous covert cerebrovascular lesions that are typically categorized as covert brain infarcts, White Matter Hyperintensities (WMHs), Cerebral Microbleeds (CMBs), and Perivascular Spaces (PVSs).[8] Covert strokes, therefore, fall within this spectrum of Covert Cerebrovascular Diseases (CCD).[9] CCD includes focal covert cortical infarctions, often due to atherothrombotic disease, and white matter diseases, such as lacunes, which result from intrinsic small vessel disease, microemboli, vasculopathy, amyloid deposition, and other related factors.[9,10] The absence of clinical symptoms and only incidental imaging detection complicates understanding of the pathophysiology. The anatomical variability and the involvement of both large and small vessels suggest multiple mechanisms.[7]

Although patients with covert stroke may lack overt neurological deficits, these lesions have been linked to cognitive decline, increased risk of future strokes, and dementia. A meta-analysis carried out on the follow-up of more than 100,000 patients per year found that covert stroke was associated with an increased risk of stroke, with a crude RR of 2.94 (95% CI 2.24–3.86),[5] with an estimated annual stroke incidence of 3%, compared to less than 1% in those without. The risk of dementia is also significantly higher, 2%–3% annually, versus 0.5% in those without occult cerebrovascular disease.[9-11] These findings emphasize the potential clinical relevance of preoperative detection and management of covert stroke.

Two major prospective studies have recently investigated covert stroke in the postoperative setting. The NeuroVISION study enrolled 1,114 patients over age 65 undergoing elective non-cardiac, non-neurological surgery. Postoperative MRIs (days 2 and 9) and neurocognitive testing revealed a 7%

https://doi.org/10.1016/j.bjane.2025.844669

incidence of covert stroke. These were associated with a higher risk of delirium, postoperative cognitive dysfunction, and transient ischemic attack.[12] At one-year follow-up, 42% of patients with a covert stroke exhibited cognitive decline, compared to 29% in those without. The adjusted Odds Ratio was 1.98 (95% CI 1.22–3.20), corresponding to a 13% absolute risk increase ($p = 0.0055$).[12] In this trial, cognitive decline was defined as a reduction of two or more points on the Montreal Cognitive Assessment one year postoperatively compared to the preoperative baseline. Notably, and disappointingly, no additional risk factors were identified in that study, such as a previous history of stroke or transient ischemic attack, vascular disease, depression, anxiety, or type of surgery.[12]

The PRECISION study evaluated 934 patients over 60 years of age undergoing non-cardiac surgery, with postoperative MRI on day 7 and standardized assessments for delirium and cognitive outcomes.[13] Of note, 66% of the cohort underwent neurosurgical procedures. The incidence of covert stroke was 11.9% (95% CI: 9.8%–14.0%), well above the 7% found in the NeuroVISION study. In neurosurgical patients, the rate reached 16.3%, versus 3.4% among non-neurosurgical patients.[12,13] A key distinction between the two studies is that the NeuroVISION excluded neurosurgical cases, whereas two-thirds of PRECISION's cohort were neurosurgical, a reflection of recruitment challenges during the COVID-19 pandemic. The elevated incidence in PRECISION suggests a greater vulnerability and raises hypotheses regarding contributing factors such as brain manipulation, osmotic agents, or retractor use.

The very different patient selection in these two studies makes comparisons difficult. It also limits the ability to speculate about broader applicability to surgical populations and the extent to which they are confirmatory of each other. The incidence of covert stroke differs quite markedly in the non-neurosurgical populations, 7% vs. 3.4%, but even 3.4% is a surprising and disturbing finding.

Substantial gaps remain in understanding the timing and mechanisms underlying perioperative covert stroke, including whether these are the same or different from covert stroke unrelated to surgery. Neither study, unfortunately, was structured or powered to investigate risk factors or the contribution of intraoperative management to the incidence, including hemodynamic fluctuations and/or the generation of micro-emboli. Given that establishing a clear association between intraoperative hypotension and postoperative stroke remains challenging,[14] identifying a link with covert stroke may be even more difficult and will require an explicit research agenda. In addition to identifying risk factors, diagnostic approaches will be crucial. Questions for consideration include the role of regionally specific neurological monitors such as regional cerebral oximetry, the use of Transcranial Doppler (TCD) in detecting microemboli; whether postoperative MRI should be routinely offered to patients with preoperative risk factors; whether the more readily available CT scan would be sufficient, or could frequent structured neurological evaluations, such as the modified NIH stroke scale, improve early detection of subtle deficits.[15] Such unanswered questions highlight the very urgent need for appropriately powered prospective studies that clarify perioperative vulnerability and guide strategies within anesthetic and surgical practice.

In conclusion, covert stroke likely represents just the tip of a broader, underrecognized perioperative phenomenon. Its frequent underdiagnosis, stemming from the absence of overt symptoms and limited clinical suspicion, renders it a silent but impactful contributor to postoperative cognitive decline. This scenario calls for targeted, suitably powered research but also heightened awareness of covert stroke not only from anesthesiologists and surgeons but also from radiologists, ward physicians, ICU teams, and nursing staff involved in perioperative care. Interdisciplinary collaboration and systematic identification of at-risk patients are essential, at least initially for risk discussion. As evidence evolves, the development of robust, integrated guidelines for screening, diagnosis, and perioperative management will be key to reducing long-term neurological morbidity. Beneath the surface, the emerging concern of covert stroke in surgery demands collective recognition and deliberate action.

Authors' contributions

All 3 authors contributed equally to the concept, literature review, and manuscript writing. All authors approved the final manuscript.

Conflicts of interest

AWG is a past president of the World Federation of Societies of Anesthesiologists, and has a consulting relationship with Medtronic, and Haisco Pharma; all unrelated to this document.

Associate Editor

Maria José Carmona

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Received 23 June 2025; Accepted 2 August 2025
Available online 21 August 2025

Brazilian Journal of Anesthesiology 2025;75(5): 844653

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

VCISpain: protocol for a prospective multicenter observational study to validate a standardized classification tool for tracheal intubation using videolaryngoscopy

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https://doi.org/10.1016/j.bjane.2025.844653

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Received 11 February 2025; accepted 4 June 2025
Available online 18 June 2025

KEYWORDS
Airway management;
Patient care;
Reproducibility of results;
Tracheal intubation;
Video-assisted techniques and procedures

Abstract
Background and objective: Videolaryngoscopy have transformed airway management by improving intubation success rates compared to direct laryngoscopy. However, its widespread adoption has been hindered by the lack of standardized classification tools for documentation and communication. This manuscript outlines the rationale and study design of the VCISpain project, which aims to evaluate the interobserver reproducibility of the Video Classification of Intubation (VCI) scale in the context of airway management using videolaryngoscopy in Spain.
Methods: This manuscript presents the planned methodology of the VCISpain study, a prospective, observational, multicenter, open-label study. The study will collect data on tracheal intubations performed in operating rooms, intensive care units, and emergency departments. In each case, two anesthesiologists will independently apply the VCI scale to assess blade type, Percentage of Glottic Opening (POGO), and ease of intubation.
Ethics and registration: The study was approved by the University of Navarra Ethics Committee (2022.079 mod1) and registered on ClinicalTrials.gov (NCT06537531). It is endorsed by the

Spanish Society of Anesthesiology, Resuscitation and Pain Therapy (SEDAR) and the European Airway Management Society (EAMS).
Conclusions: VCISpain seeks to establish a standardized classification tool for documenting and communicating findings related to videolaryngoscopy in airway management. By presenting the study rationale and design, this protocol aims to promote transparency, ensure methodological rigor, and encourage broader discussion to refine the study prior to implementation.

Introduction

Tracheal Intubation (TI) remains a cornerstone of airway management in both anesthesia and critical care, despite its routine use.[1,2] Difficult intubation occurs in approximately 5%–8% of cases, while failed TI is reported in 0.05%–0.35% of cases.[3] Recent data indicate a decline in these rates – 1.6 and 0.06 per 1,000 cases, respectively – primarily due to advances such as Videolaryngoscopy (VL).[4] Nonetheless, airway management complications remain a significant cause of morbidity and mortality.[5,6]

Direct Laryngoscopy (DL) has traditionally been the gold standard for visualizing the glottis and guiding tracheal tube placement.[7] The advent of VL in 2001 marked a significant milestone, reducing rates of difficult and failed airways.[8] Consequently, several national and international societies – including the American Society of Anesthesiologists (ASA), the Canadian Airway Focus Group (CAFG), and the Spanish Society of Anesthesiology and Resuscitation (SEDAR) – now recommend VL as a first-line technique for TI due to its ability to reduce complications and improve clinical outcomes.[9-11]

Traditional classification tools – such as the Cormack-Lehane scale, its modification by Yentis and Cook, and the Percentage of Glottic Opening (POGO) – remain the most commonly used methods for assessing intubation difficulty.[7,12-14] However, these tools were originally developed for direct laryngoscopy and may not fully capture the specific challenges associated with VL.[15] For example, excellent glottic visualization (e.g., 100% POGO) during VL does not always guarantee procedural success[16,17] due to difficulties in maneuvering and inserting the tube through the glottis.[18-20] Although alternative scales have been proposed to overcome these limitations, none have gained widespread acceptance.[16,21]

The Video Classification of Intubation (VCI) scale was developed to address this gap, providing a standardized classification tool for documenting VL intubations. It evaluates three components: blade type (Macintosh [M] or Hyperangulated [H]), Percentage of Glottic Opening (POGO), and ease of intubation (Easy [E], Difficult [D], or Failed [F]).[22] The VCISpain study is a national, multicenter initiative aimed at evaluating the interobserver reproducibility and clinical applicability of the VCI scale in real-world practice across Spain. The study is endorsed by the Spanish Society of Anesthesiology, Resuscitation, and Pain Therapy (SEDAR) and the European Airway Management Society (EAMS). This manuscript presents the study rationale and design to promote transparency, ensure methodological rigor, and encourage constructive feedback prior to implementation.[23]

Methods

Objectives

Primary Aim

The primary aim of this study is to evaluate the interobserver reproducibility of the VCI scale during tracheal intubation using videolaryngoscopy across multiple centers in Spain.

Secondary aims

1. To assess the correlation between the Percentage of Glottic Opening (POGO) and the difficulty of tracheal intubation.
2. To evaluate the impact of the operator's experience level on intubation-related outcomes.
3. To determine the incidence of complications associated with tracheal intubation using videolaryngoscopy.

Study design

The VCISpain study is a prospective, observational, multicenter, and open-label study. This design enables data collection across a diverse range of hospital settings, enhancing the external validity and generalizability of the findings. This protocol was developed in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

Study setting

The project involves 35 hospitals located across various autonomous communities in Spain. These centers encompass a wide array of clinical contexts, levels of care complexity, and technological capabilities, thereby ensuring a heterogeneous and representative sample. Additionally, the study includes anesthesiologists with varying levels of experience, offering a comprehensive and realistic analysis of the VCI scale's application in clinical practice.

The list of participating hospitals is as follows:

1. Clínica Universidad de Navarra (Madrid).
2. Clínica Universidad de Navarra (Pamplona).
3. Complejo Asistencial Universitario de Salamanca (Salamanca).
4. Complejo Hospitalario Universitario de A Coruña (A Coruña).
5. Complejo Asistencial de Zamora (Zamora).
6. Consorcio Hospital General de Castellón (Castellón).
7. Hospital Clínic de Barcelona (Barcelona).

8. Hospital del Bidasoa (Irún).
9. Hospital de Galdakao-Usansolo (Galdakao).
10. Hospital General de Requena (Valencia).
11. Hospital Infanta Sofía (Madrid).
12. Hospital Sant Joan Despí (Barcelona).
13. Hospital Universitari Dr. Peset (Valencia).
14. Hospital Universitario de Álava (HUA-Vitoria).
15. Hospital Universitario de Basurto (Bilbao).
16. Hospital Universitario de Getafe (Madrid).
17. Hospital Universitario de Navarra (Pamplona).
18. Hospital Universitario Donostia (San Sebastián).
19. Hospital Universitario Fundación Alcorcón (Madrid).
20. Hospital Universitario Infanta Leonor (Madrid).
21. Hospital Universitario La Fe (Valencia).
22. Hospital Universitario Lucus Augusti (Lugo).
23. Hospital Universitario Virgen de la Arrixaca (Murcia).
24. Hospital Universitario Virgen del Rocío (Sevilla).
25. HM Hospitales (Madrid).
26. Hospital Universitario La Paz (Madrid).
27. Consorcio Hospital General Universitario Valencia.
28. Hospital Universitario Torrecárdenas (Almería).
29. Hospital Universitario Gregorio Marañón (Madrid).
30. Hospital Universitario Puerta de Hierro (Madrid).
31. Hospital Son Llátzer (Mallorca).
32. Hospital Clinico de Valencia.
33. Hospital FREMAP (Madrid).
34. Hospital Universitario Ramón y Cajal (Madrid).
35. Hospital Universitario Virgen Macarena (Sevilla).

This extensive network of hospitals ensures a comprehensive representation of the variability and complexity encountered in airway management across Spain.

Pre-data collection preparations

To ensure consistent and standardized application of the VCI scale across all centers, a comprehensive training and coordination strategy was implemented before the initiation of data collection. All participating anesthesiologists completed a structured, one-hour virtual training session led by the principal investigator (MFV) and study coordinators (PC, MV). The session included a detailed review of the study protocol, proper completion of the Case Report Form (CRF), and specific guidance on applying the VCI scale. Emphasis was placed on protocol adherence, data quality, and ethical considerations.

Each participating hospital received a complete study package containing the CRF, informed consent templates, and all necessary supporting documentation for protocol implementation. To ensure ongoing support, a dedicated online discussion forum was created to allow investigators to submit questions and receive timely clarifications. In addition, monthly virtual meetings are being held with all site investigators to reinforce protocol adherence, resolve methodological concerns, and ensure consistency in the interpretation and documentation of the VCI scale across centers.

All participating centers obtained approval from their ethics committees, ensuring compliance with applicable ethical and regulatory standards throughout the study.

Eligibility criteria

This study will include adult patients (≥ 18-years-old) with an American Society of Anesthesiologists (ASA) physical status classification of I to III who require TI in a variety of clinical contexts, including diagnostic, therapeutic, or surgical procedures, as well as airway management in the operating room, Post-Anesthesia Care Unit (PACU), Intensive Care Unit (ICU), or emergency department. Eligible patients must undergo TI performed by an anesthesiologist or anesthesia resident participating in the study, and written informed consent must be obtained from the patient or their legal representative prior to the procedure.

Intervention in the VCISpain study

The intervention begins during the pre-anesthetic consultation or in the anesthetic-surgical preparation area (preoperative holding area), where eligible patients are provided with a detailed information sheet outlining the study objectives, methodology, and potential risks. The investigator anesthesiologists explain the protocol, address any questions or concerns, and ensure patient understanding before obtaining written informed consent.[24] Participants are informed of their right to withdraw consent at any time. If consent is withdrawn, the participant's data will be excluded from analysis in accordance with ethical guidelines, thereby respecting their autonomy (Appendices 1–2).

The clinical procedure follows standard practices (Fig. 1). TI is performed using a videolaryngoscope selected based on patient characteristics and the resources available at each center. The responsible anesthesiologist evaluates the TI using the VCI scale, which comprises the following components (Fig. 2):[22]

1. Blade Type: The videolaryngoscope is classified as either Macintosh (M) or hyperangulated (H).
2. Percentage of Glottic Opening (POGO): The POGO score is recorded at a standardized time point – immediately before advancing the endotracheal tube into the glottis. This measurement reflects the actual glottic view under the force and positioning used during intubation. Investigators are instructed not to record the initial or best view, but rather the view observed at the moment of tube insertion, to ensure consistency and clinical relevance.
3. Ease of Intubation: This is categorized as easy (E), difficult (D), or failed (F).
   a) Easy refers to successful tracheal intubation using the manufacturer's standard technique for the selected videolaryngoscope, without the need for adjuncts or external assistance.
   b) Difficult is defined as intubation requiring the use of adjuncts such as a bougie, stylet, or other guiding devices to facilitate tube placement.
   c) Failed refers to the inability to intubate the trachea using the initially selected videolaryngoscope, necessitating the use of a different videolaryngoscope or an alternative device (e.g., fiberoptic bronchoscope, supraglottic airway, or surgical airway).

Simultaneously, a second anesthesiologist observes the tracheal intubation procedure and independently records the VCI score to assess interobserver reproducibility.

Complications will be prospectively recorded based on predefined clinical criteria, including:[25] Hypoxemia (SpO_2 <

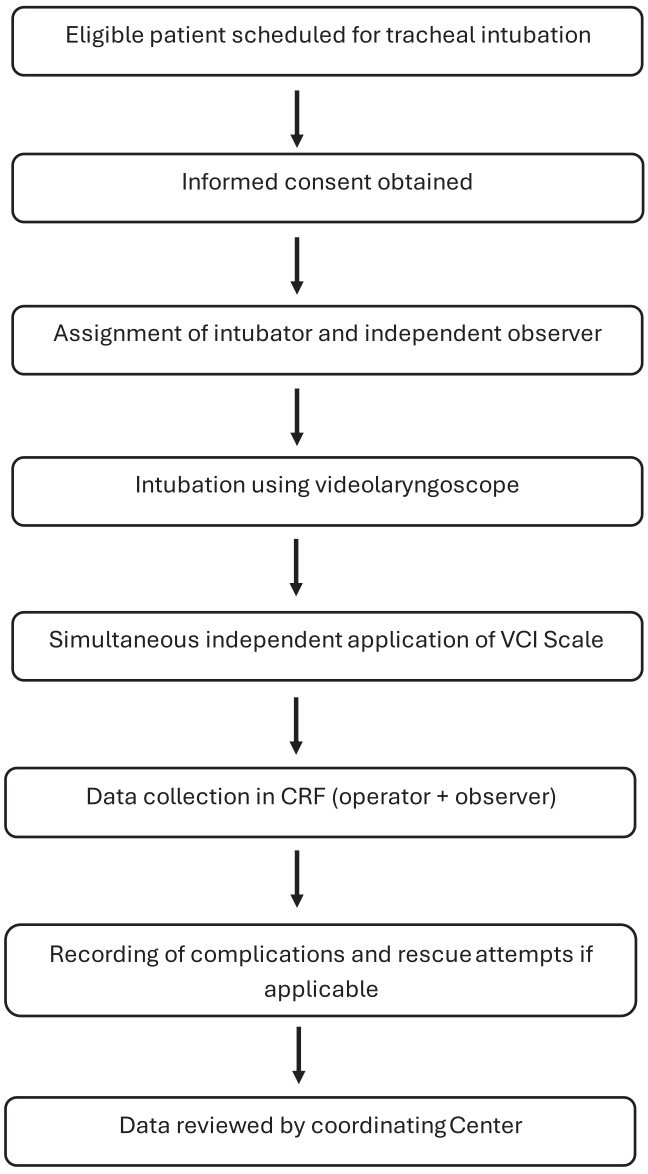

Figure 1 Flowchart.

90% for ≥ 10 seconds); Esophageal intubation (confirmed by capnography or clinical signs); Dental injury (visible tooth damage); Laryngeal trauma (presence of blood on the blade or tube, hoarseness, or stridor); Bronchospasm or laryngospasm (clinically diagnosed); Failed intubation (requiring a change in device or technique).

If a serious adverse event related to the videolaryngoscope is suspected, the attending physician may temporarily suspend the patient's participation in the study. Throughout the process, patient safety is prioritized, and each center's standard protocols will be followed in the event of any incident.

Outcome measures

Primary outcome

The primary outcome is the inter-rater agreement and reproducibility of the VCI scale, defined as the level of concordance between the VCI scores assigned by the anesthesiologist performing the tracheal intubation and an independent observer.

Secondary outcomes

1. The correlation between the Percentage of Glottic Opening (POGO) score and the difficulty of tracheal intubation.
2. The impact of operator experience on VCI scale outcomes, including the influence of training level and prior videolaryngoscopy experience on interobserver agreement and VCI scoring.
3. The incidence of tracheal intubation–related complications. While complications such as hypoxemia and laryngeal trauma are included as secondary outcomes, their expected low frequency means that related analyses will remain exploratory and descriptive in nature.

Exploratory data

The study will collect essential data in the following domains (Table 1) (Appendix 3):

1) Patient Demographics: Includes age, sex, weight, height, Body Mass Index (BMI), and ASA status.
2) Operator Characteristics: Documents the experience of the intubator or observer categorized by role (resident or specialist), years of experience (< 4, 4–8, > 8), and the number of prior intubations with VL: < 25, 25–50, > 50.
3) Procedure Setting: Documents the clinical environment, including operating theater, ICU, Post-Anesthesia Care Unit (PACU), or emergency department.
4) Videolaryngoscope Characteristics: Captures the type of videolaryngoscope used during the procedure.
5) Data Related to the VCI Scale: a) VCI score: Includes blade type (Macintosh or hyperangulated), POGO (categorized as < 25%, 25%–50%, 50%–75%, > 75%), and difficulty (easy, difficult, failed); b) Rescue Devices: If a rescue device is used, a new VCI score will be recorded.
6) Complications: these include hypoxemia, esophageal intubation, dental injury, laryngeal trauma, bronchospasm or laryngospasm, and failed intubation.

Data collection and management

Data will be collected using a standardized and anonymized physical CRF, independently completed by both the intubating anesthesiologist and the observer during and immediately after the intubation procedure. The collected data will then be managed through the secure electronic platform Research Electronic Data Capture (REDCap), hosted at the University of Navarra (UNAV), ensuring stringent patient confidentiality and data integrity. REDCap offers validated data capture and a transparent audit trail through its comprehensive logging features.

Data management workflow

Initial Data Capture: after each procedure, the anesthesiologist will complete the CRF, recording demographic data, procedure variables, and any observed complications.

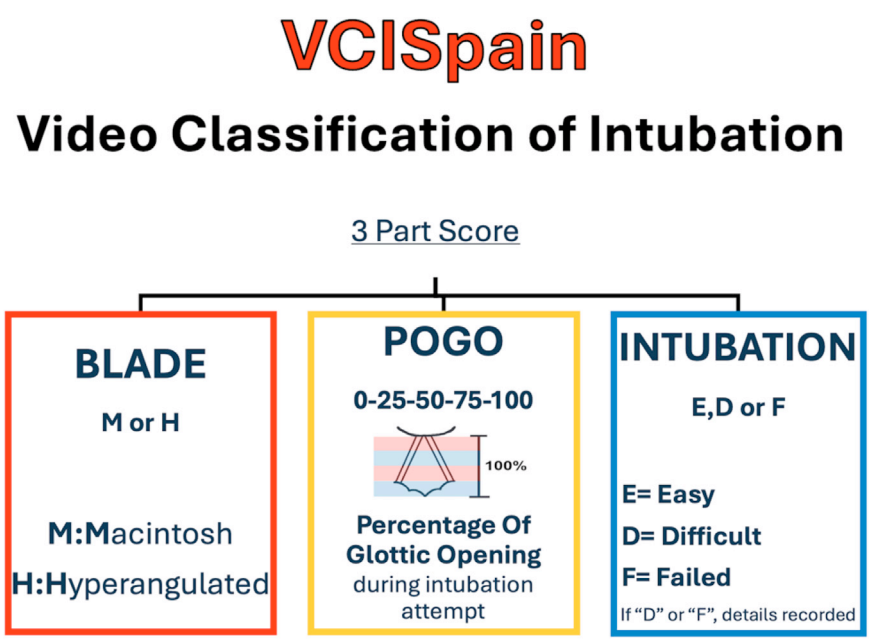

Figure 2 VCISpain (Video Classification of Intubation).

- Data Transfer to REDCap: the pseudo-anonymized data will be entered into the secure REDCap platform. Each patient will be assigned a unique encoding code that is not directly linked to their personal information, ensuring confidentiality.
- Ethical and Regulatory Compliance: all data will be collected and stored in full compliance with Good Clinical Practice (GCP) guidelines and current data protection regulations.

Data protection and quality assurance

Data Protection: the database will be encrypted and accessible only via individual passwords assigned to each investigator, ensuring robust security.

- Protocol Supervision: a designated clinical investigator will oversee the implementation of the study protocol, thoroughly documenting any deviations, adverse events, or protocol violations.
- Audits: the coordinating team and the principal investigator will conduct regular audits to verify data integrity and quality, maintaining high research standards.

Data access and oversight

- Centralized Access: the principal investigator (MFV) and two coordinators (PC and MV) will manage centralized access to the data, ensuring supervision of data security, quality, and statistical analysis.
- Access for Participating Centers: data will be made available to all participating centers to promote transparency and foster collaboration during analysis.
- Centralized Oversight: the principal investigator will coordinate the processes of data collection, storage, and analysis.

Statistical methods

A comprehensive statistical analysis will be conducted to describe the study's quantitative and qualitative variables. Quantitative variables will be summarized using measures of central tendency and dispersion (mean $\pm$ standard deviation or median [interquartile range]), depending on the distribution of data. Qualitative variables will be presented as absolute frequencies and percentages.

To evaluate the interobserver reproducibility of the VCI scale among anesthesiologists, the Cohen's Kappa coefficient will be used to measure the level of agreement between the anesthesiologist performing the tracheal intubation and the independent observer. Interpretation of agreement will follow standard criteria ($\leq$ 0.20 poor, 0.21 $-$0.40 fair, 0.41$-$0.60 moderate, 0.61$-$0.80 substantial, and $>$ 0.80 almost perfect).

Binary logistic regression analysis will be performed to explore associations between key variables, specifically to assess the relationship between the Percentage of Glottic Opening (POGO) and the ease or difficulty of Tracheal Intubation (TI). Results will be reported as Odds Ratios (OR) with their corresponding 95% Confidence Intervals (95% CI).

Statistical significance will be determined using a p-value threshold of $<$ 0.05. Data analyses will be performed using Stata 18 (StataCorp, College Station, TX, USA), a software providing advanced modeling and data-processing capabilities to ensure the precision and validity of the results.

Sample size

The study will enroll a total of 1,395 patients, accounting for a 5% dropout rate. The sample size calculation is based on achieving a precise estimate of the expected interobserver agreement measured by Cohen's Kappa coefficient, assumed to be 0.80, with a desired precision of $\pm$ 0.11 and a confidence interval of 95%. Additionally,

Table 1 CRF VCISpain. VIDEO CLASSIFICATION OF INTUBATION VCISpain — Case Report Form (CRF).

General Information	
Date	
Intubator's e-mail	
Patient Demographics	
Age	
Sex/Gender	
ASA status	
Weight (kg)	
Height (cm)	
Intubation Setting	
Place of Intubation	Operating Room / ICU / Emergency / Other
Videolaryngoscope Details	
Videolaryngoscope Model	McGrath / C-MAC / Airtraq / Glidescope / Others
Intubator Data	
Role	Resident / Specialist
Years of experience	< 4 / 4—8 / > 8
Prior VL intubations	< 25 / 25—50 / > 50
Intubator VCI	
Blade type	Macintosh / Hyperangulated
POGO score	< 25% / 25—50% / 50—75% / > 75%
Ease of intubation	Easy / Difficult / Failed
If Difficult	Stylet / Bougie / Other adjunct
If Failed	Rescue device used + Rescue VCI
Observer Data	
Role	Resident / Specialist
Years of experience	< 4 / 4—8 / > 8
Prior VL intubations	< 25 / 25—50 / > 50
Observer VCI	
Blade type	Macintosh / Hyperangulated
POGO score	< 25% / 25—50% / 50—75% / > 75%
Ease of intubation	Easy / Difficult / Failed
If Difficult	Stylet / Bougie / Other adjunct
If Failed	Rescue device used + Rescue VCI
Complications	
Desaturation	< 92%
Esophageal intubation	Yes / No
Dental damage	Yes / No
Other	Specify
Rescue VCI (If applicable)	
Blade type	Macintosh / Hyperangulated
POGO score	< 25% / 25—50% / 50—75% / > 75%
Ease of intubation	Easy / Difficult / Failed

assuming a 10% incidence of difficult Tracheal Intubation (TI), this sample size will ensure adequate representation for meaningful secondary analyses.[6] Patient recruitment is anticipated to take between 12 and 18 months, starting in September 2024.

Ethics and dissemination

Ethical approval of research

The VCISpain study complies with the principles outlined in the Declaration of Helsinki and the GCP Guidelines. Ethical approval has been granted by the Research Ethics Committee of the University of Navarra (session of September 5, 2024, reference 2022.079 mod1). The study was registered at ClinicalTrials.gov (NCT06537531), ensuring adherence to transparency and high ethical standards. Oversight of ethical compliance will be managed by the principal investigator and coordinators in collaboration with the University of Navarra (UNAV).

Confidentiality

To uphold participant confidentiality, all original records will be securely stored at the participating centers for five years after the study's completion. The electronic database will be thoroughly cleaned, anonymized, and retained for this period; this approach guarantees compliance with data protection regulations and ensures the safeguarding of participant information.

Discussion

Airway management is a cornerstone of anesthetic practice; however, difficult tracheal intubation remains a significant concern, as highlighted by a recent audit in the United Kingdom.[6] The introduction of VL has transformed airway management by providing superior glottic visualization, increasing first-attempt success rates, and reducing complications associated with multiple intubation attempts, such as hypoxemia, laryngeal trauma, and esophageal intubation.[25] Nevertheless, the widespread adoption of VL continues to be limited by challenges related to training,[26] financial constraints, and, notably, the lack of a standardized classification tool for documenting and communicating VL findings.[23]

The VCISpain study aims to bridge this gap by validating the VCI scale. This tool is designed to establish a standardized and reproducible language for airway management with videolaryngoscopy, addressing the limitations of traditional classification systems such as the Cormack-Lehane scale. Unlike these conventional tools, the VCI scale captures the unique features of videolaryngoscopy, particularly the "you see, and you fail" phenomenon, in which excellent glottic visualization does not necessarily ensure successful intubation.[17] By standardizing communication, the VCI scale can enhance planning for future airway treatments, ultimately promoting patient safety.

The VCI scale integrates three key components: blade type (Macintosh or hyperangulated), the POGO score, and the ease or difficulty of the intubation procedure. This tool not only enhances documentation but also facilitates communication among clinicians, while supporting training and standardization in advanced airway management.

A previous study demonstrated the accuracy and reproducibility of the VCI scale in describing VL intubations.[22] With its multicenter design – encompassing 35 Spanish hospitals and anesthesiologists with varying levels of experience – the VCISpain study provides a representative reflection of

real-world clinical practice in Spain. Moreover, standardized training on the study protocol and the use of the VCI scale will help ensure the quality and reproducibility of the collected data.

This study offers several strengths, including the pioneering evaluation of the VCI scale in a multicenter setting, providing robust data on its reproducibility and clinical utility. Its pragmatic design minimizes interference with standard care, enhancing its relevance to everyday clinical practice.

Despite certain limitations – such as heterogeneity among participating centers and variability in videolaryngoscope models and operator experience – these factors may, in fact, increase the external validity of the findings by reflecting real-world clinical diversity.

One notable limitation is the absence of a direct comparison with existing classification systems, which prevents definitive conclusions regarding the superiority of the VCI scale over other tools.[16] However, although not directly compared in this study, the VCI scale may offer advantages by integrating blade type, glottic view, and ease of intubation into a single, videolaryngoscopy-specific tool. It enhances clinical communication and documentation, not by replacing traditional scales, but by complementing them with context-specific information relevant to modern airway management.

The VCISpain study represents a significant step toward standardizing the communication of information related to videolaryngoscopy-guided tracheal intubation.[27] Validation of the VCI scale has the potential to establish a new benchmark for both national and international clinical practice, informing future airway management guidelines. Integrating the VCI scale into routine care may improve patient safety, foster interdisciplinary collaboration, and support continuous professional development.

Conclusion

In conclusion, VCISpain represents a cultural shift in airway management through the use of videolaryngoscopy. By establishing a common language, it has the potential to promote interprofessional collaboration, support clinical education, and improve airway management planning. It also paves the way for future research in anesthesiology.

Beyond its practical applications, the VCI scale reflects a broader commitment to continuous improvement and innovation in patient care, emphasizing safety and effective clinical communication as cornerstones of modern anesthetic practice.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Miguel Ángel Fernández-Vaquero served as the principal investigator, conceived the study, and wrote the initial draft of the manuscript. Pedro Charco-Mora and Marc Vives-Santacana acted as study coordinators, provided critical input in the study design, and contributed to drafting and revising the manuscript. Miguel Ángel García-Aroca, Manuel Ángel Gómez-Ríos, and José Alfonso Sastre-Rincón contributed significantly to the study design and collaborated on writing and refining the manuscript.

The remaining authors served as the principal investigators at their respective centers, contributing to the implementation and oversight of the study. All authors reviewed, revised, and approved the final version of the manuscript for submission.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844653.

Associate Editor

Maria José Carmona

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Brazilian Journal of Anesthesiology 2025;75(5): 844642

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Comparison of automatic versus constant CPAP in elderly patients after major abdominal surgery: a randomized noninferiority trial

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Received 9 January 2025; accepted 3 May 2025
Available online 17 May 2025

KEYWORDS
Continuous positive airway pressure;
Elderly;
Laparotomy;
Patient comfort;
Pulmonary function tests

Abstract

Background: Geriatric patients undergoing major open abdominal surgery are at high risk for postoperative pulmonary complications and hypoxemia. Continuous Positive Airway Pressure (CPAP) after surgery may improve postoperative lung function. This randomized controlled trial compared two CPAP techniques – automatic via nasal mask and constant via facial mask – regarding pulmonary function and patient tolerance.

Methods: Sixty patients (≥ 60 years) were randomized (1:1) to receive either automatic CPAP (2−10 cm H_2O) via a nasal mask (Group A) or constant CPAP (7.5 cm H_2O) via a facial mask (Group C) upon arrival in the post-anesthesia care unit. Oxygenation (PaO_2, PaO_2/FiO_2, SpO_2) and spirometry (FVC, FEV_1, PEF) were assessed preoperatively, postoperatively, and one hour after treatment. Comfort scores (0−10, with 0 indicating the best comfort) and complications were recorded.

Results: PaO_2/FiO_2 improvement was lower in Group A (32.6 ± 26.3 mmHg) than in Group C (52.9 ± 40.1 mmHg; p = 0.023). FVC improvement was also lower in Group A (3.7% ± 4.0%) than in Group C (6.7% ± 4.9%; p = 0.012). However, Group A had better tolerance, with lower comfort scores (2 [2−3] vs. 3 [2−4], p = 0.002). Pulmonary function benefits were more pronounced in patients over 70 and those undergoing upper abdominal surgery.

Abbreviations: CPAP, Continuous Positive Airway Pressure; PACU, Post-Anesthesia Care Unit; FiO_2, Fraction of Inspiratory Oxygen; MAC, Minimum Alveolar Concentration; PCV-VG, Pressure-Controlled Volume Guarantee; TOF, Train-Of-Four; SpO_2, Saturation of Peripheral Oxygen; PaO_2, Arterial Partial Pressure of Oxygen; $P(A\text{-}a)O_2$, Alveolar-Arterial Gradient; $PaCO_2$, Arterial Partial Pressure of Carbon Dioxide; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in the first second; PEF, Peak Expiratory Flow; NRS, Numeric Rating Scale; COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index; ASA, American Society of Anesthesiology.

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https://doi.org/10.1016/j.bjane.2025.844642

Conclusion: Both CPAP techniques prevent pulmonary decline in geriatric patients post-surgery. While automatic CPAP provides better comfort, constant CPAP improves oxygenation. Although our findings are short-term, they suggest that CPAP mode selection should be tailored based on patient-specific needs.

Introduction

Postoperative pulmonary complications frequently arise following major abdominal surgery, significantly contributing to higher morbidity, extended hospitalization, and elevated mortality rates.[1,2] Hypoxemia and respiratory alterations reach their peak in the initial hours post-surgery, potentially leading to acute respiratory failure – an occurrence observed in 30% to 50% of individuals after upper abdominal surgery.[3] This issue is particularly pronounced in the aging population, where surgical volume is rising.[4] The deleterious physiological changes associated with aging, coupled with the damaging effects of comorbidities on the pulmonary system, result in a heightened risk of perioperative pulmonary outcomes among geriatric patients.[3,5] The incidence rates of postoperative pulmonary complications in geriatric patients range from 1% to 23%, depending on surgical factors.[6] This underscores the importance of timely and effective treatment during the early postoperative period to prevent hypoxemia and its associated complications in these populations.

Postoperative Continuous Positive Airway Pressure (CPAP) application may effectively reduce the risk of pulmonary complications in both preventive and therapeutic settings.[7-9] CPAP involves utilizing a high-pressure gas source or machine to deliver positive pressure during both inspiration and expiration. This pressure can be consistently delivered or varied through a nasal airway or face mask.[10] Constant CPAP via a face mask may be poorly tolerated, especially over extended periods, and requires frequent staff adjustments to prevent air leakage, particularly in elderly patients with age-related facial changes.[11] Nasal automatic CPAP devices, providing positive pressure in response to abnormalities in the breathing pattern, have proven effective, well-tolerated, and widely applied for sleep apnea-hypopnea syndrome patients.[12] This highlights the potential benefits of automatic CPAP for postoperative care. However, while most CPAP studies focus on pulmonary function improvement, fewer address discomfort during treatment. Additionally, although CPAP is widely used postoperatively, limited evidence exists comparing automatic and constant CPAP in geriatric patients, particularly regarding oxygenation and patient tolerance.

This study assesses the impact of nasal automatic CPAP compared to face mask constant CPAP on postoperative oxygenation, respiratory mechanics, and comfort in geriatric patients undergoing major open abdominal surgery.

Method

This single-center randomized controlled trial, approved by the Vietnam Military Medical University Ethics Committee (n° 3977/QĐ-HVQY) and registered on ClinicalTrials.gov (NCT06260826), followed the Declaration of Helsinki and CONSORT guidelines. All patients provided informed consent.

Patient population

We enrolled 60 patients over 60 years old undergoing major open abdominal surgery (e.g., gastrectomy, colectomy, proctocolectomy, hepatectomy) from December 2021 to August 2022. Exclusion criteria included preoperative non-invasive ventilation, airway deformities, bullous emphysema, suspected bronchopleural fistula, facial abnormalities, delayed extubation (> 4 hours), non-epidural anesthesia, or inability to consent. Additionally, we excluded patients with suspected sleep apnea syndrome based on clinical symptoms and risk factors, such as obesity (BMI > 30), loud snoring, and witnessed apneas during sleep.

Anesthesia protocol

Patients received standardized anesthetic management per hospital protocols. Before induction, an epidural catheter was placed in the epidural space at D7−9 for upper abdominal surgery and at L1−3 for lower abdominal surgery. A 0.2% bupivacaine solution was initially administered as a 5 mL bolus and maintained at 5 $mL.h^{-1}$ during surgery. General anesthesia was induced with propofol (1−2 $mg.kg^{-1}$), fentanyl (1−2 $\mu g.kg^{-1}$), and rocuronium (0.6−0.8 $mg.kg^{-1}$), followed by intubation after 3 minutes of manual ventilation. Anesthesia was maintained with sevoflurane (0.5−0.8 MAC) and oxygen/air (FiO_2 = 0.4). Rocuronium was given based on TOF (train-of-four) monitoring. Fentanyl and epidural rates were adjusted to maintain the Surgical Pleth Index at 40−70. Intraoperatively, fluid balance was managed with Ringer's lactate and colloid solutions, based on urine output, blood loss, and central venous pressure.

The ventilator was set in Pressure-Controlled Volume Guarantee (PCV-VG) mode with tidal volume 6−8 $mL.kg^{-1}$ (ideal body weight), inspiration: expiration ratio of 1:2, positive end-expiratory pressure of 5 cm H_2O, and the respiratory rate (9−12 per minute) was adjusted to maintain $EtCO_2$ between 35−40 mmHg. Alveolar recruitment maneuvers were performed every 30−45 minutes. The patient was extubated when fully awake, spontaneously breathing, and TOF > 90%. Nausea and vomiting were prophylactically managed with dexamethasone (4 mg) and ondansetron (4 mg). Postoperative pain was managed with continuous epidural analgesia (bupivacaine 0.125% + fentanyl 2 $\mu g.mL^{-1}$), paracetamol (15 $mg.kg^{-1}$), and nefopam (20 mg).

Randomization and interventions

After extubation, all patients were positioned with a 30° upper body elevation. CPAP treatment began as soon as

patients could cough and clear phlegm. Randomization into Group A or Group C (1:1 ratio) was performed using a computer-generated list, with allocation concealed in numbered, sealed, opaque envelopes opened by a research nurse upon the patient's arrival at the PACU.

Group A: automatic CPAP (JPAP system, Metran, Japan) delivered via a nasal mask with a reference pressure of 7 cm H_2O during a 5-minute ramp time (in 0.5 cm H_2O increments). After that, the pressure was allowed to vary within a 2—10 cm H_2O range during treatment, with O_2 at 6 $L.min^{-1}$.

Group C: constant CPAP (O2-Max Trio, Pulmodyne, USA) delivered via a facial mask with a pressure set at 7.5 cm H_2O and FiO_2 at 30%, both fixed throughout the treatment.

Patients received 1 hour of CPAP therapy. Those unable to tolerate it were treated according to standard PACU protocols and excluded from further analysis. PACU discharge was determined using a modified Aldrete score.[13]

Outcome measures

The primary outcome was the PaO_2/FiO_2 ratio. Arterial blood gas was measured at three time points: before surgery, at fixed postoperative intervals – including upon arrival at the PACU – and immediately after CPAP treatment using the Cobas B221 blood gas machine (Roche, Basel, Switzerland) for all patients.

Secondary outcome measures included spirometry parameters (forced vital capacity-FVC, forced expiratory volume in the first second-FEV1, FEV1/FVC ratio, and peak expiratory flow-PEF), assessed using Spirobank II Advanced (Medical International Research, Roma, Italia) in a 45° upper body elevation position, concurrently with blood gas assessment. After CPAP treatment, patients rated their overall comfort on a numeric rating scale (NRS, 0—10, where 0 indicated the best comfort and 10 the worst), and other complications related to CPAP were recorded.

Sample size and statistical analysis

According to previous studies that have reported oxygenation improvements (ΔPaO_2) of 15 mmHg (SD = 18 mmHg) and a reduction in postoperative respiratory failure with CPAP or non-invasive ventilation compared to traditional oxygen therapy in morbidly obese postoperative patients,[14-16] the sample size was calculated to be 48 (24 per group) using an alpha of 0.05 and a power of 0.8. After accounting for a 20% dropout rate, 60 patients were included, with 30 in each group.

Data are presented as mean ± SD and range for continuous variables or as numbers and percentages for categorical variables. Variable distribution was assessed using histograms and the Kolmogorov-Smirnov test. Group differences were analyzed using Student's *t*-test or Mann-Whitney *U* test. Within-group variations for continuous variables were assessed using two-way repeated measure ANOVA with Tukey's post hoc tests. Categorical variables were analyzed using Chi-Squared or Fisher's exact tests. IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, N.Y., USA), was used for statistical analyses. A p-value < 0.05 was considered statistically significant.

Results

After randomization, 30 patients were included in each group, with no cases excluded due to CPAP intolerance or incomplete follow-up, as presented in the CONSORT-compliant flow diagram (Fig. 1). There were no significant differences between the groups regarding preoperative characteristics, surgery, and anesthesia features (Table 1).

Figure 2 illustrates the oxygenation parameters. Post-surgery, PaO_2, PaO_2/FiO_2, and SpO_2 values before CPAP (pre-CPAP) significantly decreased in all patients compared to pre-surgery (pre-op), with no differences between groups. Following CPAP treatment (post-CPAP), PaO_2 (Fig. 2A) improved in both groups (adjusted p = 0.011 in Group A, < 0.001 in Group C; within-group comparison), showing an interaction between group and time [F(2, 58) = 3.67, p = 0.031]. PaO_2 in Group C was higher than in group A (p = 0.004, between groups). PaO_2/FiO_2 values (Fig. 2B) exhibited a pattern similar to PaO_2.

After surgery, the alveolar-arterial gradient ($P(A\text{-}a)O_2$, Fig. 2C) significantly increased in both Groups A and C (adjusted p < 0.001 and 0.012, respectively). CPAP treatment effectively reversed this increase, with adjusted p-values of 0.014 (Group A) and < 0.001 (Group C). A significant group and time interaction was observed [F(2, 58) = 6.11, p = 0.004], and Group C showed a significantly lower $P(A\text{-}a)O_2$ than Group A (p = 0.001, between groups).

The pulse oximetry values (SpO_2) displayed a similar pattern to the PaO_2 parameter (Fig. 2D).

Figure 3 illustrates respiratory mechanics parameters. Postoperative FEV1 (Fig. 3A), FVC (Fig. 3B), and PEF (Fig. 3D) values decreased compared to preoperative levels in both groups, with improvement following CPAP application. No significant group differences were observed in FEV1, FEV1/FVC (Fig. 3C), and PEF at all measurement time points. However, there was an interaction between group and time in FVC values [F(2, 58) = 6.02, p = 0.004].

After CPAP treatment, the improvement in PaO_2/FiO_2 ($\Delta PaO_2/FiO_2$ = post-CPAP PaO_2/FiO_2 value − pre-CPAP PaO_2/FiO_2 value) in Group A (32.6 ± 26.3 mmHg) was lower than in Group C (52.9 ± 40.1 mmHg) with p = 0.023 (Fig. 4A). Similarly, the improvement in FVC (ΔFVC = post-CPAP FVC value − pre-CPAP FVC value) in Group A (3.7 ± 4.0%) was lower than in Group C (6.7 ± 4.9%) with p = 0.012 (Fig. 4B). Notably, the difference between CPAP treatment groups in $\Delta PaO_2/FiO_2$ (mmHg) was more pronounced in patients aged ≥ 70 (95% CI: 2.88—53.30) than those < 70 (95% CI: -16.70 to 23.45) and in upper (95% CI: 2.79—46.12) vs. lower abdominal surgery (95% CI: -21.79 to 39.79), despite similar intraoperative ventilation settings and opioid use across subgroups. A similar trend was observed in ΔFVC (%) for upper (95% CI: 0.30—6.25) vs. lower abdominal surgery (95% CI: -1.01 to 5.82).

Postoperative complications and comfort data are detailed in Table 2. While some Group A patients reported device noise as a concern, discomfort in Group C was more commonly associated with pressure, mouth dryness, and mask contact with the face. Overall, patients treated with automatic CPAP reported greater comfort than those receiving constant CPAP.

No patient experienced gastric distension, conjunctival congestion, pneumothorax, or hypotension due to CPAP

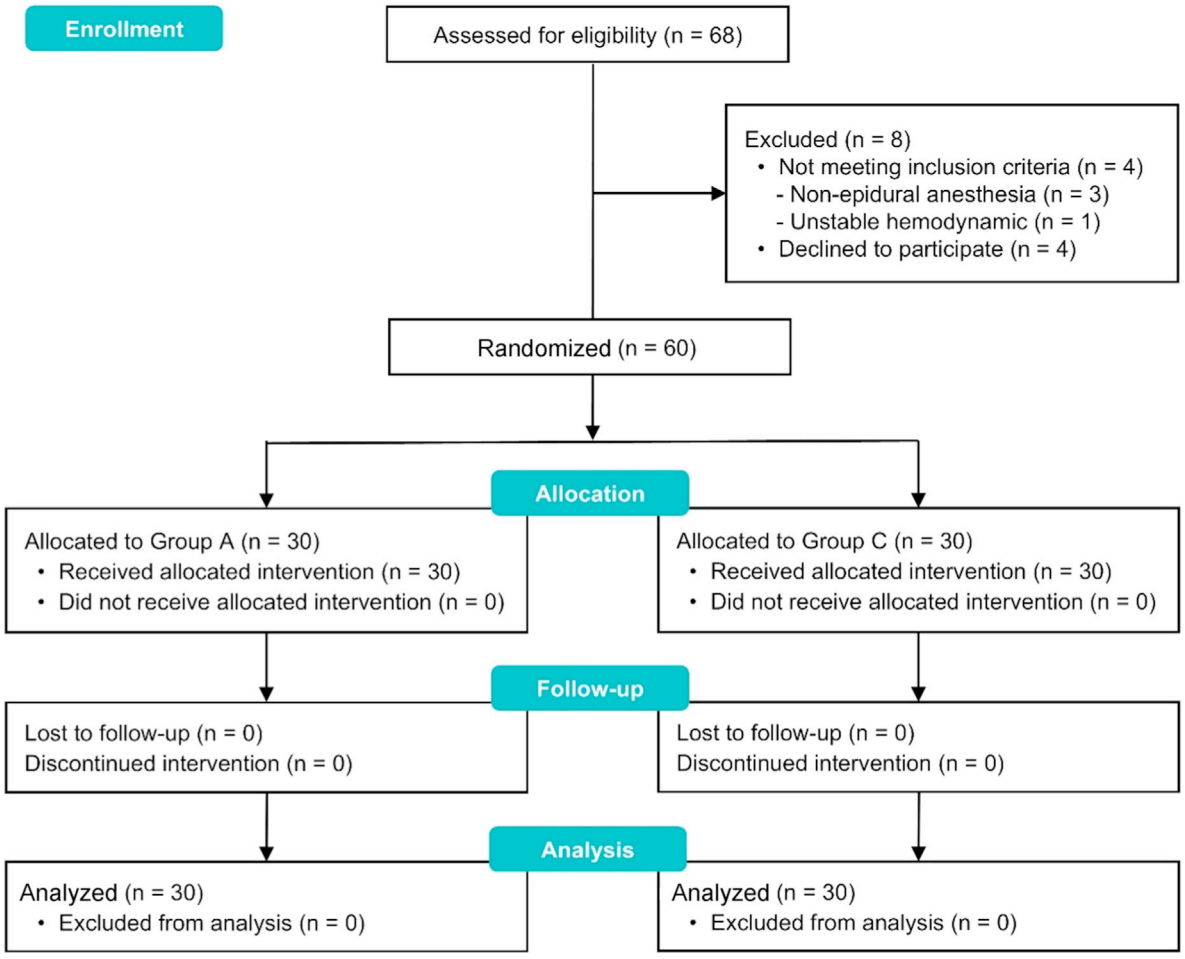

Figure 1 CONSORT diagram.

Table 1 Demographic data.

	Group A (n = 30)	Group C (n = 30)	p-value
Age (yr)	73.1 ± 8.3 [62–88]	73.7 ± 7.0 [60–86]	0.775
Weight (kg)	59.0 ± 8.7 [42–80]	58.8 ± 7.9 [42–75]	0.926
Height (cm)	163.2 ± 6.5 [150–175]	161.7 ± 5.3 [150–171]	0.366
BMI	22.1 ± 2.6 [16.8–27]	22.4 ± 2.3 [17.8–26.9]	0.637
Gender (Male/Female)	25/5	24/6	0.739
ASA grade (II/III)	10 /20	11/19	0.787
Preoperative respiratory disease			
Asthma, n (%)	0	1 (3.3)	1
COPD, n (%)	1 (3.3)	0	1
Smoker, n (%)	9 (30)	9 (30)	1
Surgical site			1
Upper abdominal, n (%)	22 (73.3)	22 (73.3)	
Lower abdominal, n (%)	8 (26.7)	8 (26.7)	
Surgery length (min)	178 ± 50 [90–315]	162 ± 60 [80–310]	0.253
Anesthesia length (min)	209 ± 49 [115–340]	187 ± 59 [110–345]	0.129
Anesthetic agents			
Fentanyl (μg)	100	100	1
Rocuronium (mg)	55.2 ± 17.2 [40–110]	51.7 ± 10.2 [40–110]	0.343
Sevoflurane (mL)	53.0 ± 13.0 [27–85]	46.6 ± 14.1 [23–78]	0.071

Data are expressed as mean ± SD and [range]; BMI, Body Mass Index; ASA, American Society of Anesthesiology, COPD, Chronic Obstructive Pulmonary Disease. Student's *t*-test, Chi-Squared test, or Fisher's exact test.

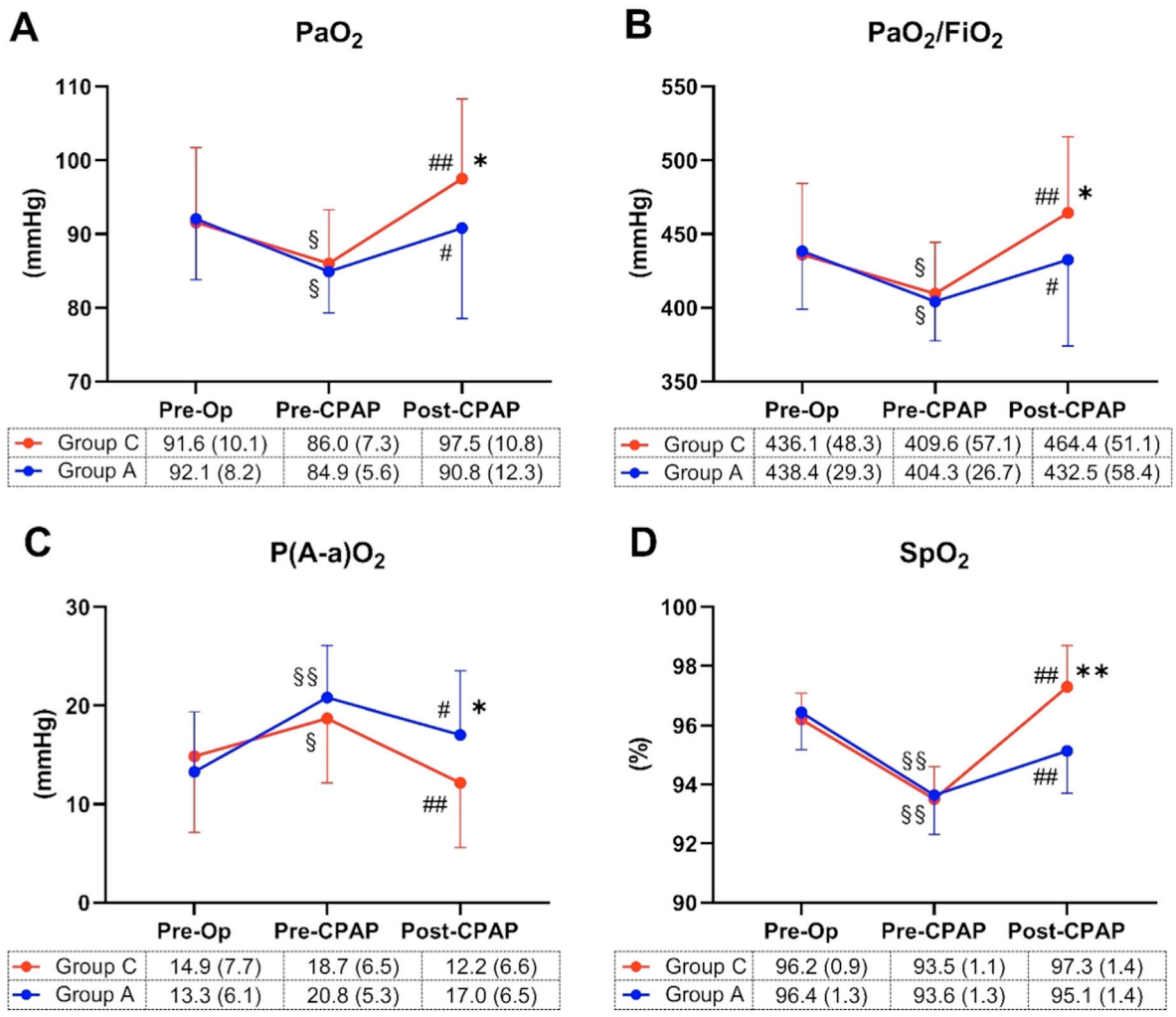

Figure 2 Blood gas analyses and pulse oximetry values. The arterial partial pressure of oxygen (PaO_2; A), the ratio of PaO_2 to the fraction of inspired oxygen (PaO_2/FiO_2; B), the alveolar-arterial gradient ($P(A\text{-}a)O_2$; C) and the saturation of peripheral oxygen (SpO_2; D) were recorded before anesthesia (Pre-Op), after anesthesia before applying CPAP (Pre-CPAP) and after CPAP (Post-CPAP). All measurements were taken after 5 minutes of breathing room air. Data are expressed as means with SD. Differences were estimated by two-way repeated-measures ANOVA with Tukey's post-hoc test (*$p < 0.05$, **$p < 0.001$, between groups; $^{\S}p < 0.05$, $^{\S\S}p < 0.001$, within the group between Pre-CPAP and Pre-Op; $^{\#}p < 0.05$, $^{\#\#}p < 0.001$; within the group between Post-CPAP and Pre-CPAP).

application during PACU time, and the length of PACU stay was similar between groups. Additionally, no patients in either group developed severe pulmonary complications requiring reintubation or ICU readmission for respiratory failure within 48 hours postoperatively. The hospital mortality rate was similar between groups.

Discussion

Our study shows that both automatic and constant CPAP techniques improve gas exchange and respiratory mechanics in geriatric patients undergoing major open abdominal surgery. Constant CPAP leads to greater improvements in oxygenation and FVC compared to automatic CPAP, while the latter provides higher comfort scores during treatment.

CPAP treatment, whether automatic or constant, improved postoperative oxygenation in geriatric patients. The observed decline in postoperative pulmonary function can be attributed to hypoventilation,[3] atelectasis,[17] and an increased alveolar-arterial gradient.[18] Here, we found that after 1 hour of CPAP, PaO_2/FiO_2 and FVC improved by 52.9 mmHg and 6.7% with the constant technique and 32.6 mmHg and 3.7% with the automatic technique. Our findings with constant CPAP are consistent with previous studies after major abdominal surgery, though data specifically on elderly patients remain limited. Hatice Yağlıoğlu et al. reported a 137-mmHg increase in PaO_2/FiO_2 and a 14.6% rise in expiratory tidal volume in patients (mean age 60–61 years) with COPD comorbidities, which may explain their greater improvement.[19] Similarly, a 32 mmHg increase was observed in younger, morbidly obese patients (mean age 42.6 years),[20] whereas in older patients (mean age 67–68 years) after major abdominal surgery, PaO_2/FiO_2 improved by only 10 mmHg despite 6 hours of CPAP.[21] This may be due to intermittent mask CPAP rather than continuous application.[21] The lung expansion effects of CPAP – preventing airway collapse, promoting alveolar recruitment, and reducing the

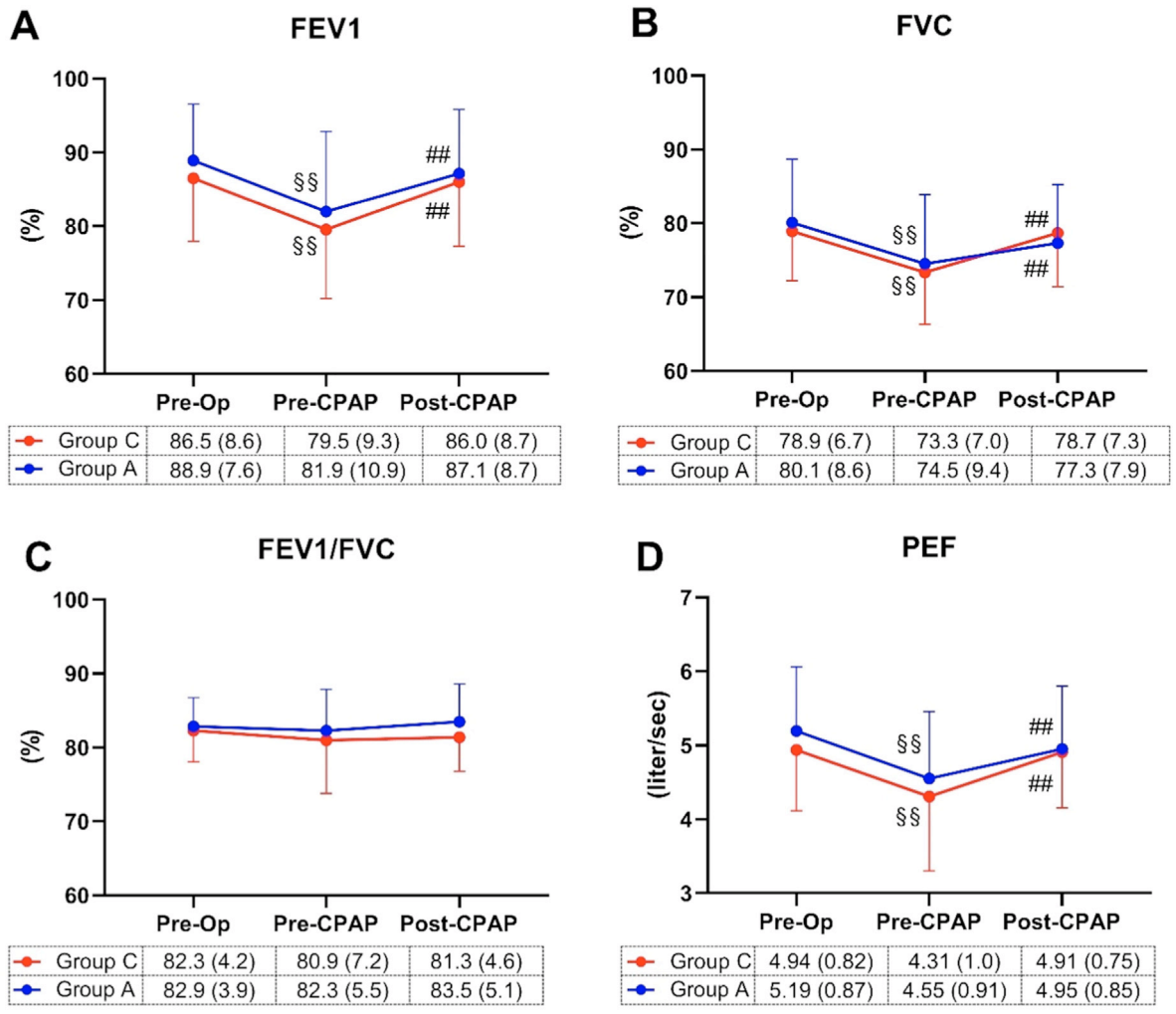

Figure 3 Respiratory Mechanics. The Forced Expiratory Volume in the first second (FEV1; A), Forced Vital Capacity (FVC; B), FEV1/FVC (C), and Peak Expiratory Flow (PEF; D) values were recorded before Anesthesia (Pre-Op), after anesthesia before applying CPAP (Pre-CPAP) and after CPAP (Post-CPAP). Data are expressed as means with SD. Differences were estimated by two-way repeated-measures ANOVA with Tukey's post-hoc test ($^{\S}p < 0.05$, $^{\S\S}p < 0.001$, within the group between Pre-CPAP and Pre-Op; $^{\#}p < 0.05$, $^{\#\#}p < 0.001$; within the group between Post-CPAP and Pre-CPAP).

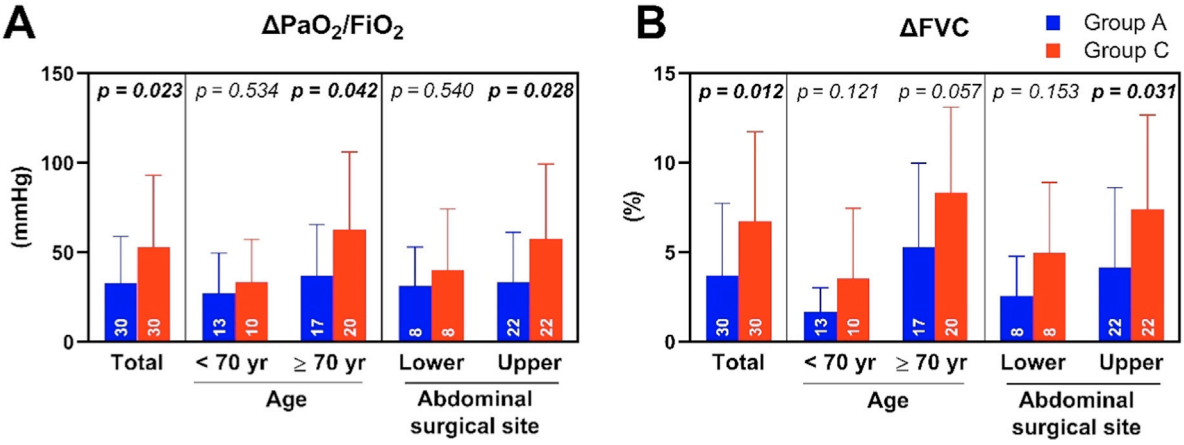

Figure 4 The change in lung function after applying CPAP and subgroup. The change induced by applying CPAP (Post-CPAP − Pre-CPAP) in the ratio of the Arterial Partial pressure of Oxygen to the Fraction of Inspired Oxygen ($\Delta PaO_2/FiO_2$; A) and Forced Vital Capacity (ΔFVC; B) were subgrouped by age and abdominal surgical site. Data are expressed as means with SD. Differences were estimated by Student's *t*-test. Numbers inside the bars indicate the number of participants.

Table 2 Patient-reported comfort and complications.

	Group A (n = 30)	Group C (n = 30)	p-value
Comfort Score, median (IQR)	2 (2−3)	3 (2−4)	**0.002**
Uncomfortable due to			
Noise, n (%)	5 (16.7)	1 (3.3)	0.194
Pressure, n (%)	1 (3.3)	9 (30)	**0.012**
Dryness of mouth, n (%)	1 (3.3)	5 (16.7)	0.194
Facial erythema	0	3 (10)	0.237
Length of PACU stay, h	5.4 ± 1.2	5.6 ± 1.3	0.765
Hospital mortality, n (%)	1 (3.3)	1 (3.3)	1

Numeric Rating Scale (NRS), 0−10: with the number 0 indicating the best possible comfort and 10 the worst.
Mann-Whitney *U* test, Fisher's exact test, Student's *t*-test.

work of breathing – likely contributed to the observed improvements in FEV_1, FVC, and PEF with both automatic and constant CPAP in our study. A similar 5.7% increase in FVC was reported by Joana Guimarães et al. with constant CPAP.[22] However, some studies have found no significant improvement in FVC and FEV_1 with CPAP compared to conventional oxygen therapy postoperatively.[20,22,23] These discrepancies may be due to differences in treatment duration[23] or patient characteristics.[20,22] To date, the effect of postoperative automatic CPAP on pulmonary function has not been published. Our findings suggest that the pulmonary function benefits of CPAP vary depending on patient characteristics.

The observed differences in oxygenation and lung function improvement between the automatic CPAP and constant CPAP groups may be attributed to variations in the delivered airway pressure, which play a primary role in lung expansion. The lower pressure may not be sufficient to open micro-atelectasis areas.[24] A study on sleep apnea-hypopnea syndrome patients found that patients using automatic CPAP slept at a mean pressure lower than those using constant CPAP.[25,26] While the airway pressure is maintained with the constant CPAP, the effective pressure with automatic CPAP can vary within a given subject in each breath cycle, depending on body position, fatigue level, sedative stage, and upper airway characteristics.[26] Alveolar pressure created by CPAP can vary across the respiratory cycle among different patients. Our population study is mostly within the normal or lower range of BMI, Mallapati levels 1 and 2, and lying in a head-up position resulting in the pressure delivered in Group A possibly being lower than the pressure in Group C. Additionally, patients in Group A used nasal masks, which can lead to air leakage through the mouth, further contributing to differences in effective pressure between the groups.

Although constant CPAP resulted in greater pulmonary function improvements than automatic CPAP, we found that automatic CPAP treatment with a nasal mask provided patients with higher comfort scores than constant CPAP with a face mask. Moreover, no patients required a break or exhibited non-adherence during the 1-hour treatment in either group. Various studies have evaluated patient tolerance when comparing automatic and constant CPAP for the treatment of obstructive sleep apnea, consistently reporting a preference for automatic CPAP.[27] Poor compliance with face mask constant CPAP therapy is a well-recognized issue, particularly in long-term treatment, with non-adherence rates ranging from 46% to 83%.[28] Our study is the first to evaluate patient comfort during automatic versus constant CPAP treatment in the acute postoperative setting. Discomfort with constant CPAP was more commonly associated with pressure and mask contact with the face. In a study by Jens T. F. Osterkamp et al.,[21] the overall comfort score had a median (IQR) of 2 (1−3), with 27% of patients reporting discomfort due to pressure – similar to our findings. However, skin trauma or facial erythema was not reported in their study, possibly because the face mask was applied intermittently. The pressure variation in automatic CPAP devices provides greater comfort for patients compared to constant pressure. Additionally, using a nasal mask can reduce mouth dryness and benefit patients with mask fit issues, postoperative delirium, anxiety, or claustrophobia. Enhanced comfort with nasal automatic CPAP may support prolonged treatment duration, contributing to hemodynamic stability and improved lung function.

Notably, the more significant benefit of both CPAP techniques on lung function improvement was found in patients aged over 70 and/or those undergoing upper abdominal surgery. Age, identified as an independent risk factor for postoperative pulmonary complications, exhibits an increasing odds ratio (95% CI) of 2.1 (1.7−2.6) for individuals aged 60 to 69 compared to those under 60, with the risk further escalating with advanced age.[18] This susceptibility is attributed to their limited physiological reserve, age-related frailty, higher airway closing capacity, and lower ventilation-perfusion ratios.[29] Furthermore, the diaphragm undergoes more cephalad displacement and splinting during upper abdominal surgery, combined with limited respiratory excursion induced by pain, exacerbating the reduction in functional residual capacity[30] and postoperative hypoxemia. High-risk patients, with advanced age as a contributing factor, also derived more benefits from CPAP treatment after lung resection surgery.[31] Therefore, we assert that the prophylactic use of CPAP holds greater clinical relevance for advanced-age patients and/or those undergoing upper abdominal surgery.

Our study has some limitations. We applied CPAP for one-hour post-extubation and evaluated its short-term effects on pulmonary function and patient tolerance in the PACU. Longer CPAP applications and more detailed assessments of pulmonary complications using lung imaging could provide stronger evidence regarding the benefits and risks of these techniques in postoperative settings. Among the excluded subjects, some may have had poor CPAP tolerance, potentially biasing the overall patient tolerance results. Additionally, our study population primarily consisted of elderly patients, which may limit its generalizability. Further research on individuals with

specific comorbidities, particularly pre-existing lung diseases, could provide valuable insights into these unique populations. Moreover, a larger sample size would strengthen the reliability of our findings and allow for more robust subgroup analyses.

Nevertheless, our study provides initial evidence to guide anesthesiologists in selecting a CPAP technique for postoperative patients, balancing lung function improvement with patient comfort. While constant CPAP offers superior gas exchange benefits, making it ideal for patients at high risk of immediate postoperative hypoxemia and reduced functional residual capacity, automatic CPAP may be preferable for those prioritizing comfort with lower risks, and longer CPAP application may further enhance its benefits.

Conclusion

Both automatic and constant CPAP techniques enhance respiratory function, including gas exchange and mechanical respiration, in elderly patients undergoing major open abdominal surgery, with particularly notable benefits in advanced age and upper abdominal surgery patients. While both CPAP techniques effectively improve postoperative oxygenation, automatic CPAP may be preferable for patients prioritizing comfort, whereas constant CPAP provides superior gas exchange improvements. Further research is needed to determine optimal duration and patient selection criteria.

Availability of data and materials

Data for this study are available from the corresponding author upon reasonable request.

Authors' contributions

Concept and study design: Nguyen Thi Thuy, Nguyen Dang Thu, Le Sau Nguyen, Cong Quyet Thang, Nguyen Ngoc Thach.

Data acquisition: Nguyen Thi Thuy, Le Sau Nguyen.

Data analysis and interpretation: Nguyen Dang Thu, Nguyen Thi Thuy.

Writing-original draft: Nguyen Dang Thu, Nguyen Thi Thuy.

Writing, review, and editing: Nguyen Dang Thu, Nguyen Thi Thuy, Le Sau Nguyen, Cong Quyet Thang, Nguyen Ngoc Thach, Nguyen Trung Kien.

All authors are anaesthesiologists and have read and approved the final manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Clinical Trial.gov identified NCT06260826 (15/02/2024) https://clinicaltrials.gov/study/NCT06260826

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors respectfully acknowledge the late Professor Cong Quyet Thang, President of the Vietnam Society of Anesthesiologists, for his invaluable scientific guidance and supervision. As a co-author of this study, his passing represents a profound loss to both the research team and the broader medical community.

Associate Editor

Luiz Marcelo Malbouisson

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Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Comparison of pericapsular nerve group block and anterior quadratus lumborum block for hip fracture surgery: a randomized clinical trial

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Received 10 February 2025; accepted 3 May 2025
Available online 23 May 2025

KEYWORDS
Anesthesia;
Arthroplasty;
Hip fractures;
Nerve block;
Postoperative pain

Abstract
Objective: This study compared the Pericapsular Nerve Group (PENG) block combined with the Lateral Femoral Cutaneous Nerve (LFCN) block to the anterior Quadratus Lumborum Block (QLB) in patients undergoing Total Hip Arthroplasty (THA).
Methods: In this prospective, double-blind trial, 80 adults scheduled for THA under spinal anesthesia were randomized to receive either an anterior QLB (n = 40) with 30 mL of 0.25% bupivacaine or a combined PENG + LFCN block (n = 40) using 25 mL of 0.25% bupivacaine for PENG and 5 mL for LFCN. The primary outcome was cumulative 24 hour postoperative intravenous morphine consumption. Secondary outcomes included pain scores, quadriceps strength, patient satisfaction and side effects.
Results: No significant differences were observed between the groups in morphine consumption or pain scores during the first 12 hours ($p > 0.05$). At 24 hours, the PENG + LFCN group demonstrated significantly lower morphine consumption ($p = 0.027$) and resting VAS scores ($p < 0.001$). Quadriceps weakness occurred in 15% (6/40) of anterior QLB patients at 6 hours ($p = 0.026$), whereas no weakness was observed in the PENG + LFCN group within 24 hours. Patient satisfaction and the incidence of complications were comparable between the groups.
Conclusion: Both anterior QLB and PENG + LFCN blocks provide effective analgesia for up to 12 hours post-THA. However, the PENG + LFCN combination offers prolonged analgesia, reduced opioid requirements and better preservation of quadriceps strength.

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https://doi.org/10.1016/j.bjane.2025.844643

Introduction

Total Hip Arthroplasty (THA) is one of the most common orthopedic procedures in the United States, with over 400,000 surgeries performed annually. The numbers are expected to increase due to the aging population.[1] There is growing interest in the perioperative analgesia of THA surgery to optimize early postoperative mobilization and discharge.[2] Peripheral nerve and fascial plane blocks are critical to multimodal analgesia, reducing opioid use, side effects (e.g., respiratory depression, nausea), and hospital stays while accelerating mobilization.[3,4] However, the hip joint's complex innervation and the need to preserve motor function complicate optimal analgesia for THA and the optimal postoperative regional analgesia technique for THA remains debated.[5] Among emerging options, two recently described motor-sparing techniques have gained prominence: the anterior Quadratus Lumborum Block (QLB)[6] and the Pericapsular Nerve Group (PENG) block.[7]

The anterior QLB, which involves the injection of local anesthetic in the plane between the Quadratus Lumborum (QL) and Psoas Major (PM) muscles, with potential spread to the lumbar plexus, has been shown to effectively control THA pain.[8-10] The PENG block selectively blocks sensory innervation to the anterior hip capsule – a region predominantly comprised of nociceptive fibers – via branches of the obturator, accessory obturator, and femoral nerves.[7,11] Postoperative PENG blocks have been shown to reduce pain scores, opioid consumption, and the time to first mobilization following THA.[12,13] When the PENG block is combined with the Lateral Femoral Cutaneous Nerve (LFCN) block, which provides sensory innervation to the lateral thigh, the missing dermatome blockade area is completed.[14,15]

Although a few previous studies have compared these two blocks, our study has key differences. Most are focused on elective total hip arthroplasty rather than traumatic hip fractures.[16-18] Additionally, some did not combine the LFCN block with the PENG block,[16,17,19,20] a combination we routinely use and recommended.[14,15] Furthermore, one study used the lateral QLB instead of the anterior QLB,[18] and another had a retrospective design.[20]

This study aims to compare the effectiveness of the PENG + LFCN block with the anterior QLB in reducing postoperative opioid consumption, improving analgesia, and preserving quadriceps muscle strength in patients undergoing total hip arthroplasty.

Materials and methods

This trial was registered on ClinicalTrials.gov (NCT05654519) prior to patient enrollment. Following approval from the Institutional Review Board (IRB n° 2021/541), written and verbal informed consent was obtained from all participants. This single-center, prospective, randomized study was conducted in the operating rooms of a university-affiliated hospital. The manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Patients aged 45—85 years, with American Society of Anesthesiologists (ASA) physical status I—III, scheduled for unilateral total hip arthroplasty due to hip fracture, were included. Exclusion criteria comprised: contraindications to regional anesthesia or peripheral nerve blockade, cognitive impairment/communication barriers, weight < 50 kg or > 100 kg, Body Mass Index (BMI) > 40 kg.m^{-2} (due to concerns regarding altered anesthetic pharmacokinetics and technical challenges in block administration), peripheral neuropathy, coagulation disorders, chronic pain, severe hepatic/cardiac/renal failure, active opioid use, revision arthroplasty, diabetes mellitus, or pregnancy.

Enrollment occurred between April 2022 and April 2023. Consenting subjects were randomized to receive either the anterior QLB or the combined PENG + LFCN block using a closed opaque-envelope technique. Envelopes were opened by an independent researcher prior to block administration. All research staff, care team members (except the regional anesthesia team), and patients remained blinded to group allocation. Standardized protocols for block performance and postoperative care were implemented to minimize bias.

Preoperative assessment included the evaluation of pain intensity using the 10-point Visual Analog Scale (VAS, 0 cm = no pain, 10 cm = worst possible pain) and the explanation of how to use the Patient-Controlled Analgesia (PCA) device. Demographic data, including sex, age, height, weight, BMI, and ASA scores, were recorded for all patients. The anesthesia method and monitoring techniques used were standard routine practices with no study-specific interventions. Prior to the procedure, standard non-invasive monitoring (ECG, NIBP, and SpO_2) was applied, and oxygen was administered via a nasal cannula while intravenous sedation was administered with 0.03 mg.kg^{-1} midazolam and 1 mcg.kg^{-1} fentanyl. To maintain blinding, aseptic skin preparation was applied to both block sites, irrespective of group assignment. A 10 cm, 21-gauge echogenic needle was used for both block groups.

PENG block

While the patient was in a supine position, a low-frequency convex (2–5 MHz) transducer was used to visualize the anterior inferior iliac spine, iliopsoas tendon, iliopubic eminence, and femoral artery. As described previously, an echogenic needle was advanced laterally to medially (in-plane) until it reached the lateral and inferior edge of the iliopsoas tendon.[7] Bupivacaine hydrochloride (25 mL, 0.25%) was then injected in 5 mL increments with intermittent negative aspiration between the iliopsoas tendon and iliopubic eminence (Fig. 1A).

LFCN block

The LFCN was located/identified medial and inferior to the anterior superior iliac spine and laterally or superficially to the sartorius muscle. An echogenic needle was then advanced laterally to medially (in-plane) into the plane containing the nerve, and bupivacaine hydrochloride (5 mL, 0.25%) was injected. The spread of the local anesthetic around the nerve was visualized (Fig. 1B).

Anterior QLB

This block was performed with the patient in the lateral decubitus position, with the surgical site positioned upward. A convex transducer (2–5 MHz) was placed transversely

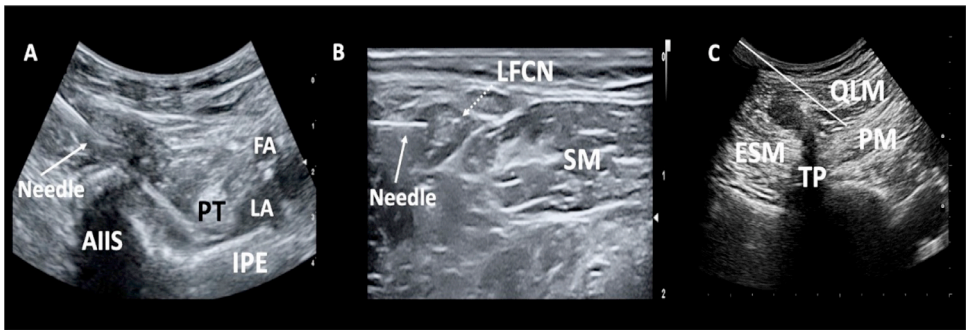

Figure 1 Sonoanatomy of (A) pericapsular nerve group block (B) lateral femoral cutaneous nerve block and (C) anterior quadratus lumborum block. Solid white line indicates the trajectory of the needle for local anesthetic placement. AIIS, Anterior Inferior Iliac Spine; FA, Femoral Artery; IPE, Iliopubic Eminence; PT, Tendon of Psoas muscle; LA, Local Anesthetic; LCFN, Lateral Femoral Cutaneous Nerve; SM, Sartorius Muscle, QLM, Quadratus Lumborum Muscle; ESM, Erector Spinae Muscle, PM, Psoas Muscle, TP, Transverse Process.

along the mid-axillary line at the L4 level to obtain a "shamrock sign". In this position, the QL, psoas major, and erector spinae muscles, as well as the L3 and L4 transverse processes, were visualized (Fig. 1C). The echogenic needle was advanced in-plane from posterior to anterior until it pierced the ventral fascia of the QL muscle. Bupivacaine (30 mL, 0.25%) was then injected into the plane between the QL and PM muscles, and the spread was visualized.

In cases of ineffective or incomplete blocks – defined as a VAS reduction < 3 or VAS ≥ 5 at rest 30 minutes post-block – it was preemptively planned to administer rescue analgesics and exclude the patient from the final analysis.

Anesthesia and postoperative analgesia

Thirty minutes after the block procedures, the same spinal anesthetic regimen, consisting of 2.5 mL of 0.5% hyperbaric bupivacaine (12.5 mg) and 25 mcg fentanyl, was administered to all patients. In case of failure of spinal anesthesia (inadequate/absent sensory block requiring supplemental analgesia/sedation) general anesthesia was applied, and the patient was excluded from the study.

Standardized postoperative care orders were implemented in the PACU as part of a multimodal analgesia protocol: all patients received 0.1 $mg.kg^{-1}$ Intravenous (IV) dexamethasone (maximum 8 mg) and 1000 mg IV paracetamol. For the first 24 hours postoperatively, 10 $mg.kg^{-1}$ IV paracetamol (maximum 1000 mg) was administered every 6 hours, supplemented with morphine via Patient-Controlled Analgesia (PCA) (1 mg bolus with a 10-minute lockout interval) as rescue medication.

At the 24^{th} postoperative hour, PCA was discontinued, and oral paracetamol was continued until discharge, within the multimodal analgesia protocol. For breakthrough pain (VAS > 3), tramadol 1 $mg.kg^{-1}$ (administered at $\geq$ 4-hour intervals, maximum 300 $mg.day^{-1}$) was used as the first-line rescue analgesic.

Primary and secondary outcome measures

- Primary Outcome:

Cumulative morphine consumption within the first 24 hours postoperatively, measured at predefined intervals (4, 12, and 24 hours).

- Secondary Outcomes:

1. Pain Intensity:
   - At rest: Assessed preoperatively (baseline), 30 minutes post-block, and at 4, 12, and 24 hours postoperatively using the Visual Analog Scale (VAS).
   - Movement-evoked pain: Evaluated at 24 hours postoperatively using a standardized walk test, per institutional surgical protocol (mobilization delayed until 24 hours).
2. Quadriceps muscle strength was measured via isometric knee extension at 6, 12, and 24 hours postoperatively. This assessment was conducted in a standardized supine position (hips flexed at 45°, knees at 90° flexion) without requiring active mobilization (e.g., standing/walking).[21]
3. Patient satisfaction was rated at 24 hours postoperatively using a 5-point Likert scale: 1 = Terrible, 2 = Poor, 3 = Satisfactory, 4 = Good, 5 = Excellent.
4. Adverse effects were documented between 0 and 24 hours postoperatively, including nausea, vomiting, pruritus, respiratory depression (respiratory rate $\leq$ 8 min), and urinary retention. No interim analysis was performed.

Statistical analysis

No previous studies have compared pain scores between patients receiving the PENG block and anterior QLB. Sample size calculation for our study was based on a study by He et al.,[22] which compared cumulative opioid consumption in patients who received anterior QLB after THA. The cumulative morphine consumption in the anterior QLB group was 16 mg over 24 hours. With a 5% alpha error and 80% power, a 15% reduction in cumulative opioid consumption was expected after the PENG block. The minimum required sample size per group was 36 patients. Considering potential dropouts and variability in standard deviation, we calculated a sample size of 40 patients per group.

Data were presented as percentages (%), frequencies (n), mean $\pm$ Standard Deviation (SD), minimum, median, and maximum values, with no missing data. The Chi-square and Fisher's exact tests were used for categorical variables, while independent *t*-tests were used for normally distributed parametric data. For non-parametric data, the Mann-Whitney *U* test was applied. All statistical analyses were performed using SPSS for Windows version 22. A significance level of $p < 0.05$ was considered statistically significant.

Results

During the study period, data from 96 patients were recorded. Some patients were excluded due to the presence of cognitive impairment, refusal of spinal anesthesia, or technical issues with the PCA device (Fig. 2). The final study population consisted of 80 subjects, with equal numbers in each group.

Participant demographic and baseline characteristics (sex, age, BMI, ASA score, surgical duration, and approach) are summarized in Table 1, and there were no significant differences between the groups ($p > 0.05$).

Primary outcome

The cumulative opioid consumption over 24 hours postoperatively is shown in Figure 3. No significant differences were found between the groups at 4 and 12 hours postoperatively. However, at the 24-hour postoperative mark, the cumulative intravenous morphine consumption in the PENG + LFCN group was significantly lower than in the anterior QLB group (10.25 ± 4.76 vs. 12.80 ± 5.36, Cohen's $d = 0.50$, 95% Confidence Intervals 0.1 to 0.9; $p = 0.027$) (Fig. 3).

Secondary outcomes

Visual Analog Scores (VAS) at 24 hours postoperatively, the resting VAS scores in the PENG + LFCN group were significantly lower compared to the anterior QLB group (2.93 ± 1.14 vs. 4.20 ± 1.54, Cohen's $d = 0.94$, 95% Confidence Intervals 0.47 to 1.40; $p < 0.001$) (Fig. 4). Other VAS scores measured at rest and during movement at different time points were similar between the two groups ($p > 0.05$). Quadriceps weakness occurred in 15% (6/40) of anterior QLB patients at 6 hours, whereas no weakness was observed in the PENG + LFCN group within 24 hours (Odds Ratio = 0.06, 95% CI 0.3 to 1.1; $p = 0.026$). No quadriceps weakness was observed at any other time points in either group.

There were no significant differences between the groups in terms of opioid-related side effects, including nausea ($p = 0.59$), vomiting ($p = 0.74$), or pruritus ($p = 0.50$). No adverse events or complications were observed in either group. Furthermore, patient satisfaction scores were comparable between the groups (Table 2).

Discussion

This study compared the postoperative pain scores, morphine consumption, and quadriceps muscle strength between PENG and LFCN blocks versus anterior QLB in patients undergoing THA after hip fracture. Patients in the PENG + LFCN group had lower resting VAS scores and consumed less morphine at 24 hours postoperatively compared to the anterior QLB group. Additionally, quadriceps weakness was detected in 15% of the anterior QLB group during early postoperative hours.

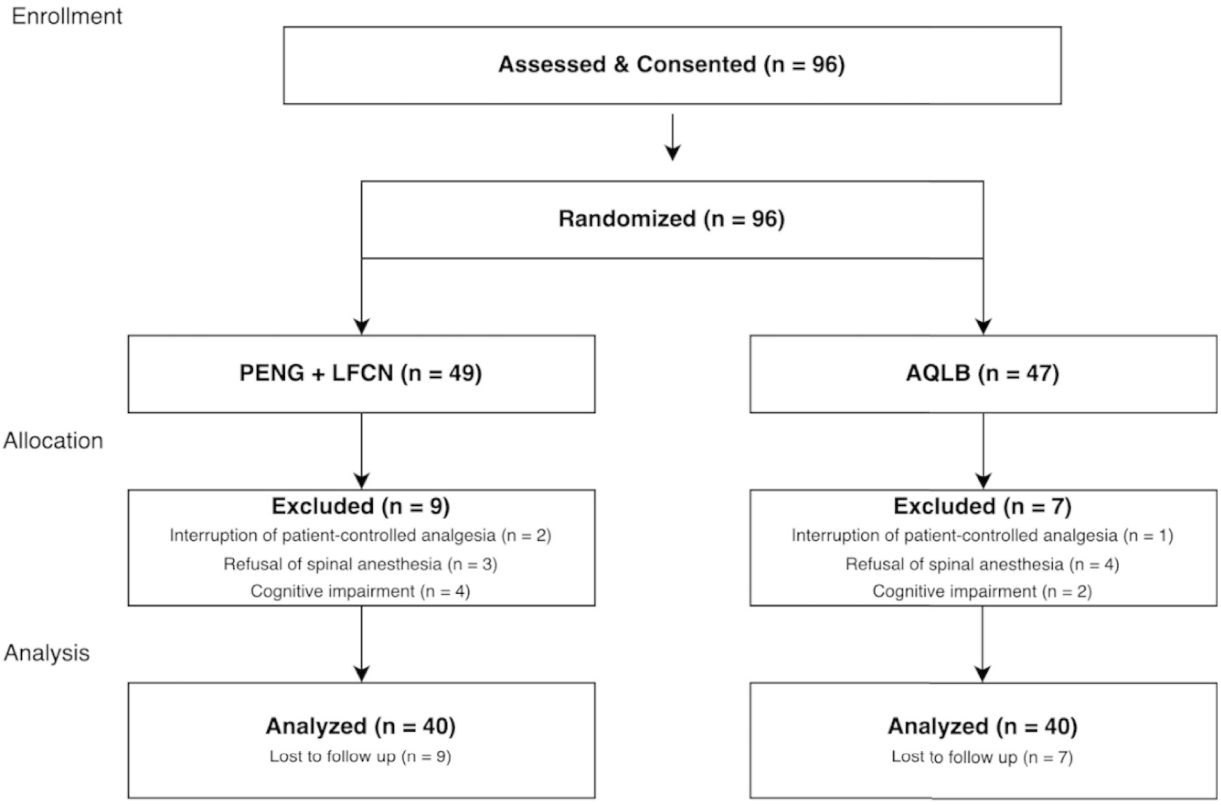

Figure 2 Consolidated Standards of Reporting Trials flow diagram. LFCN, Lateral Femoral Cutaneous Nerve; PENG, Pericapsuler Nerve Group; AQLB, Anterior Quadratus Lumborum Block.

Table 1 Baseline characteristics of patients.

	AQLB (n = 40)	PENG (n = 40)	p-value
Sex (male), n (%)	17 (42.5)	19 (47.5)	0.653[a]
Age (years), mean ± SD	69.55 ± 6.06	68.95 ± 8.09	0.708[b]
BMI (kg.m^{-2}), mean ± SD	28.67 ± 3.68	27.65 ± 3.24	0.190[b]
ASA (1/2/3), n (%)	0/19 (47.5) /21 (52.5)	2 (5) /15 (37.5) /23 (57.5)	0.299[c]
Duration of Surgery, mean ± SD	155.53 ± 18.77	150.07 ± 19.19	0.203[b]
Surgical approach			
Right / Left, n (%)	24 (60) /16 (40)	20 (50)/20 (50)	0.369[a]

ASA, American Society of Anesthesiologists; PENG, Pericapsular Nerve Group + Lateral femoral cutaneous nerve block, AQLB, Anterior Quadratus Lumborum Block; BMI, Body Mass Index.
[a] Chi-Square analysis.
[b] *t*-test.
[c] Fisher's Exact test.

In a study by He et al., which included 88 patients undergoing hip arthroplasty, the analgesic efficacy and safety of anterior QLB were compared to a control group. They found that postoperative resting and dynamic VAS scores were significantly lower in the anterior QLB group until 48 hours postoperatively.[22] Nassar et al. compared the analgesic effectiveness and motor block profiles of transmuscular QLB and Suprainguinal Fascia Iliaca Block (SIFIB) in hip arthroplasty patients and found that both groups had similar postoperative pain scores and analgesia durations, with lower opioid consumption in the SIFIB group.[23]

Chung et al. demonstrated that PENG block significantly reduced cumulative opioid consumption and pain scores at 24 hours after hip surgery.[24] Mosaffa et al. compared the postoperative analgesic effectiveness of PENG block and FIKB in hip fracture surgery. They reported that 15 minutes post-block and at 12 hours postoperatively, the PENG block group had lower VAS scores and less opioid consumption over the 24-hour postoperative period.[25] Huda et al. conducted a meta-analysis and found that PENG block significantly reduced 24-hour opioid consumption after hip surgery, delayed the time to the first analgesic request, and resulted in less motor block risk.[26] Aliste et al. compared PENG block to SFIB in 40 patients undergoing THA under spinal anesthesia and found that the PENG block group had lower quadriceps

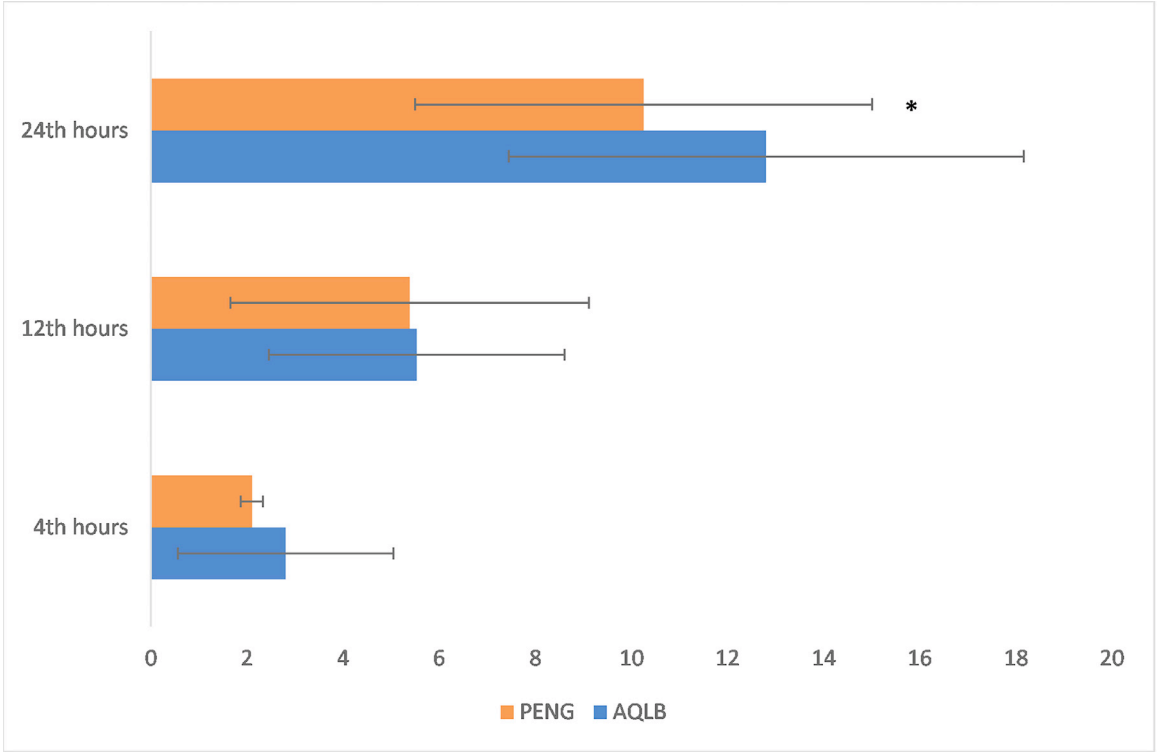

Figure 3 Comparison of the cumulative morphine consumption among the study groups. PENG, Pericapsuler Nerve Group + Lateral Femoral Cuteneous Nerve Block; AQLB, Anterior Quadratus Lumborum Block. *p = 0.027.

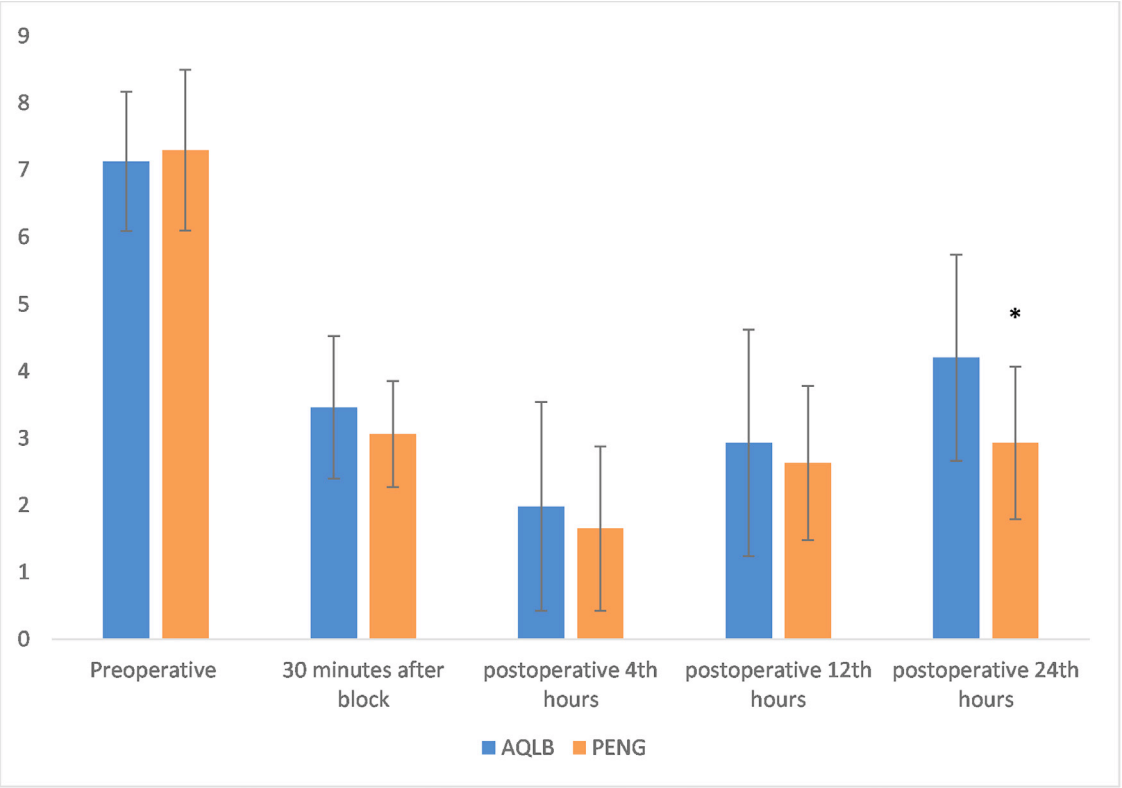

Figure 4 Comparison of the pain scores among the study groups. PENG, Pericapsuler Nerve Group + Lateral Femoral Cuteneous Nerve Block; AQLB, Anterior Quadratus Lumborum Block. * $p < 0.05$.

motor block at 3 hours (45% vs. 90%) and 6 hours (25% vs. 85%).[27]

Previous studies comparing anterior QLB and PENG blocks in hip surgery have shown similar outcomes, although some contradictory results have been reported. Differences in drugs, volumes, anesthesia methods, and whether LFCN block was included or not may have contributed to these results, as there is no standardization in the methodology. In a study by Tayfun Et et al., which compared PENG, anterior QLB, and intra-articular blocks for primary THA, they found similar analgesic effects between PENG and anterior QLB.[16] This may be due to differences in drug volumes (30 mL of 0.5% bupivacaine for the anterior QLB group vs. 20 mL of 0.5% bupivacaine for the PENG block group) and the exclusion of LFCN block in the PENG group. Similar to our study, they reported better preservation of quadriceps muscle strength postoperatively in the PENG group compared to anterior QLB.

Table 2 Additional outcomes of interest.

Postoperative		AQLB (n = 40)		PENG (n = 40)		p-value
		n	%	n	%	
Quadriceps Weakness	6th Hours	6	15	0	0.0	0.026[a]
	12th Hours	0	0.0	0	0.0	
	24th Hours	0	0.0	0	0.0	
Patient Satisfaction	Unsatisfied	0	0.0	0	0.0	0.280[a]
	Satisfied	5	12.5	4	10.0	
	Good	22	55.0	16	40.0	
	Excellent	13	32.5	20	50.0	
Nousea		10	25	8	20	0.59[a]
Vomiting		5	12.5	6	15	0.74[a]
Pruritus		3	7.5	2	5	0.50[a]

AQLB, Anterior Quadratus Lumborum Block; PENG, Pericapsular Nerve Group + Lateral Femoral Cutaneous Nerve Block.
[a] Chi-Square analysis.

Braun et al. performed a retrospective study comparing PENG and anterior QLB after THA and found no difference in morphine consumption at 24 and 48 hours postoperatively.[20] Abdelsalam et al. compared PENG and anterior QLB methods in hip arthroplasty and found no differences in resting and dynamic pain scores, cumulative opioid consumption, or time to first analgesic request between the two groups.[17] In these studies, unlike ours, LFCN block was not added to the PENG block.

Wang et al. reported significantly lower maximum pain scores in the PENG group and significantly lower pain scores at 3 hours after surgery at rest and during movement at 3 and 6 hours postoperatively. However, they found no significant differences in morphine consumption, hospital length of stay, pain levels one year postoperatively, or complication incidence between the groups.[19] Both groups did not show quadriceps weakness. Hay et al. compared PENG and lateral QLB after THA and observed lower cumulative opioid consumption and lower pain scores during movement between 36 and 72 hours postoperatively in the lateral QLB group.[18]

Ritesh Roy et al. concluded that combining PENG block with LFCN block provided superior analgesia with lower pain scores than PENG block alone.[15] In our study, we found that the addition of LFCN block to the PENG block resulted in prolonged analgesic duration and reduced morphine consumption. We hypothesize that without the LFCN block, the PENG block alone may provide incomplete dermatomal blockade, resulting in insufficient analgesia.

In this study, we observed lower quadriceps strength at 6 hours postoperatively in the anterior QLB group when compared to the PENG + LFCN group. This is likely due to the fact that the PENG block only targets the joint branches of the FN, ON, and AON. On the other hand, higher volumes or intramuscular needle placement during PENG block might result in unintended spread and quadriceps weakness.[28] One possible explanation for these results is that the better vascularization of the anterior QLB region may lead to a shorter duration of analgesia. Additionally, increased drug diffusion toward neural structures could contribute to motor blockade. At the L4 vertebral level, when a local anesthetic is injected between the Quadratus Lumborum (QL) and Psoas Major (PM) muscles, it may spread medially toward the ventral rami of L2 and L3, laterally toward the lateral cutaneous nerve of the thigh, and caudally beneath the fascia iliaca.[29] However, previous studies have reported an inconsistent distribution following anterior QLB, which may explain both the variable outcomes observed in prior research and the motor weakness seen in some patients in this study.[29,30]

Limitations

This study had some limitations. First, the effect of spinal anesthesia may have influenced the early postoperative assessment of motor strength. Second, the study did not include a normal control group. However, both blocks have been previously compared with control groups, showing superior results compared to placebo. Third, although the study was prospective and randomized, and preoperative sedation was administered, patients may not have been completely blinded since they were awake during the block procedure. However, based on postoperative assessment questions, we found that patients were unaware of which block was performed. Fourth, information on pain scores during movement before the 24-hour mark, discharge times, pain scores and analgesic consumption after 24 hours could not be obtained.

Conclusions

In conclusion, while both anterior QLB and PENG + LFCN blocks are effective analgesic methods for up to 12 hours postoperatively in patients undergoing THA after fracture, our findings suggest that the PENG + LFCN combination provides significantly longer-lasting analgesia, preserves quadriceps muscle strength, and reduces opioid consumption compared to anterior QLB. Based on these results, the PENG + LFCN block may be a preferable option for THA analgesia, particularly in clinical settings prioritizing early mobilization and opioid-sparing strategies. However, further multicenter studies with larger sample sizes are needed to confirm these findings and determine the clinical significance of the differences.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mustafa Aslan, Alper Kilicaslan, Funda Gok, Ahmet Fevzi Kekec, Tahsin Sami Colak. The first draft of the manuscript was written by Mustafa Aslan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Associate Editor

Florentino Fernandes Mendes

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Prevention of shivering post spinal anesthesia: Ondansetron vs. Nefopam – a prospective randomized controlled trial

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Received 25 December 2024; accepted 29 May 2025
Available online 11 June 2025

KEYWORDS
Nefopam;
Ondansetron;
Shivering;
Spinal anesthesia

Abstract

Background: Post Spinal Anesthesia Shivering (PSAS) is common and linked to increased morbidity. While various methods exist to prevent it, no study has compared Nefopam and Ondansetron. This study aims to compare Ondansetron and Nefopam in preventing PSAS.

Methods: A prospective, randomized, controlled, and double-blind trial was conducted in the operating room of a tertiary university hospital from April 5, 2021 to April 30, 2022. It included patients aged between 18 and 65 years scheduled for surgery under spinal anesthesia. Patients received either 8 mg of Ondansetron or 20 mg of Nefopam administered intravenously over 30 min before spinal anesthesia. Main outcome measures included the number and grades of shivering episodes post spinal anesthesia at 15-minute intervals until post-anesthesia care unit discharge. Secondary outcomes included number of episodes of hypotension, bradycardia, nausea and/or vomiting. Tympanic temperature and pain at the injection site were also recorded.

Results: The study included 150 patients, evenly divided between the two groups. The Ondansetron group had a higher incidence of shivering compared to the Nefopam group (23.9 % vs. 16 %; $p = 0.038$), as well as higher incidences of hypotension (16 % vs. 5.3 %; $p = 0.035$) and bradycardia (13.3 % vs. 2.7 %; $p = 0.016$). The Ondansetron group had a significantly lower incidence of nausea and vomiting (12 % vs. 1.3 %; $p = 0.010$). More patients in the Nefopam group (45.3 %) reported pain during drug infusion.

Conclusions: Nefopam seems to be more effective than Ondansetron in preventing PSAS with fewer cardiovascular side effects. However, Ondansetron reduces the incidence of nausea and vomiting and causes no pain during administration.

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https://doi.org/10.1016/j.bjane.2025.844650

Introduction

Spinal anesthesia is commonly used in many surgical procedures.[1] This effective anesthesia technique is, however, associated with some undesirable side effects. Among them, shivering can affect up to 40 % to 60 % of patients.[2,3] Shivers occur in response to disturbances of the homeostatic system triggered by spinal anesthesia. The underlying mechanism is lower limb vasodilation, inducing rapid heat loss and redistribution of body heat from the central to the peripheral compartment, thus resulting in hypothermia and shivering.[4]

Shivers are uncomfortable for patients and also challenging for anesthesiologists as they interfere with monitoring parameters. Moreover, they can lead to a cascade of physiological changes. Shivering increases metabolic activity, oxygen consumption, and induces arterial hypoxemia, potentially amplifying the risk of ischemic events, as well as, increasing intracranial and intraocular pressure, increasing cardiac output and peripheral vascular resistance, and inducing lactic acidosis.[5–7] All these factors are associated with increased morbidity, especially in elderly and fragile patients.

Many non-pharmacological and pharmacological methods are available to prevent and treat Post Spinal Anesthesia Shivering (PSAS) such as Ondansetron, Pethidine or other opioids, Physostigmine, Nefopam, Ketamine, and Doxapram.[5,8]

Ondansetron, initially used to treat nausea and vomiting, has recently shown encouraging results in reducing PSAS by attenuating the drop in core temperature, a potential trigger for shivering.[9,10] On the other hand, Nefopam, a non-opioid analgesic, has also demonstrated its effectiveness in preventing post spinal anesthesia shivers, with a distinct mechanism of action.[5]

To our knowledge, no prospective and randomized study has yet been conducted to specifically compare Nefopam with Ondansetron in PSAS prevention.

Materials and methods

Ethics

Ethical approval for this study (CEHDF 1589) was provided by the Ethical Committee of Hôtel-Dieu de France Hospital, Beirut, Lebanon (Chairperson Prof. Sami Richa) on September 24, 2020.

Written informed consent was obtained from all study participants. The Helsinki declarations of 1963 were considered: respect, confidentiality, and patient anonymity.

We conducted a prospective randomized, controlled, double-blind trial with 2 parallel groups comparing the impact of Ondansetron and Nefopam administration on the incidence and intensity of PSAS when used as prophylaxis in non-obstetric surgeries. This is a superiority trial between Nefopam and Ondansetron.

The study protocol (trial number: NCT04870541) was registered in ClinicalTrials.gov (https://clinicaltrials.gov./study/NCT04870541?term=NCT04870541&rank=1).

Study estimates and sampling

We included patients aged between 18 and 65 years-old, who were scheduled for surgery under spinal anesthesia at Hôtel-Dieu de France, a university hospital in Beirut, Lebanon, between April 5, 2021, and April 30, 2022. The study was conducted in a small country, with minimal ethnic or geographic diversity.

Exclusion criteria were pregnancy, breastfeeding, presence of allergy to any of the drugs used, patients with long QT syndrome, renal or hepatic insufficiency, epilepsy or Parkinson's disease, glaucoma, or phenylketonuria.

Randomization

After informed consent, patients were randomized into 2 groups:

- Group A: patients receiving 8 mg of Ondansetron diluted in 20 mL of 0.9 % Saline Solution administered intravenously over 30 min before spinal anesthesia.
- Group B: patients receiving 20 mg of Nefopam diluted in 20 mL of 0.9 % Saline Solution administered intravenously over 30 min before spinal anesthesia.

Whenever the patients reported pain with a score greater than 3 on a 10-point Numeric Rating Scale (NRS) during drug infusion, we decreased the speed of drug administration by half.

Randomization was performed using a computer-generated random number concealed in sealed opaque envelopes, which remained opaque even when held to the light. The random sequence was generated using *R* (package: randomizeR) and was prepared by an independent statistician who was not involved in participant recruitment or data collection. The patients were included in one of the two groups according to the randomization sequence. To minimize selection bias, the envelopes were sequentially numbered and opened only after participant enrollment, ensuring allocation concealment. Once the patient was recruited, the sealed envelope was opened by a single nurse who prepared the drugs and presented them as coded syringes. The nurse was not aware of the study protocol. The patient, the anesthesiologist in the Operating Room (OR), and in the Post Anesthesia Care Unit (PACU) were blinded to the content of the syringe.

Procedure

After admission to the OR, routine standard monitoring was used in all patients in the form of non-invasive blood pressure, pulse oximetry and Electrocardiogram (ECG). Room temperature in the operating rooms was maintained at 20°–22 °C.

The attending anesthesiologist in charge of patient anesthesia was blinded to the study drug and not involved in data acquisition. The study protocol drug was started immediately upon arrival to the operating room. Spinal anesthesia was done at either L2/L3, L3/L4 or L4/L5 interspace with 0.5 % hyperbaric or isobaric bupivacaine and Sufentanil 2.5 μg. After completion of spinal anesthesia, oxygen was administered via a nasal cannula (2 L/min) till the end of the procedure.

Intraoperatively, all patients were covered at the shoulder level with a forced air warming blanket started immediately after spinal anesthesia and until transfer to PACU. Tympanic temperature was monitored by Braun® thermoscan thermometer every 15 min, and hemodynamic parameters every 3 min, until motor blockade resolution.

Data

Data entry was performed by an independent person and included demographic characteristics, types of surgery, characteristics of spinal anesthesia (drugs used and sensory blockade level) as well as:

- Number of episodes of shivering and their grades post spinal anesthesia until PACU discharge. Shivering was graded from 0 to 3: 0 = No shivering; 1 = visible tremors of head and neck with ECG modifications with no arm movement; 2 = visible tremors in more than one muscle group and 3 = intense shivering, tremors of the whole body.
- Number of episodes of hypotension (defined as Systolic Blood Pressure [SBP] < 90 mmHg or less than 25 % of baseline SBP) post spinal anesthesia until PACU discharge.
- Number of episodes of bradycardia (defined as Heart Rate [HR] < 50 min or less than 25 % of initial HR) post spinal anesthesia until PACU discharge.
- Number of episodes of nausea and/or vomiting intra and postoperatively.
- Monitoring of tympanic temperature every 15 min post spinal anesthesia and in PACU to detect hypothermia (defined as temperature lower than 35.5 degrees Celsius).
- Presence of pain at site of injection during intravenous study drug infusion. Pain is defined as a score greater than 3 on a 10-point NRS, where 0 represents no pain and 10 represents the worst possible pain.

Outcomes

The primary outcome was comparing the incidence of PSAS, as well as the intensity of PSAS, in non-obstetric surgeries between patients receiving Ondansetron vs. Nefopam.

Secondary outcomes included evaluation of hemodynamic variations (hypotension and bradycardia), incidence of nausea and vomiting intraoperatively and in PACU, incidence of hypothermia intraoperatively and in PACU, and intensity of pain at site of injection during study drug infusion.

Statistics

Distribution of continuous variables was checked using the Shapiro-Wilk normality test and visual inspection of Quantile-Quantile plots. Categorical data were presented as frequency, percentage, and 95 % Confidence Intervals. Continuous data that did not deviate from normality were presented as mean ± Standard Deviation ($m \pm SD$); ordinal data and continuous data that significantly deviate from normality were presented as Median (Med) and interquartile range [Q1–Q3]. Categorical data were compared using Fisher's exact test. Normally distributed data were compared using Student's *t*-test for independent samples. Non-normally distributed continuous data and ordinal data were compared using the Mann-Whitney non-parametric test. All tests are two-tailed, and the first type error risk is set at 5 % without adjustment for multiplicity.

Results

A consort flow diagram detailing the screening, recruitment, and analysis of the participants is shown in Figure 1. The study included 150 patients, evenly distributed between the 2 groups. All patients included were followed up in the OR and PACU (no exclusions after randomization). Demographic characteristics of patients are described in Table 1. No significant differences were observed regarding age, sex, and other relevant demographic parameters between the studied groups. Likewise, we noted a balanced distribution of surgeries between the 2 groups (Supplemental Table 1), as well as, homogeneity of the sensory blockade level, administered anesthetic drugs, and duration of spinal anesthesia (Table 2).

Post spinal anesthesia shivering

Patients in the Ondansetron group showed a higher incidence of shivering compared with the Nefopam group (18 [23.9 %] vs. 12 [16 %] patients; $p = 0.038$) (Figure 2). The Risk Ratio (RR) with its corresponding 95 % Confidence Intervals (95 % CI) is 1.83 (95 % CI 0.98—3.43). This means that the incidence of shivering was 83 % higher in the Ondansetron group compared to the Nefopam group. Although higher grades of shivering were also observed in the Ondansetron group, this difference was not statistically significant ($p = 0.064$) (Figure 3).

Cardiovascular effects and sensory levels

Significant differences were noted in cardiovascular responses between the two groups (Table 3). The Ondansetron group showed a higher incidence of hypotension episodes (12 [16 %] vs. 4 [5.3 %] patients; $p = 0.035$) and bradycardia episodes (10 [13.3 %] vs. 2 [2.7 %] patients; $p = 0.016$) compared with the Nefopam group, although sensory levels after spinal anesthesia were comparable between the two groups ($p = 0.941$).

Nausea, vomiting, and perioperative hypothermia

We noted a significant decrease in the incidence of nausea and vomiting in the Ondansetron group compared with the Nefopam group (9 [12 %] vs. 1 [1.3 %] patients; $p = 0.010$). The frequency of perioperative hypothermia was similar between the two groups (31 [41.3 %] in Ondansetron vs. 32 [42.7 %] patients in Nefopam group; $p = 0.717$) (Table 3).

Reactions to the product and associated pain

A significantly higher percentage of patients in the Nefopam group (34 patients [45.3 %]) reported painful sensations during drug infusion compared with those in Ondansetron group (4 patients [5.3 %]) ($p = 0.000$).

Discussion

Spinal anesthesia is a safe anesthetic technique practiced commonly worldwide.[1] However, PSAS is a commonly encountered side effect. Multiple pharmaco-therapeutic

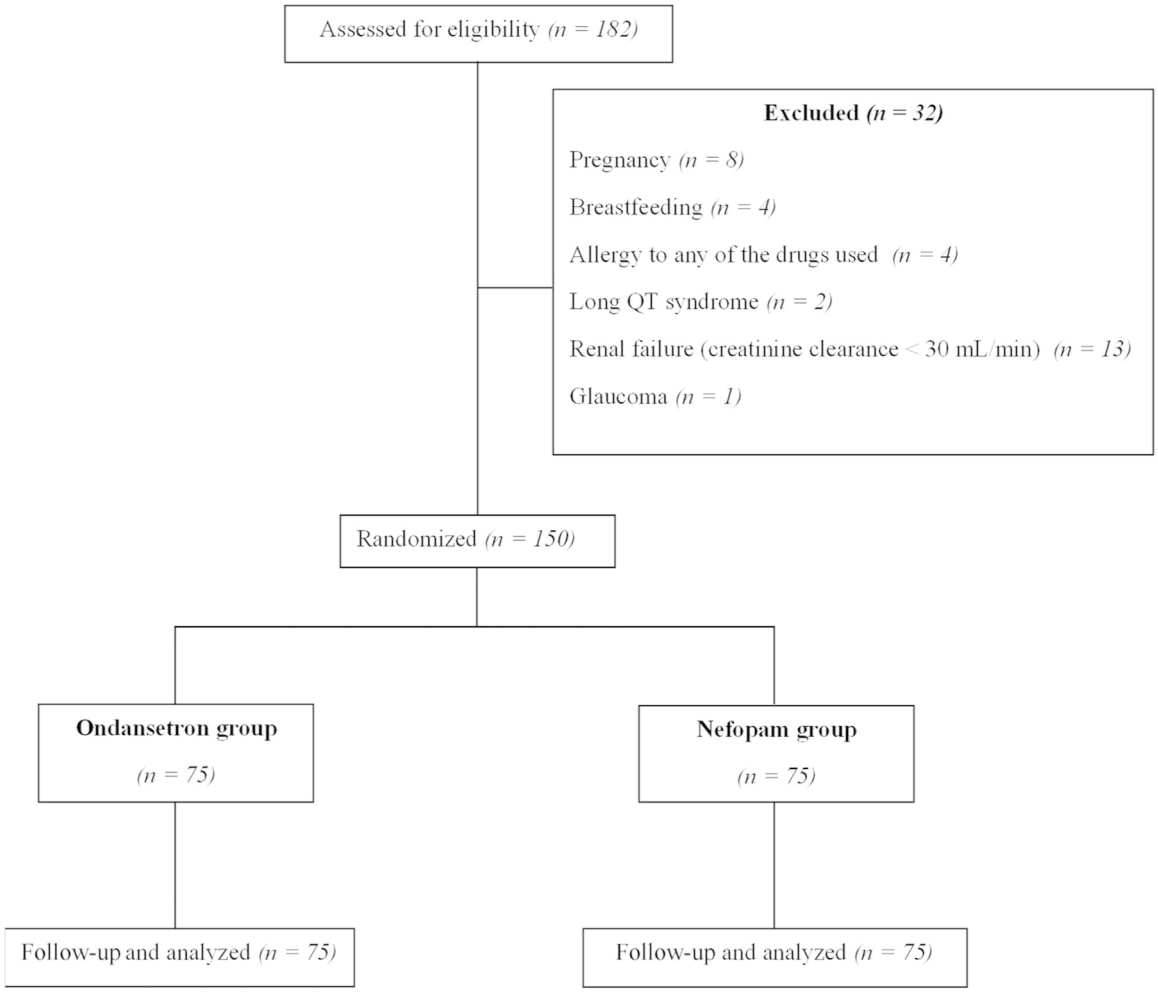

Figure 1 CONSORT flow diagram.

drugs have been studied for prevention of PSAS.[5,8] Among them, Ondansetron and Nefopam have emerged as promising options. To our knowledge, this is the first study to compare the effect of these drugs on preventing PSAS.

The dose of 8 mg Ondansetron was selected based on prior studies demonstrating its efficacy in similar contexts. Kelsaka et al.[11] showed that Ondansetron 8 mg intravenously administered immediately before spinal anesthesia had antishivering effects. The doses of Nefopam in the literature vary between 0.15 mg/kg and 0.2 mg/kg.[12,13] We opted for a fixed dose of 20 mg, as it aligns with the standard practice in our institution for analgesia, ensuring consistency and practical applicability in our clinical setting.

Table 1 Patients' demographics across Nefopam and Ondansetron groups.

		Nefopam Group (n = 75)	Ondansetron Group (n = 75)
Age (years, mean ± SD)		45.1 ± 11.5	46.7 ± 13.1
Weight (Kg, mean ± SD)		76.1 ± 18.2	77.4 ± 17
BMI (Kg/m^2, mean ± SD)		26.5 ± 5.1	27.7 ± 5.6
Sex female, n (%) [95 % CI]		49 (65.3 %) [54.1–75.4 %]	48 (64 %) [52.8–74.2 %]
ASA, n (%) [95 % CI]	1	32 (42.7 %) [31.9–54 %]	37 (49.3 %) [38.2–60.5 %]
	2	41 (54.7 %) [43.4–65.6 %]	37 (49.3 %) [38.2–60.5 %]
	3	2 (2.7 %) [0.6–8.3 %]	1 (1.3 %) [0.1–6.1 %]
APFEL Score, n (%) [95 % CI]	0	11 (14.7 %) [8.1–23.9 %]	17 (22.7 %) [14.3–33.1 %]
	1	37 (49.3 %) [38.2–60.5 %]	24 (32 %) [22.3–43.1 %]
	2	19 (25.3 %) [16.6–36 %]	32 (42.7 %) [31.9–54 %]
	3	6 (8 %) [3.4–15.7 %]	2 (2.7 %) [0.6–8.3 %]

CI, Confidence Interval; MWU, Mann-Whitney U; SD, Standard Deviation.

Table 2 Spinal anesthesia characteristics across Nefopam and Ondansetron groups.

		Nefopam Group (*n* = 75)	Ondansetron Group (*n* = 75)	p
Sensory block level, n (%) [95 % CI]	T4	–	1 (1.4 %) [0.1–6.2 %]	0.941
	T5	2 (2.7 %) [0.6–8.5 %]	–	
	T6	4 (5.5 %) [1.9–12.5 %]	2 (2.7 %) [0.6–8.5 %]	
	T7	3 (4.1 %) [1.2–10.6 %]	7 (9.6 %) [4.4–17.9 %]	
	T8	5 (6.8 %) [2.7–14.4 %]	8 (11 %) [5.3–19.6 %]	
	T9	6 (8.2 %) [3.5–16.2 %]	3 (4.1 %) [1.2–10.6 %]	
	T10	51 (69.9 %) [58.7–79.5 %]	49 (67.1 %) [55.8–77.1 %]	
	T11	2 (2.7 %) [0.6–8.5 %]	3 (4.1 %) [1.2–10.6 %]	
Duration of spinal anesthesia (min) [95 % CI]		90 [60–120]	100 [60–120]	0.720
Hyperbaric Bupivacaine, n (%) [95 % CI]		62 (82.7 %) [72.9–89.9 %]	66 (89.2 %) [80.6–94.8 %]	0.347
Bupivacaine dose (mg ± SD)		8.6 ± 1	8.4 ± 1.1	0.397

CI, Confidence Interval; MWU, Mann-Whitney *U* test; min, minutes; SD, Standard Deviation.

In the present study, the incidence of PSAS was significantly reduced with Nefopam when compared with Ondansetron. Shivers' intensity seemed also lower with Nefopam even though not statistically significant. The primary outcome included two independent variables: the incidence of PSAS and their intensity. Since these variables were analyzed separately and the results of shivering intensity showed no statistically significant difference, no correction was applied to the statistical tests. However, it is important to note that results associated with multiple analyses should be interpreted carefully.

Concerning side effects, Ondansetron was associated with more episodes of hypotension and bradycardia and Nefopam was associated with higher incidence of nausea, vomiting and pain during drug infusion. We did not compare the 2 groups of drugs to a placebo group, since it has been well established that both drugs are beneficial on preventing shivering after spinal anesthesia.[9,14] Moreover, it is important to note that pethidine, the gold standard anti-shivering drug, as well as other opioid drugs could be associated with opioid related side effects as over-sedation, respiratory depression, nausea and vomiting, itching, constipation, and postoperative opioid induced hyperalgesia.[8,15,16] The main advantage of both Ondansetron and Nefopam is that they are devoid of these adverse effects.

When it comes to anti-shivering effects, Nefopam has been described as causing a small increase in the core temperature by lowering the shivering threshold and without influencing sweating and vasoconstriction thresholds, therefore minimizing heat loss.[17] Nefopam also affected thermoregulatory response via α2-adrenoceptors.[18] Ondansetron has a central mechanism in reducing the shivering response by inhibition of serotonin reuptake at the level of the preoptic anterior hypothalamic region. As a matter of fact, its anti-shivering effect is independent of the intraoperative core temperature, as observed by Powell and Buggy.[19] Incidence of shivering across both groups in this study showed no correlation with the incidence of hypothermia, as

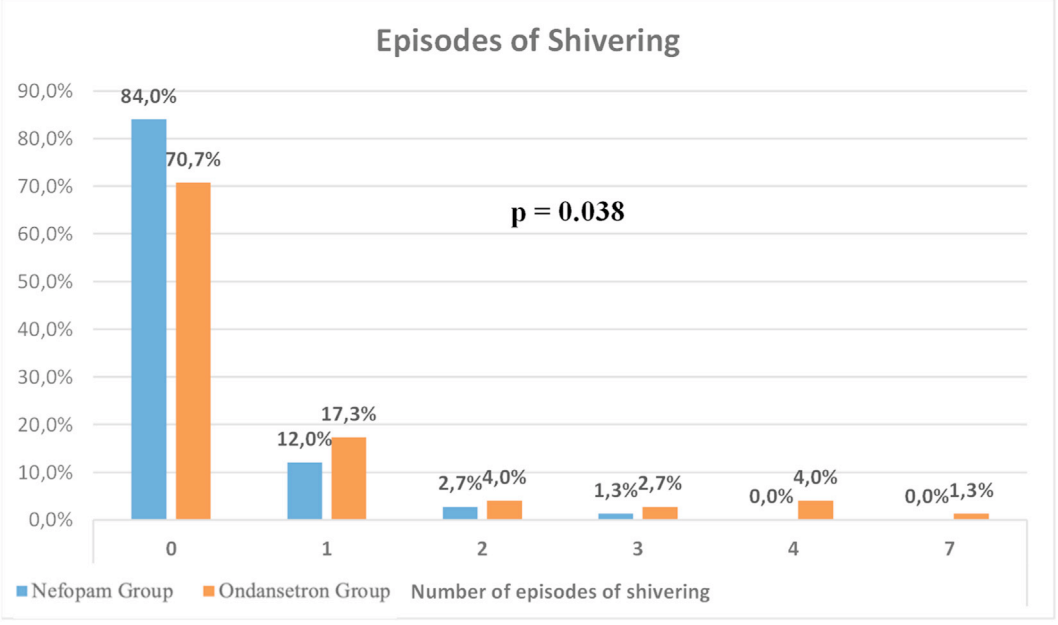

Figure 2 Number of shivering episodes across Nefopam and Ondansetron groups.

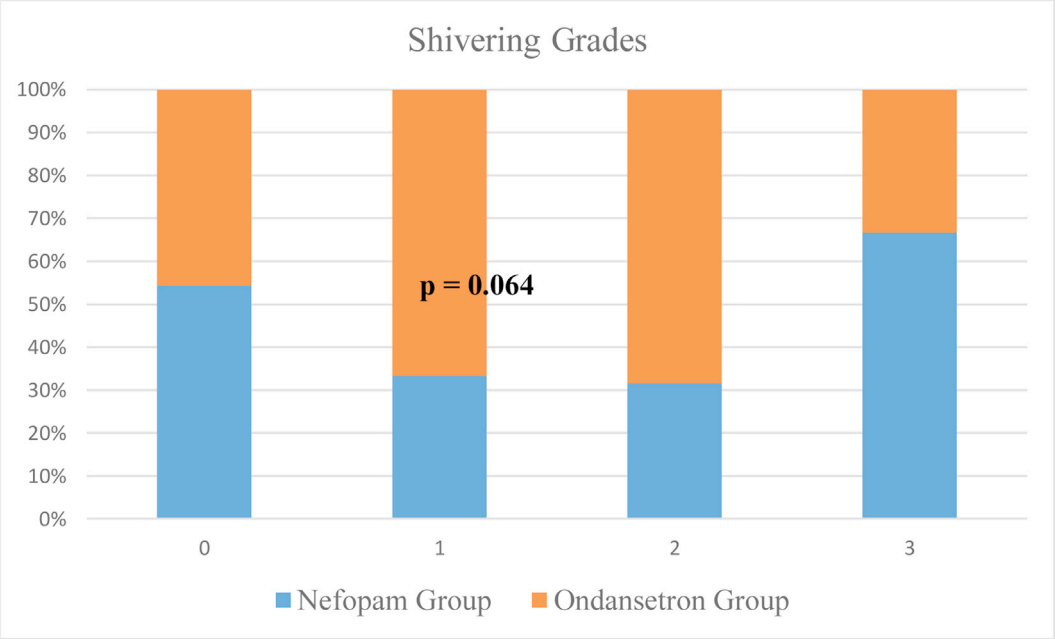

Figure 3 Grades of Shivering. Grades of shivering: 0 = No shivering; 1 = Visible tremors of head and neck with ECG modifications with no arm movement; 2 = Visible tremors in more than one muscle group, and 3 = Intense shivering, tremors of the whole body.

hypothermia incidence was comparable between the 2 groups. This finding is comparable to other studies that found no correlation between shivering and hypothermia.[10,20]

The findings of the current trial go in agreement with results of other studies that concluded that prophylactic administration of Ondansetron showed a substantial reduction in the incidence and scores of shivering in both non-obstetric[14,21] and obstetric surgeries.[22] Likewise, many studies showed that the prophylactic administration of Nefopam decreased the incidence of PSAS.[5,16,23]

Our results highlight the difference in action mechanisms of both Ondansetron and Nefopam. In fact, Nefopam is a non-opioid, non-steroidal centrally acting analgesic. It acts by inhibiting the reuptake of serotonin, noradrenaline, and dopamine.[24,25] It also possesses action on α2-adrenergic[26] and is a noncompetitive NMDA receptor antagonist.[27] Hence, it has sympathomimetic and anticholinergic effects, which explains the fewer episodes of hypotension and bradycardia described in our study. These results are concordant with other studies that described hemodynamic stability with the use of Nefopam.[16,23] On the other hand, Ondansetron acts as a 5HT-3 (5-hydroxytryptamine-3) receptor antagonist, which explains its efficacy in reducing nausea and vomiting.[28] This finding is comparable to other studies that found a decrease in nausea and vomiting with Ondansetron even at a lower

Table 3 Drugs' associated side effects.

		Nefopam Group (n = 75)	Ondansetron Group (n = 75)	p
Hypotension episodes, n (%) [95 % CI]	**0**	71 (**94.7 %**) [87.8–98.2 %]	6 3 (**84 %**) [74.5–90.9 %]	**0.035**
	1	2 (2.7 %) [0.6–8.3 %]	7 (9.3 %) [4.3–17.5 %]	
	2	2 (2.7 %) [0.6–8.3 %]	2 (2.7 %) [0.6–8.3 %]	
	3	–	1(1.3 %) [0.1–6.1 %]	
	4	–	2 (2.7 %) [0.6–8.3 %]	
Bradycardia episodes, n (%) [95 % CI]	**0**	73 (**97.3 %**) [91.7–99.4 %]	65 (**86.7 %**) [77.6–92.9 %]	**0.016**
	1	1 (1.3 %) [0.1–6.1 %]	5 (6.7 %) [2.6–14 %]	
	2	1 (1.3 %) [0.1–6.1 %]	1 (1.3 %) [0.1–6.1 %]	
	3	–	2 (2.7 %) [0.6–8.3 %]	
	4	–	1 (1.3 %) [0.1–6.1 %]	
	6	–	1 (1.3 %) [0.1–6.1 %]	
Nausea and Vomiting episodes, n (%) [95 % CI]	**0**	66 (**88 %**) [79.2–93.9 %]	74 (**98.7 %**) [93.9–99.9 %]	**0.010**
	1	5 (6.7 %) [2.6–14 %]	–	
	2	4 (5.3 %) [1.8–12.2 %]	1 (1.3 %) [0.1–6.1 %]	
Pain during drug infusion, n (%) [95 % CI]		34 (**45.3 %**) [34.4–56.6 %]	4 (**5.3 %**) [1.8–12.2 %]	**0.000**
Hypothermia, n (%) [95 % CI]		32 (42.7 %) [31.9–54 %]	31 (41.3 %) [30.7–52.6 %]	1.000

CI, Confidence Interval; MWU, Mann-Whitney *U* test.

dose of 4 mg.[9,10] Even though, few studies described that Ondansetron may possess protective potentials against spinal anesthesia induced hypotension.[29] Others concluded that Ondansetron had no actual capabilities to reduce the incidence of hypotension and shivering during cesarean section after spinal anesthesia, but could efficiently decrease incidence of nausea, vomiting, and bradycardia.[30,31] In this study, results showed that Nefopam was superior to Ondansetron in reducing hypotension and bradycardia.

Finally, when it comes to pain during injection of the compared drugs, this study showed that 45 % of patients reported pain during infusion of Nefopam which was significantly higher than with Ondansetron (5.3 %). These results are in agreement with other studies that also described pain during infusion of Nefopam in patients under spinal anesthesia.[17,23] It has been suggested that injection pain was associated with rapid increases in cerebral concentration of Nefopam.[32]

Limitations

This study has a few limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of our findings. The sample size was calculated based on the formula: $n = \frac{(Z\alpha/2 + Z\beta)2 \left(p1\ (1 - p1) + p2(1 - p2)\right)}{(p1-p2)2}$, where $p_1 = 0.40$ (baseline shivering rate, determined based on the review of literature) and $p_2 = 0.20$ (we wanted to detect a 50 % decrease in the shivering rate). The sample size, adequate for primary outcomes, may be suboptimal for detailed secondary analyses. However, the authors believe that the prospective randomized double-blind design decreased the possibility of bias.

Second, the study population was limited to patients undergoing non-obstetric surgeries, so the findings may not be applicable to obstetric surgeries.

Third, a limitation of this study is the fixed dosing of Ondansetron (8 mg) and Nefopam (20 mg), which were selected based on commonly used clinical regimens and prior studies demonstrating their efficacy in similar contexts. However, different dosing strategies could potentially influence the outcomes, and we did not explore dose-response relationships, and this is an important consideration for future research.

Fourth, this study lacked quantification of administered fluids and the use of intravenous fluids. While our study aimed to reflect real-world clinical practice, we recognize that variations in fluid management may have affected hemodynamic outcomes. In future studies, we could consider standardized fluid administration protocols to better assess the independent effect of Nefopam and Ondansetron on hemodynamic stability. However, it is important to note that no difference in temperature was observated between the 2 groups.

Conclusion

This study provides valuable insights into the comparative effectiveness of Ondansetron and Nefopam for PSAS prevention. While Nefopam demonstrates superior efficacy in preventing shivering with fewer cardiovascular side effects, Ondansetron offers advantages in reducing the incidence of nausea and vomiting with no pain during administration. Future research should explore larger, multicenter studies including obstetric surgeries to further elucidate whether different doses and rate of administration of both drugs impact PSAS and their side effects.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

JT, JC and CD have given substantial contributions to the conception or the design of the manuscript and have participated in writing the original draft; HAZ, RM, MAI to acquisition, analysis and interpretation of the data; NN, KJ, CD to reviewing and editing the final draft of the manuscript. All authors read and approved the final version of the manuscript.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844650.

Associate Editor

Neuber Martins Fonseca

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Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Comparison of the effect of intra-cuff normal saline, dexamethasone or ketamine for prevention of postoperative sore throat: a randomized controlled trial

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Received 23 December 2024; accepted 8 June 2025
Available online 13 June 2025

KEYWORDS
Cough;
Dexamethasone;
Hoarseness;
Ketamine;
Pain;
Postoperative

Abstract

Background: Postoperative Sore Throat (POST) may result in patient dissatisfaction and distress, which could possibly delay discharge. Various pharmacological and non-pharmacological approaches have been explored, yet effective techniques remain elusive. This research evaluates the impact of intra-cuff Dexamethasone, Ketamine, and normal saline on alleviating POST symptoms.

Methods: In this randomized controlled trial, 405 adult patients aged 18–60 years undergoing short pelvic laparoscopic surgeries under general anesthesia for 1–3 h requiring endotracheal intubation were enrolled. Patients were randomized into Group N (intra-cuff normal saline), Group D (intra-cuff Dexamethasone), and Group K (intra-cuff Ketamine). The primary outcome of this study was the incidence and severity of POST at 2, 6, 12, and 24 hours after extubation. Secondary outcomes were the incidence and severity of postoperative hoarseness of voice and postoperative cough at various time intervals.

Results: There were more patients in Group D without symptoms of POST (92.59 %) than in Group K (74.07 %) and Group N (67.41 %) ($p < 0.0001$) at 2 h. Similarly, more patients had no symptoms of postoperative hoarseness of voice (93.33 %) and postoperative cough (93.33 %) in Group D at 2 h. Furthermore, Group D consistently exhibited the lowest incidence of POST, postoperative hoarseness of voice, and postoperative cough at various time intervals.

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https://doi.org/10.1016/j.bjane.2025.844651

Conclusions: Intra-cuff Dexamethasone appears to be a favourable intervention for symptom alleviation of POST, postoperative hoarseness of voice, and postoperative cough during the early postoperative period.
Clinical Trial Registry Number: CTRI/2022/08/044,664.

Introduction

Postoperative Sore Throat (POST) is a usual complication after general anesthesia with endotracheal tube intubation. The prevalence of sore throat after tracheal intubation in the postoperative phase ranges from 21 % to 65 %.[1] Despite a self-limiting condition, it may postpone discharge after day-care procedures. It eventually leads to unpleasant memories and dissatisfaction in patients in the postoperative period.[2] POST is known to be an aseptic inflammatory process due to localized trauma to the mucosa during airway manipulation.

POST may be prevented using a variety of pharmacological and non-pharmacological strategies. Among non-pharmacological methods, the use of small-size tracheal tubes, supra-glottic devices, meticulous airway instrumentation, gentle suction of the oropharynx, application of water-soluble jelly over the tracheal tube, and low intra-cuff pressure has been studied in the literature.[3] Among pharmacological agents, Dexamethasone, lignocaine, and magnesium sulfate have been used in various studies.[4]

Studies have shown that a peripherally administered N-Methyl-D-Aspartate (NMDA) receptor antagonist like Ketamine has demonstrated anti-nociceptive and anti-inflammatory effects. Dexamethasone is a potent corticosteroid with anti-inflammatory action. Because of its ability to modulate tissue edema and discomfort, it has been used to treat sore throats caused by tracheal irritation.[5–7]

The present study aimed to compare intra-cuff normal saline, Dexamethasone, and Ketamine to reduce Postoperative Sore Throat (POST) in patients undergoing surgery under general anesthesia with endotracheal intubation. We hypothesized that there is no difference in the incidence and severity of POST in the three groups.

Methods

Study settings

The present study was conducted within the operation theatres of an academic tertiary hospital. Following clearance from the ethics committee (AIIMS/IEC/2022/3906), this trial was subsequently registered with the Clinical Trials Registry of India (CTRI/2022/08/044,664) (https://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=67,337&EncHid=49,341.90645&modid=1&compid=19).

Patients

Adult patients aged between 18 and 60 years of either sex with American Society of Anesthesiologists (ASA) physical status 1–2 with Mallampati grades I or II undergoing short pelvic laparoscopic surgeries with a duration greater than 1 hour and lasting less than 3 h under general anesthesia in supine position requiring endotracheal intubation were recruited in this study. The exclusion criteria were patient's refusal to participate, history of pre-operative sore throat, smoker, oral and nasal surgeries, upper respiratory tract infection, pregnant females, patients with chronic obstructive pulmonary disease, known allergies to study drugs, anticipated airway instrumentation difficulty with Mallampati grades III/IV, and patients who required more than one attempt for intubation.

Interventions

Patients were randomized into Group N (intra-cuff normal saline), Group D (intra-cuff Dexamethasone), and Group K (intra-cuff Ketamine) by a web-based randomization program (www.randomizer.org), and the randomization sequence was kept inside serially numbered opaque-sealed envelope. Sealed envelopes were opened to reveal allocation before inducing the patient for general anesthesia. Both the patients and assessors were blinded to group allocation.

A standardized protocol was followed to administer general anesthesia. All patients had preoxygenation for 3 min with 100 % oxygen prior to the administration of anesthesia. Induction in all patients was accomplished with Intravenous (IV) fentanyl at 1.5–2 $\mu g.kg^{-1}$, IV propofol at 2–2.5 mg.kg^{-1}, IV atracurium at a dosage of 0.5 mg.kg^{-1}, and 100 % oxygen. After mask ventilation for 3 min, participants were intubated by a swift and gentle laryngoscopy that lasted no more than 15 s, using a low-pressure, high-volume, cuffed polyvinyl chloride Endotracheal Tube (ETT). In male patients, ETT with an internal diameter of 8 mm was used, whereas, in female patients, ETT with a 7 mm internal diameter was utilized. Endotracheal intubation was performed by two anesthesiologists (A.M. and A.S.), who had more than five years of experience and was verified by bilateral air entry upon auscultation and a consistent end-tidal capnographic waveform.

Two other anesthesiologists (P.K. and D.R.) filled the study drug in the endotracheal tube cuff with the minimum volume required to prevent an audible leak. Patients in the N, D, and K groups received intra-cuff normal saline, 0.1 mg.kg^{-1} of Dexamethasone, and 0.5 mg.kg^{-1} of Ketamine, respectively. In groups D and K, the estimated doses of Dexamethasone and Ketamine were first administered to the endotracheal tube cuff, followed by the desired amount of saline. Anesthesia was maintained using a mixture of oxygen and air (1:2) containing 1 %–1.2 % isoflurane (end-tidal, 0.7 to 1 MAC). After surgery, ondansetron 0.1 mg.kg^{-1} was administered intravenously, and residual muscle paralysis was reversed with neostigmine 0.05 to 0.07 mg.kg^{-1} and glycopyrrolate 10 $\mu g.kg^{-1}$ IV. In all patients, following mild

oropharyngeal suctioning, extubation was carried out after completion of surgery. All patients were administered 1 g of paracetamol intravenously at an 8-hour interval. Patients were assessed and graded for POST, hoarseness of voice, and postoperative cough at 2, 6, 12, and 24 hours postoperatively by independent anesthesiologists who were not part of this study using a scoring chart (Suppl. File 1).

The primary outcome of this research was the occurrence and intensity of POST at 2, 6, 12, and 24 hours post-extubation. Secondary outcomes were the incidence and severity of postoperative hoarseness of voice and postoperative cough at various time intervals.

Sample size

Rajan S et al. have reported 24-hour POST in 36.7 % of the saline group and 0 % in the Dexamethasone group.[8] To estimate a 50 % decrease in the incidence of post-op sore throat, we estimated a sample size of 135 per group at 95 % CI, 80 % power adjusted for three groups, and 10 % contingency.

Data analysis

The data was entered into a Microsoft Excel spreadsheet, and the final analysis was performed with the Statistical Package for Social Sciences (SPSS) software, IBM, Chicago, USA, version 25.0. The categorical variables were reported as numbers and percentages. The quantitative data were provided as means ± SD and median, along with the 25th and 75th percentiles (interquartile range). The comparison of the quantitative variables was analyzed using the Analysis of Variance (ANOVA) test with Bonferroni correction. The comparison of the qualitative variables was analyzed using the Chi-Square test and Fisher's exact test. For statistical significance, a *p*-value of less than 0.05 was considered statistically significant. The analysis was performed after the sample size was completed and relevant follow-up was performed.

Results

Initially, 418 patients were enrolled in the trial; however, 13 were excluded after randomization due to surgery lasting more than 3 h or the patient being kept under mechanical ventilation after the procedure (4 in the N group, 4 in the D group, and 5 in the K group). Following the per-protocol analysis, a total of 405 patients were included in the final analysis and allocated to three study groups, with 135 patients in each group (Figure 1). The excluded 13 patients were managed at the discretion of the anesthesiologist posted in the operation theatre. All three study groups had similar demographic characteristics (Table 1).

In the following two hours, in Group D, 92.59 % of patients had no symptoms (Grade 0) for POST, followed by Group K (74.07 %) and Group N (67.41 %). There was a significant

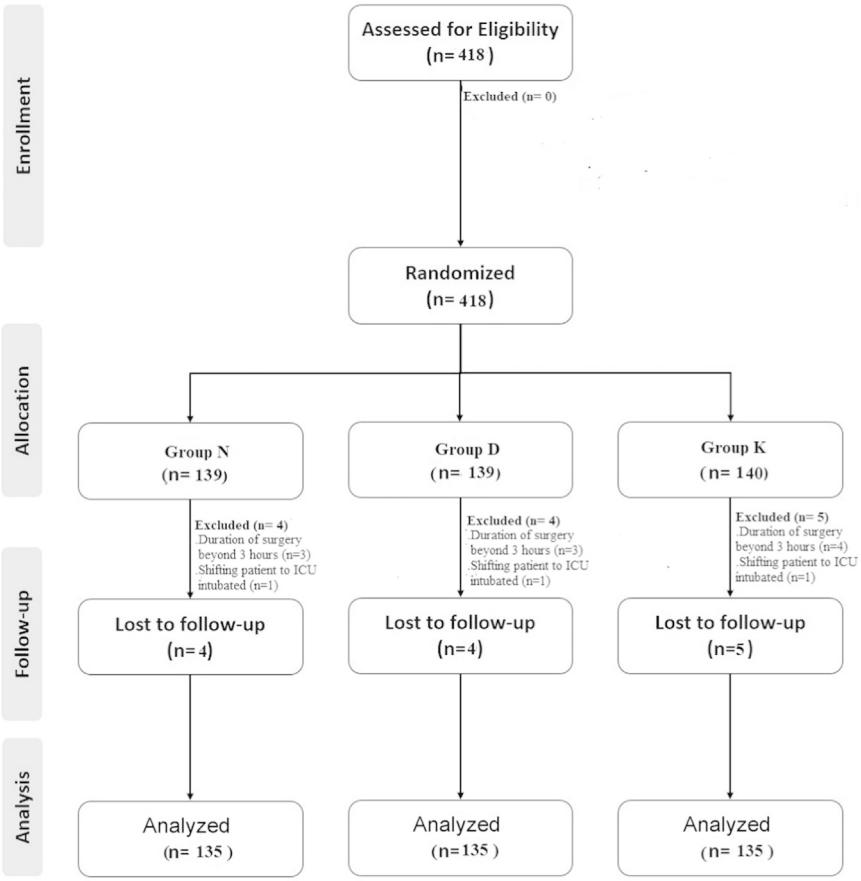

Figure 1 Consort diagram.

Table 1 Comparison of various characteristics between the groups.

Parameters		Group N (n = 135)	Group D (n = 135)	Group K (n = 135)	Total	p-value
Age (years)		42.43 ± 11.08	43.28 ± 12.2	43.98 ± 10.76	43.23 ± 11.35	0.534
Gender	M	71 (52.59 %)	69 (51.11 %)	70 (51.85 %)	210 (51.85 %)	0.971
	F	64 (47.41 %)	66 (48.89 %)	65 (48.15 %)	195 (48.15 %)	
Height (cm)		168.56 ± 6.11	170.56 ± 7.02	165.34 ± 9.05	168.15 ± 7.78	0.074
Weight (Kg)		66.24 ± 16.02	67.27 ± 13.09	65.43 ± 12.15	66.31 ± 13.84	0.550

M, Male, F, Female.
Group N, D, and K: Group Normal saline, Dexamethasone, and Ketamine, respectively.

difference between Group N and Group D ($p < 0.0001$) and between Group D and Group K ($p = 0.0002$) at 2 h. However, there was no significant difference between Group N and Group K ($p = 0.352$) at this time. After 6 h, similar trends were observed, with Group D having no symptoms of POST (Grade 0) in 94.81 % of patients, followed by Group K (74.81 %) and Group N (72.59 %). At 12 h, in Group D, 97.78 % had no symptoms of POST, followed by Group K (89.63 %) and Group N (80 %). At 24 h, in Group D, 99.26 % had no POST symptoms (Grade 0), followed by Group K (97.78 %) and Group N (93.33 %). At 24 h, there was a substantial difference between groups N and D ($p = 0.019$). In contrast, no significant differences were observed between Group N and Group K ($p = 0.137$) or between Group D and Group K ($p = 0.622$) at this time. There were no patients in Grade 3 POST in any of the groups (Figure 2, Table 2).

For postoperative hoarseness, at 2 h, Group D had Grade 0 hoarseness (93.33 %), followed by Group K (82.96 %) and Group N (77.78 %). There was a significant difference between Group N and Group D ($p = 0.001$) and between Group D and Group K ($p = 0.004$). At 6 h, Group D showed Grade 0 hoarseness (99.26 %), followed by Group K (91.11 %) and Group N (82.96 %). At 12 h, Group D had Grade 0 hoarseness (100 %), followed by Group K (96.30 %) and Group N (90.37 %). At 24 h, no significant differences were observed between any of the groups at this time point (Table 3).

For postoperative cough, at 2 h, Group D had Grade 0 cough (93.33 %), followed by Group N (76.30 %) and Group K (74.81 %). There was a significant difference between Group N and Group D ($p < 0.0001$) and between Group D and Group K ($p < 0.0001$), but not between Group N and Group K ($p = 0.558$) at this time. At 6 h, Group D had Grade 0 cough (97.78 %), followed by Group K (82.22 %) and Group N (74.07 %). At 12 h, Group D had Grade 0 cough (99.26 %), followed by Group K (95.56 %) and Group N (82.96 %). At 24 h, Group D had Grade 0 cough (100 %), followed by Group K (99.26 %) and Group N (94.07 %). There was a significant difference between Group N and Group D ($p = 0.007$), between Group N and Group K ($p = 0.036$), but not between Group D and Group K ($p = 1$) (Table 4). The absolute risk reductions and Number Needed to Treat (NNT) for clinically relevant outcomes are represented in Suppl. Tables 1, 2, and 3.

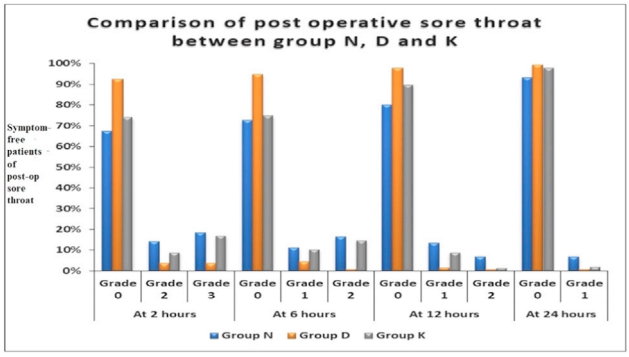

Figure 2 Comparison of post-operative sore throat among groups N, D and K at various intervals.

Discussion

The present study demonstrated a significant reduction in the incidence of POST, postoperative coughing, and hoarseness of voice at various time intervals post-extubation among patients who underwent surgeries of duration 1 to 3 h and received intra-cuff inflation with Dexamethasone compared to intra-cuff use of Ketamine and normal saline. These findings suggest that Group D may offer the most favorable outcomes in mitigating postoperative sore throat, hoarseness, and cough at various intervals.

Endotracheal intubation ensures safety by safeguarding the airway; however, it increases susceptibility to POST. The proposed mechanisms involve an aseptic inflammatory response triggered by the irritation of the pharyngeal mucosa during laryngoscopy and persistent irritation of the tracheal mucosa caused by the presence of the endotracheal tube cuff. An additional significant factor is the potential for trauma to occur during intubation.[9] Prevention of POST has been attempted through a variety of drugs and administration techniques.

Lipophilic medications permeate through the endotracheal tube cuff via diffusion. A small quantity of the drug traverses the cuff and has an anti-inflammatory effect on the mucosa. The cuff would serve as a reservoir for the medicines, facilitating diffusion. The suggested action of intracuff Dexamethasone and Ketamine likely relies on its anti-inflammatory properties, which include preventing leukocyte migration, preserving cell membrane integrity, and diminution of lysosomal release.[8]

Naqvi et al. conducted research including 70 patients, revealing that intra-cuff alkalinized lidocaine substantially reduced the intensity of POST, cough, hoarseness, and laryngeal spasm in the postoperative period compared to intracuff Ketamine.[10] In a study of 80 patients, Bhat et al. compared the beneficial effects of Ketamine and alkalinized lidocaine injection in the endotracheal tube cuff to reduce

Table 2 Comparison of post-operative sore throat between groups N, D, and K.

Symptom-free patients of post-operative sore throat	Group N (*n* = 135)	Group D (*n* = 135)	Group K (*n* = 135)	*p*-value (effect size)
At 2 h				
Grade 0	91 (67.41 %) [59.11, 74.74]	125 (92.59 %) (86.90, 95.93)	100 (74.07 %) (66.09, 80.73)	< 0.0001[b] N vs. D: < 0.0001[b] (0.315)
Grade 2	19 (14.07 %) [9.20, 20.94]	5 (3.70 %) (1.59, 8.38)	12 (8.89 %) (5.16, 14.89)	N vs. K: 0.352[b] (0.087) D vs. K: 0.0002[b] (0.252)[b]
Grade 3	25 (18.52 %) [12.87, 25.91]	5 (3.70 %) [1.59, 8.38]	23 (17.04 %) [11.63, 24.27]	
At 6 h				
Grade 0	98 (72.59 %) [64.52, 79.41]	128 (94.81 %) [89.68, 97.47]	101 (74.81 %) [66.88, 81.38]	< 0.0001[b] N vs. D: < 0.0001[b] (0.316)
Grade 1	15 (11.11 %) [6.85, 17.52]	6 (4.44 %) [2.05, 9.36]	14 (10.37 %) [6.28, 16.66]	N vs. K: 0.916[b] (0.025) D vs. K: < 0.0001[b] (0.295)[b]
Grade 2	22 (16.30 %) [11.02, 23.44]	1 (0.74 %) [0.13, 4.08]	20 (14.81 %) [9.80, 21.78]	
At 12 h				
Grade 0	108 (80 %) [72.46, 85.88]	132 (97.78 %) [93.67, 99.24]	121 (89.63 %) [83.34, 93.72]	< 0.0001[a] N vs. D: < 0.0001[b] (0.282)
Grade 1	18 (13.33 %) [8.60, 20.09]	2 (1.48 %) [0.41, 5.24]	12 (8.89 %) [5.16, 14.89]	N vs. K: 0.041[b] (0.153) D vs. K:0.007[a] (0.171)
Grade 2	9 (6.67 %) [3.55, 12.18]	1 (0.74 %) [0.13, 4.08]	2 (1.48 %) [0.41, 5.24]	
At 24 h				
Grade 0	126 (93.33 %) [87.82, 96.45]	134 (99.26 %) [95.92, 99.87]	132 (97.78 %) [93.67, 99.24]	0.027[a] N vs. D: 0.019[a] (0.137)
Grade 1	9 (6.67 %) [3.55, 12.18]	1 (0.74 %) [0.13, 4.08]	3 (2.22 %) [0.76, 6.33]	N vs. K: 0.137[a] (0.089) D vs. K: 0.622[a] (0.030)

[a] Fisher's exact test.
[b] Chi-Square test.
Values are in n (%) and 95 % Confidence Interval (95 % CI) of percentage.
Group N, D, and K: Group Normal saline, Dexamethasone, and Ketamine, respectively.

POST in adult patients undergoing general anesthesia. They noted that alkalinized lidocaine was more effective than intra-cuff Ketamine.[11] Similarly, in the present study, we noted that intra-cuff Dexamethasone was more effective than intra-cuff Ketamine in preventing POST. Dexamethasone permeates the cuff membrane and provides a prolonged local anti-inflammatory impact on the tracheal mucosa when delivered through the ETT cuff.[8] This intervention markedly diminishes mucosal inflammation, post-extubation sore throat, and cough. Conversely, Ketamine predominantly acts as an N-Methyl-D-Aspartate (NMDA) receptor antagonist and has modest anti-inflammatory characteristics.[10] Although Ketamine can alleviate airway irritation and inhibit reflex reactions like coughing, its effects are transient and mainly facilitated by local analgesia rather than significant anti-inflammatory actions. From a pharmacokinetic perspective, Dexamethasone's increased lipophilicity and extended duration of action confer a prolonged therapeutic window. Ketamine, while beneficial for immediate symptom alleviation, possesses a shorter duration of action and may be absorbed more rapidly. These combined mechanistic and pharmacokinetic benefits justify the preference for intra-cuff Dexamethasone over Ketamine in addressing post-extubation airway complications.

Rajan et al., in their study of 60 patients undergoing minor pelvic laparoscopic operations lasting less than two hours, discovered that intra-cuff Dexamethasone dramatically lowers the frequency and severity of POST, postoperative cough, and hoarseness of voice, which occur after general anesthesia with endotracheal intubation.[8] Rafiei et al., in their study on 180 patients, found that using Dexamethasone to inflate the endotracheal tube cuff for mitigating post-extubation responses was as effective as lidocaine, although superior to normal saline.[12] They considered it in clinical practice to enhance a patient's tolerance to anesthesia, particularly in cardiovascular illness, intracranial and intraocular hypertension, or pulmonary hyperreactivity. We discovered that intra-cuff Dexamethasone substantially decreased the incidence of POST and postoperative coughing and hoarseness at different time intervals after extubation.

Oliveira et al., in their study involving 154 children aged 4 to 12 years undergoing general anesthesia for elective tonsillectomy and adenotonsillectomy, discovered that intracuff alkalinized lidocaine, in conjunction with intravenous Dexamethasone, may effectively diminish sore throat 24 h postoperatively compared to air as the cuff insufflation medium.[6] Magnesium, an N-methyl-D-aspartate receptor antagonist, possesses anti-nociceptive and anti-inflammatory effects. Singh et al. conducted a systematic review and

Table 3 Comparison of post-operative hoarseness between groups N, D and K.

Symptom-free patients of postoperative hoarseness	Group N (n = 135)	Group D (n = 135)	Group K (n = 135)	p-value (effect size)
At 2 h				
Grade 0	105 (77.78 %) [70.76, 84.79]	126 (93.33 %) (89.13, 97.54)	112 (82.96 %) [76.62, 89.30]	0.002[a] N vs D: 0.001[a] (0.235)
Grade 1	12 (8.89 %) [4.09, 13.69]	6 (4.44 %) [0.97, 7.92]	5 (3.70 %) [0.52, 6.89]	N vs K: 0.372[a] (0.109) D vs K: 0.004[a] (0.212)
Grade 2	14 (10.37 %) [5.23, 15.51]	3 (2.22 %) [0.00, 4.71]	13 (9.63 %) [4.65, 14.61]	
Grade 3	4 (2.96 %) [0.10, 5.82]	0 (0 %) [0.00, 0.00]	5 (3.70 %) [0.52, 6.89]	
At 6 h				
Grade 0	112 (82.96 %) [76.62, 89.30]	134 (99.26 %) [97.81, 100.00]	123 (91.11 %) [86.31, 95.91]	0.0001[b] N vs. D: < 0.0001[a] (0.286)
Grade 1	14 (10.37 %) [5.23, 15.51]	1 (0.74 %) [0.00, 2.19]	6 (4.44 %) [0.97, 7.92]	N vs. K: 0.116[b] (0.126) D vs. K: 0.003[a] (0.192)[a]
Grade 2	9 (6.67 %) [2.46, 10.87]	0 (0 %) [0.00, 0.00]	6 (4.44 %) [0.97, 7.92]	
At 12 h				
Grade 0	122 (90.37 %) [85.39, 95.35]	135 (100 %) [100.00, 100.00]	130 (96.30 %) [93.11, 99.48]	< 0.0001[a] N vs. D: 0.0002[a] (N.C.)
Grade 1	13 (9.63 %) [4.65, 14.61]	0 (0 %) [0.00, 0.00]	3 (2.22 %) [0.00, 4.71]	N vs. K: 0.01[a] (0.177) D vs. K: 0.06[a] (0.137)
Grade 2	0 (0 %) [0.00, 0.00]	0 (0 %) [0.00, 0.00]	2 (1.48 %) [0.00, 3.52]	
At 24 h				
Grade 0	133 (98.52 %) [96.48, 100.00]	135 (100 %) [100.00, 100.00]	131 (97.04 %) [94.18, 99.90]	0.214[a] N vs. D: 0.498[a] (N.C)
Grade 1	2 (1.48 %) [0.00, 3.52]	0 (0 %) [0.00, 0.00]	3 (2.22 %) [0.00, 4.71]	N vs. K: 0.684[a] (0.067) D vs. K: 0.122[a] (0.122)
Grade 2	0 (0 %) [0.00, 0.00]	0 (0 %) [0.00, 0.00]	1 (0.74 %) [0.00, 2.19]	

[a] Fisher's exact test.
[b] Chi-square test.
N.C., Not Computable.
Values are in n (%) and 95 % Confidence Interval (95 % CI) of percentage.
Group N, D, and K: Group Normal saline, Dexamethasone, and Ketamine, respectively.

meta-analysis of seven trials with 726 participants, revealing that the incidence of POST at 24 h was significantly reduced in the topical magnesium group (26 out of 363) compared to both the active and non-active control groups (89 out of 363); p = 0.00, RR = 0.22 (95 % CI 0.12–0.39, I^2 = 0 %).[13]

Reducing POST enhances the patient's tolerance to anesthesia, especially in cardiovascular disease, intracranial and intraocular hypertension, and pulmonary hyperreactivity. It minimizes the need for additional pain medication and may reduce hospital stays, enhancing the overall perioperative experience and quality of care. However, these factors were not measured in the current investigation. There can be potential side effects of intra-cuff medications, such as local tissue irritation or systemic absorption risks.[8] However, we did not observe any adverse effects in the present study.

Limitations

The present study has certain limitations. First, it was impossible to determine whether the reported throat pain was due to endotracheal intubation alone, as it may be associated with Ryle's tube position. However, the clinical benefit on the first postoperative day was noted either way. Furthermore, there may be inter-observer variability in assessing POST scores. Secondly, as the study was conducted in adult patients, some pain information was subjectively provided by patients. Patients may underestimate their sore throat pain without objective pain scales compared to surgical site pain. We could not assess the intra-cuff pressure due to fluid intrusion into the manometer, which might compromise the apparatus. No cuff pressure measurement device was used, which can introduce variability in drug diffusion and mucosal irritation. Further, pain related to airway management during intubation is directly related to cuff pressure, which can be a bias in this study.[14] There was no control group (a placebo group with air in the cuff). Moreover, we did not measure any of the drug (Ketamine, Dexamethasone) serum concentrations. We also did not conduct long-term follow-up for the occurrence of laryngeal injuries or prolonged hoarseness beyond 24 h. Further studies are necessary to address these limitations in the future.

Table 4 Comparison of postoperative cough between groups N, D, and K.

Symptom-free patients of postoperative cough	Group N (*n* = 135)	Group D (*n* = 135)	Group K (*n* = 135)	*p*-value (effect size)
At 2 h				
Grade 0	103 (76.30 %) [69.12, 83.47]	126 (93.33 %) [89.13, 97.54]	101 (74.81 %) [67.49, 82.14]	0.0005[b] N vs. D: < 0.0001[a] (0.269) N vs. K: 0.558[b] (0.087) D vs. K: < 0.0001[a] (0.268)
Grade 1	4 (2.96 %) [0.10, 5.82]	4 (2.96 %) [0.10, 5.82]	7 (5.19 %) [1.44, 8.93]	
Grade 2	18 (13.33 %) [7.60, 19.07]	5 (3.70 %) [0.52, 6.89]	21 (15.56 %) [9.44, 21.67]	
Grade 3	10 (7.41 %) [2.99, 11.83]	0 (0 %) [0.00, 0.00]	6 (4.44 %) [0.97, 7.92]	
At 6 h				
Grade 0	100 (74.07 %) [66.68, 81.47]	132 (97.78 %) [95.29, 100.26]	111 (82.22 %) [75.77, 88.67]	< 0.0001[a] N vs. D: < 0.0001[a] (0.344) N vs. K: 0.031[a] (0.171) D vs. K: < 0.0001[a] (N.C)
Grade 1	19 (14.07 %) [8.21, 19.94]	3 (2.22 %) [−0.26, 4.71]	20 (14.81 %) [8.82, 20.81]	
Grade 2	15 (11.11 %) [5.81, 16.41]	0 (0 %) [0.00, 0.00]	4 (2.96 %) [0.10, 5.82]	
Grade 3	1 (0.74 %) [−0.71, 2.19]	0 (0 %) [0.00, 0.00]	0 (0 %) [0.00, 0.00]	
At 12 h				
Grade 0	112 (82.96 %) [76.62, 89.30]	134 (99.26 %) [97.81, 100.71]	129 (95.56 %) [92.08, 99.03]	< 0.0001[a] N vs. D: < 0.0001[a] (0.286) N vs. K: 0.001[a] (0.206) D vs. K: 0.120[a] (N.C)
Grade 1	21 (15.56 %) [9.44, 21.67]	1 (0.74 %) [−0.71, 2.19]	6 (4.44 %) [0.97, 7.92]	
Grade 2	2 (1.48 %) [0.56, 3.52]	0 (0 %) [0.00, 0.00]	0 (0 %) [0.00, 0.00]	
At 24 h				
Grade 0	127 (94.07 %) [90.09, 98.06]	135 (100 %) [100.00, 100.00]	134 (99.26 %) [97.81, 100.71]	0.003[a] N vs. D: 0.007[a] (0.174) N vs. K: 0.036[a] (0.145) D vs. K: 1[a] (N.C.)
Grade 1	7 (5.19 %) [1.44, 8.93]	0 (0 %) [0.00, 0.00]	1 (0.74 %) [−0.71, 2.19]	
Grade 2	1 (0.74 %) [−0.71, 2.19]	0 (0 %) [0.00, 0.00]	0 (0 %) [0.00, 0.00]	

[a] Fisher's exact test.
[b] Chi-Square test.
N.C., Not Computable
Values are in n (%) and 95 % Confidence Interval (95 % CI) of percentage.
Group N, D, and K: Group Normal saline, Dexamethasone, and Ketamine, respectively.

Conclusion

Intra-cuff Dexamethasone appears to have the lowest incidence of postoperative sore throat, hoarseness, and cough at most time points during the early postoperative period, indicating its potential as an effective intervention for reducing postoperative discomfort.

Declaration of competing interest

The authors declare no conflicts of interest.

Ethics approval

IRB approval was taken from the Institutional Ethics Committee (IEC Reg n° AIIMS/IEC/2022/3096 dated 03/03/2022).

The study was registered with Clinical Trial Registry – India (CTRI Reg. n° CTRI/2022/08/044,664).

Authors' contributions

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Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844651.

Associate Editor

Luís Vicente Garcia

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Brazilian Journal of Anesthesiology 2025;75(5): 844665

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Pain thresholds in elderly individuals: a cross-sectional observational study of the influence of gender and chronic non-cancer pain☆

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Received 13 November 2024; accepted 8 June 2025
Available online 29 July 2025

KEYWORDS
Aging;
Chronic pain;
Elderly;
Gender;
Pain measurement;
Pain threshold

Abstract

Background: The older population is growing, and it is estimated that, by 2050, people aged 60 years or more will have reached two billion. The increased life expectancy has led to a higher incidence of chronic degenerative diseases, contributing to increased pain complaints. This study aims to compare the pain threshold after mechanical stimulation in older adults according to gender and presence or absence of chronic pain and find the prevalence and intensity of chronic pain in this population.

Methods: This was a cross-sectional observational study with a convenience sample in the outpatient clinic at two research centers. All participants answered sociodemographic and clinical questionnaires, and the Pressure Pain Threshold (PPT) was assessed with an algometer. Patients reporting chronic pain answered the Geriatric Pain Measure (GPM) questionnaire.

Results: The sample consisted of 230 individuals, aged 60 to 96 years, 67.8% women and 32.2% men. Chronic pain prevalence was 47.8%, 29.7% in men and 56.4% in women. PPT was significantly lower in women (4.49 ± 1.78 kg) than in men (6.41 ± 1.92 kg). PPT in older individuals presenting chronic pain (4.58 ± 1.93 kg) was lower than in older individuals without chronic pain

☆ The study was approved (data 29/09/2016) by the Ethics Committee for Analysis of Research Projects of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (n° 1.751.968), link file:///C:/Users/aquila.g/Downloads/PB_PARECER_CONSUBSTANCIADO_-CEP_1751968_E1.pdf. The study was registered at clinicaltrials.gov (43535915.0.0000.0068).

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https://doi.org/10.1016/j.bjane.2025.844665

(5.58 ± 2.01 kg). There was no significant difference between genders in pain assessment by GPM.
Conclusions: Pressure pain threshold was lower in older women and in patients with chronic pain, the association between gender and lower pain threshold was stronger than observed with chronic pain.

Introduction

Aging of the world population is an evident and fast-paced phenomenon, and it is expected that, by 2050, the number of people aged 60 years or more reaches two billion.[1] Changes resulting from aging lead to increased incidence of chronic degenerative diseases, contributing to pain complaints.[2]

Pain exhibits variability according to gender and sex and, usually, women report more intense, frequent and persistent pain symptoms than men,[3] which has been confirmed in epidemiological studies of prevalence and characteristics of chronic pain.[4,5] These differences between women and men are influenced by genetic, social, psychological and hormonal factors.[5]

Changes in gonadal hormone levels as a result of aging play an important role in pain sensitivity and tolerance. Reduced levels of estrogen in women (postmenopausal) and testosterone in older men may influence pain perception.[6] Gonadal hormones are related to increased pain perception in animals.[7] In older women, in menopause, when female gonadal hormones have decreased secretion, there are questions about how women behave in relation to pain.[8-10]

Studies show that aging appears to alter the pain threshold.[11,12] With aging, sensitivity to pain is reduced, confirming that pain thresholds increase with age,[13] with men having a higher pain threshold for mechanical stimuli. However, there are no studies addressing the influence of chronic pain in conjunction with gender in older people.

We hypothesized that pain threshold after mechanical stimulation in older women would be similar to that of older men due to decreased gonadal hormones in menopausal women. This study aimed to compare pain threshold after mechanical stimulation in older individuals according to gender and presence or absence of chronic pain and establish the prevalence and intensity of chronic pain in the population.

Methods

This was a cross-sectional observational study with convenience sample. The study was approved by the Ethics Committee for Analysis of Research Projects of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (#1.751.968) and registered at clinicaltrials.gov (NCT06855797).

The study was carried out in two geriatric outpatient centers: Geriatric Outpatient Clinic of the Central Institute of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, and Geraldo de Paula Souza School Health Center of the Faculdade de Saúde Pública da Universidade de São Paulo, centers serving geriatric outpatients.

People aged 60 years or more were considered older adults, according to the definition used in Brazil and recommended by the World Health Organization for developing countries.[14] Although chronic pain is defined as pain that persists or recurs for more than 3 months,[15] this study included patients presenting pain for at least 6 months, and the data collection instrument adopted was the measurement of pain in geriatric patients (Geriatric Pain Measure-GPM).[16]

Inclusion criteria

Individuals aged 60 years or more without cognitive impairment assessed using the Mini Mental State Examination (MMSE) were included. Cutoff values varied according to education, as follows: 20 for illiterate individuals, 25 for 1- to 4 years of schooling, 26 for 5 to 8 years of schooling, 28 for 9 to 11 years of schooling, and 29 for more than 11 years of schooling.[17]

Exclusion criteria

Participants presenting cognitive difficulty understanding and answering the questionnaires or with cancer pain were excluded.

Data collection

Data collection lasted for the period necessary to reach the number of subjects calculated for the study (07/2017 to 12/2019).

After signing the informed consent form, participants were interviewed. All participants answered the Questionnaire for Assessment of Sociodemographic and Clinical Characteristics. Patients reporting chronic pain for six months or more answered the Geriatric Pain Measure (GPM) questionnaire, and pain threshold was assessed by mechanical stimulus.

Pressure pain thresholds were assessed using a pressure algometer (Push Pull Force Gauge – Model 12-0304), which measures force exerted between 1 and 10 $kg.cm^{-2}$. The device was applied on the right or left Trapezius muscle, on the suprascapular portion of the muscle, then pressure was applied, and participants reported the moment they felt pain or discomfort. Each subject was tested three times with 5 min intervals and the mean of the three measurements was recorded as the pressure pain threshold.

Sample size

Sample size was calculated as 230 patients, assuming a standard deviation of 2.0 points on the pain threshold scale,[18] with an expected allocation of one man for every two women, with 90% power to detect an average difference of 1 point on the pain threshold scale at a significance level of 5%.

Statistical analysis

Quantifiable variable values were described by mean and standard deviation, minimum and maximum values. Variables were summarized and segmented by gender and presence of chronic pain. Categorical variables were compared by Fisher's exact test and, for continuous variables, by Student's *t*-test, when normal distribution was present. Otherwise, variables were compared using the non-parametric Mann-Whitney test.

The assessment of the primary outcome, pressure pain threshold, was performed using the linear regression model considering the interaction between gender and chronic pain. Sensitivity analyses adjusted for age and interactions with gender and pain were also performed. Analysis was performed using the R4.0.2 program (R Core Team, 2020). The significance level in the statistical tests was 5%.

Results

Two hundred and eighty-three individuals were eligible for the study, forty-seven declined to participate in the study, two were excluded for not meeting minimum MMSE scores, and four opted out of the study. Two hundred and thirty subjects were assessed, 67.8% (n = 156) women and 32.2% (n = 74) men. The participants' average age was 75.8 years, 76.2 years in women and 74.9 years in men. Participants aged 60 — 74 years were the most frequent, 45.7% (n = 105), and older individuals aged 75 — 84 years, 37.8% (n = 87). The youngest participant was 60 years old and the oldest participant was 96 years-old (Table 1).

The most frequent morbidities in the sample were: systemic arterial hypertension, 49.1% (n = 113); diabetes mellitus, 22.6% (n = 52), and osteoarthritis, 13.5% (n = 31). Chronic pain prevalence in the sample was 47.8% (n = 110), 56.4% (n = 88) among women and 29.7% (n = 22) among men. Chronic pain was about twice more frequent in women than in men (56.4% vs. 29.7%, $p < 0.001$) (Table 2). Chronic pain intensity, using GPM score, was not different between men and women, 42.8 ± 24.4 in men and 51.0 ± 25.6 in women, meaning moderate pain (Table 2). Prevalent sites of pain were lower limbs, 58.2% (n = 64); lumbar region, 40.9% (n = 45), and shoulders 38.2% (n = 42).

PPTs found in women (4.49 ± 1.78 $kg.cm^{-2}$) were lower than in men (6.41 ± 1.92 $kg.cm^{-2}$) ($p < 0.001$) (Table 3). Pain thresholds in chronic pain participants (4.58 ± 1.93 $kg.cm^{-2}$) were lower than in participants without chronic pain (5.58 ± 2.01 $kg.cm^{-2}$) ($p < 0.001$), (Fig. 1, Table 3).

The interaction between female gender and chronic pain was assessed, since pain was more prevalent in women, and a linear regression model for PPT according to gender and presence of chronic pain showed no interaction effect (p = 0.82) (Table 4). Another linear regression model verified the independent association of gender, presence of chronic

Table 1 Sample distribution according to gender and age.

Parameter	Male (n = 74)	Female (n = 156)	Total (n = 230)	p-value
Age (mean ± SD)	74.9 ± 8.4	76.2 ± 8.0	75.8 ± 8.2	0.234[a]
Age group				
60 — 74 years	37 (50%)	68 (43.6%)	105 (45.7%)	0.665[b]
75 — 84 years	26 (35.1%)	61 (39.1%)	87 (37.8%)	
85 years or more	11 (14.9%)	27 (17.3%)	38 (16.5%)	

[a] Student's *t*-test.
[b] Fisher's exact test.
* Significance level: $p < 0.05$.
Values are presented as mean ± standard deviation or number (%).

Table 2 Sample distribution according to gender and chronic pain prevalence, and Geriatric Pain Measure according to gender.

Parameter	Gender			p-value
	Male (n = 74)	Female (n = 156)	Total (n = 230)	
Chronic pain				
Yes	22[c] (29.7)	88[c] (56.4%)	110 (47.8%)	< 0.001[a]
No	52[c] (70.3%)	68[c] (43.6%)	120 (52.2%)	
Pain assessment GPM	(n = 22)	(n = 88)	(n = 110)	
GPM Total (0–100)	42.8 ± 24.4	51.0 ± 25.6	49.4 ± 25.5	0.18[b]

[a] Fisher's exact test.
[b] Student's *t*-test.
[c] Significance level: $p < 0.05$.
Values are presented as mean ± standard deviation or number (%).

Table 3 Sample distribution according to mean pressure pain threshold, gender and presence or absece of chronic pain.

Variables	Number of participants (n = 230)	PPT ($kg.cm^{-2}$)	p-value[a]
Gender			
Male	74	6.41 ± 1.92	< 0.001
Female	156	4.49 ± 1.78	
Chronic pain			
No	120	5.58 ± 2.01	< 0.001
Yes	110	4.58 ± 1.93	

[a] Student's *t*-test.
PPT, Pressure Pin Threshold ($kg.cm^{-2}$).
Values are presented as mean ± standard deviation.

pain with pain threshold. It was estimated that women had an average value of 1.76 $kg.cm^{-2}$ lower pain threshold than men (95% CI 1.24−2.28, $p < 0.01$). Chronic pain also reduced pain threshold by an average of 0.59 $kg.cm^{-2}$ (95% CI 0.11 −1.07, p = 0.02) (Supplementary Material). Female gender was more associated to lower pressure pain threshold than chronic pain. There was no difference in pressure pain threshold and estimates of gender and chronic pain according to age stratification (Supplementary Material).

Discussion

This cross-sectional study compared pressure pain threshold between older men and women with or without chronic pain and assessed the prevalence of chronic pain in older outpatients.

PPT in older adults was different between males and females, and in those with or without chronic pain. Our initial hypothesis was that older women in menopause, without the influence of female gonadal hormones, would have a pain threshold similar to men, due to the absence of the pronociceptive effects of gonadal hormones. However, the pain threshold was, on average, 1.76 $kg.cm^{-2}$ lower in women than in men. Similarly, patients with chronic pain had decrease in pain threshold of 0.59 $kg.cm^{-2}$ compared to those without chronic pain. Both female gender and chronic pain were associated to lower pain thresholds; however, interestingly, being female was more associated to lower pain threshold than presenting chronic pain.

Testosterone, present in males, can contribute with a protective or analgesic effect of the hormone,[9,10] while social, psychological or cultural factors also influence pain perception in females, with women seemingly presenting more catastrophizing and less self-efficacy behaviors, leading to increased pain perception.[19] Seemingly, decreased gonadal female hormones are less important than gender.

Although findings on this issue are controversial, our results were similar to previous studies on PPT between

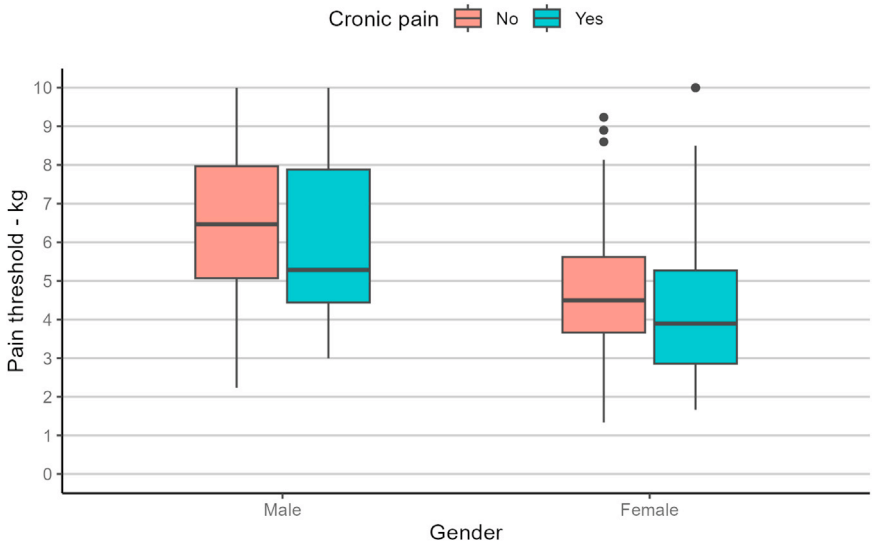

Figure 1 Mean pressure pain threshold between genders and chronic pain.

Table 4 Linear regression model for pain threshold according to gender and chronic pain interaction.

Factor	Coefficient	Standard error	*t*-value	p
Intercept	6.56	0.25	26.10	< 0.01
Female	−1.72	0.33	−5.14	< 0.01
Chronic pain	−0.50	0.46	−1.09	0.28
Interaction Gender (F): Pain (Yes)	−0.12	0.55	−0.23	0.82

[2] = 21.6%.

genders in healthy older individuals without chronic pain, with a lower pain threshold in women than in men.[11,13] One small study (n = 40) showed no difference between older men and women; however, the study has no report of the number of older men and women in the study.[12] Pain thresholds after heat are also lower in older women compared to older men,[20] and pain thresholds for different pain stimuli may also be lower in women.

As in most studies involving older adults, most subjects were female (67.8%) and the prevalence of chronic pain in this population was 47.8%, similarly to other studies on community-dwelling older individuals, which range from 28.7% to 60.4%.[21-23]

Although chronic pain prevalence was higher in women than in men, the characterization of chronic pain according to GPM was not different between the genders, with pain intensity showing moderate intensity in both genders, similarly to a previous study.[16] Prior to this study, GPM had not been used for comparisons between genders, and there are still no elements to state that the instrument is adequate to assess the role of gender on intensity of pain in older adults.

This study has some limitations due to its adoption of a convenience sample of participants, which may have introduced selection bias, sometimes overrepresenting certain patient profiles, creating difficulty in applying the results to the general older population. Due to this being a cross-sectional study, we can only show the association but not causality between gender, chronic pain and lower PPT.

We found no previous study of older individuals presenting chronic pain. An interesting and intriguing result was the lower association of previous chronic pain compared to gender on pain threshold. Older women showed higher decrease in pain threshold than older individuals presenting chronic pain. It has been well established that individuals with chronic pain, for example, chronic low back pain, have lower PPT than healthy individuals.[24] Chronic pain would be expected to impact pain threshold more than gender. It is difficult to consider this result without further studies to confirm and explain this finding and, in our opinion, it is still early to apply these findings to clinical practice, in treatments of acute and chronic pain in the older population; however, gender and chronic pain will probably be addressed in the future for customized pain treatments.

Conclusion

Gender was the main factor associated with decreased pressure pain threshold. PPT was lower in older women than in older men. Chronic pain was also associated with lower pain threshold, which was lower in people presenting chronic pain, and PPT was lower in women than in individuals with chronic pain. Chronic pain was more prevalent in older women.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844665.

Associate Editor

Maria José Carmona

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Brazilian Journal of Anesthesiology 2025;75(5): 844646

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Effect of propofol and sevoflurane anesthesia on the optic nerve sheath: systematic review and meta-analysis

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Received 20 December 2024; accepted 23 May 2025
Available online 4 June 2025

KEYWORDS
Intracranial pressure;
Laparoscopy;
Optic nerve;
Propofol;
Robotic surgical procedures;
Sevoflurane

Abstract
Background: To facilitate the surgical view, laparoscopic and robotic pelvic surgeries require a pneumoperitoneum with the Trendelenburg position, which may result in elevated Intracranial Pressure (ICP). The choice of anesthetic agents may also influence ICP. Ultrasonographic evaluation of the Optic Nerve Sheath Diameter (ONSD) is a promising way to evaluate ICP. In this systematic review, we aimed to evaluate the ONSD, as an indirect estimation of ICP, in patients undergoing laparoscopic/robotic surgeries under pneumoperitoneum and Trendelenburg position.
Methods: A literature search was performed to identify prospective randomized clinical trials in which the primary endpoint was the evaluation of the ONSD using sevoflurane or propofol anesthesia after the onset of pneumoperitoneum and Trendelenburg position. The mean and the standard deviation of the ONSD in each intervention group were extracted from the included trials for analysis. Mean difference with 95% Confidence Interval (95% CI) was calculated.
Results: Five randomized controlled trials, with 277 subjects, were allocated to this study. Compared with the baseline, there was an increase in ONSD from 0.5h to 3 hours ($p < 0.05$) in both propofol and sevoflurane groups. Furthermore, propofol reduced the ONSD compared to sevoflurane (mean difference: -0.23 mm, 95% CI: -0.37 to -0.10; studies = 5; $I^2 = 23\%$).

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https://doi.org/10.1016/j.bjane.2025.844646

Conclusion: There is evidence indicating, through ultrasonographic analysis of the ONSD, that propofol probably reduces ICP compared to sevoflurane in robotic and laparoscopic pelvic surgeries.

Introduction

Every three years, the prevalence of cancer in the United States is estimated using the Surveillance, Epidemiology, and End Results Cancer Registries (SEER) database. In 2022, more than 3.5 million North American men were affected by prostate cancer and 268490 new patients were diagnosed with the disease.[1] Minimally invasive radical prostatectomies first occurred in the 1990s.[2] The "da Vinci" robotic platform became the available model most used by doctors in the world today.[3] In the USA, more recent data indicate that more than 85% of radical prostatectomies are performed with robotics (RARP).[4]

In the past 20-years, pelvic laparoscopic and robotic surgeries have become the method of choice due to their oncological benefits and the reduction in perioperative complications. They were previously performed using open techniques. However, these procedures require the establishment of pneumoperitoneum with Carbon Dioxide (CO_2) and Trendelenburg position, which lead to physiological changes in the cardio-respiratory system and impact on Intracranial Pressure (ICP). Pulmonary and cardiovascular repercussions are known and monitored. On the other hand, the traditional measurement of ICP proved to be an impracticable magnitude to be implemented perioperatively due to its complexity. In the past two decades, studies that measure the diameter of the Optic Nerve Sheath (ONSD) by ultrasonography have proven to be an easy-to-implement and noninvasive approach to detect ICP.[5-7]

Anesthetic agents may influence ICP during surgery. Under propofol anesthesia, a decrease in cerebral blood flow, cerebral metabolic rate, and ICP has been reported.[8-10] Conversely, sevoflurane is a vasodilator with the potential to increase ICP.[11] The effects of anesthetics on ICP, through pneumoperitoneum and the steep Trendelenburg position, require more in-depth knowledge. The objective of this systematic review is to investigate whether there is a difference between the anesthetics propofol and sevoflurane regarding the diameter of the optic nerve sheath, measured by ocular ultrasonography, as an indirect predictor of ICP, in simple laparoscopic and robotic pelvic surgeries.

Methods

The study was registered in PROSPERO, CRD42023387503 (www.crd.york.ac.uk/Prospero), with the planned analyses performed. The PICO Diagram[12] listed is P: Adult patients undergoing surgery in the Trendelenburg position and use; I: Anesthetic maintenance with propofol; C: Anesthetic maintenance with sevoflurane; O: Ultrasound diameter of the optic nerve sheath; S: Randomized Controlled Clinical Trials (RCTs).

Criteria for inclusion: patients between 19 and 79 years of age with an American Society of Anesthesiologists (ASA) physical status of I—III who were underwent elective laparoscopic or robot-assisted pelvic surgery. Patients with a previous neurological disease or cerebrovascular disease that could increase ICP, history of allergy to anesthetic drugs, pregnancy and patients with a history of ophthalmological disease were excluded.

A timeless search strategy with high sensitivity and moderate specificity and precision was developed between November 2021 and December 2022, according to the Cochrane Manual for Systematic Reviews of Interventions, version 6.3.[13] STRING was built through an advanced search on the leading web platforms: PubMed; Embase; Cochrane; Virtual Health Library (VHS) Portal. Other sources, sites, and meta-search tools were part of the strategy: Handsearch (manual search); Grey Literature (Wordwidescience.org, Qinsight, Oasis.br, Grey Literature Report); Preprints: MedRxiv, Scielo preprint; Tripdatabase, ClinicalTrail.gov (ongoing clinical trials, records); University of York; Scielo; BMJ Clinical Evidence; Epistemonikos; Scopus; CINAHL (Cumulative index to nursing and allied health literature); BDTD (Portal of the Digital Library of Theses and Dissertations at USP); and Google Scholar (Appendix 1).

The searched terms and descriptors were: "surgery", "Trendelenburg position or cephalo-declined", and "intracranial pressure". The MeSH terms used were: "Head-Down Tilt", "Trendelenburg Position", "Surgery", "Surgery, General", "Surgical Procedures, Operative", "Intracranial Pressure", "Intracranial Hypertension", and "Papilledema".

The studies were filtered to include all randomized clinical articles in English, Portuguese, Spanish, and others (Fig. 1). Two independent authors (VTC and NCJ) analyzed all relevant studies for selection and data extraction, and the discrepancies were solved by a third author (MFV). Data was managed using the Rayyan *software*.[10,14-17]

Data were extracted from methods (study design and definition), identification data (source of sponsorship, country, and details of authors such as name, institution, e-mail, and address), data on the characteristics of the participants (number of randomized participants, number of assessed participants, and number lost from follow-up with reasons described, basic data characteristics, inclusion criteria), interventions (number of participants within each intervention group and intervention description), outcome measures (type of outcome report, breadth, measurement unit, direction, and observations), study design characteristics (and risk of bias assessment), and any other relevant information.

Two authors (VTC and NCJ) independently assessed the risk of bias of each included study using version 2 of the Cochrane' Risk of Bias' tool (RoB2) according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions version 6.3.[13]

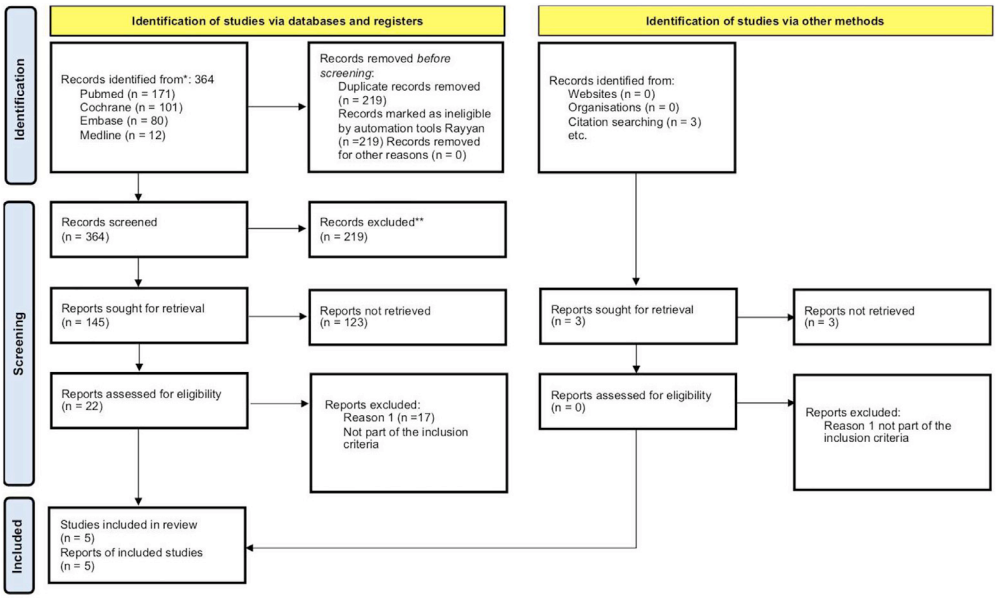

Figure 1 PRISMA 2020, Flow diagram for new systematic reviews, which included searches of databases, registers and other sources.

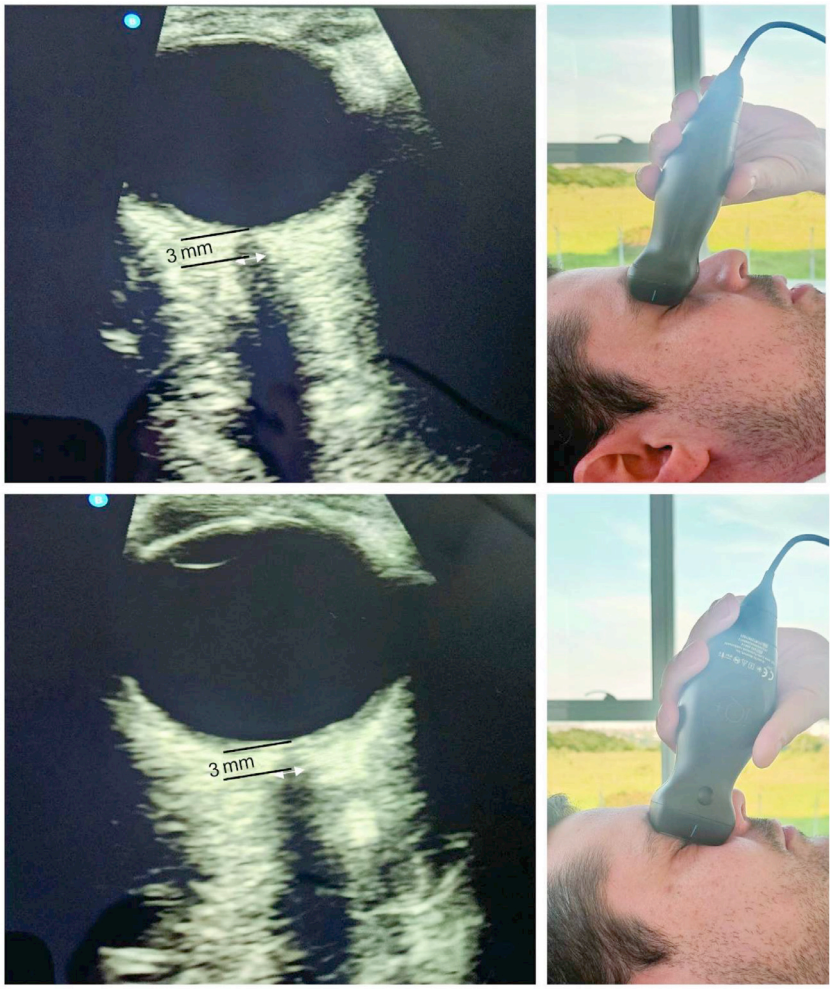

Figure 2 Ocular ultrasound: 3 views [transverse (top), sagittal (middle) and bottom (bottom)], diameter of red optic nerve sheath (inside diameter), diameter of yellow optic nerve sheath (outside diameter), green distance 3 mm behind the globe (Kishk and Ebraheim, 2019; Raval et al., 2020).

The primary outcome was the change in ONSD, measured by ultrasound[18] from 0.5h to 3 hours after the onset of pneumoperitoneum and cephalon decline compared to the baseline values after anesthesia (Fig. 2). The mean, Standard Deviation (SD), and number of participants in each intervention group from the included trials were extracted for continuous data. When trials reported any other measure of dispersion (e.g., confidence interval or standard error), the SD was calculated according to the instructions in the Cochrane Handbook for Systematic Reviews of Interventions version 6.3.13 Data extraction was based on intention-to-treat analysis when possible. The data were summarized using meta-analysis, the inverse generic variance method and the random effects model since one of the studies presented the results separated by eye, which were later grouped following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions version 6.313. In the present study, a cut-off value of 5 mm was used to predict a high ICP (above 20 mmHg).

The analysis unit considered was each individual (randomization was used from each participant, individually). When several points in time were reported in the same study, the data were related to the most extended follow-up of the surgical time the patient was undergoing pneumoperitoneum (the exception was the study by Sujata et al.,[14] in which the extracted data concerned the highest value found, due to data availability).

Possible clinical heterogeneity was assessed considering participants, interventions, outcomes, and study characteristics for the included trials. Statistical heterogeneity was visually inspected in the forest plots, and the Chi^2 test was used. In addition, the I^2 statistic was used to describe the proportion of variation in the effect estimates that is due to variability between studies and not to sampling error, following the recommendations of chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions version 6.3.[13]

Regarding the assessment of the certainty of the evidence, two authors (VTC and NCJ) used the approach proposed by the GRADE Working Group and the recommendations of chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions version 6.3.[13] The GradePro GDT software was used to analyze the overall certainty of the evidence. The investigation of publication bias was planned with the funnel chart. The subgroup and sensitivity analysis was designed for studies with high risk of bias.

Results

A total of 277 patients were allocated to this study. The sample consisted of 16 women undergoing robotic gynecological surgery and 115 men, in whom robotic-assisted radical prostate surgery predominated (Table 1). Weight and age were presented as mean ± standard deviation. There were no statistically significant differences between the propofol and sevoflurane groups ($p > 0.05$) regarding the variables number of patients, weight and age (Table 2). In studies E2 and

Table 1 Identification of studies.

Study	Source/Type	Title	Surgery	Authors	DOI https://doi.org/
E1	J Robot Surg (2019) RCT	A randomized trial to compare the increase in intracranial pressure as correlated with the optic nerve sheath diameter during propofol versus sevoflurane-maintained anesthesia in robotic-assisted laparoscopic pelvic surgery	RAGS, RAGS	Sujata N. et al.[14]	10.1007/s11701-018-0849-7
E2	BMC Anesthesiol (2021) RCT	Effects of sevoflurane and propofol on the optic nerve sheath diameter in patients undergoing laparoscopic gynecological surgery: a randomized controlled clinical study	LGS	Geng W. et al.[15]	10.1186/s12871-021-01243-7
E3	Anesth Pain Med (2019) RCT	Optic nerve sheath diameter changes during gynecologic surgery in the Trendelenburg position: comparison of propofol-based total intravenous anesthesia and sevoflurane anesthesia	RAGS	Lee YY. et al.[16]	10.17085/apm.2019.14.4.393
E4	Biomed Res Int (2019) RCT	Kim Y, Choi S, Kang S, Park B. Propofol Affects Optic Nerve Sheath Diameter Less than Sevoflurane during Robotic Surgery in the Steep Trendelenburg Position	RARP	Kim Y. et al.[10]	10.1155/2019/5617815
E5	BMC Anesthesiol (2018) RCT	Propofol attenuates the increase of sonographic optic nerve sheath diameter during robot- assisted laparoscopic prostatectomy: a randomized clinical trial	RARP	Yu J. et. al.[17]	10.1186/s12871-018-0523-7

DOI, Digital Object Identifier; RAGS, Robotic-Assisted Gynecologic Surgery; RARC, Robotic-Assisted Radical Cystectomy; LGS, Laparoscopic Gynecologic Surgery; RARP, Robotic-Assisted Radical Prostatectomy; RCT, Randomized Clinical Trail.

Table 2 Demographic data.

	N total	N PROP	N SEVO	Age (years) PROP Mean ± SD	Age (years) SEVO Mean ± SD	Weight (kg) PROP Average ± SD	Weight (kg) SEVO Average ± SD
E1	49	25 (1 ♀)	24 (1 ♀)	62.88 ± 8.14	65.33 ± 8.51	72.56 ± 9.78	78.54 ± 14.84
E2	110	55 ♀	55 ♀	40.53 ± 1.08	41.15 ± 10.26	59 (54.5, 63)	56 (51.9, 60)
E3	50	25 ♀	25♀	45 ± 13.80	44 ± 11.90	58 ± 6.80	56 ± 9.80
E4	32	16 ♂	16 ♂	64.38 ± 7.86	68.44 ± 7.97	69.38 ± 10.25	66.69 ± 8.65
E5	36	18 ♂	18 ♂	66.1 ± 7.20	63.6 ± 7.90	72.3 ± 6.50	69.80 ± 10.60

PROP, Propofol; SEVO, Sevoflurane; SD, Standard deviation; ♀, Female; ♂, Male.

E3, lower mean ages were observed in the propofol and sevoflurane groups compared to the other articles.

Anesthetic and surgical data were recorded during the perioperative period following the parameters: fluid volume; physical status according to the American Society of Anesthesiology (ASA); Peak Inspiratory Pressure (PIP); Blood Pressure (BP); end-tidal carbon dioxide ($ETCO_2$); end-tidal effect-site concentration (Ce); incline (all parameters $p > 0.05$). The only exception occurred with the heart rate variable, which showed higher levels in the sevoflurane group in studies E3 and E5.

The ONSD of the groups are shown in Table 3. Although E1 recruited patients with console time < 5 hours, the period analyzed to search for effects on ONSD reached comparisons up to 180 minutes after anesthetic induction due to the consistency of the information provided by the included articles.

When comparing the baseline optic nerve sheath diameters at anesthetic induction in relation to the values achieved after the introduction of pneumoperitoneum and head tilt, in all articles statistical significance was reached regarding the effect of increasing ONSD, regardless of the type of anesthetic used, considering the mean values ± SD. Also in the studies, results in ONSD were found with a statistically significant difference between the groups after establishing pneumoperitoneum with carbon dioxide and the Trendelenburg position ($p < 0.05$), except for study E3.

ONSD variation over time, which exceeded the limit value of 5 mm (presumed ICP > 20 mmHg), was observed in the sevoflurane group in E1, E3, and E5.

The risk of bias assessments for each included study was directly expressed in the meta-analysis, and the decisions considering the different types of bias are presented in Figure 3.

Applying the GRADE criteria, we found moderately certain evidence that propofol probably slightly reduces intracranial pressure compared to sevoflurane (lowered once due to imprecision). Publication bias assessment was not possible since less than ten trials were included in the meta-analysis. Sensitivity and subgroup analyses were not required considering no study was assessed as a high risk of general bias.

Although E1 recruited patients with < 5 hours console time, the analyzed period used to search for effects on ONSD reached comparisons up to 180 minutes after anesthetic induction. When comparing the basal optic nerve sheath diameters in anesthetic induction concerning the values achieved after the introduction of pneumoperitoneum and head-declined position, all articles showed statistical significance regarding the effect of increasing ONSD, regardless of anesthetic type, considering the mean values ± SD. Propofol causes less elevation intracranial pressure compared to sevoflurane (mean difference: -0.23 mm, 95% CI -0.37 to -0.10; studies = 5; $I^2 = 23\%$) (Fig. 4).

A sensitivity and subgroup analysis was planned for studies with high risk of bias, however it was not necessary because no study was classified as having high risk of bias overall. Furthermore, due to the low importance of the heterogeneity found in the articles, the investigation was once again shown to be unnecessary.

Discussion

Robot-assisted prostatectomy has become the dominant surgical approach for prostate cancer treatment, mainly in developed countries. More recent data indicate that more than 85% of radical prostatectomies in the United States are performed laparoscopically or are robotically-assisted.[4] RARP - robotic-assisted radical prostatectomy — allows for many benefits when we consider oncological outcomes and perioperative complications compared to open surgery. Thus, new challenges arise concerning understanding the impact on the physiological phenomena related to the method. Despite the technique's effectiveness, research is necessary to ensure greater safety for surgical patients.

ONSD ultrasonographic measurement has been known as a simple and non-invasive surrogate instrument for ICP monitoring. A distensible subarachnoid space surrounds the retrobulbar optic nerve; therefore, the nerve sheath expands when the ICP rises.[19] Mehrpaur et al.[20] demonstrated that optic nerve sonography as a ONSD parameter is a real-time technique for detecting intracranial hypertension. A pooled sensitivity of 0.90 and pooled specificity of 0.85 were observed in the NO sonographic evaluation.[10,21]

As a technique, ocular ultrasonography can be quickly learned. Tayal et al.[22] and Sujata et al.[14] showed that, for an experienced operator, ten scans, including three abnormal scans, should be sufficient training to learn the method. At the same time, 25 ultrasounds may be necessary for new sonographers. In addition to these findings, both eyes are measured in less than 4 minutes. Just as anesthesiologists monitor a patient's cardiorespiratory condition, they can learn to handle the ultrasound device in the operating room.

Table 3 Comparative data of optic nerve sheath diameters.

Studies	POST-IND SDPROP (mm)	POST-IND SDSEVO (mm)	Ta10 min SDPROP (mm)	Ta10 min SDSEVO (mm)	Ta30 min SDPROP (mm)	Ta30 min SDSEVO (mm)	Ta60 min SDPROP (mm)	Ta60 min SDSEVO (mm)	Ta120 min SDPROP (mm)	Ta120 min SDSEVO (mm)	Ta180 min SDPROP (mm)	Ta180 min SDSEVO (mm)
E1	3.6 ± 0.3	3.5 ± 0.3	–	–	3.8	3.8	3.8	3.8	3.8	3.9	3.8 ± 0,4	4.1 ± 0.4
E2	4.06 ± 0.45	4.05 ± 0.45	4.64 ± 0.48	4.50 ± 0.29	4.77 ± 0.45	4.62 ± 0.28	4.83 ± 0.43	4.66 ± 0.28	4.82 ± 0.41	4.71 ± 0.28	–	–
E3	4.6	4.7	4.9	5.1	5.15	5.20	–	–	–	–	–	–
E4	3.6 ± 0.32	3.6 ± 0.16	–	–	3.73 ± 0.23	4.0 ± 0.23	3.6 ± 0.29	3.8 ± 0.2	–	–	3.62 ± 0.52	3.89 ± 0.3
E5	4.75 ± 0.37	4.74 ± 0.42	–	–	5.22 ± 0.34	5.42 ± 0.36	5.27 ± 0.35	5.57 ± 0.28	–	–	–	–

POST-IND, Post-anesthetic Induction; SDPROP, Sheath Diameter with Propofol; SDSEVO, Sheath Diameter with Sevoflurane; Ta, Anesthesia time.

Trends in the diameter of the optic nerve sheath were investigated at different time intervals (0.5h to 3 hours) in the five publications considered for this systematic review. No statistically significant differences were identified between the groups ($p > 0.05$) in the various variables that affect the ICP. The only exception occurred with the heart rate variable, which showed higher levels in the sevoflurane group in studies E3 and E5, with no direct correlation with the increase in MAP and its fractions.

Pneumoperitoneum causes hypercapnia, cerebrovascular dilatation, increased intracranial blood flow, and increased intracranial pressure.[23] While these effects rarely result in serious complications such as cerebral hemorrhage and edema, mild neurological complications, such as nausea, vomiting, and headaches, sometimes occur.[15,24] Pandey et al.[24] reported two cases of robotic radical cystectomy with perioperative neurological complications and documented neurological deterioration after extubation, probably due to cerebral edema. They suggested that the duration and placement be optimized. Weber et al.[25] reported postoperative visual loss due to a prolonged steep Trendelenburg position during prostatectomy. Lee et al.[16] considered that reversible neurological deficits, such as a transient ischemic attack, may not be detected due to a lack of postoperative course follow-up.

In studies E1, E3, E5, the 5 mm ONSD values measurements did not result in any adverse postoperative neurological or ophthalmological sequel. However, the absence of a specific population (with glaucoma, retinopathy, previous cerebrovascular diseases, with console time greater than 4 hours and age greater than 79 years) compromises the external validity for this population.

When applying the GRADE criteria for assessing the risk of bias in the studies, the result was categorized as a "moderate certainty of evidence". The domains named as routes due to deviations from planned interventions and bias in results selection raised some concerns. Heterogeneity was present in the data used for the meta-analysis, but the value of I^2 = 23% was regarded as unimportant (0 to 40%). Factors such as differences in patient characteristics, types of surgery, positions and angles, insufflation pressures, and the complex mechanisms for raising ICP and compensation may be considered possible causes for heterogeneity. In addition, the level of experience or skill in performing ocular sonography may affect measurement results in the ONSD. Possibly, this may explain the findings pointed out by Yu et al.[17] (2018) and Lee et al.[16] concerning larger measurements of ONSD at baseline and after anesthetic induction, reproducing high ICPs (ICP 20 mmHg and ONSD 5 mm).

Sevoflurane presents a dose-dependent effect on intrinsic cerebral vasodilation activity. The cerebral blood flow increases significantly, and, as a result, ICP may rise. On the other hand, propofol decreases cerebral metabolic rate and local blood perfusion, which causes less impact on ICP.[17] Thus, ICP increases with both anesthetics. However, with a lower impact on ONSD, propofol reached a negative mean difference of -0.23 mm (0.37 less to 0.1 less) compared to sevoflurane.

Although there were differences in anesthetic techniques, Trendelenburg angles and surgery time, heterogeneity was low.

In short, anesthetic agents can influence ICP. The results obtained by this review favor the use of anesthetic maintenance with propofol. Through the concept of indirect evidence, it is also possible to expand the recommendation for

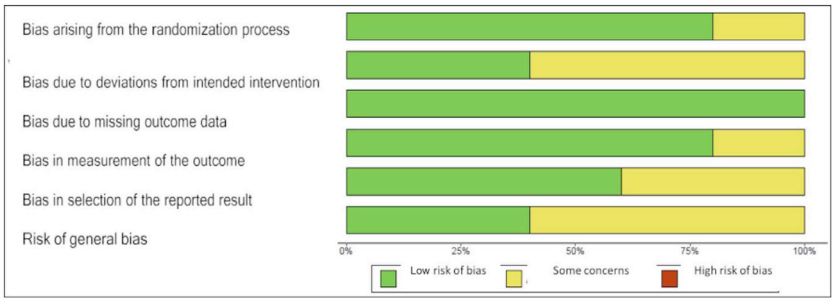

Figure 3 Risk of general bias of studies included in the systematic review.

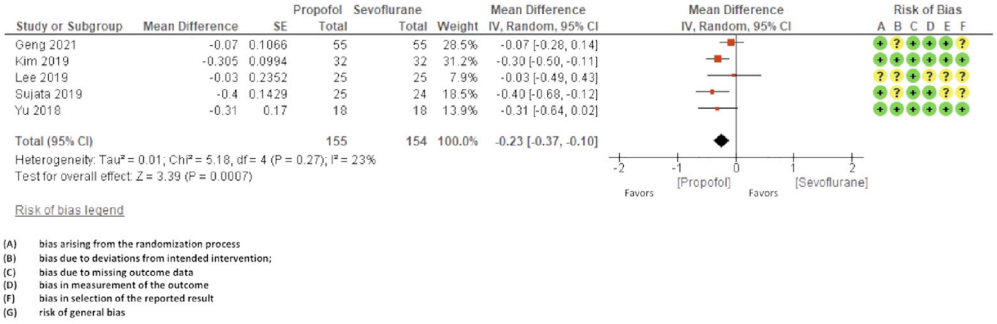

Figure 4 Forest plot of the comparison: propofol versus sevoflurane, outcome: intracranial pressure and GRADE.

the benefit of propofol to elderly patients (> 80-years-old) and/or with higher neurological and ophthalmological risks.

Conclusion

There is evidence to demonstrate, through optic nerve sheath diameter ultrasonographic analysis, that propofol causes less elevation to intracranial pressure compared to sevoflurane in the context of pure robotic and laparoscopic pelvic surgery.

There are limitations regarding the number of primary studies, which makes it impossible to broaden the discussion about the safety of minimally invasive pelvic surgeries in more specific settings, such as elderly patients, patients with ophthalmopathy, and neuropathies. Further studies must be encouraged to overcome these uncertainties.

Registry

PROSPERO: https://www.crd.york.ac.uk/PROSPERO/#CRD42023387503

https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=387503

Date of first submission: 21 February 21st, 2023

Date of registry: 4 March 4th, 2023

Authors' contributions

Rodolfo Otávio Tomaz Bertti: Conception and design of the study; Acquisition of data, analysis and interpretation of data; Drafting and revising the manuscript.

Luiz Antonio Vane: Conception and design of the study, Acquisition of data, analysis and interpretation of data; Drafting and revising the manuscript; General supervision of the study.

José Mariano Soares de Moraes: Revising the manuscript.

Paulo do Nascimento Junior: Analysis and interpretation of data; Drafting and revising the manuscript.

Lucas Fachini Vane: Analysis and interpretation of data; Drafting and revising the manuscript.

Norma Sueli Pinheiro Módolo: Revising the manuscript.

Matheus Fachini Vane: Analysis and interpretation of data; drafting and revising the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844646.

Associate Editor

Gabriel Magalhães Nunes Guimarães

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Brazilian Journal of Anesthesiology 2025;75(5): 844647

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Serratus posterior superior intercostal plane block versus thoracic paravertebral block for pain management after video-assisted thoracoscopic surgery: a randomized prospective study

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Received 4 February 2025; accepted 28 May 2025
Available online 3 June 2025

KEYWORDS
Nerve block;
Pain;
Serratus posterior superior intercostal plane block;
Thoracic paravertebral block;
Video-assisted thoracic surgery

Abstract

Background: Video-Assisted Thoracoscopic Surgery (VATS) is a minimally invasive procedure associated with faster recovery and fewer complications compared to open thoracotomy. Effective postoperative pain management is important for optimizing recovery. This study compares the analgesic efficacy of the Serratus Posterior Superior Intercostal Plane Block (SPSIPB) and Thoracic Paravertebral Block (TPVB) for postoperative pain following VATS.

Methods: In this randomized, prospective, double-blind study, 70 patients aged 18–65 years (ASA I–III) undergoing VATS were randomly assigned to Group TPVB (n = 35) or Group SPSIPB (n = 35). The primary outcome was the 24-hour postoperative Visual Analog Scale (VAS) pain score at rest. Secondary outcomes included VAS pain scores during coughing, time to first opioid request, total opioid consumption within 24 hours, patient satisfaction, and Quality of Recovery-15 (QoR-15) scores. Opioid consumption was assessed using intravenous tramadol through Patient-Controlled Analgesia (PCA), with additional morphine, if required.

Results: The mean age of the patients was 52 ± 11 years, and 64.2% were male. VAS pain scores were evaluated at 24 hours and at seven time points. There was no significant difference between groups ($p > 0.05$) except at 1 hour postoperatively, where the TPVB group had a significantly lower resting VAS score (19 [8–28] vs. 26 [18.5–33], $p = 0.031$). The total 24 hour tramadol consumption was 220 mg (135–260) in the TPVB group versus 150 mg (110–230) in the SPSIPB group ($p = 0.129$). The proportion of patients requiring additional analgesia was 25.7% in the

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https://doi.org/10.1016/j.bjane.2025.844647

TPVB group versus 28.5% in the SPSIPB group (p = 0.788). Preoperative and postoperative QoR-15 scores were similar between the groups (preoperative: 137 vs. 136, p = 0.878; postoperative: 133 vs. 132, p = 0.814). Patient satisfaction scores were also comparable (8 [7—10] vs. 9 [7—10], p = 0.789).

Conclusion: SPSIPB provides analgesic efficacy similar to TPVB for VATS, with comparable pain scores, opioid consumption, and recovery outcomes. Given its ease of use and safety profile, SPSIPB represents a promising alternative to TPVB in multimodal analgesia for minimally invasive thoracic surgery.

Introduction

Surgical intervention via Video-Assisted Thoracoscopic Surgery (VATS) is accomplished through the utilization of two to three incisions (2—3 cm) in the skin, accompanied by the deployment of an endo-camera and surgical instruments within the thoracic cavity. In recent years, VATS has gained prominence as the conventional minimally invasive surgical technique for pulmonary procedures.[1] Compared to open thoracotomy, VATS offers advantages such as expedited recovery, reduced hospital stays, and a lower risk of complications.[2] Although VATS is considered less painful than thoracotomy, both acute and chronic pain remain significant concerns following VATS surgery.[3] Thoracic Epidural Analgesia (TEA), the gold standard for pain management after thoracotomy,[4] is less commonly used for analgesia following VATS. However, given the relatively limited nature of pain associated with VATS, thoracic wall blocks may be more effective for this patient population.[3,5] The challenges associated with TEA, including difficulties in application and side effects such as hypotension, urinary retention, and nausea/vomiting, have led to the increasing acceptance of less invasive analgesic techniques for minimally invasive surgery.[6]

In recent years, regional block techniques have become an indispensable component of multimodal analgesia for postoperative pain management. Thoracic Paravertebral Block (TPVB), Erector Spinae Plane Block (ESPB), and Serratus Anterior Plane Block (SAPB) are commonly used as regional anesthesia procedures in thoracic surgery.[1,5] TPVB has long been established in the literature as the first-line regional technique for VATS surgery.[7] In addition, the Serratus Posterior Superior Intercostal Plane Block (SPSIPB), performed under Ultrasound (US) guidance, was described by Tulgar et al.[8] in 2023 and has since become a routine interfascial plane block for suitable patients undergoing thoracic surgery.[9] This block involves injection between the serratus posterior superior muscle and the rib at the level of the second or third rib.[10] The SPSIPB has been shown to provide analgesia for a range of conditions, including interscapular pain, chronic myofascial pain syndromes, scapulocostal syndrome, and shoulder discomfort.[10] The serratus posterior superior muscle attaches to the lateral edges of the second to fifth ribs and is located between the C7 and T2 vertebral levels. It receives its innervation primarily from the ventral rami of the upper intercostal nerves (T2—T5) and the lower cervical spinal nerves, reflecting its anatomical location between the cervical and upper thoracic vertebral levels.[10] The potential of SPSIPB to effectively target these nerves has been demonstrated by Tulgar et al. in a cadaver study, which demonstrated the efficacy of SPSIPB in providing analgesia for thoracic procedures, including persistent myofascial pain, breast surgery, thoracic surgery, and shoulder surgery.[8]

To date, no randomized trials have been reported in the literature comparing the efficacy of SPSIPB with TPVB for postoperative analgesia following VATS. This study aimed to evaluate the postoperative analgesic efficacy of ultrasound guided SPSIPB compared to TPVB in patients undergoing VATS, based on the hypothesis that SPSIPB is non-inferior to TPVB.

Materials and methods

Study design and patients

This study is a two-center, prospective, randomized, double-blind, and observational trial. After obtaining approval from the Ethics Committee of the Faculty of Medicine at Hitit University (approval n° 2023-181), 70 patients scheduled for VATS surgery were included in the study. Inclusion criteria were patients aged 18—65 years, with an American Society of Anesthesiologists (ASA) physical status classification of I—III, a Body Mass Index (BMI) of < 35 kg.m^{-2}, and who had read and signed the informed consent form. The study was registered on ClinicalTrials.gov with reference number NCT06219369 (January 23, 2024). The recruitment period was between January 31, 2024, and August 15, 2024, and included patients who underwent surgery at both Ankara Ataturk Sanatorium Training and Research Hospital and Hitit University Erol Olcok Training and Research Hospital.

Patients were excluded from the study if they could not communicate in Turkish, declined consent, had technical problems with the Patient-Controlled Analgesia (PCA) device, or were unable to use the Visual Analog Scale (VAS) or complete the Quality of Recovery-15 (QoR-15) questionnaire. Other exclusion criteria included allergy to local anesthetics or study-specific analgesics; pregnancy or breastfeeding; uncontrolled anxiety or substance dependence; history of thoracic surgery, trauma, neuromuscular or peripheral nerve disorders; diabetes mellitus, hepatic or renal insufficiency, or coagulation abnormalities; chronic opioid or steroid use; widespread pain; anticoagulant therapy; infection at the block insertion site; early termination of surgery; or no planned postoperative extubation.

Patient enrollment and allocation followed the Consolidated Standards of Reporting Trials (CONSORT) flow chart, as illustrated in Figure 1. Patient confidentiality was protected in accordance with the Declaration of Helsinki.

Interventions

Patients enrolled in the study were randomly assigned to the TPVB and SPSIPB groups using a computer-generated randomization table prepared by a researcher not involved in the study. To ensure blinding, each patient was assigned a random code, which was placed in a sealed envelope. The anesthetist in the operating room retrieved the appropriate sealed envelope from a file, specifying the block to be administered to each randomized patient. The patient, surgeon, and individuals overseeing postoperative pain management were unaware of the patient's group assignment. During the preoperative examination, the patients were educated on pain assessment and the implementation of Patient-Controlled Analgesia (PCA). Standard anesthesia monitoring, including noninvasive arterial blood pressure monitoring, heart rate monitoring, electrocardiography, and peripheral oxygen saturation testing, was performed once the patients were admitted to the operating room. A 20G catheter was inserted to establish intravenous access, and the time of anesthesia initiation was recorded. Premedication was 0.03 $mg.kg^{-1}$ of midazolam, followed by induction of anesthesia with 2 $mg.kg^{-1}$ of propofol and 1 $mcg.kg^{-1}$ of fentanyl after preoxygenation. After administering 0.6 $mg.kg^{-1}$ of rocuronium bromide Intravenous (IV) for muscle relaxation, intubation was performed using a left double-lumen endotracheal tube. All patients underwent radial artery cannulation for arterial monitoring and lung-protective single-lung ventilation. Mechanical ventilation was performed with a target end-tidal CO_2 of 35—40 mmHg. A mixture of O_2/air (FiO_2 = 0.50), sevoflurane (minimum alveolar concentration 0.8—1), and an IV infusion of remifentanil (adjusted according to the patient's hemodynamic data) was used to maintain anesthesia. The remifentanil infusion was planned in a dose range of 0.01–0.2 $mcg.kg^{-1}.min^{-1}$ to maintain the patient's mean arterial blood pressure within 20% of baseline. Thirty minutes before the end of surgery, all

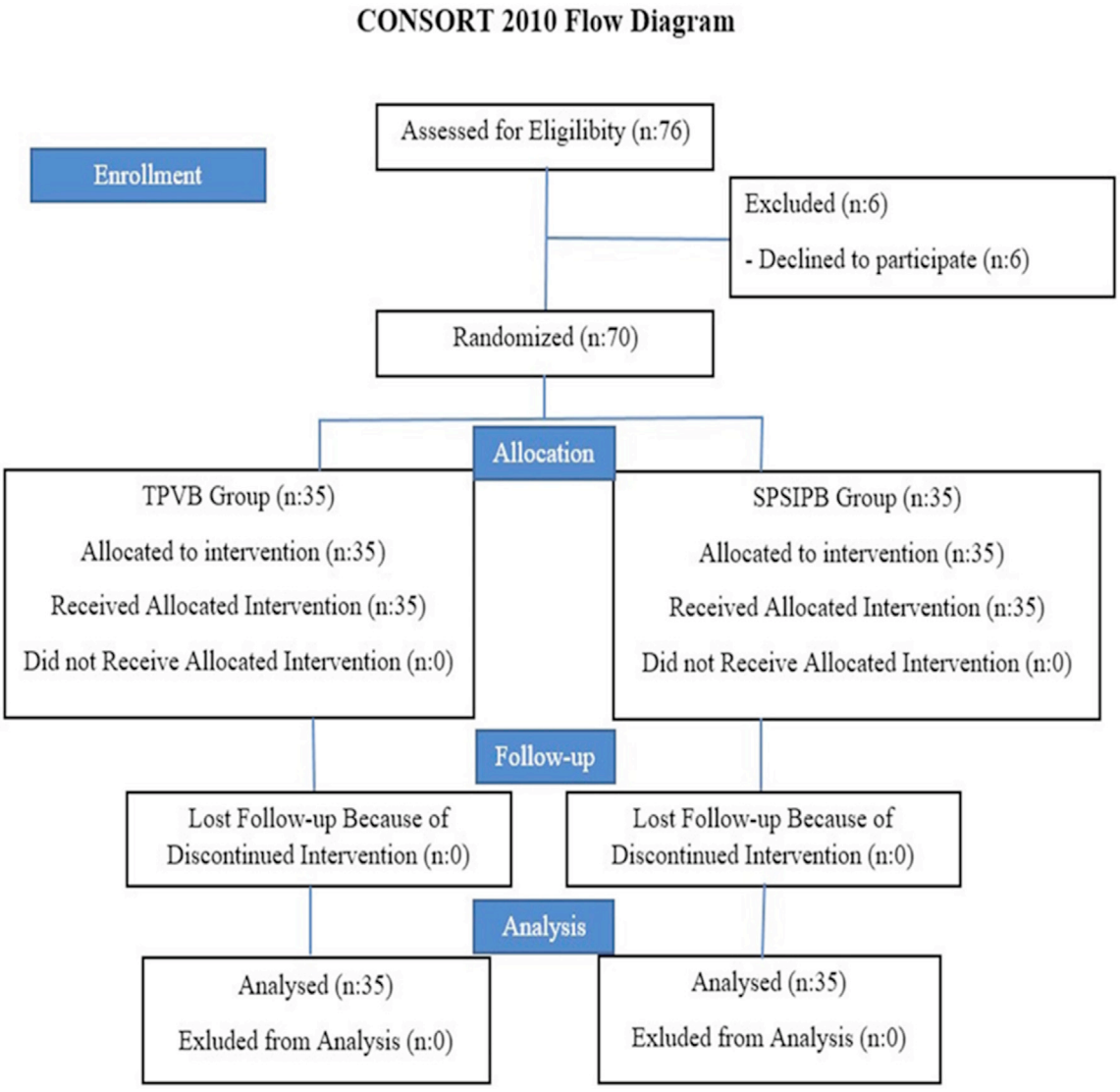

Figure 1 Consort flow chart. TPVB, Thoracic Paravertebral Block; SPSIPB, Serratus Posterior Superior Intercostal Plane Block.

patients received 1 g of paracetamol and 1 mg.kg^{-1} of tramadol for analgesia, along with 4 mg of ondansetron IV for nausea and vomiting prophylaxis. Following the conclusion of the surgical procedure and the closure of the skin incision, regional anesthesia was administered. After the specified block procedure was completed, general anesthesia was terminated, and the neuromuscular blockade was reversed with 4 mg.kg^{-1} of sugammadex. Once adequate respiratory effort was observed, patients were extubated. Postoperatively, patients were transferred to the intensive care unit for close monitoring and advanced surveillance.

The duration of the regional anesthesia, the time the block was performed, the end time of surgery, and the end time of anesthesia were all noted. The blocks were performed by anesthesiologists experienced in ultrasound and the routine application of blocks in clinical practice.

Block procedures applied

Thoracic paravertebral block

The procedure was performed using an 80 mm peripheral block needle (Braun 360°) with the patient in the lateral decubitus position in accordance with the guideline definitions.[11] A high-frequency sterile ultrasound linear probe (6—13 MHz) was placed 2—3 cm lateral to the T5 spinous process. After visualizing the transverse process, the muscular structures up to the transverse process, the paravertebral space, the internal intercostal membrane, and the pleura, the needle was advanced using the in-plane technique until it reached the paravertebral space. After confirming the accuracy of needle placement with the transverse technique, 30 mL of 0.25% bupivacaine was injected into this area (Fig. 2a).

Serratus posterior superior intercostal plane block

As described by Tulgar et al.,[8] the block was performed after completion of the surgical procedure but before the patient was awakened. A high-frequency sterile linear ultrasound probe (6—13 MHz) and an 80 mm block needle (Braun 360°) were used. The procedure was performed with the patient in the lateral decubitus position. After slight lateral displacement of the scapula, the spine of the scapula was visualized with ultrasound and the probe was moved medially. Once the end of the scapular spine was located, the probe was placed sagittally at the superior angle of the scapula and the third rib was visualized. The block needle was advanced in the craniocaudal direction, entering between the serratus posterior superior muscle and the third rib. A 2 mL saline injection was administered to confirm the correct placement of the block. After confirming the block site, 30 mL of 0.25% bupivacaine was injected (Fig. 2b).

Postoperative analgesia protocol and pain assessment

Postoperative pain monitoring was performed by a blind pain assessment nurse or the anesthetist responsible for postoperative pain management, who was unaware of the patient's group allocation. VAS was used to assess the patient's perception of pain, which was converted into a numerical format (scaled from 0 to 100 mm; 0 = no pain and 100 mm = unbearable pain). The VAS score was evaluated under both resting and active movement conditions (e.g., during coughing). VAS scores were recorded at 0, 1, 3, 6, 12, 18, and 24 hours postoperatively.

All patients received IV paracetamol at a dosage of 1 g every 8 hours, with postoperative analgesia provided through PCA using IV tramadol. Our PCA protocol was

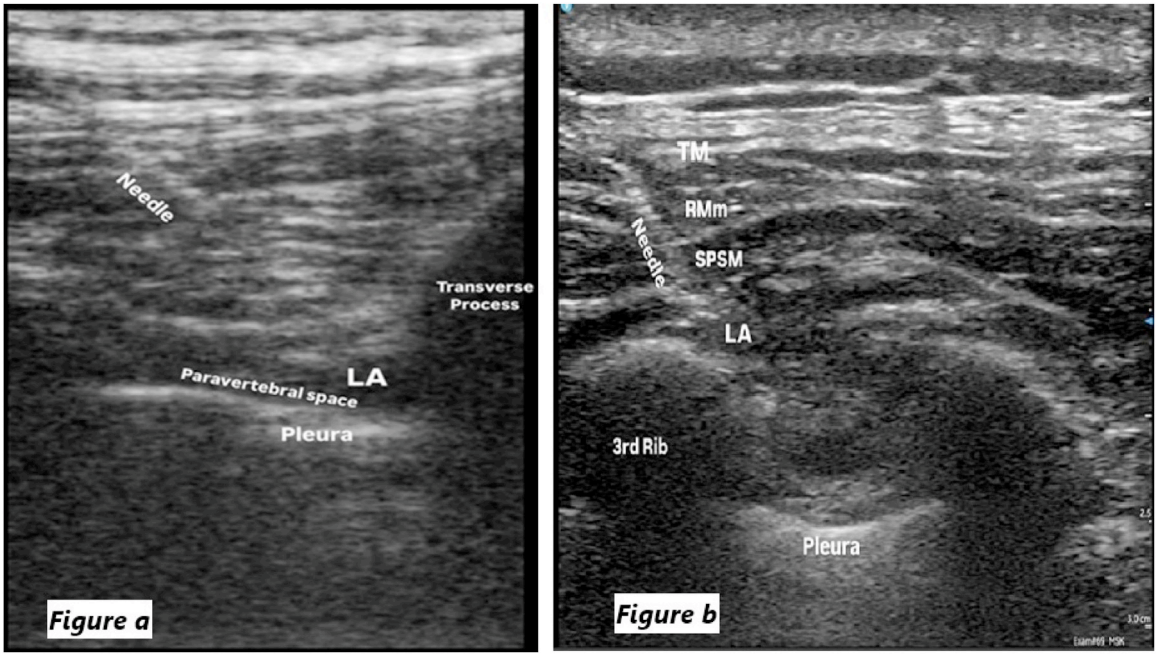

Figure 2 (a) Sono-anatomy and spread of LA during Thoracic paravertebral block (LA, Local Anesthetic). (b) Sono-anatomy and spread of LA during SPSIPB (Tm, Trapezius muscle; RMm, Rhomboid Major muscle; SPSN, Serratus Posterior Superior muscle; LA, Local Anesthetic).

designed to deliver a 10 mg bolus of tramadol on demand without baseline infusion, with a maximum dose of 400 mg/day and a lockout period of 20 minutes. Tramadol consumption was recorded for intervals of 0−1 hour, 1−12 hours, 12−24 hours, and a total of 24 hours. During the pain monitoring periods, intravenous morphine was administered as a slow infusion at a dose of 0.05 $mg.kg^{-1}$ to patients with a VAS score of 40/100 mm or above and the number of applications was documented. In addition, the total morphine consumption was converted to tramadol equivalents (morphine consumption in mg × 10 = tramadol in mg)[12] and added to the total tramadol consumed during the patient's follow-up period by PCA.

The time of the patient's first postoperative opioid analgesic requirement and the total amount of opioid analgesics administered during the first 24 hours were recorded. Nausea and vomiting during the first 24 hours were monitored using the Postoperative Nausea and Vomiting (PONV) scale: PONV1 (no nausea or vomiting), PONV2 (nausea present, no vomiting), PONV3 (one episode of vomiting or persistent nausea), PONV4 (two or more vomiting episodes or severe/continuous retching). Patients with a nausea score of 2 or higher received 4 mg of ondansetron via IV infusion. The total dose of ondansetron administered over 24 hours was recorded.

To evaluate the quality of postoperative recovery, patients completed the QoR-15 scale, a self-reported questionnaire, twice: once in the waiting area on the morning of surgery and again 24 hours postoperatively. Patient demographics were recorded before surgery, while postoperative data included the time of first oral intake, time to gas/stool passage, and the duration until the first mobilization (unassisted standing).

Outcomes

The primary outcome measure was the postoperative 24-hour VAS pain score in the TPVB and SPSIPB groups. Other outcome measures included resting and cough VAS pain scores between the two groups, opioid consumption during the first 24 hours postoperatively, side effects associated with opioid use (such as allergic reaction, nausea, and vomiting), patient satisfaction at 24 hours postoperatively, and preoperative and postoperative QoR-15 scale scores.

Sample size

The sample size for this study was calculated using G*Power software, version 3.1.9.6. The effect size employed in the calculation was derived from the study by Qiu et al., which compared SAPB with a single injection of 30 mL local anesthetic to TPVB.[13] The study by Qiu et al.[13] reported that the mean 24-hour resting VAS score for TPVB was 19 ± 11 mm and the mean cough VAS score was 35 ± 14 mm. The minimum clinically significant change in pain as measured by VAS was determined to be 13 mm, which is widely accepted in the literature.[14] Consequently, to detect a minimum difference of 13 mm between the SPSIPB and TPVB groups, a minimum sample size of 27 was calculated for each treatment arm, with a type-1 error level of 0.05 and a study power of 90% (effect size: 0.9). Given that SPSIPB is a novel block, a margin of error of approximately 20% was added for each treatment arm to account for potential deviations from the protocol. It was determined that 35 patients would be included in each treatment arm.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to evaluate the normality of the distribution of continuous variables, while the Levene test was applied to assess the homogeneity of variances. Continuous variables were presented as mean ± Standard Deviation (SD) for normally distributed data and as median (Q1−Q3) for non-normally distributed data, unless otherwise specified. Categorical variables were expressed as numbers and percentages [n (%)]. Comparisons between two independent groups were made using Student's *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables were compared using Pearson's Chi-Square test; however, when the expected frequency in any cell of the contingency table was less than 5, Fisher's exact test was used to ensure the validity of the results. Missing data were handled by complete case analysis, and no imputation methods were used. A p-value of less than 0.05 was considered statistically significant.

Graphical representations were generated using Jamovi version 2.3.21.0 software (Sydney, Australia).

Results

Between January 31, 2024, and August 15, 2024, a total of 76 patients were screened for eligibility at two participating centers. After the exclusion of six patients who declined to participate, 70 patients were randomized and included in the final analysis, with 35 patients in the TPVB group and 35 patients in the SPSIPB group (Fig. 1).

The mean age of the patients was 52 ± 11 years, and 64.2% (n = 45) were male. Table 1 presents the distribution of age, gender, BMI, ASA classification, comorbidities, anesthesia duration, and surgical duration by group. There were no statistically significant differences between the two groups regarding these parameters. Table 2 displays the VAS scores during rest and coughing at different time points. When comparing the VAS rest scores between the groups, no statistically significant differences were observed (0 hours, p = 0.688; 3 hours, p = 0.282; 6 hours, p = 0.571; 12 hours, p = 0.564; 18 hours, p = 0.934; 24 hours, p = 0.572). However, the VAS rest score at 1 hour was statistically lower in the TPVB group (p = 0.031). In analyzing the VAS cough scores, no statistically significant differences were found between the groups (0 hours, p = 0.948; 1 hour, p = 0.267; 3 hours, p = 0.434; 6 hours, p = 0.902; 12 hours, p = 0.809; 18 hours, p = 0.972; 24 hours, p = 0.737). The median amount of tramadol requested via PCA postoperatively was 200 mg in the TPVB group and 150 mg in the SPSIPB group, with no statistically significant difference in tramadol demand between the groups (p = 0.183, Table 3). Regarding requests for additional analgesia, 9 (25.7%) patients in the TPVB group and 10 (28.5%) patients in the SPSIPB group requested it within the first 24 hours postoperatively (p = 0.788). There was no

Table 1 Comparison of demographic data between groups.

	TPVB (n = 35)	SPSIPB (n = 35)	p-value
Age, year, median (Q_1 – Q_3)	57 (47.0 – 59.5)	58 (44.5 – 61.5)	0.902[b]
Sex, n (%)			0.454[δ]
Female	11 (31.43%)	14 (40.0%)	
Male	24 (68.57%)	21 (60.0%)	
BMI, kg.m^{-2}, mean ± SD	25.81 ± 3.53	26.31 ± 5.02	0.630[a]
ASA, n (%)			0.730[δ]
ASA I	4 (11.43%)	2 (5.71%)	
ASA II	17 (48.57%)	17 (48.57%)	
ASA III	14 (40.0%)	16 (45.72%)	
Comorbidities, n (%)			0.584[δ]
No	10 (28.57%)	8 (22.86%)	
Yes	25 (71.43%)	27 (77.14%)	
Anesthesia Procedure Duration (min), mean ± SD	189.9 ± 55.5	186.3 ± 55.3	0.786[a]
Surgical Procedure Duration (min), mean ± SD	159.3 ± 54.3	161.0 ± 54.6	0.897[a]

Categorical variables are expressed as either [δ] Frequency (n) or percentage (%), while continuous variables are expressed as [a] The mean ± Standard Deviation (SD) or [b] The median (Q1; 25 Percentile – Q3; 75 Percentile). Pearson's Chi-Square test or Fisher's exact test were used to compare categorical variables, while the student *t*-test or the Mann-Whitney *U* test were used to compare continuous variables. p-values that are statistically significant are in bold. TPVB, Thoracic Paravertebral Block; SPSIPB, Serratus Posterior Superior Intercostal Plane Block; BMI, Body mass index; ASA, American Society of Anesthesiologists; SD, Standard Deviation; min, minute.

statistically significant difference in the amount of additional analgesia consumed between the groups (p = 0.890). The total amount of tramadol consumed within 24 hours was a median of 220 mg in the TPVB group and 150 mg in the SPSIPB group, with no statistically significant difference (p = 0.129, Table 3). When evaluating the total amount of tramadol consumed in the first 6 hours, the TPVB group consumed less, but the difference was not statistically significant (p = 0.307).

When examining the maximum PONV scores at follow-up for the groups, no statistically significant difference was found (p = 0.743). In the TPVB group, ondansetron was administered to 1 patient (2.8%) within 24 hours, while in the SPSIPB group, it was administered to 3 patients (8.5%) (p = 0.614). After 24 hours of follow-up, patient satisfaction was assessed, and both groups reported high satisfaction levels; the TPVB group had a median score of 8 (7—10), while the SPSIPB group had a median score of 9 (7—10) (p = 0.789). The preoperative and postoperative QoR-15 score changes for the patients are detailed in Figure 3. In the TPVB group, the preoperative QoR-15 score was a median of 137, while at the 24 hour postoperative mark, it was a median of 133. In the SPSIPB group, the preoperative QoR-15 score was a median of 136 and at the end of the 24 hour postoperative period, it was a median of 132. There was no statistically significant difference in the changes in QoR-15 scores between

Table 2 Comparison of VAS data between groups.

	TPVB (n = 35) Median (Q1 – Q3)	SPSIPB (n = 35) Median (Q1 – Q3)	p-value
VAS rest, mm			
0 hour	17 (2 – 32.5)	20 (8 – 31)	0.688[a]
1 hours	19 (8 – 28)	26 (18.5 – 33)	**0.031**[a]
3 hours	18 (7.5 – 23.5)	20 (14 – 25.50)	0.282[a]
6 hours	16 (7 – 22)	18 (10 – 23)	0.571[a]
12 hours	21 (13 – 25)	22 (15 – 26)	0.564[a]
18 hours	21 (16 – 26.5)	22 (17 – 25)	0.934[a]
24 hours	19 (12 – 23)	16 (10.5 – 24)	0.572[a]
VAS cough, mm			
0 hour	31 (15.5 – 46)	32 (16 – 42)	0.948[a]
1 hours	31 (17 – 39.5)	32 (26 – 44)	0.267[a]
3 hours	28 (14.5 – 34)	26 (21.5 – 38)	0.434[βa]
6 hours	26 (16.5 – 32)	25 (16 – 34.5)	0.902[a]
12 hours	28 (22.5 – 32.5)	28 (21 – 34.5)	0.809[a]
18 hours	27 (24 – 33)	30 (24 – 32.5)	0.972[a]
24 hours	26 (19.5 – 32)	24 (18 – 34)	0.737[a]

The [a]median is used to express continuous variables (Q1; 25 Percentile-Q3; 75 Percentile). The Mann-Whitney *U* test was used for comparisons between continuous variables. p-values that are statistically significant are in bold. TPVB, Thoracic Paravertebral Block; SPSIPB, Serratus Posterior Superior Intercostal Plane Block; VAS, Visual Analog Scale.

Table 3 Comparison of analgesic consumption, patient satisfaction, and QoR scores between groups.

	TPVB (n = 35)	SPSIPB (n = 35)	p-value
PCA Tramadol Consumption, mg, median (Q_1 – Q_3)			
0 – 1 hour	20 (10 – 30)	20 (10 – 30)	0.695[b]
1 – 12 hours	60 (30 – 80)	40 (20 – 65)	0.262[b]
12 – 24 hours	120 (95 – 155)	100 (60 – 125)	0.065[b]
Total	200 (135 – 260)	150 (110 – 230)	0.183[b]
Request for Additional Analgesia, n (%)			0.788[a]
No	26 (%74.29)	25 (%71.43)	
Yes	9 (%25.71)	10 (%28.57)	
Additional Morphine, mg, median (Q_1 – Q_3)	0 (0 – 1.5)	0 (0 – 1.5)	0.890[b]
Total Tramadol Consumption, mg, median (Q_1 – Q_3)			
0 – 6 hours	50 (20 – 60)	50 (30 – 80)	0.307[b]
0 – 24 hours	220 (135 – 260)	150 (110 – 230)	0.129[b]
PONV score, max, n (%)			0.743[a]
1	34 (97.14%)	32 (91.43%)	
2	0	2 (5.71%)	
3	1 (2.86%)	1 (2.86%)	
Patient Satisfaction, median (Q_1 – Q_3)	8 (7 – 10)	9 (7 – 10)	0.789[b]
Preoperative QoR-15 score	137 (130 – 141)	136 (132 – 142)	0.878[b]
Postoperative QoR-15 score	133 (126 – 137.5)	132 (129 – 138)	0.814[b]

Categorical variables are expressed as either [a] frequency (n) or percentage (%), while continuous variables are expressed as * the mean ± Standard Deviation (SD) or [b] the median (Q1; 25 Percentile – Q3; 75 Percentile). Pearson's Chi-Square test or Fisher's exact test were used to compare categorical variables, while the student *t*-test or the Mann-Whitney *U* test were used to compare continuous variables. p-values that are statistically significant are in bold. TPVB, Thoracic Paravertebral Block; SPSIPB, Serratus Posterior Superior Intercostal Plane Block; QoR-15, Quality of Recovery-15.

the groups (p-values: preoperative 0.878, postoperative 0.814) (Table 3).

Discussion

The results of our study evaluating two different thoracic body blocks in patients undergoing VATS indicate that both TPVB and the relatively new plane block, SPSIPB, demonstrate similar analgesic and clinical outcomes.

Minimally invasive thoracic surgery significantly improves patient comfort while limiting potential complications, thus facilitating early discharge. However, despite all these advances in minimally invasive surgery, early postoperative pain and the risk of developing chronic pain due to inadequate management remain current issues.[15] To address this, multimodal analgesic techniques have significant potential due to their ability to reduce the incidence of side effects and their different mechanisms of action. The contribution of thoracic body blocks, in addition to systemic analgesia, cannot be overlooked. It is well established that TPVB provides effective postoperative analgesia.[16] There are even studies suggesting that TPVB achieves similar analgesic efficacy in thoracotomies.[17] Although TPVB is easier to perform compared to TEA, the proximity of the paravertebral space to the pleura and other vascular and nerve structures can complicate the procedure and increase complication rates. Recently, thoracic plane blocks have been widely used in clinical practice due to their ease of application and similar analgesic efficacy.[17]

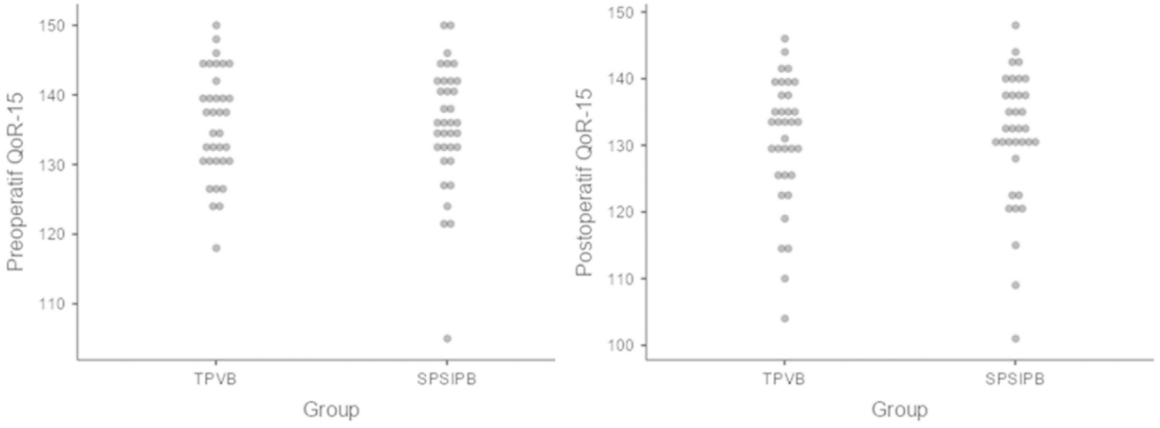

Figure 3 Graphs of preoperative and postoperative QoR-15 scores in the groups (TPVB, Thoracic Paravertebral Block; SPSIPB, Serratus Posterior Superior Intercostal Plane Block; QoR-15, Quality of Recovery-15).

In 2007, Henrik Kehlet and the Procedure-Specific Postoperative Pain Management (PROSPECT) study group classified both TEA and TPVB as Class A evidence based on randomized clinical trials.[18] A protocol for managing postoperative pain after thoracotomy, which includes recommendations for regional analgesic methods, is available through PROSPECT. Among the recommended regional analgesic techniques for VATS surgery, TPVB and ESPB ranked first, followed by SAPB.[19] ESPB has inconsistent distribution in radiological and cadaver studies, which means that different distribution and dermatomal involvement may occur in each patient. In this regard, SPSIPB may serve as an alternative to ESPB.[20] The long-held perception of TEA as the 'gold standard' is increasingly being challenged. Literature reviews have concluded that TPVB provides postoperative analgesia comparable to TEA.[21] A 2016 Cochrane study by Yeung et al. found moderate-quality evidence indicating similar analgesic efficacy between the two approaches. A protocol for managing postoperative pain after thoracotomy, including recommendations for regional analgesic methods, is available through PROSPECT.[22] Furthermore, rhomboid intercostal block has been demonstrated to be a viable alternative for this purpose.

In 2023, Tulgar et al. introduced SPSIPB, a novel planar block that may serve as an alternative for postoperative pain management after thoracotomy due to its ease of application and effective analgesia.[8] Cadaver studies have demonstrated that local anesthetics are widely used in the thoracic area. This suggests that local anesthesia may provide analgesia during VATS procedures. In a single prospective randomized study of 24 patients, Avcı et al. compared VATS patients who received SPSIPB + IV tramadol PCA with those who received IV tramadol PCA alone.[23] They found that effective analgesia was achieved in patients who received SPSIPB. At the same time, the use of SPSIPB as a component of multimodal analgesia in postoperative pain management in thoracic surgery is increasing. In their case report, Celik et al.[24] used SPSIPB as a component of multimodal analgesia in a patient with a clavicle fracture and achieved effective analgesia in the first eight hours of postoperative follow-up without the need for additional analgesic interventions. They also noted that the superficial and easily accessible nature of the SPSIPB application provided a significant advantage during its administration. In a separate study, Ciftci et al.[25] initially planned to use ESPB as a regional anesthetic technique in pediatric patients undergoing posterior instrumentation between T2 and L1 for thoracic scoliosis. However, due to difficulty distinguishing transverse processes under US in the postoperative period, they administered SPSIPB instead. During the postoperative follow-up, the researchers reported a numerical rating score below 3 and noted that no additional analgesic drugs or opioids were required. These data suggest that SPSIPB may be a viable alternative for managing multimodal analgesia in patients undergoing thoracic surgery, given its ease of administration and efficacy. In our results, the overall analgesic effect and the incidence of side effects were similar, and our QoR-15 results were comparable. This suggests that the application of SPSIPB could serve as an alternative in multimodal analgesia management for VATS surgery.

Many studies have compared TPVB with other planar blocks with quite different results. Sertcakacılar et al. showed in their study that single-injection TPVB provided superior analgesia compared to ESPB in patients undergoing single-port VATS and demonstrated a greater opioid-sparing effect by reducing morphine consumption in the TPVB group.[26] In contrast, Zengin et al. found lower VAS scores in the ESPB group compared to the TPVB group in a randomized controlled study comparing ESPB, TPVB, and the combination of ESPB + TPVB in VATS patients.[27] Similarly, Çiftçi et al. found that both ESPB and TPVB provided more effective analgesia compared to the control group in VATS patients. They also noted that ESPB had a shorter duration of performance and a higher single-puncture success rate than TPVB.[28] Other studies comparing SAPB with TPVB have indicated that SAPB can be safely and quickly used in VATS patients, providing analgesia as effective as TPVB and potentially serving as an alternative.[29] While TPVB has been compared with SPSIPB in terms of postoperative analgesic efficacy in studies of breast surgery and minimally invasive cardiac surgery,[30,31] to the best of our knowledge, there is no study in the literature comparing TPVB with SPSIPB in patients undergoing VATS. Our study results show that SPSIPB provides analgesic outcomes similar to TPVB in VATS patients. Although we did not evaluate duration, we can state that we observed a rapid application, which is in alignment with the literature. We attribute this ease of identification of anatomical structures to ultrasound, as is the case with other planar blocks.

One of the intriguing findings of our study, although not statistically significant, is that during the early postoperative period (first hour), opioid consumption was more restricted in the TPVB group, while it was lower in the SPSIPB group within 24 hours. It is well known that the analgesic effect of thoracic fascial blocks differs from that of TPVB. The dermatomal spread of regional anesthetic blocks plays an important role in their analgesic efficacy, especially in thoracic surgery. TPVB has been documented to provide analgesia by delivering local anesthetic into the paravertebral space, affecting both the dorsal and ventral rami of the spinal nerves.[17] Typically, TPVB results in unilateral segmental spread from T2 to T6, though cadaver and infrared thermography tests have demonstrated dermatomal spread from T2 to T10, varying by volume and technique used.[32,33] In contrast, the mechanism of action of the more recently introduced SPSIPB is more complicated. It provides analgesia by targeting the interfascial plane between the serratus posterior superior muscle and the intercostal nerves at the T2–T5 levels, with its effect extending along the upper intercostal and lower cervical nerves. Cadaver studies have shown spread between C7 and T7 levels.[8] Although there are limited data in the literature, a dermatomal analysis study has also reported spread between C3 and T7.[8] Unlike TPVB, which has a more predictable diffusion into the paravertebral space, SPSIPB primarily provides analgesia through interfascial diffusion, which may lead to variability in its mechanism of action. Future studies comparing the consistency of dermatomal spread between these two blocks could clarify their relative efficacy in thoracic analgesia. In TPVB, local anesthetic acts through the paravertebral space, affecting nerve roots and the epidural area.[17] This allows for faster and more effective diffusion of analgesia compared to the thoracic paravertebral area's potential space. However, the transition through the fascial pores that delimit the paravertebral space, as well as quick access to the epidural space and nerve roots, allows for rapid analgesic effects.

Conversely, in planar blocks, the diffusion of local anesthetics applied to fascial planes is thought to occur via neurovascular bundles passing through the fascial layers.[34] This could result in a more prolonged effect on dorsal and ventral nerves. Our findings suggest that limited opioid consumption at the 24 hour mark in the TPVB group supports this notion. Although the difference in opioid consumption did not achieve statistical significance, it may still hold clinical relevance by contributing to an overall opioid-sparing effect in the postoperative period. Notably, the VAS rest score was significantly lower in the TPVB group at 1 hour postoperatively, indicating a potential advantage in early-phase analgesia. However, this early difference did not persist at later time points and was not accompanied by reductions in overall opioid consumption, patient satisfaction, or quality of recovery scores. Therefore, while this short-term benefit may not alter routine practice, it could be clinically relevant in specific contexts such as early mobilization, physiotherapy, or postoperative imaging, where superior immediate pain control is advantageous. Together, these findings suggest that TPVB may offer superior early-phase analgesia, while SPSIPB may provide advantages in sustained analgesic efficacy and reduced opioid requirements over time. These observations illustrate the potential complementary roles of these techniques in multimodal analgesia strategies for thoracic surgery. Further studies with larger sample sizes and extended follow-up are warranted to corroborate these findings and elucidate their implications for long-term postoperative outcomes, including the incidence of chronic postsurgical pain.

In our study, in addition to assessing VAS scores, opioid consumption, and side effects, we also evaluated the QoR-15 questionnaire to ensure the reliability of the results. As is well known, the QoR-15 provides a multidimensional assessment of postoperative recovery, and the resulting scores are recommended as an endpoint in clinical studies focusing on postoperative pain.[35] The QoR-15 is now increasingly being used as an effective tool in postoperative applications[36] and is used to evaluate the effectiveness of Enhanced Recovery After Surgery (ERAS) protocols, which are being applied more frequently in thoracic anesthesia.[37] The QoR-15 has indicated a significant correlation between postoperative pain and postoperative recovery.

Another important consideration in the clinical application of SPSIPB is the optimal volume of local anesthetic required to achieve effective analgesia. In the present study, a volume of 30 mL of 0.25% bupivacaine was used for SPSIPB to ensure adequate interfascial spread and dermatomal coverage. However, the optimal volume for this block technique remains unclear in the literature. Recent studies, including the report by Ciftci et al.,[9] have demonstrated that lower volumes, such as 20 mL, may provide sufficient analgesic efficacy while potentially minimizing the risk of Local Anesthetic Systemic Toxicity (LAST). These findings suggest that further research is needed to determine whether reduced volumes can maintain analgesic efficacy while improving the safety profile of SPSIPB. Future randomized trials comparing different local anesthetic volumes may provide valuable evidence to optimize the balance between efficacy and safety for this novel regional technique.

Our study has several limitations. First, the absence of a control group prevented the evaluation of outcomes of both block techniques compared to a standard care group without regional anesthesia. Second, although the study was conducted at two centers, patient follow-up was standardized by assessing outcomes during the first 24 hours in the postoperative intensive care unit. However, a longer follow-up period could have provided additional insight into the prolonged effects of these blocks on acute postoperative pain. Furthermore, we did not evaluate chronic pain development. Another limitation is the lack of dermatome mapping, as sensory coverage was not evaluated after SPSIPB was performed; therefore, the extent of sensory blockade could not be confirmed. The potential influence of individual thoracic anatomy, BMI, and prior opioid exposure on block efficacy in our study population cannot be discounted; however, these variables were not analyzed in detail. Future studies should consider a stratified analysis to determine whether specific patient subgroups respond differently to SPSIPB compared to TPVB. Furthermore, although we used a standardized volume of local anesthetic, different volumes or concentrations may result in different analgesic outcomes. Finally, the duration of the sensory blockade and the evaluation of regression patterns were not assessed in this study.

Conclusion

This randomized controlled trial demonstrated that SPSIPB provides postoperative analgesia comparable to that of TPVB in patients undergoing VATS. While TPVB was associated with lower resting pain scores during the early postoperative period, no significant differences were observed between the two groups in terms of overall pain scores, total opioid consumption, patient satisfaction, or QoR-15 outcomes within the first 24 hours postoperatively.

SPSIPB appears to be a promising alternative to TPVB for postoperative analgesia in minimally invasive thoracic surgery, offering a technically simpler, safer, and comparably effective option. Its superficial anatomical location and ease of administration may make it a particularly attractive choice in multimodal analgesia strategies. Further studies with larger sample sizes, extended follow-up, and more diverse surgical populations are warranted to validate these findings and to better define the role of SPSIPB in routine clinical practice.

Declarations

Ethical approval: This study was approved by the Hitit University Faculty of Medicine Ethics Committee (Approval n° 2023-181).

ClinicalTrials.gov identifier: NCT06219369 (January 23, 2024).

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

Data availability

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

Authors' contributions

Güvenç Doğan, Onur Küçük, Selçuk Kayır and Bahadır Çiftçi: Conception and design of the study. Güvenç Doğan, Musa Zengin and Ali Alagöz: Data acquisition. Gökçe Çiçek Dal, Selçuk Kayır, Ali Alagöz and Bahadır Çiftçi: Writing/manuscript preparation. Güvenç Doğan, Musa Zengin and Gökçe Çiçek Dal: Supervision.

Funding

The study had no funding source.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

None.

Editor

Liana Azi

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Preemptive regional nerve blocks for sternotomy in pediatric cardiac surgery: a Bayesian network meta-analysis

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Received 11 March 2025; accepted 8 June 2025
Available online 20 June 2025

KEYWORDS
Cardiovascular anesthesia;
Network meta-analysis;
Pediatric anesthesia;
Perioperative care;
Regional anesthesia

Abstract

Background: Effective pain management and expedited recovery are critical in pediatric cardiac surgery. While regional anesthesia techniques provide targeted pain control and may reduce opioid use and related complications, comparative evidence among regional nerve blocks in this population is limited. This study aimed to conduct a systematic review and network meta-analysis to support clinical decision-making for optimal analgesia.

Methods: We conducted a Bayesian Network Meta-Analysis (NMA) including Randomized Controlled Trials (RCTs) of pediatric patients (0—12 years) undergoing cardiac surgery by sternotomy and receiving preemptive regional nerve blocks. Primary outcomes included pain scores, opioid consumption and extubation time. Both direct and indirect evidence were synthesized to rank interventions probabilistically. This study was registered on PROSPERO (CRD42024585785) and followed PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.

Results: The NMA incorporated 12 RCTs, comprising 969 participants, and evaluated seven regional nerve blocks. Among the techniques studied, transversus Thoracis Muscle Plane Block (TTPB) consistently ranked among the most effective for pain relief and recovery. Other blocks, including thoracic retrolaminar block and thoracic paravertebral block, also demonstrated notable performances. Adverse events were infrequent but inconsistently reported, preventing an adequate analysis.

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https://doi.org/10.1016/j.bjane.2025.844652

Conclusion: This NMA identified TTPB as a consistently top-performing technique across outcomes. These findings provide promising support for its inclusion in ERAS protocols, although further high-quality trials are needed.
Registration: PROSPERO ID: CRD42024585785.

Introduction

The perioperative management of pediatric cardiac surgery is critical for modulating the physiological response to surgical stress and influencing postoperative outcomes. Triggers such as median sternotomy, tissue trauma, and surgical drains activate the sympathetic and endocrine systems, resulting in a heightened stress response.[1] Inadequate analgesia may lead to complications like delayed recovery, respiratory compromise, psychological distress, and increased risk of chronic pain syndromes.[2-4]

Opioid-based regimens have traditionally been the cornerstone of pain management but often provide suboptimal analgesia and cause side effects such as delayed extubation, respiratory and cardiovascular issues, nausea, pruritus, and opioid dependence.[5,6] Despite advances, significant variability remains in managing postoperative pain in these patients.[7] Multimodal analgesia, central to Enhanced Recovery After Surgery (ERAS) protocols, aims to reduce opioid reliance while optimizing pain control.[4] Neuraxial anesthesia, although effective, is limited by risks like hemodynamic instability and perimedullary hematoma, especially in patients undergoing cardiopulmonary bypass and those with postoperative coagulopathy.[8] Consequently, regional nerve blocks have emerged as promising alternatives for pain control and opioid minimization, with improved recovery outcomes.[9,10] Advances in perioperative ultrasound have further enhanced their safety and efficacy in pediatric settings.[6]

Most studies have focused on individual techniques rather than direct comparisons, limiting the understanding of nerve blocks' roles within multimodal analgesia bundles and the development of evidence-based ERAS protocols.[10] This study aims to systematically evaluate and compare the efficacy of preemptive regional nerve blocks in pediatric cardiac surgery using Bayesian network meta-analysis, focusing on pain control, opioid consumption, and recovery outcomes.

Methods

This systematic review and Bayesian NMA was registered under the PROSPERO database (CRD42024585785) and adheres to the guidelines outlined in the Cochrane Handbook, following the criteria recommended by PRISMA-NMA guidelines.[11-13]

Search methods

A comprehensive literature search was conducted across multiple electronic databases, including Medline, Embase, Web of Science, and Cochrane Library, from September 4 to October 2024, without language restriction. The search strategy was initially developed and rigorously tested in Medline, then adapted for the other databases maintaining core structure and logic (Supporting Information S3). Additionally, searches of relevant clinical trial registries identified ongoing trials and study protocols. We contacted authors to inquire about unpublished results or additional data. References from included studies were screened to capture potentially relevant articles. Finally, we removed the duplicates among the identified documents using Rayyan.[14]

Eligibility criteria

Inclusion criteria

Eligible studies included Randomized Controlled Trials (RCTs) published in peer-reviewed journals that evaluated pediatric patients (0–12 years) undergoing cardiac surgery by sternotomy and receiving preemptive regional nerve blocks. Studies were required to report pain, or opioid consumption, or recovery outcomes. Studies were required to be prospectively registered in a national or international clinical trials database. There were no restrictions on the publication date for inclusion or language of publication. The eligibility criteria were designed to maximize transitivity by ensuring that included populations, interventions, and outcomes were sufficiently comparable across studies.

Exclusion criteria

We excluded non-randomized studies, studies without protocols, and studies that performed postoperative regional blocks. We also excluded studies involving patients undergoing cardiac procedures without comparable pain stimulus, such as percutaneous interventions, pacemaker implantation, or catheter-based procedures.

Interventions

Intervention group

The interventions considered included the following regional nerve blocks: Erector Spinae Plane Block (ESPB), Medial Transversus Plane Block (MTPB), Multiple Injection Costotransverse Block (MICB), Pectoral Interfacial Block (PIFB), Thoracic Paravertebral Block (TPVB), Thoracic Retrolaminar Block (TRLB), and Transversus Thoracis Muscle Plane Block (TTPB).

Comparator group

Placebo and non-placebo control groups were initially analyzed as separate nodes. However, sensitivity analyses demonstrated that Surface Under the Cumulative Ranking (SUCRA) scores, effect estimates, and the overall ranking of interventions remained consistent when these groups were merged. Therefore, for the final model, they were combined

into a single reference node ('NoBlock') to facilitate interpretation and streamline comparisons across treatment strategies.

Outcomes evaluated

The primary outcomes of interest in this review included extubation time, intraoperative fentanyl-equivalent consumption, and pain scores at 12 hours postoperatively. Secondary outcomes included pain scores at 24 hours postoperatively, postoperative mean fentanyl-equivalent consumption at 24 hours, time to the first request for rescue analgesia, length of hospital and ICU stay, and the incidence of adverse effects, including Postoperative Nausea and Vomiting (PONV) and pruritus.

In the included studies, pain scores were reported using the Modified Observer's Pain Scale (MOPS), a 10-point scale with 1-point increments; the Face, Legs, Activity, Cry, Consolability Scale (FLACC), a 10-point scale with 2-point increments; the Visual Analogue Scale (VAS); and the Numeric Rating Scale (NRS).[15]

Study selection and data extraction

Two authors (BW and GW) independently screened the titles and abstracts of all identified records based on the eligibility criteria. Full texts of potentially relevant citations were retrieved and evaluated for inclusion. Any discrepancies were resolved through consensus. Two reviewers (BW and GW) independently extracted data using a standardized spreadsheet in Google Sheets. When reported data was unavailable for direct extraction, the corresponding author was contacted for clarification. The primary data source consisted of numerical values presented in tables and figures. Data presented only in graphical format were extracted using WebPlot Digitizer version 4.7.[16]

Statistical analysis

All analyses were conducted using R software, employing a Bayesian framework

Relative treatment effects were estimated for each outcome. Binary outcomes were reported as Risk Ratios (RR), while continuous outcomes were expressed as Mean Differences (MD). Standardized Mean Differences (SMDs) were used for pain scores to account for variation in measurement scales, while Mean Differences (MDs) were calculated for fentanyl-equivalent consumption.

Network modelling and consistency

Non-informative priors were used to minimize bias, ensuring that posterior estimates were primarily driven by observed data. Various configurations of iteration counts, burn-in periods, and thinning intervals were systematically tested to optimize precision and ensure model convergence. The most suitable configuration was selected based on convergence diagnostics, including Gelman-Rubin-Brooks diagnostics, trace plots, and auto correlograms, which confirmed adequate mixing, stable oscillations around the posterior mean, and low autocorrelation. Model adequacy was evaluated through posterior predictive checks and Deviance Information Criterion (DIC), with lower DIC values indicating superior model fit.

Final simulations were conducted using Markov Chain Monte Carlo (MCMC) techniques with a sufficiently high number of iterations. Node-splitting models were employed to assess incoherence between direct and indirect evidence.

To enhance graphical representations and to improve assessment of evidence confidence, we repeated all statistical analysis on the Confidence in Network Meta-Analysis (CINeMA) web application.[17] Due to expected mean age differences between studies, we performed a covariate analysis with shared coefficients using the MetaInsight web application controlling for age for all included outcomes.[18] The MetaInsight web application was also used to enhance the graphical representation of SUCRA scores by generating Litmus rank-o-grams, which integrate SUCRA values into rank distributions to visually summarize the relative performance of each treatment.[19,20]

The methodology presented here is not exhaustive. A detailed description of statistical analysis is available in Supporting Information S1, which provides detailed instructions for interpreting our methods and findings.

Assessment of quality of evidence

Risk of bias

Two independent reviewers (BW and JA) assessed the methodological quality of the included trials using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2).[21] Any discrepancies were resolved by consensus, and if consensus could not be reached, a third reviewer (GW) was consulted.

Confidence in estimates

Confidence was evaluated using the CINeMA framework,[17] which considers within-study bias (from the Risk of Bias assessment), reporting bias (including selective outcome reporting via Egger's test and the Risk of Bias in Multi-Endpoint Network [RoB-MEN] framework), indirectness, imprecision, heterogeneity, and incoherence. Imprecision was determined by whether confidence intervals, derived from CINeMA framework, crossed the null effect or indicated opposing clinical effects.[22] Heterogeneity was assessed using prediction intervals provided by CINeMA. Predefined thresholds for minimal clinically important differences were set as follows: an SMD of 1 for pain severity,[15,23] an MD of 4 $\mu g.kg^{-1}$ for fentanyl consumption,[24] and a relative risk of 1.2 for increased adverse effects. Clinically relevant differences for key secondary outcomes were defined as a 4-hour difference for extubation time and time to rescue analgesia, a 6-hour difference for ICU stay, and 0.5 days for hospital stay. These thresholds provided a structured basis for interpreting the clinical significance of the observed effects.

GRADE assessment

The GRADE approach was employed to systematically evaluate the quality of evidence for each outcome, categorizing it into four levels: high, moderate, low, and very low.[25] This assessment incorporated insights from CINeMA, integrating considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias. By combining these elements within the structured framework of GRADE, we

provided a structured and transparent evaluation of the certainty in the estimated treatment effects.[17,21,25]

Results

Study selection

Our comprehensive literature search identified 3,771 records. After the exclusion of 469 duplicates, 3,302 unique records remained. Title and abstract screening yielded 52 records for full-text review. Ultimately, 12 studies comparing seven different regional blocks in pediatric cardiac surgery, comprising 969 participants, met the inclusion criteria.[26-37] These studies included 11 two-arms studies,[26,27,29-37] with 2 head-to-head comparisons,[26,27] and one three-arm study,[28] adding one more head-to-head comparison. No study was excluded solely due to lack of prospective registration, as all studies meeting the remaining inclusion criteria were registered and therefore eligible for inclusion (Fig. 1).

Study characteristics

The characteristics of the included studies are detailed in Supporting Information S3. The mean (Standard Deviation [SD]) sample size across the studies was 80.8 (37.2), with a mean (SD) age of 3.71 (2.88) years. Of the total participants, 50.2% were female. The mean (SD) length of surgery was 149.30 (46.5) minutes. All twelve trials were conducted between 2020 and 2024, predominantly in Egypt (58.3%), followed by China (16.7%), India (16.7%), and Turkey (8.3%).

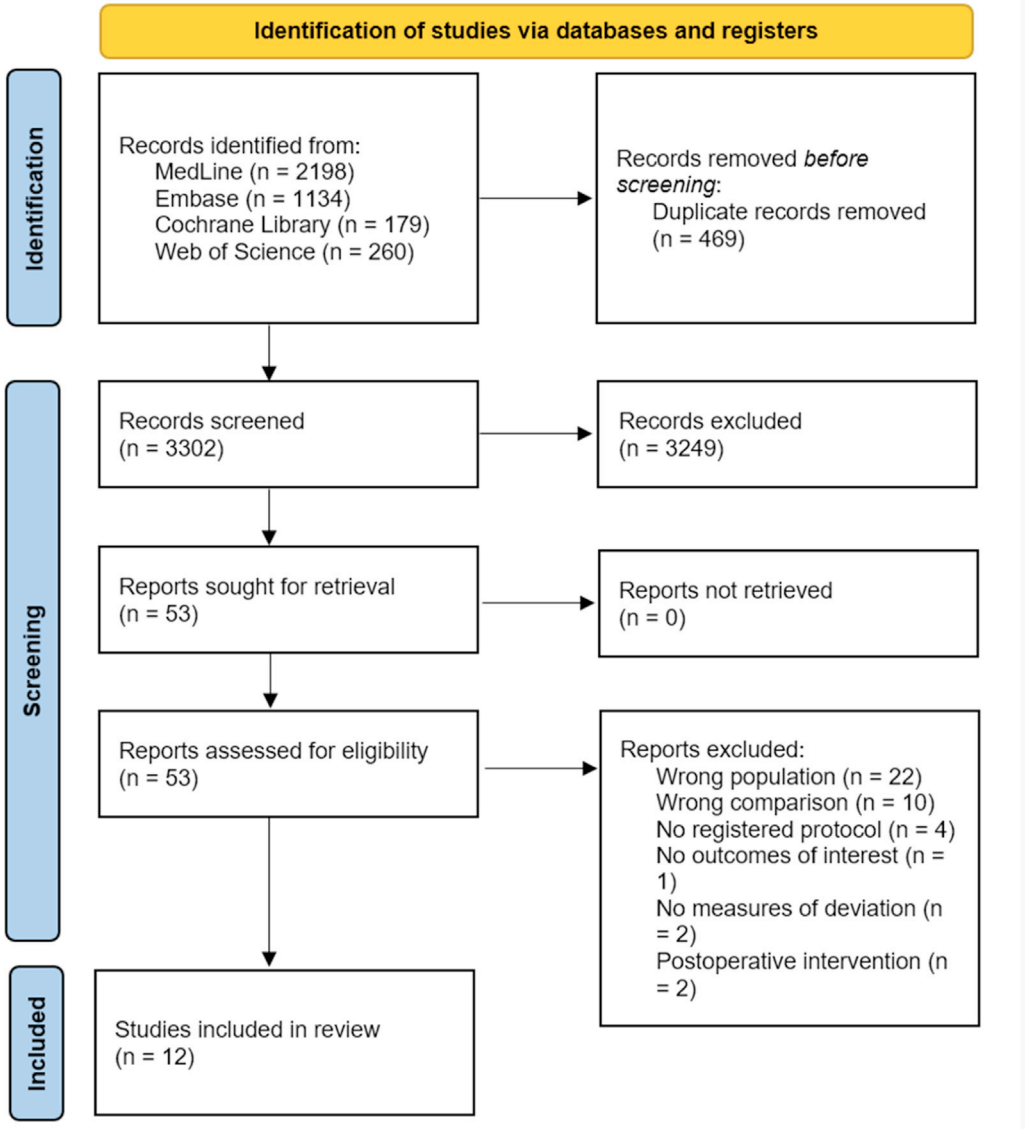


Figure 1 PRISMA flowchart.

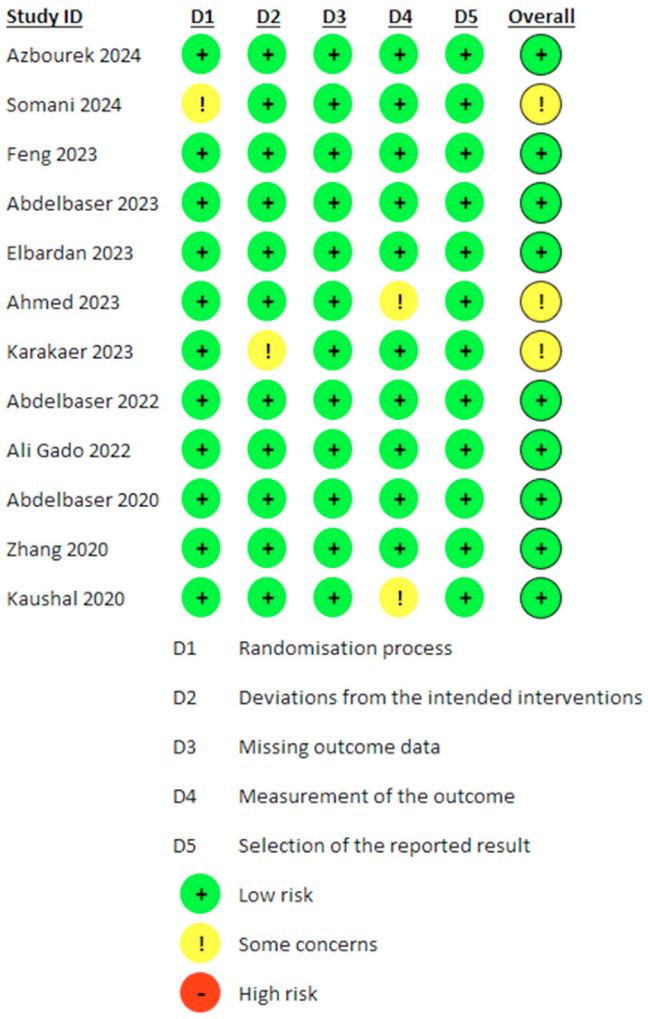


Figure 2 Risk of bias plot.

Risk of Bias

Synthesis of results

Opioid consumption Fig. 2

Post-operative cumulative fentanyl-equivalents consumption at 24 hours

Analysis included seven studies, involving 434 patients. Five studies reported fentanyl consumption, and two studies reported morphine consumption. TRLB ranked highest for reducing fentanyl-equivalent consumption (SUCRA 82.6%, MD -9.66 μg.kg^{-1}, 95% CrI -21.12 to 1.69). TTPB ranked second (SUCRA 78.7%, MD -8.61 μg.kg^{-1}, 95% CrI -20.04 to 2.83) – Table 1.

Time to rescue analgesia

Analysis included seven studies, involving 563 patients. TRLB ranked highest for delaying rescue analgesia (SUCRA 78%, MD 4.99 hours, 95% CrI -0.82 to 10.83). TTPB ranked second (SUCRA 65%, MD 3.99 hours, 95% CrI -1.85 to 9.79) – Table 1.

Intraoperative fentanyl-equivalents consumption

Analysis included twelve studies, involving 969 patients. PIFB ranked highest for reducing intraoperative fentanyl consumption (SUCRA 91.4%, MD -40.91 μg.kg^{-1}, 95% CrI -86.19 to 1.07). TTPB ranked second (SUCRA 68.2%, MD -19.37 μg.kg^{-1}, 95% CrI -54.93 to 15.01). Supporting Information S3.

Pain-scales

Pain scores were measured at rest or without specification, by FLACC scale (1 study),[29] or MOPS (10 studies).[26-28,30-33,35-37] One study reported pain scores measured by VAS but did not provide deviation measurements.[34]

Pain scores

At 12 hours

Analysis included ten studies, involving 720 patients. TTPB ranked highest for pain reduction (SUCRA 99.9%, SMD -4.39, 95% CrI -5.57 to -3.16), representing a clinically significant reduction in pain scores. ESPB, MICB and "No Block" had the lowest probability of reducing pain – Table 1.

At 24 hours

Analysis included eight studies, involving 596 patients. TTPB ranked highest for pain reduction at 24 hours (SUCRA 91.9%, SMD -1.97, 95% CrI -3.28 to -0.65). PIFB ranked second (SUCRA 78.2%, SMD -1.58, 95% CrI -2.89 to -0.28) — Table 2.

Recovery outcomes

Extubation time

Analysis included nine studies, involving 707 patients. TRLB ranked highest for reducing extubation time (SUCRA 88.4%, MD -3.47 hours, 95% CrI -7.85 to 0.91). TTPB ranked second (SUCRA 78.6%, MD -2.25 hours, 95% CrI -5.36 to 0.8). ESPB and MTPB had moderate SUCRA scores. Lower-ranked interventions like ESPB and PIFB had the lowest probability of reducing extubation time (Table 3).

ICU stay

Analysis included twelve studies, involving 791 patients. TTPB ranked highest for reducing ICU stay (SUCRA 86.9%, MD -6.93 hours, 95% CrI -11.57 to -2.35). TRLB was also likely to contribute to a reduction in ICU stay (SUCRA 80.3%, MD -6.5 hours, 95% CrI -13.11 to 0.15). Lower-ranked interventions, such as PIFB and No Block, were likely to have minimal impact on reducing ICU stay length (Table 3).

Hospital stay

The analysis included four studies, involving 410 patients. TTPB ranked highest for reducing hospital stay (SUCRA 95.5%, MD -2.5 days, 95% CrI -5.12 to 0.11). TPVB was likely to have a minimal impact on reducing Hospital Stay. Supporting Information S3.

Adverse effects

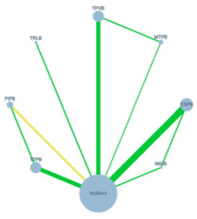
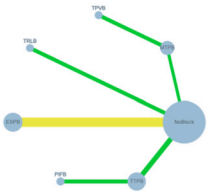
PONV Incidence

PONV was reported in nine studies, involving 779 patients. ESPB ranked highest for reducing PONV risk (SUCRA 76.9%, RR 0.41, 95% CrI 0.11 to 1.35). PIFB ranked lowest. Supporting Information S3.

Pruritus incidence

Pruritus was reported as an outcome in six studies, involving 394 patients. TPVB ranked highest for reducing pruritus (SUCRA 68.1%, RR 0.45, 95% CrI 0.05 to 3.96). ESPB ranked

Table 1 Bayesian network summary of findings: fentanyl-equivalent consumption.

Bayesian Network Meta-Analysis Summary of Findings	**Intraoperative Fentanyl consumption**	**Postoperative Fentanyl consumption at 24 hours**
Fentanyl consumption		
Patients: Pediatric Cardiac Patients, 0-12 years **Intervention:** Erector Spinae Plane Block (ESPB); Medial Transversus Plane Block (MTPB); Multiple Injection Costotransverse Block (MICB); Thoracic Paravertebral Block (TPVB); Thoracic Retrolaminar Block (TRLB); Transversus Thoracis Muscle Plane Block (TTPB). **Comparator:** No block or Placebo **Outcome:** Pain Scores at 24 hours reported in Face, Legs, Activity, Cry, Consolability Scale (FLAC) or Modified Observer's Pain Scale (MOPS). Cumulative Fentanyl consumption at 24 hours postoperatively.		

Intervention	**Intraoperative Fentanyl, MD†, (95% CrI), mcg.kg^{-1}**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**Postoperative Fentanyl MD†, (95% CrI), mcg.kg^{-1}**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**Interpretation §****
PIFB	-40.91 (-86.19, 1.07)	1st, 0.914	⊕⊕⊕◯b	67 (2)	-4.74 (-20.83, 11.62)	3rd, 0.537	⊕⊕◯◯f	30 (1)	🟢
TTPB	-19.37 (-54.93, 15.01)	2nd, 0.682	⊕⊕⊕◯d	70 (2)	-8.61 (-20.04, 2.83)	2nd, 0.787	⊕⊕⊕⊕	67 (2)	🟢
TPVB	-5.74 (-50.92, 39.22)	3rd, 0.456	⊕⊕⊕⊕	29 (1)	-1.83 (-17.92, 14.37)	5th, 0.384	⊕⊕◯◯f	29 (1)	🟡
MTPB	-4.86 (-50.18, 39.92)	4th, 0.440	⊕⊕⊕⊕	119 (2)	-1.61 (-12.93, 9.83)	6th, 0.352	⊕⊕◯◯f	52 (2)	🟡
TRLB	-3.16 (-58.53, 52.19)	5th, 0.416	⊕⊕⊕⊕	29 (1)	-9.69 (-21.12, 1.69)	1st, 0.826	⊕⊕⊕⊕	29 (1)	🟠
MICB	-2.26 (-52.42, 47.77)	6th, 0.401	⊕⊕⊕⊕	18 (1)	-	-	-		🟠
ESPB	-1.21 (-28.68, 26.63)	7th, 0.365	⊕⊕⊕⊕	19 (1)	-2.43 (-11.5, 5.16)	4th, 0.425	⊕⊕◯◯f	70 (2)	🔴
No Block	Reference	8th, 0.323	-	327 (9)	Reference	7th, 0.105	-	157 (5)	-

Cr.I, credible interval; MD, mean difference; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking.

‡ Estimates are reported as Standardized mean difference with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

† Estimates are reported as mean difference (hours) with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

‡ The ranking of interventions is determined using SUCRA scores. The top-ranked intervention is the most likely to be the best option for the outcome under consideration.

§ The interpretation of findings incorporates the effect estimate size and precision, certainty in the evidence, and the SUCRA score.

****Interpretation**: 🟢: major probability of benefit; 🟡: moderate probability of benefit; 🔴: unclear probability benefit; 🟠: inconclusive.

GRADE: ⊕⊕⊕⊕ (High) - True effect likely close to estimate; ⊕⊕⊕◯ (Moderate) - Some uncertainty; ⊕⊕◯◯ (Low) - Limited confidence; ⊕◯◯◯ (Very Low) - Effect may differ significantly.

Clinical Relevance Threshold: Fentanyl consumption reduction > 4 mcg.kg^{-1}.

Downgrading Factors According to CINeMA:

a. Downgrading for risk of bias: more than half of the comparisons involved studies with some concerns of bias.

b. Downgrading for incoherence: we downgraded when major concerns of incoherence was detected between direct and indirect evidence or when incoherence could not be measured.

c. Downgrading for heterogeneity: we downgraded when prediction intervals conflicted with confidence intervals, extending into clinically important effects in both directions. Not downgraded when prediction intervals extended into clinically unimportant effects or when prediction intervals were concordant with confidence intervals.

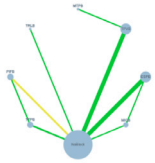
d. Downgrading for imprecision: we downgraded for imprecision when 95% confidence intervals comprised clinically relevant effects on both directions.

e. Publication bias: we downgraded for publication bias when it was detected by ROB-MEN.

f. When heterogeneity or imprecision could not be assessed by CINeMA approach, we used credible intervals as metrics for imprecision. In this case, we double downgraded for imprecision when the 95% credible intervals were both wide and comprised clinically relevant effects in both directions.

There was no significant indirectness between studies.

Table 2 Bayesian network summary of findings: pain management.

Bayesian Network Meta-Analysis Summary of Findings	**Pain At 12 Hours**	**Pain At 24 Hours**
Pain Management		
Patients: Pediatric Cardiac Patients, 0-12 years **Intervention:** Erector Spinae Plane Block (ESPB); Medial Transversus Plane Block (MTPB); Multiple Injection Costotransverse Block (MICB); Pectoral Interfacial Block (PIFB); Thoracic Paravertebral Block (TPVB); Thoracic Retrolaminar Block (TRLB); Transversus Thoracis Muscle Plane Block (TTPB). **Comparator:** No block or Placebo **Outcome:** Pain Scores at 12 hours and at 24 hours reported in Face, Legs, Activity, Cry, Consolability Scale (FLAC) or Modified Observer's Pain Scale (MOPS).		

Intervention	**Pain Scores at 12 hours SMD‡ (95% CrI)**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**Pain Scores at 24 hours SMD‡ (95% CrI)**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**Interpretation §****
TTPB	-4.39 (-5.57, -3.16)	1st ,0.996	⊕⊕⊕⊕	67 (2)	-1.97 (-3.28, -0.65)	1st, 0.919	⊕⊕⊕⊕	67 (2)	◍
PIFB	-1.41 (-2.44, -0.26)	2nd, 0.671	⊕⊕⊕◯a	70 (2)	-1.58 (-2.89, -0.28)	2nd, 0.782	⊕⊕⊕◯a	70 (2)	◍
TRLB	-1.34 (-2.64, -0.02)	3rd, 0.639	⊕⊕⊕⊕	29 (1)	-0.4 (-1.99, 1.2)	5th, 0.330	⊕⊕◯◯b,c	29 (1)	◍
TPVB	-1.21 (-2.39, -0.04)	4th, 0.597	⊕⊕⊕⊕	119 (2)	-0.61 (-1.81, 0.7)	4th, 0.431	⊕⊕⊕◯c	119 (2)	◍
MTPB	-1.21 (-2.95, 0.52)	5th, 0.588	⊕⊕⊕⊕	29 (1)	-0.41 (-1.67, 0.94)	6th, 0.320	⊕⊕⊕◯c	52 (2)	◍
ESPB	-0.17 (-0.84, 0.52)	6th, 0.220	⊕⊕⊕◯c	29 (1)	-1.08 (-2.76, 0.59)	3rd, 0.608	⊕⊕◯◯a, b	20 (1)	◍
MICB	-0.08 (-1.05, 0.9)	7th, 0.171	⊕⊕⊕◯c	28 (1)	-	-	-	-	◍
No Block	Reference	8th, 0.174	-	327 (9)	Reference	7th, 0.105	-	259 (7)	-

Cr.I, credible interval; MD, mean difference; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking.

‡ Estimates are reported as Standardized mean difference with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

† Estimates are reported as mean difference (hours) with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

‡ The ranking of interventions is determined using SUCRA scores. The top-ranked intervention is the most likely to be the best option for the outcome under consideration.

§ The interpretation of findings incorporates the effect estimate size and precision, certainty in the evidence, and the SUCRA score.

****Interpretation**: ◍: major probability of benefit; ◍: moderate probability of benefit; ◍: unclear probability benefit; ◍: inconclusive.

GRADE: ⊕⊕⊕⊕ (High) - True effect likely close to estimate; ⊕⊕⊕◯ (Moderate) - Some uncertainty; ⊕⊕◯◯ (Low) - Limited confidence; ⊕◯◯◯ (Very Low) - Effect may differ significantly.

Clinical Relevance: Pain relief - SMD ≥ 1.

Downgrading Factors According to CINeMA:

a. Downgrading for risk of bias: more than half of the comparisons involved studies with some concerns of bias.

b. Downgrading for incoherence: we downgraded when major concerns of incoherence was detected between direct and indirect evidence or when incoherence could not be measured.

c. Downgrading for heterogeneity: we downgraded when prediction intervals conflicted with confidence intervals, extending into clinically important effects in both directions. Not downgraded when prediction intervals extended into clinically unimportant effects or when prediction intervals were concordant with confidence intervals.

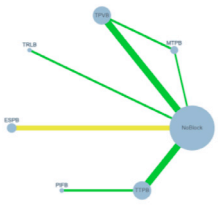
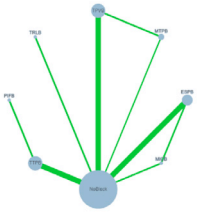
d. Downgrading for imprecision: we downgraded for imprecision when 95% confidence intervals comprised clinically relevant effects on both directions.

e. Publication bias: we downgraded for publication bias when it was detected by ROB-MEN.

f. When heterogeneity or imprecision could not be assessed by CINeMA approach, we used credible intervals as metrics for imprecision. In this case, we double downgraded for imprecision when the 95% credible intervals were both wide and comprised clinically relevant effects in both directions.

There was no significant indirectness between studies.

Table 3 Bayesian network summary of findings: postoperative recovery – extubation time and time of ICU Stay.

Bayesian Network Meta-Analysis Summary of Findings Postoperative Recovery	**Extubation Time**	**ICU Stay**
Patients: Pediatric Cardiac Patients, 0-12 years **Intervention:** Erector Spinae Plane Block (ESPB); Medial Transversus Plane Block (MTPB); Multiple Injection Costotransverse Block (MICB); Pectoral Interfacial Block (PIFB); Thoracic Paravertebral Block (TPVB); Thoracic Retrolaminar Block (TRLB); Transversus Thoracis Muscle Plane Block (TTPB). **Comparator:** No block or Placebo **Outcome:** Mean Extubation Time and time of ICU Stay		

Intervention	**Extubation time, MD‡ (95% CrI), hours**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**ICU Stay, MD†, (95% CrI), hours**	**Rank, SUCRA‡**	**GRADE**	**N (RCTs)**	**Interpretation §****
TRLB	-3.47 (-7.85, 0.91)	1st, 0.884	⊕⊕⊕⊕	29 (1)	-6.5 (-12.56, -0.43)	2nd, 0.811	⊕⊕⊕⊕	29 (1)	◍
TTPB	-2.25 (-5.36, 0.8)	2nd, 0.786	⊕⊕⊕⊕	120 (3)	-6.9 (-11.21, -2.73)	1st, 0.875	⊕⊕⊕⊕	120 (3)	◍
MTPB	-0.8 (-4.34, 2.75)	3rd, 0.542	⊕⊕⊕◯c	52 (2)	-4.17 (-9.36, 0.56)	3rd, 0.596	⊕⊕⊕⊕	52 (2)	◍
TPVB	-0.21 (-3.79, 3.35)	4th, 0.418	⊕⊕⊕◯c	119 (2)	-2.58 (-7.69, 2.06)	5th, 0.501	⊕⊕⊕⊕	119 (2)	◍
No Block	Reference	5th, 0.364	-	334 (9)	Reference	8th, 0.082	-	362 (10)	-
ESPB	0.23 (-2.85, 3.37)	6th, 0.333	⊕⊕⊕◯c	63 (2)	-3.52 (-7.55, 0.67)	6th, 0.379	⊕⊕⊕⊕	91 (3)	◍
PIFB	1.65 (-3.75, 6.96)	7th, 0.169	⊕⊕⊕⊕	30 (1)	-1.09 (-8.52, 6.11)	7th, 0.241	⊕⊕⊕⊕	30 (1)	◍
MICB	-	-	-	-	-3.6 (-9.24, 2.09)	4th, 0.511	⊕⊕⊕⊕	28 (1)	◍

Cr.I, credible interval; MD, mean difference; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking.

‡ Estimates are reported as Standardized mean difference with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

† Estimates are reported as mean difference (hours) with associated credible intervals in parenthesis for likelihood of event in comparison to reference group.

‡ The ranking of interventions is determined using SUCRA scores. The top-ranked intervention is the most likely to be the best option for the outcome under consideration.

§ The interpretation of findings incorporates the effect estimate size and precision, certainty in the evidence, and the SUCRA score.

****Interpretation**: ◍: major probability of benefit; ◍: moderate probability of benefit; ◍: unclear probability benefit; ◍: inconclusive.

GRADE: ⊕⊕⊕⊕ (High) - True effect likely close to estimate; ⊕⊕⊕◯ (Moderate) - Some uncertainty; ⊕⊕◯◯ (Low) - Limited confidence; ⊕◯◯◯ (Very Low) - Effect may differ significantly.

Clinical Relevance: Extubation time - SMD ≥ 4h; ICU Stay - MD ≥ 6h.

Downgrading Factors According to CINeMA:

a. Downgrading for risk of bias: more than half of the comparisons involved studies with some concerns of bias.

b. Downgrading for incoherence: we downgraded when major concerns of incoherence was detected between direct and indirect evidence or when incoherence could not be measured.

c. Downgrading for heterogeneity: we downgraded when prediction intervals conflicted with confidence intervals, extending into clinically important effects in both directions. Not downgraded when prediction intervals extended into clinically unimportant effects or when prediction intervals were concordant with confidence intervals.

d. Downgrading for imprecision: we downgraded for imprecision when 95% confidence intervals comprised clinically relevant effects on both directions.

e. Publication bias: we downgraded for publication bias when it was detected by ROB-MEN.

f. When heterogeneity or imprecision could not be assessed by CINeMA approach, we used credible intervals as metrics for imprecision. In this case, we double downgraded for imprecision when the 95% credible intervals were both wide and comprised clinically relevant effects in both directions.

There was no significant indirectness between studies.

second (SUCRA 56.9%, RR 0.63, 95% CrI 0.08 to 4.29). TTPB ranked lowest. Supporting Information S3.

Other adverse events

Other adverse events were sparse and inconsistently documented. Isolated cases of pneumothorax, paravertebral hematoma, fever, bradycardia, hypotension, respiratory depression, reintubation, local anesthetic toxicity, and neurological deficits were assessed. Supporting Information S3 provides a detailed description of these adverse events, including absolute frequencies by intervention group.

Cumulative SUCRA scores

Figure 3 presents a comprehensive overview of comparative intervention performance by combining SUCRA data for pain management and recovery parameters.

Each bar's height corresponds to the probability that a given treatment ranks among the most effective options for its respective outcome. Interventions exhibiting taller bars across multiple domains suggest a more consistent benefit probability. However, not all interventions contributed data for every outcome. As a result, some bars may appear shorter due to incomplete outcome reporting. This limitation underscores the need for cautious interpretation, as the comparative performance of certain interventions may be underestimated due to incomplete data availability across domains. Ranking interpretation should also consider the corresponding effect sizes and their uncertainty. Further details on SUCRA calculations and individual outcome rankings, including Litmus rank-o-grams, are available in Supplementary Information S2 and S4 (Fig. 3).

Heterogeneity and transitivity evaluation

In node-splitting analyses (Supporting Information S4), only three comparisons – TTPB versus NoBlock, PIFB versus NoBlock and TTPB versus PIFB for intraoperative fentanyl consumption – showed discrepancies between direct and indirect estimates, while overall outcome heterogeneity remained low (I^2 ranged from 0% to 11%). Despite these discrepancies, we found no discernible link between the inconsistent comparisons and any clinical or methodological characteristic.

As detailed in Table 1, key effect modifiers – mean patient age (1.5–7 years), sternotomy technique, and block-specific protocols (local anesthetic type, volume, ultrasound approach and timing) – were evenly distributed across all studies, with no clear link to the inconsistent comparisons. Uniform preemptive block administration, blinded outcome assessment and standardized methodology further support the transitivity assumption.

Covariate analysis

Although our protocol initially planned for covariate adjustments in the network meta-analysis, the limited number of studies relative to the number of interventions precluded their reliable inclusion. Conducting a meta regression in this context would have increased the risk of overfitting, yielded unstable estimates with wide credible intervals, and compromised the robustness of the findings, potentially leading to misleading conclusions. The meta-regression conducted using MetaInsight web application reflected these limitations, showing inconsistent trends and wide credible intervals.[18] For instance, the direction of age-related effects differed at 12 and 24 hours, despite stable treatment rankings. This inconsistency suggested that the observed trends were not robust and could be misleading.

To avoid overinterpretation of inconclusive results, we decided not to present the age-adjusted results. Therefore, our primary conclusions were based solely on the main network meta-analysis without age adjustment.

This limitation, stemming from the paucity of available studies rather than a methodological choice, prevented an objective evaluation of age as an effect modifier. Nonetheless, mean patient age was relatively homogeneous across trials – eight studies reported means between 4.29 and 7 years, and four studies between 1.30 and 2.49 years. However, given the broad age range of 0–12 years, the potential for residual confounding by age cannot be entirely excluded and should be considered when interpreting the results.

Discussion

This network meta-analysis compared regional nerve blocks in pediatric cardiac surgery, highlighting variability in their performance across outcomes such as analgesia, opioid consumption, recovery, and adverse effects. TTPB consistently ranked among the most effective techniques for pain relief and recovery. Other blocks, such as TRLB and TPVB, also showed notable performances, particularly in pain relief and recovery metrics, suggesting their potential role in optimizing postoperative care in pediatric cardiac surgery.

Postoperative pain after cardiac surgery is multifactorial, with median sternotomy causing intense discomfort due to tissue disruption, rib retraction, and sternal manipulation. Inadequate pain control can impair respiratory function, increasing the risk of complications such as atelectasis, pneumonia, and prolonged mechanical ventilation [4] The anterior chest wall is mainly innervated by the anterior branches of intercostal nerves (T2–T6), while irritation from surgical drains and rectus abdominis involvement further contribute to pain.[38] Reducing opioid consumption, facilitating early extubation, and accelerating overall recovery rely on effectively targeting these neural pathways, particularly through regional nerve blocks.

Pediatric patients with congenital heart disease frequently require multiple surgical interventions, resulting in cumulative opioid exposure and a heightened risk of tolerance, dependence, and long-term adverse effects. Effective strategies that reduce opioid consumption while maintaining adequate analgesia are essential to optimize perioperative care, and regional anesthesia techniques have emerged as a key component of such multimodal approaches. TTPB, by targeting the anterior branches of the intercostal nerves, provides effective analgesia for the sternum and anterior chest wall, making it particularly beneficial in managing pain after median sternotomy. TRLB involves the injection of local anesthetic into the retrolaminar plane, adjacent to the dorsal surface of the thoracic vertebrae, allowing for spread to the paravertebral space and resulting in analgesia of the posterior and lateral thoracic wall.

Early extubation is a critical postoperative objective, associated with reduced cardiopulmonary complications, shorter Intensive Care Unit (ICU) stays, and improved hemodynamic stability.[39] Spontaneous breathing diminishes the need for fluid resuscitation and inotropic support while mitigating the adverse effects of prolonged mechanical ventilation.[39,40] These benefits are particularly relevant in cavopulmonary surgeries – such as the Glenn or Fontan procedures – where maintaining spontaneous breathing enhances cardiac output.[2,39,41] However, achieving early extubation requires adequate analgesia to prevent agitation, which can increase the risk of bleeding and cardiovascular instability.[41] Moreover, inadequate analgesia can delay

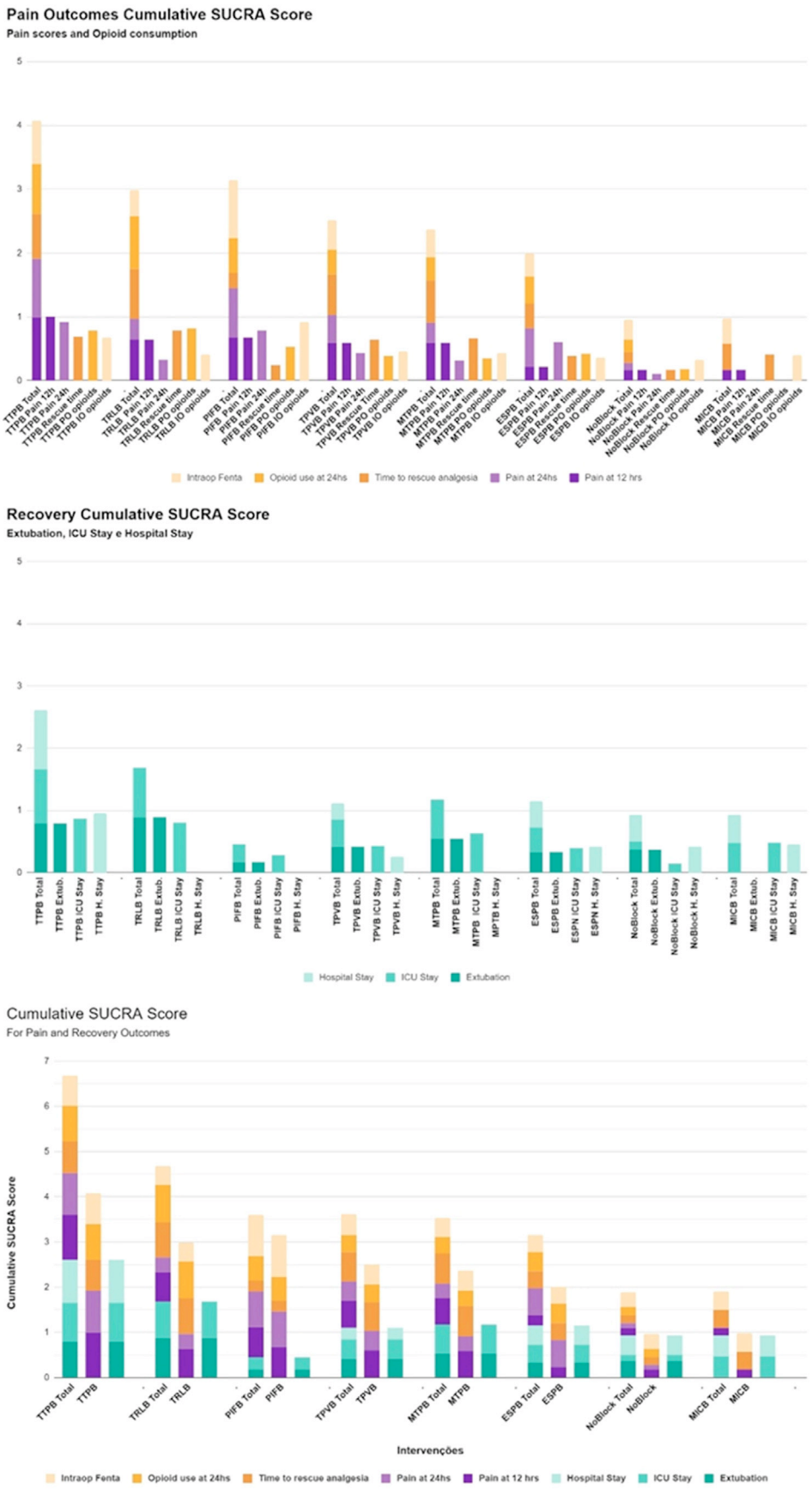


Figure 3 Cumulative SUCRA scores for pain outcomes highlight TTPB as the most effective intervention across all metrics, including pain at 12/24 hours and opioid consumption (intraoperative and at 24 hours). TRLB and PIFB demonstrate moderate efficacy, while

extubation, prolong mechanical ventilation, and increase the likelihood of complications such as ventilator-associated pneumonia. Notably, extubation failure has been linked to a tenfold increase in postoperative mortality.[39]

Beyond immediate postoperative concerns, prolonged hospitalization and delayed recovery pose additional risks, particularly in neonates and infants, whose immature brains are more susceptible to neurotoxicity.[42] Notably, over 40% of children with congenital heart defects exhibit preoperative brain injuries, and approximately one-third sustain new neurological postoperative injuries.[42,43] Therefore, optimizing analgesia and expediting recovery are critical components in mitigating these neurodevelopmental risks.

This study also underscores the distinct profiles of individual regional nerve blocks. For example, the PIFB ranked well in terms of postoperative pain management in cardiac surgery. However, the recovery metrics in this analysis – such as time to extubation, ICU stay, and hospital length of stay – reflect broader aspects of recovery beyond pain control alone. Despite effective analgesia, PIFB showed a potentially limited impact on these recovery outcomes. By targeting the intercostal nerves through the injection of local anesthetic between the pectoralis major and intercostal muscles, PIFB provides analgesia to the anterior chest wall.[44] However, its limited performance on recovery metrics suggests that PIFB may not fully address the complex factors influencing postoperative recovery following cardiac surgery.

Selecting specific interventions aims to optimize both pain relief and recovery outcomes. Techniques such as TTPB and TRLB demonstrated a favorable balance, effectively combining analgesia with improved recovery metrics. These findings highlight the importance of tailoring regional block strategies to individual patients by accounting for factors such as comorbidities, surgical approaches, and patient-specific needs. Such an individualized approach is essential for providing the best care for pediatric patients.

Although adverse effects were infrequently reported, their evaluation remains critical for assessing the safety of regional blocks.[45] The variability in adverse event reporting across studies highlights the need for standardized safety assessments in future trials. While this NMA provides comparative insights into the performance of different blocks, further data on adverse events is necessary to provide a more precise understanding of the risk-benefit balance associated with each technique.

Strengths of the study

This review has several strengths, including a pre-registered protocol, a comprehensive literature search that encompassed trial protocols, and rigorous methodology, with duplicate and independent screening and data extraction. The network meta-analysis integrated both direct and indirect evidence, while GRADE assessments evaluated the certainty of the findings. High transitivity was observed, with comparable mean ages across studies and all procedures involving sternotomies. Furthermore, low heterogeneity enhances the reliability of results. Collectively, these factors establish this study as the most comprehensive and up-to-date synthesis of evidence on regional blocks for sternotomy in pediatric cardiac surgery.

Limitations

Despite these strengths, certain limitations should be acknowledged. Most included studies were conducted in a limited geographical scope, with a concentration in a few countries (notably Egypt, India, and China), which may affect the generalizability of the findings. In addition, small sample sizes were common, further limiting generalizability and also reducing the precision of effect estimates. Additionally, the absence of age-stratified analyses in most studies may limit applicability across pediatric subgroups.[46-48] Long-term outcomes, particularly chronic postoperative pain, were insufficiently assessed, representing a gap in current evidence. Furthermore, adverse events were inconsistently reported across studies, often without clear definitions or standardized timeframes, which hinders a robust comparative safety assessment of the interventions analyzed.

Future research should address these limitations to enhance the reliability and applicability of findings. Large-scale, multicenter studies are needed to ensure adequate sample sizes, increase statistical power and reduce the risk of type II errors. Stratification by surgery type and pediatric age groups is essential to capture developmental differences in pain perception and recovery and to minimize age-related bias. Furthermore, standardized reporting of long-term outcomes, including chronic postoperative pain, should be incorporated into study protocols to provide a more comprehensive understanding of postoperative recovery. Addressing these gaps will strengthen the evidence base and advance pediatric cardiac surgery practices.

Conclusion

This network meta-analysis identified several effective regional analgesia techniques for pediatric cardiac surgery. While credibility intervals overlapped in some comparisons, TTPB consistently ranked among the most effective across multiple outcomes. These findings align with ERAS principles, supporting improved pain management, reduced opioid consumption, and enhanced recovery. By optimizing regional block strategies, this evidence may inform the refinement of perioperative protocols and advance pediatric surgical care. Nonetheless, prospective, multicenter

lower-ranked blocks, such as MICB and NoBlock, show minimal impact on pain and opioid-related outcomes. Cumulative SUCRA scores for recovery outcomes (extubation, ICU stay, hospital stay) show TTPB as the top-ranking intervention, followed by moderate performance from TRLB. Lower-ranked blocks, such as MICB and NoBlock, exhibit minimal contributions to recovery metrics. Cumulative SUCRA scores demonstrate TTPB's probabilistic better performance across different outcomes, including pain at 12/24 hours, hospital/ICU stay, and intraoperative fentanyl use. ESPB, Erector Spinae Plane Block; Fenta, Fentanyl; ICU, Intensive Care Unit; Intraop, Intraoperative; MTPB, Medial Transversus Plane Block; MICB, Multiple Injection Costotransverse Block; PIFB, Pectoral Interfacial Block; SUCRA, Surface Under the Cumulative Ranking; TPVB, Thoracic Paravertebral Block; TRLB, Thoracic Retrolaminar Block; TTPB, Transversus Thoracis Muscle Plane Block.

randomized controlled trials with age-stratified analyses are warranted – particularly to assess long-term outcomes such as chronic postoperative pain and potential neurodevelopmental effects.

Conflicts of interest

The authors declare no conflicts of interest.

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

During the preparation of this work the author(s) used ChatGPT-4.0 in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Funding

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

Associate Editor

Maria José Carmona

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Brazilian Journal of Anesthesiology 2025;75(5): 844649

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Effectiveness of the hypotension prediction index in non-cardiac surgeries: a systematic review, meta-analysis and trial sequential analysis

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Received 7 February 2025; accepted 23 May 2025
Available online 10 June 2025

KEYWORDS
Hypotension prediction index;
Intraoperative hypotension;
Meta-analysis;
Non-cardiac surgery;
Randomized controlled trials;
Trial sequential analysis

Abstract

Background: The efficacy of the Hypotension Prediction Index (HPI) for reducing Intraoperative Hypotension (IOH) among patients undergoing non-cardiac surgeries remains unclear. We aimed to perform a systematic review, meta-analysis, and trial sequential analysis to determine whether the HPI is effective for adult patients undergoing non-cardiac surgeries. This study was prospectively registered in the PROSPERO database (CRD42024571931).

Methods: PubMed, Embase, and Cochrane were systematically searched for Randomized Controlled Trials (RCTs) comparing HPI-guided therapy with standard care in non-cardiac surgeries. We computed Mean Difference (MD) and Risk Ratios (RR) for continuous and binary outcomes, respectively, with 95 % Confidence Intervals (95 % CI). Statistical analyses were performed using R Software, version 4.2.3.

Results: We included 11 RCTs, comprising a total of 789 patients, of whom 395 (50.1 %) received HPI-guided management. HPI significantly reduced the Time-Weighted Average (TWA) of Mean Arterial Pressure (MAP) < 65 mmHg (MD = -0.23 mmHg.min^{-1}; 95 % CI -0.35 to -0.10; $p < 0.01$) and the Area Under the Curve (AUC) of MAP < 65 mmHg (MD = -97.2 mmHg.min^{-1}; 95 % CI -143.4 to -50.98; $p < 0.01$). HPI also decreased the duration of MAP < 65 mmHg (MD = -16.22 min; 95 % CI -25.87 to -6.57; $p < 0.01$) and the number of hypotensive episodes per patient (MD = -3.38;

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https://doi.org/10.1016/j.bjane.2025.844649

95 % CI -5.38 to -1.37; $p < 0.01$). No significant differences were observed in the number of hypotensive events, phenylephrine use, or AKI incidence ($p > 0.05$).
Conclusion: In adult patients undergoing non-cardiac surgeries, HPI use was associated with a reduction in the duration and severity of IOH, with no significant difference for adverse events. Limitations include significant heterogeneity across studies, differences in HPI implementation, and lack of long-term outcome data.

Introduction

Intraoperative Hypotension (IOH) is a common and serious complication during surgical procedures, characterized by a significant drop in blood pressure.[1] Inadequate management of IOH can lead to detrimental effects such as organ dysfunction, prolonged hospital stay, and increased mortality.[2,3] Therefore, ensuring hemodynamic stability is essential, particularly considering recent rapid recovery protocols that aim to minimize the impact of hypotension on patient outcomes.[4]

Current strategies for managing IOH primarily rely on standard hemodynamic monitoring techniques, such as intermittent blood pressure measurements and continuous monitoring with or without advanced cardiac output measurements.[5] However, these methods are inherently reactive, responding to hypotensive episodes only after they occur. This reactive nature often results in delayed interventions and potentially preventable complications.[6] To overcome these limitations, the Hypotension Prediction Index (HPI), commercially developed by Edwards Laboratories, provides a preemptive approach to hypotension management by predicting and preventing hypotensive events before they are consistent.[7,8]

HPI systems work by analyzing over 2.6 million features from a single arterial waveform and comparing them to 133 million waveform patterns to predict hypotensive events. This comprehensive monitoring capability allows the HPI system to provide continuous predictive insights and early warnings of potential IOH up to 15 min before the event with high sensitivity and specificity.[9] Several Randomized Controlled Trials (RCTs) have demonstrated that HPI-guided monitoring can effectively reduce the duration and severity of hypotensive episodes compared to standard monitoring practices.[10–13] Therefore, we aimed to perform a systematic review, meta-analysis, and trial sequential analysis to compare the efficacy of HPI versus standard monitoring in patients undergoing non-cardiac surgeries compared to standard hemodynamic monitoring.

Methods

This systematic review and meta-analysis was conducted following Cochrane recommendations and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[14,15] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under protocol number CRD42024571931.

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met the following eligibility criteria: (I) RCT; (II) Among adult patients undergoing non-cardiac surgeries; (III) Comparing HPI with standard monitoring; and (IV) Reporting at least one outcome of interest. Exclusion criteria included studies with (I) Non-adult population (< 18 years), (II) Patients undergoing cardiac surgeries, or (III) Observational, retrospective, or unpublished studies.

Search strategy and data extraction

We systematically searched PubMed, Embase, and Cochrane Library databases from inception to July 2024, with the following search terms: "Hypotension Prediction Index", "HPI", "intraoperative hypotension", "hemodynamic management", "goal-directed therapy", "vasopressors", "postoperative hypotension", "mortality", "fluid administration", "blood products". No language restrictions were used. References from all included studies, previous systematic reviews and meta-analyses were also manually searched to identify any additional studies. Two authors (V.F., I.Q.) independently extracted data from the selected studies. A template was developed for data extraction of relevant items, including study details (first author, publication year, study design, sample size, type of surgery), participants baseline characteristics (population characteristics, age, sex, ASA physical status), intervention (HPI protocol), control (type of monitorization), and outcome measures. Disagreements were resolved by consensus. Other databases such as Web of Science and Scopus were not included due to overlap in indexed studies and feasibility constraints.

Handling of missing data

Missing data were managed through sensitivity analyses and, when possible, by contacting study authors. If data remained unavailable, an available-case analysis was conducted to minimize bias. Studies with a high proportion of missing data were flagged for quality and risk of bias assessment.

Endpoints

The outcomes were Time-Weighted Average (TWA) of Mean Arterial Pressure (MAP) < 65 mmHg, duration of MAP < 65 mmHg, Area Under the Curve (AUC) for MAP < 65 mmHg, hypotension per patient, colloids use, crystalloids use, noradrenaline use, phenylephrine use, and ephedrine use, as well as the incidence of Acute Kidney Injury (AKI), hospital

length of stay, blood loss, and the number of hypotensive events.

Risk of bias assessment

Two authors (A.T., L.B.) independently assessed the risk of bias. Disagreements were resolved with a third author (V.F.). The Cochrane Collaboration's Risk of Bias-2 (RoB-2) tool was used to evaluate the risk of bias in randomized trials. RoB-2 has 5 domains, specifically selection, performance, detection, attrition, and reporting.[16]

Publication bias was assessed by funnel-plot analysis to evaluate the symmetric distribution of trials with similar weights. No quantitative assessment of small studies or publication bias was performed due to the small number of studies included in each individual outcome.[17]

Sensitivity analyses

We performed leave-one-out sensitivity analyses for the primary outcomes to assess the impact of individual studies on the pooled estimates. Studies were sequentially excluded, and the meta-analyses recalculated to ensure the robustness of the findings. Although univariable meta-regression analyses were conducted, multivariable meta-regression was not performed due to the limited number of studies per covariate ($\kappa < 10$), which would increase the risk of overfitting.[15]

Statistical analysis

We pooled Risk Ratios (RR) and Mean Differences (MD) with 95 % Confidence Intervals (95 % CI) for categorical and continuous outcomes, respectively. DerSimonian and Laird random-effects models were employed for all endpoints due to the heterogeneity in methodology and demographics across the individual studies.[18,19] We assessed heterogeneity with I^2 statistics and Cochran *Q* test; p-values < 0.10 and $I^2 > 25$ % were considered significant for heterogeneity.[18] All statistical analyses were performed using *R* software version 4.3.2 (R foundation, Vienna, Austria). Statistical analyses were performed using R Software, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Trial sequential analysis

To evaluate whether the cumulative evidence had adequate statistical power, we performed a Trial Sequential Analysis (TSA) for the primary outcome. Our methodology included two-sided hypothesis testing, with a type I error set at 5 % and a type II error at 20 %. We established both conventional and Trial Sequential Monitoring Boundaries (TSMB) for the HPI and standard groups. The sequential analysis accounted for heterogeneity using a variance-based correction, and a random effects model was applied. A z-score curve was generated to assess the strength and reliability of the evidence. Additionally, we estimated the number of patients required in a meta-analysis to determine whether the intervention should be accepted or rejected. TSA enhances the robustness of findings by ensuring that conclusions are supported either when the sample size surpasses the required threshold or when the z-curves cross the TSMBs before reaching the necessary patient count.[20]

Results

Study selection and characteristics

In July 2024, the initial search identified 873 studies. After eliminating duplicates and applying the eligibility criteria, 31 studies were selected for full-text review, as illustrated in Figure 1.[10–13,21–27] A total of 11 studies met the inclusion criteria for the meta-analysis. The mean age of participants varied between 55 and 70.9 years. Overall, the baseline characteristics of the included studies were largely comparable, as presented in Table 1.

Hypotensive outcomes

The use of HPI was associated with significantly lower TWA < 65 mmHg (MD = −0.23 mmHg; 95 % CI −0.35 to −0.1; $p < 0.01$; I^2 = 86 %; Figure 2A) and lower AUC < 65 mmHg (MD = −97.20 mmHg.min^{-1}; 95 % CI −143.42 to −50.98; $p < 0.01$; I^2 = 91 %; Figure 2B) compared with the standard group. Additionally, HPI resulted in a reduced duration of MAP < 65 mmHg (MD = −16.22 min; 95 % CI −25.87 to −6.57; $p < 0.01$; I^2 = 90 %; Figure 2C) and a decrease in hypotension per patient (MD −3.38; 95 % CI −5.38 to −1.37; $p < 0.01$; I^2 = 72 %; Figure 3A). However, no significant differences were observed between the groups regarding the number of hypotensive events (RR=0.72; 95 % CI 0.46 to 1.12; p = 0.14; I^2 = 94 %; Figure 3B) or blood loss (MD = 69.87 mL; 95 % CI −10.27 to 150.02; p = 0.09; I^2 = 75 %; Figure 3C).

Drugs

There was no significant difference between HPI and standard care in the use of phenylephrine (MD = −0.01 mg; 95 % CI −0.17 to 0.15; p = 0.91; I^2 = 0 %; Figure 4A) or noradrenaline (MD = 0.17 mg; 95 % CI −0.06 to 0.39; p = 0.15; I^2 = 35 %; Figure 4B) intraoperatively. HPI was associated with a lower use of crystalloids (MD = −229.15 mL; 95 % CI −412.29 to −46.01; p = 0.01; I^2 = 0 %; Figure 4C) and an increased use of colloids (MD = 142.86 mL; 95 % CI 3.71 to 282.01; p = 0.04; I^2 = 69 %; Figure 4D).

Acute kidney failure

Incidence of AKI (RR = 0.81; 95 % CI 0.48 to 1.36; p = 0.42; I^2 = 0 %; Supplementary Fig. S1) was similar between patients who underwent surgery with HPI and patients who underwent surgery with the standard monitorization.

Hospital length of stay

There were no significant differences between groups for hospital length of stay (MD = 0.12 days; 95 % CI −0.49 to 0.74; p = 0.69; I^2 = 0 %; Supplementary Fig. S2).

Sensitivity analyses

Leave-one-out sensitivity analysis for the outcome of TWA < 65 mmHg revealed consistent results after omitting each individual study. The results for the sensitivity analysis are presented in Supplementary Figure S3.

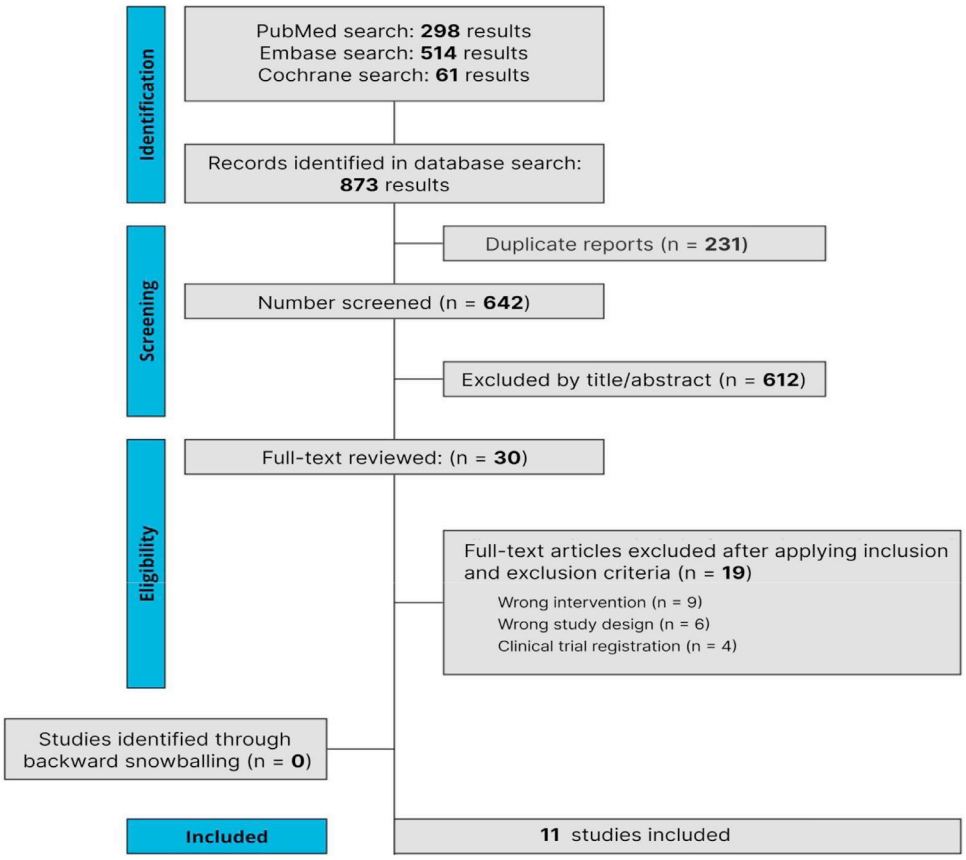

Figure 1 PRISMA flow diagram illustrating the selection process for studies included in the systematic review and meta-analysis.

Trial sequential analysis

TSA showed that there is sufficient evidence for the reduction in TWA < 65 mmHg with HPI when compared to standard monitoring, as the cumulative z-curve crosses both the TSMB and the required information size (Supplementary Fig. S4).

Risk of bias assessment

Among the 11 included RCTs, 10 were classified as having an overall low risk of bias.[10–13,21–27] However, one study was identified as having some concerns regarding the randomization process and was rated as presenting an overall moderate risk of bias (Supplementary Fig. S5).[13]

The funnel plot for TWA < 65 mmHg (Supplementary Fig. S6) showed no apparent asymmetry, suggesting no strong evidence of publication bias. This finding was further supported by Egger's test, which indicated no significant small-study effects.

Discussion

In this systematic review and meta-analysis of 11 Randomized Controlled Trials (RCTs), we evaluated the effectiveness of the Hypotension Prediction Index (HPI) compared to standard monitoring in patients undergoing non-cardiac surgeries. Our findings demonstrated that HPI significantly reduced both the incidence and duration of Intraoperative Hypotension (IOH) across diverse surgical contexts. Specifically, HPI was associated with reductions in the Time-Weighted Average (TWA) of Mean Arterial Pressure (MAP) below 65 mmHg, the Area Under the Curve (AUC) for MAP below 65 mmHg, the number of hypotensive events per patient, and crystalloid administration (approximately 230 mL less compared to standard care). Conversely, no significant differences were identified regarding adverse events such as hypertension or Acute Kidney Injury (AKI) between HPI-guided and standard care groups.[10–13,21–27]

Technological advancements in Artificial Intelligence (AI) increasingly transform clinical practice by enabling real-time analysis of patient data to anticipate adverse outcomes. HPI leverages AI to analyze arterial waveforms, predicting potential hemodynamic instability up to 15 min in advance, thereby shifting intraoperative management from reactive to proactive.[28–30] Maheshwari et al. evaluated the algorithm in adult patients over 45 years of age undergoing moderate- to high-risk non-cardiac surgery, initially finding no significant difference in hypotension duration unless clinical interventions were actively executed following HPI alerts, highlighting the importance of prompt responses to predictive warnings.[25] Similarly, Wijnberge and colleagues, in the HYPE trial involving non-cardiac surgical patients, confirmed significant reductions in hypotensive episodes associated with HPI use.[22] These findings collectively underscore the necessity of timely interventions following AI-based predictions, reinforcing the clinical value of integrating HPI technology into routine practice.

Table 1 Baseline characteristics of the included studies.

Study	N° of patients, HPI/ Stand	Male, HPI/ Stand (%)	Age, years, HPI/ Stand	ASAI and II, HPI/ Stand (%)	ASA III and IV, HPI/ Stand (%)	BMI kg.m^{-2}, HPI/ Stand	Surgery time HPI/ Stand (min)	Anesthesia time HPI / Stand (min)	Surgery Type	
									LPT HPI / Stand (%)	LPS HPI / Stand (%)
Wijnberge et al. 2020	31/29	68/45	68/62	80.65/93.10	19.35/6.90	24.2/24.7	256/259	302/300	61/45	7/17
Frassanito et al. 2023	30/30	0/0	55/59	80/ 83.33	20/16.67	23/22	N/A	298/305	50/80	50/20
Koo et al. 2022	35/33	31.4/48.5	64/63	100/100	0/0	N/A	207.9/208	N/A	100/100	0/0
Lai et al. 2024	30/30	76.7/76.7	60.17/23.3	36.7/59.7	36.7/50	22.2/21.7	517.5/491.4	N/A	N/A	N/A
Maheshwari et al. 2020	105/108	55.2/60.2	67/66	4.8/1.9	95.2/98.2	29/29	342/372	N/A	N/A	N/A
Murabito et al. 2022	20/20	50/60	69/ 70.5	45/50	55/50	25.3/25.6	207/237	N/A	N/A	N/A
Schneck et al. 2020	25/24	48/54	66/60	72/92	28/8	28.5/27.9	144/148	190/195	N/A	N/A
Sribar et al. 2023	40/40	65/60	60/59	72/92	28/8	26/28.4	81/82	169/185	N/A	N/A
Tsompa et al. 2021	49/50	53/58	66/70	86/90	14/10	27.7/27.4	207/207	240/240	N/A	N/A
Yoshikawa et al. 2024	30/30	40/47	68/67	93/93	7/7	22/21	272/316	380/316	43/43	57/57

ASA, American Society of Anesthesiologist Physical Status Classification System; BMI, Body Mass Index; LPT, Laparotomy: LPS, Laparoscopy.

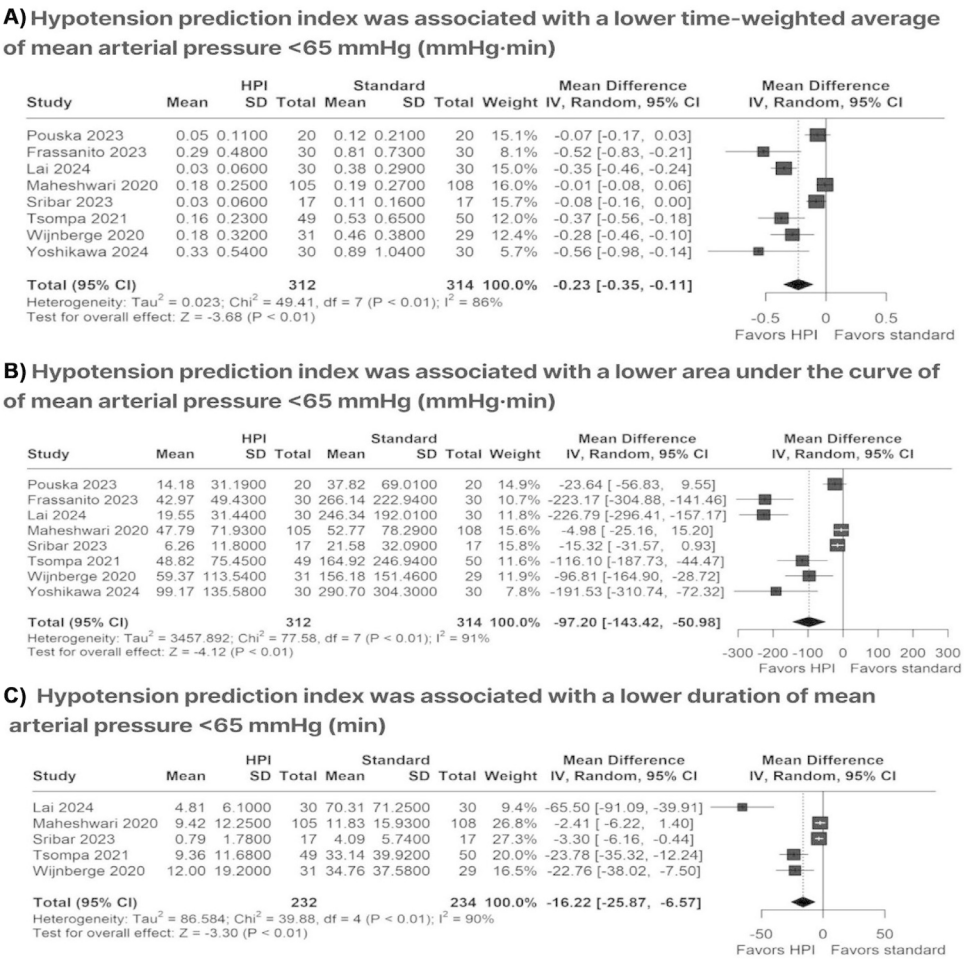

Figure 2 Forest plots comparing HPI-guided versus standard monitoring for (A) Time-Weighted Average (TWA) of MAP < 65 mmHg, (B) Area Under the Curve (AUC) for MAP < 65 mmHg, and (C) duration of MAP < 65 mmHg. MAP, Mean Arterial Pressure; TWA, Time-Weighted Average; AUC, Area Under the Curve.

Our analysis consistently demonstrated that HPI-guided management significantly reduced hypotensive episodes during surgery, corroborating prior studies that also reported significantly lower TWA of MAP below 65 mmHg compared to standard care.[22,25] Clinically, even brief episodes of hypotension are linked with increased risks of acute kidney injury, myocardial ischemia, and neurological complications.[3,6,31] Gregory et al. previously showed that incremental decreases in MAP correlate with significantly increased risks for postoperative adverse events.[32] Thus, the observed reduction of approximately 16.22 min in hypotension duration with HPI use is clinically relevant, potentially decreasing cumulative organ hypoperfusion and minimizing the risks associated with IOH, although these specific outcomes were not statistically significant in our meta-analysis.

Despite these promising findings, our meta-analysis showed substantial heterogeneity (I^2 frequently above 70 %), potentially due to differences in protocols, anesthetic techniques, surgical populations, and varying operational definitions of IOH across studies. Future subgroup analyses or meta-regression could clarify sources of heterogeneity, helping to identify specific patient populations or surgical contexts that benefit most from HPI-guided management.

Additionally, although our analysis revealed significant reductions in crystalloid administration, there was no observed significant difference in vasopressor use, and clinical outcomes such as AKI and hospital Length of Stay (LOS) remained unaffected. This absence of significant differences in relevant clinical outcomes could be attributed to the high heterogeneity and variability in patient populations and surgical scenarios included in our analysis. Moreover, in the context of Enhanced Recovery Protocols (ERAS), expecting significant improvements in outcomes from a single intervention, such as HPI-guided hypotension management, may be overly simplistic, given the multifactorial nature of postoperative complications.

Rather than functioning as a standalone solution, HPI can be effectively integrated into existing goal-directed therapy protocols, complementing other hemodynamic monitoring tools to enhance intraoperative management.[33] This proactive approach, when combined with fluid and vasopressor management strategies, can optimize tissue perfusion, reduce the risk of organ dysfunction, and ultimately improve patient outcomes.[33] Additionally, HPI can provide a probability score ranging from 0 to 100, indicating the likelihood of hypotension occurring within the next 5, 10, 15 min.[34]

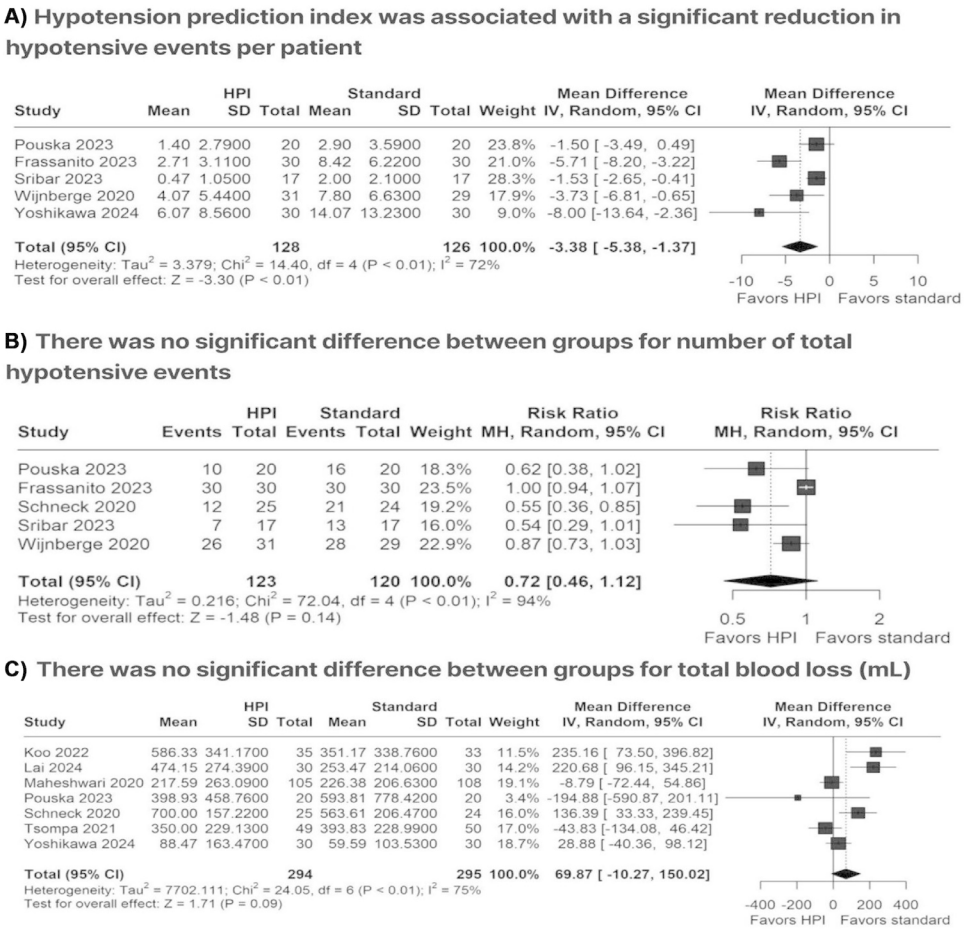

Figure 3 Forest plots showing (A) number of hypotensive episodes per patient, (B) number of hypotensive events, and (C) intraoperative blood loss.

This enables timely interventions before significant drops in MAP occur. In our meta-analysis, the HPI was associated with a reduction of 16.2 min in time spent with a MAP < 65 mmHg. This finding suggests that HPI not only reduces the occurrence of hypotension but also shortens its duration when it does occur, potentially reducing the cumulative harm from extended periods of low blood pressure.[33]

Gregory et al. showed that for every absolute maximum decrease in MAP, the odds of a major adverse event within 30 days post-surgery increased by 12 % for MAP ≤ 75 mmHg, 17 % for MAP ≤ 65 mmHg, and 26 % for MAP ≤ 55 mmHg.[32] Despite these well-established associations between IOH and adverse events, our analysis did not show significant differences for AKI between the HPI and standard care groups.[32] However, it is essential to consider the different patient profiles and surgical contexts across the included trials. Future research should focus on stratifying patient populations to determine whether HPI is more beneficial in specific subgroups, particularly those at higher risk for hemodynamic instability.

A key challenge in utilizing HPI lies in striking the right balance between preventing hypotension and avoiding overtreatment, which can result in hypertension or unnecessary fluid administration. An observational study found that patients who underwent surgery with HPI monitors had a significantly higher number of hypertensive episodes.[23] Although our meta-analysis demonstrated that HPI-guided therapy significantly reduced crystalloid use, we did not find a significant difference in vasopressor administration. These findings underscore the importance of careful calibration of interventions based on HPI predictions to avoid unnecessary fluctuations in blood pressure and excessive therapeutic measures. Overcorrecting hypotension can lead to other hemodynamic disturbances, such as hypertension, which carries its own set of risks, including postoperative bleeding and cardiovascular stress.[35]

HPI represents a significant advancement in hemodynamic management, and its evolution is paving the way for non-invasive applications.[36] Traditionally, HPI has relied on invasive arterial catheterization to obtain accurate arterial waveform data, which is essential for its predictive algorithm.[9] Recent innovations in non-invasive arterial pressure monitoring systems, such as finger-cuff technologies, are broadening HPI's clinical applicability. These non-invasive approaches demonstrate promising predictive accuracy (sensitivity and specificity of approximately 0.86 at 5 min prior to hypotension), overcoming previous limitations related to invasiveness and limited applicability highlighted by Hatib et al.[37] By integrating these non-invasive monitoring techniques with predictive HPI algorithms, clinicians may achieve proactive and precise hemodynamic management across broader clinical scenarios, enhancing patient safety and outcomes without reliance on invasive procedures.[30,38,39]

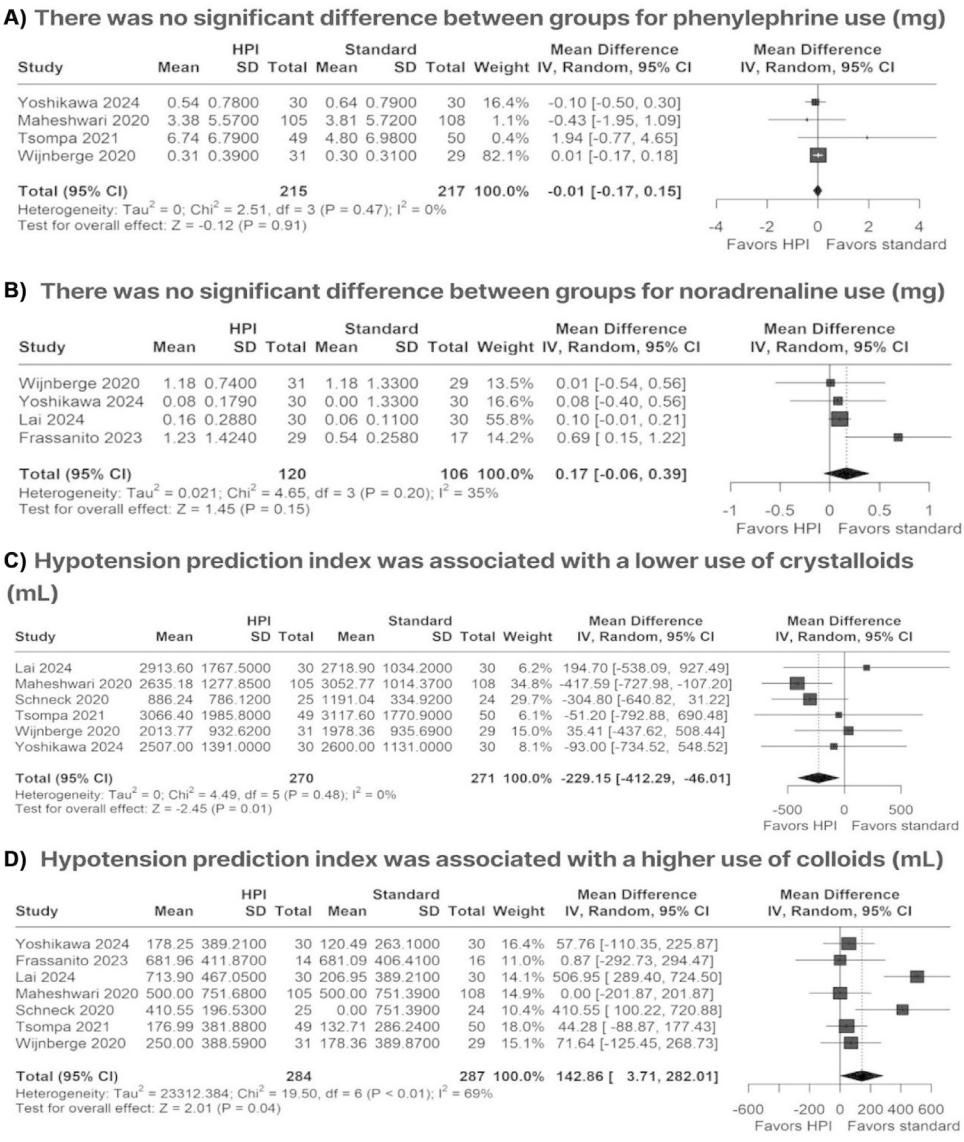

Figure 4 Forest plots comparing (A) phenylephrine use, (B) noradrenaline use, (C) crystalloid volume administered, and (D) colloid volume administered in HPI-guided versus standard care groups. HPI, Hypotension Prediction Index.

Strengths and limitations

A key strength of this meta-analysis is the comprehensive integration of recent literature evaluating HPI-guided management across varied clinical contexts, thus providing a robust synthesis of current evidence. Our analysis highlights the practical benefits of HPI implementation in reducing hypotension duration and crystalloid administration, outcomes directly linked to enhanced intraoperative management and potential clinical improvements. However, the study's hypothesis was founded on a relatively superficial exploration of existing literature concerning specific mechanisms by which HPI may influence clinical outcomes. Future studies would benefit from a deeper mechanistic understanding, clearly articulating the pathways through which HPI-guided intervention could reduce postoperative complications.

Additionally, significant heterogeneity among included trials presents limitations to the generalizability of our findings. Variability in patient populations, anesthetic practices, and definitions of hypotension contributed to the high heterogeneity observed. The limited feasibility of multivariable meta-regression further constrained our ability to explore effect modifiers. Future research using more granular subgroup analyses and robust multivariable models may help identify patients and clinical contexts that benefit most from HPI-guided management.

Conclusion

In this systematic review and meta-analysis of adult patients undergoing non-cardiac surgeries, we found that the HPI significantly reduced the incidence and duration of IOH compared to

standard monitoring. HPI was also associated with lower TWA of MAP < 65 mmHg and reduced use of crystalloids, without increasing vasopressor usage or causing adverse events.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

Vitor Felippe: Conceptualization, project management, study design, supervision of meta-analysis, data verification, manuscript writing, and editing.
Ana C. Pinho: Data extraction, risk of bias assessment, manuscript preparation.
Lucas M. Barbosa: Data extraction, figures and tables preparation.
Ivo Queiroz: Data extraction, study screening, trial sequential analysis, manuscript review.
Arthur H. Tavares: Data extraction, study screening, risk of bias assessment, manuscript editing.
Rodrigo Diaz: Critical manuscript revision.
Carlos Darcy Bersot: Statistical analysis, manuscript review, critical revision.
Jean-Louis Vincent: Critical revision for intellectual content, approval of final manuscript.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844649.

Associate Editor

Eric Benedet Lineburger

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Brazilian Journal of Anesthesiology 2025;75(5): 844662

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SHORT COMMUNICATION

Dexmedetomidine for preventing postoperative delirium in neurosurgical patients: a meta-analysis of randomized controlled trials

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Received 12 December 2024; accepted 1 June 2025
Available online 10 July 2025

KEYWORDS
Delirium;
Dexmedetomidine;
Neuroprotective agents;
Neurosurgery

Introduction

Delirium is an acute, fluctuating disturbance of attention and cognition, often with altered consciousness and perception. Postoperative Delirium (POD) commonly occurs within one week of surgery or before discharge. Its prevalence after neurosurgery ranges from 12% to 26%, averaging 19%.[1]

Although dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, is frequently recommended for POD prevention, especially in neurological surgeries, published evidence remains inconsistent. Recent studies suggest that, while dexmedetomidine may reduce the incidence of delirium in certain cases, its efficacy is not consistently observed across various surgical procedures.

Given these inconsistencies and the substantial impact of POD on patient outcomes, it is crucial to clarify the role of dexmedetomidine in preventing POD. To address this need, we performed a comprehensive meta-analysis of randomized controlled trials focusing specifically on neurosurgical patients. This study aims to evaluate the efficacy of dexmedetomidine in reducing POD incidence, offering clearer guidance for its application in neurocritical care and bridging existing gaps in the current body of knowledge.

Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[2] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The prospective meta-analysis project was registered on PROSPERO on August 18, 2024, under protocol CRD42024577345. ▫ https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=577345

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https://doi.org/10.1016/j.bjane.2025.844662

(PRISMA) guidelines.[3] The prospective meta-analysis project was registered on PROSPERO under protocol CRD42024577345. We considered studies eligible for inclusion if (1) They were RCTs; (2) Patients had undergone neurosurgical procedures; (3) They compared dexmedetomidine versus placebo; (4) They presented data regarding any of the clinical outcomes of interest. Exclusion criteria encompassed: (1) Case reports, review articles, and observational studies; (2) Lack of sufficient data for analysis.

A systematic search was conducted across PubMed, Embase, Scopus, ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials from their inception up to March, 2025. The following MeSH (Medical Subject Headings) terms were used for the MEDLINE search and were adapted as needed for other databases. The full search strategy can be found in Supplementary Table 1. The remaining relevant literature was independently screened and evaluated for inclusion in the systematic review by title and/or abstract by two authors (V.A. and B.P.A.). The first reviewer (V.A.) screened the studies for duplicates, while the second reviewer (B.P.A.) assessed the studies against the eligibility criteria. The full texts of potentially eligible studies were then retrieved and reviewed for further selection by both authors. Any disagreements were resolved through consensus between the two reviewers.

The primary outcome was the incidence of POD. We extracted the incidence rates based on the assessments and criteria utilized in each individual study. Two authors (B.P.A. and V.A.) independently extracted data according to predetermined search criteria and performed quality assessments. The risk of bias in randomized studies was evaluated using version 2 of the Cochrane Risk of Bias assessment tool.[4] The Risk Ratio (RR) was utilized to compare the intervention effect for dichotomous endpoints, presented with 95% Confidence Intervals (CIs). To assess heterogeneity, we employed the Cochrane Q test and I^2 statistics, considering $p < 0.10$ and $I^2 > 40\%$ as significant indicators of heterogeneity. We also performed sensitivity analyses with restriction of the study with the highest weight. The outcome was analyzed using a random-effects model. The statistical analysis was performed using RevMan version 8.1.1.[5]

Results

Our systematic search yielded 71 potential articles. After removing duplicates and studies that did not meet the eligibility criteria, nine studies were retrieved and reviewed in full for possible inclusion. Of these, three met all inclusion criteria and were included in our analysis, comprising a total of 526 patients (Supplementary Fig. 1). Among them, 264 patients (50.2%) received dexmedetomidine. The main characteristics of the included studies are detailed in Table 1.

The analysis of the incidence rates of POD (RR = 0.48; 95% CI 0.35–0.64; $p < 0.00001$; $I^2 = 0\%$; Fig. 1A) revealed a statistically significant reduction in the dexmedetomidine group compared to the placebo group. In the sensitivity analysis, the exclusion of the study with the highest weight (59.9%) did not significantly affect the overall result (RR = 0.49; 95% CI 0.31–0.80; $p = 0.004$; $I^2 = 0\%$; Supplementary Fig. 2). Moreover, the results illustrate a potential 52% reduction in POD risk, with an Absolute Risk Reduction (ARR) of 20.1% (95% CI 13.9%–25.1%), leading to a Number Needed to Treat (NNT) of 5 (95% CI 4–8) patients.

Among the three studies evaluated, one study[6] was found to have some concerns, specifically in the domain of bias in the selection of the reported results (Fig. 1B). The other two studies[7,8] were identified as having an overall low risk of bias across all domains. Notably, no studies were found to be at high risk of bias.

Discussion

This systematic review and meta-analysis, encompassing three studies with a total of 526 patients, is the first to assess the efficacy of dexmedetomidine in reducing POD in neurosurgical patients. The primary finding demonstrates a significant reduction in POD rates among patients treated with dexmedetomidine.

Dexmedetomidine exerts neuroprotective effects mediated by brain-derived neurotrophic factor, which inhibits Nucleotide-binding domain-Like Receptor Protein-3 (NLRP3) inflammasome, reduces macrophage infiltration, microglial migration, and neurological damage. It also modulates autophagy and decreases microtubule-associated Light Chain-3 (LC3), Beclin-1, and Nuclear Factor kappa-B (NF-κB).[9] These pathways lower pro-inflammatory cytokines, contributing to neuroinflammation control.[10]

All studies included in the meta-analysis[6-8] consistently demonstrated a lower incidence of POD in the patients who received dexmedetomidine compared to those in the placebo group. Two studies[7,8] also assessed the severity of POD in addition to its incidence. The results revealed that the dexmedetomidine group not only exhibited fewer cases but also experienced milder forms of delirium compared to the control group. These findings suggest that dexmedetomidine may offer a dual benefit in mitigating the intensity of POD.

Our findings demonstrate a statistically significant reduction in the risk of POD among patients receiving dexmedetomidine compared to those given placebo. The pooled risk ratio (RR = 0.48; 95% CI 0.35–0.64; $p < 0.00001$; $I^2 = 0\%$; Fig. 1A) indicates a 52% reduction in the incidence of delirium. This finding is further supported by the absence of significant heterogeneity among the included studies, suggesting consistency in the beneficial effects of dexmedetomidine across different patient populations and study designs.

The dosage of dexmedetomidine varies and is presented in different ways in the literature. It can be administered as a bolus (i.e., a single dose), as an infusion or as a combination of bolus followed by infusion, which is commonly continued during the postoperative period. A variable dose regimen based on the duration of surgery is also described, allowing adjustments to the dosage regimen in accordance with the anesthesiologist or patient-specific factors such as age or weight. Doses are commonly categorized as low (0–0.49 μg.kg^{-1}), medium (0.5–0.99 μg.kg^{-1}) and high ($\geq$ 1 μg.kg^{-1}).

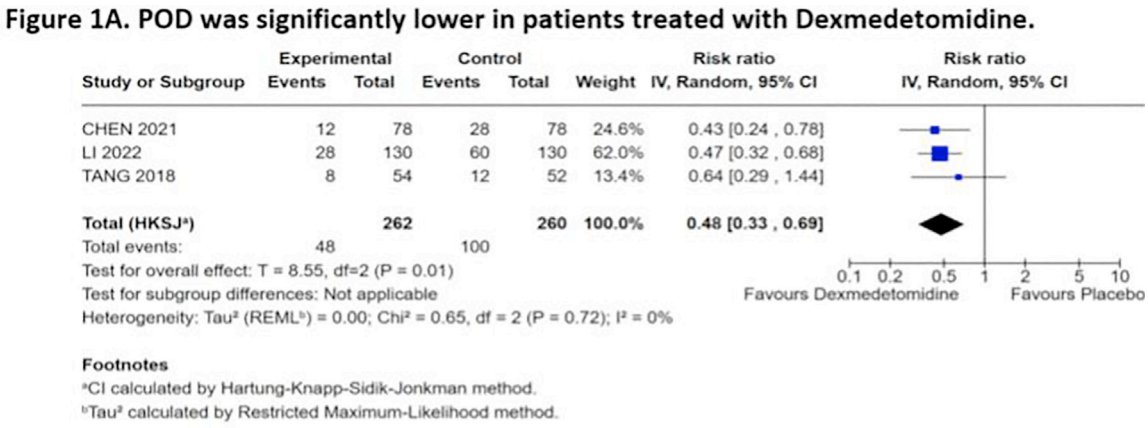
Regarding safety, across all included studies,[6-8] the main adverse events associated with dexmedetomidine administration were clinically significant bradycardia and hypotension. Nevertheless, the use of dexmedetomidine was associated with reduced mortality and shorter hospital

Table 1 Characteristics of studies included in meta-analysis.

Study	Population	No, of Patients DEX/Placebo	Female, % DEX/Placebo	ASA class (I/II/III/IV) DEX – Placebo	Delirium assessment tool[a]	DEX dosage	Surgery type
Chen 2021	Patients > 20 y who had undergone elective cranial surgery for brain tumor resection, aneurysm clipping, intracranial bypass procedure, and microvascular decompression, between April, 2017 – April, 2020	80/80	62.5/58.7	5/48/27/0 – 3/53/24/0	ICSDC	0.5 μg.kg^{-1}.h^{-1} before start of surgery and maintained until end of surgery	Brain tumor resection, aneurysm clipping, intracranial bypass procedure, and microvascular decompression
Li 2022	Patients with frontotemporal brain tumors > 18 yr old who were scheduled for elective craniotomy with general anesthesia. MMSE > 20	130/130	44.6/50.8	6/77/45/2 – 6/66/57/1	CAM-ICU	Loading dose: 0.6 μg.kg^{-1}.h^{-1}; maintenance: 0.4 μg.kg^{-1}.h^{-1} until dural close	Brain tumor resection
Tang 2018	Patients with ASA I to IV, 18–70 y, Glasgow coma scale > 11, Hunt-Hess I–III and embolization of intracranial aneurysms	54/52	44/50	16/34/2/2 – 18/32/1/1	Modified CAM-S	1 μg.kg^{-1} for 15 minutes; maintenance: 0.3 μg.kg^{-1}.h^{-1} until end of surgery	Intracranial aneurysm embolization

Y, Years; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; RCT, Randomized Controlled Trial; DEX, Dexmedetomidine; ICSDC, Intensive Care Delirium Screening Checklist; CAM-ICU, Confusion Assessment Method for Intensive Care Unit; CAM-S, Confusion Assessment Method.

[a] Description of each delirium assessment tool in Supplementary Table 2.



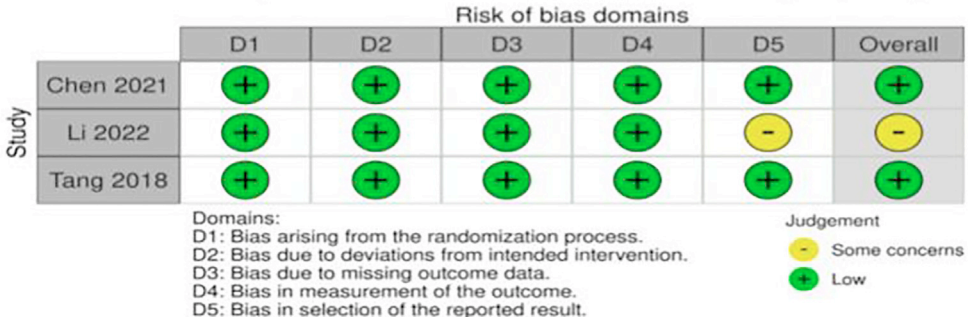


Figure 1 (A) Forest plot of studies examining outcomes between patients in dexmedetomidine intervention and saline placebo; (B) Risk of bias of this meta-analysis.

length of stay, suggesting that these hemodynamic effects likely had minimal or uncertain clinical impact. These findings highlight the need for careful perioperative management, with particular attention to potential effects on hemodynamic stability.

Our meta-analysis has several notable limitations that should be carefully considered. First, the small number of included studies significantly limits the generalizability and robustness of the findings. Although statistical analysis demonstrated consistency in the results, this cannot fully compensate for the limited dataset and its inherent weaknesses. The small sample size increases the risk of overestimating the effect size and reduces the reliability of the conclusions.

Furthermore, varying tools were used across the studies to assess POD (Supplementary Table 2), leading to potential measurement inconsistencies. To manage this variability, we categorized patients dichotomously as either experiencing delirium or not, without accounting for differences in severity or duration.

Additionally, differences in neurosurgical indications, surgical techniques, and perioperative care practices across studies introduce further heterogeneity that may have influenced the outcomes.

These limitations highlight the need for caution when interpreting the results and underscore the importance of future larger-scale studies with standardized assessment methods to confirm the role of dexmedetomidine in reducing POD in neurosurgical patients.

This meta-analysis of randomized clinical trials shows that dexmedetomidine is associated with a significant reduction in the incidence of POD in neurosurgical patients. Although these results support its potential role in improving perioperative outcomes, the underlying mechanisms remain unclear and the adverse effects uncertain, making it a likely obstacle to implementation in clinical practice.

Despite its promising potential, there is a clear need for larger multicenter trials employing standardized delirium assessments and comprehensive safety evaluations regarding its applicability. Future research should aim to determine whether the observed reduction in delirium stems from specific neuroprotective mechanisms or from ancillary factors, such as optimized sedation strategies and modulation of inflammatory responses. Additionally, studies should comprehensively assess dexmedetomidine across diverse clinical settings.

Research data availability

Data sharing does not apply to this article as no new data were created or analyzed in this study.

Authors' contributions

Virgilio Astori: Responsible for conceptualization; data curation; formal analysis; investigation; methodology; project administration; writing-original draft; writing-review & editing.
Bruno Pandolfi Arruda: Responsible for conceptualization; formal analysis; investigation; methodology; writing-original draft.

Pedro Guimarães Marcarini: Responsible for conceptualization; formal analysis; investigation; writing-original draft; writing-review & editing.
Lucas Destefani Natali: Responsible for conceptualization; formal analysis; investigation; writing-original draft; writing-review & editing.
Marcos Sampaio Meireles: Responsible for supervision.
Daniele Fernandes Holanda: Responsible for supervision and writing-review & editing.
All authors have read and approved the final version submitted and take public responsibility for all aspects of the work.

Fundings

No funding was received for this work.

Conflicts of interest

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844662.

Associate Editor

Maria José Carmona

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Perceived stress among Brazilian anesthesiologists before and after a mindfulness-based program: preliminary findings

KEYWORDS
Anesthesiologist;
Mindfulness;
Stress

Dear Editor,

Anesthesiologists are at increased risk of experiencing stress due to the high-responsibility environments in which they work within hospitals.[1] They often lack autonomy and flexibility in managing their work schedules, typically adhere to long weekly working hours, and are required to maintain sustained attention and concentration during anesthetic procedures. In addition, they bear significant responsibility for patient's clinical outcomes, must engage in complex interpersonal interactions with fellow anesthesiologists and surgeons, and frequently face fear of litigation as well as mounting pressure for productivity within surgical centers.[1]

Modifying the structural and organizational context of operating rooms and the daily routines of anesthesiologists is often more complex than equipping these professionals with strategies to respond to adversity in a less reactive, more observant and composed manner.[2] Mindfulness-based intervention programs are accessible and well-established tools that have demonstrated potential to positively impact mental health and overall well-being, enhance workplace performance, reduce the incidence of medical errors and improve patient satisfaction.[3] The aim of this study is to evaluate the impact of an eight-week Mindfulness program on perceived stress among Brazilian anesthesiologists using the PSS-10 questionnaire administered anonymously before and after the intervention.

This is a *quasi*-experimental pre-post study design involving data collection from a single group at two distinct time points: before and after the intervention. The sample size was calculated based on a paired Student's *t*-test assuming an expected effect size of 0.80, a significance level (α) of 0.05 (5 %), and a corresponding confidence level of 95 % ($1 - \alpha$), the estimated total sample size was 23 participants. The study participants were drawn from the population of 89 anesthesiologists affiliated with *Grupo Sam*, the anesthesiology team of *Rede Mater Dei* in Brazil, and exclusion criterion was regular Mindfulness practice or prior program completion.

Of the sampled population, 35 volunteers completed the initial PSS-10 questionnaire. The Mindfulness intervention was conducted between April and July 2023 in a synchronous online format, consisting of weekly 2-hour sessions over the course of eight weeks, and was delivered by NUMI (*Núcleo de Mindfulness*). Among the volunteers, 25 individuals completed both the pre and post intervention assessments. Of these, 16 participants completed the course, while 9 did not. Completion of the course is defined as attending at least 5 out of the 8 sessions with the first session being mandatory.

Data were analyzed using IBM SPSS Statistics version 26.0. Descriptive statistics were used for quantitative variables, and absolute (n) and relative (%) frequencies were used to describe categorical variables. To compare two measurements obtained from the same experimental unit at different time points a paired Student's *t*-test was applied. Effect size was assessed using Cohen's d coefficient, and results were considered statistically significant when the p-value was less than 0.05, corresponding to a 95% confidence level in the conclusions drawn.

Among participants who did not complete the course but responded to the questionnaire at both time points (n = 9), no statistically significant differences were observed in Perceived Stress Scale (PSS-10) scores between the pre and post intervention assessments (p = 0.773). The mean PSS score changed from 23.4 $\pm$ 7.1 (95% CI: 18.01 - 28.88) at baseline to 22.9 $\pm$ 3.7 (95% CI: 20.08 - 25.7) after the course, with a small effect size (d = 0.10). The median also remained stable, shifting from 20.0 (Q1—Q3: 17.5—32.0) to 22.0 (Q1—Q3: 20.0—26.5), suggesting no relevant change in perceived stress levels within this subgroup.

Among participants who completed the course (n = 16), a significant reduction in Perceived Stress Scale (PSS-10) scores was observed between the pre and post intervention assessments, with a statistically significant difference ($p < 0.001$; t (15) = 3.924) and a large effect size (d = 0.98). The mean score decreased from 21.4 $\pm$ 5.4 (95% IC: 18.55 - 24.32) before the course to 16.2 $\pm$ 4.7 (95% IC: 13.7 - 18.67) after the intervention. The median score also declined, from 22.0 (interquartile range: 17.0—25.0) at baseline to 16.5 (interquartile range: 13.0—20.3) post-intervention. Minimum and maximum values

https://doi.org/10.1016/j.bjane.2025.844638

Table 1 Comparative analysis of PSS scores between participants who completed and those who did not complete the course.

	Course	
PSS	Completed (n = 16)	Not completed (n = 9)
Pre-course		
Mean ± SD	21.4 ± 5.4	23.4 ± 7.1
Median (Q_1 – Q_3)	22.0 (17.0 – 25.0)	20.0 (17.5 – 32.0)
Minimum – Maximum	12.0 – 32.0	17.0 – 34.0
Conclusion:	p = 0.434; t_{23} = 0.797; d = 0.34 Completed = Not completed; Effect size: Small	
Post-course		
Mean ± SD	16.2 ± 4.7	22.9 ± 3.7
Median (Q_1 – Q_3)	16.5 (13.0 – 20.3)	22.0 (20.0 – 26.5)
Minimum – Maximum	8.0 – 24.0	18.0 – 29.0
Conclusion:	p = 0.001; t_{23} = 3.705; d = 1.60 Completed < Not completed; Effect size: Large	

Dataset: 25 participants.
Note: p, p-value from the independent samples Student's t-test; d, Effect size (Cohen's d).

ranged from 12.0 to 32.0 before the course, and from 8.0 to 24.0 after the course, indicating not only a reduction in mean perceived stress levels but also a decrease in score dispersion following full participation in the intervention.

When comparing Perceived Stress Scale (PSS-10) scores between participants who completed the course (n = 16) and those who did not (n = 9), the groups showed similar results at the pre-intervention time point. However, a statistically significant reduction in PSS-10 scores was observed in the post-intervention assessment among those who completed the course.

At the pre-intervention time point, the mean PSS-10 scores were 21.4 ± 5.4 for the course completion group and 23.4 ± 7.1 for the non-completion group. The difference between the groups was not statistically significant (p = 0.434; $t(23)$ = 0.797) with a small effect size (d = 0.34), suggesting baseline equivalence between the groups prior to the intervention.

At the post-intervention time point, a significant difference between the groups was observed: the mean score for the course completion group was 16.2 ± 4.7, while the non-completion group had a mean score of 22.9 ± 3.7. This difference was statistically significant (p = 0.001; $t(23)$ = 3.705) with a large effect size (d = 1.60), indicating a substantial improvement in perceived stress levels among those who completed the course.

This study demonstrated that although both subgroups exhibited similar levels of perceived stress prior to the intervention (p = 0.434; d = 0.34), only the subgroup that completed the Mindfulness course showed a statistically significant reduction in PSS-10 scores at the end of the intervention (16.2 ± 4.7), compared to the non-completion subgroup (22.9 ± 3.7). This difference was statistically significant (p = 0.001) with a large effect size (d = 1.60) (Table 1).

These results indicate that completing the Mindfulness course may be associated with a significant reduction in perceived stress, reinforcing the effectiveness of the intervention in this population of anesthesiologists.

The final sample size was small (n = 16), which implies wider confidence intervals and reduced statistical power to detect differences. Nevertheless, a statistically significant difference was observed (p < 0.001). To address limitations related to statistical power, the effect size was calculated and found to be large (d = 0.98). This suggests that the observed difference in PSS-10 scores before and after the course is clinically relevant and unlikely to be due to chance.

The *quasi*-experimental design of this study inherently presents limitations, including the potential for selection bias and regression to the mean. Without a control group or random allocation, it is difficult to establish causal inference, as the observed effects may be confounded by external variables such as seasonal fluctuations in workload or other unmeasured factors. Incorporating a control group would strengthen internal validity and allow for a more accurate estimation of the effects directly attributable to the Mindfulness intervention.

It is noteworthy that, in the present study, 45.71 % of the sampled population completed the course, while 54.29 % did not, and 28.6 % of all enrolled participants did not attend any session. Given the documented benefits of Mindfulness-based programs, it is important to identify factors that may enhance engagement and participation among healthcare teams in this type of practice.

Data on the daily meditation practice volume for each participant were not collected, therefore, it was not possible to adjust the results for the covariate "hours of meditation." Regular practice frequency is one of the core components of Mindfulness.[3]

Barriers such as workload related fatigue, personal life demands, and the course schedule, limit the feasibility of Mindfulness practice at both individual and institutional levels. Shorter interventions incorporating core components of Mindfulness may offer a viable solution for implementing the practice in the context of healthcare professionals.[4]

Additional strategies may include institutional support for conducting interventions during working hours; the creation of dedicated spaces within the workplace that encourage regular Mindfulness practice; flexible scheduling of course sessions; availability of asynchronous online courses; promotion of mobile meditation app usage; and ongoing education on the importance of mental health and the individual and institutional impact of stress on healthcare professionals.

Moreover, there is a lack of studies evaluating the long-term impact of such interventions on this professional population.[5]

The main contribution of the present study is the application of Mindfulness as an accessible tool with the potential to transform anesthesiologist's relationship with their work environment without necessarily altering the inherent characteristics or operational logic of the surgical setting.

By bringing the discussion on the impact of Mindfulness in anesthesiologists into the scientific community, this study aims to contribute to professional self-care initiatives and raise awareness among institutions responsible for the specialty regarding the relevance and feasibility of implementing Mindfulness techniques in this context.

Declaration of competing interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 21 February 2025; accepted 1 May 2025
Available online 12 May 2025

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

The role of GLP-1 agonists in perioperative care: a suspension dilemma

Dear Editor,

In the editorial of this journal, Glucagon-Like Peptide-1 Agonists in Perioperative Medicine: to Suspend or Not Suspend, That Is the Question, several tools for anesthesiologists were discussed to enhance patient safety.[1] In addition, this letter offers a commentary that synthesizes recent international consensus perspectives to refine perioperative guidance concerning the use of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) in patients undergoing anesthesia or sedation.

GLP-1RAs and the dual agonists GIP/GLP-1 (Glucose dependent Insulinotropic Polypeptide/Glucagon-Like Peptide-1) are synthetic analogues of a gut-derived incretin hormone secreted after food ingestion. Endogenous hormone has a short half-life of 2—3 minutes and plays a key role in satiety and glucose regulation. In contrast, synthetic GLP-1 RAs such as semaglutide (Ozempic®, Wegovy®) have prolonged elimination profiles — approximately 165 hours (~7 days) — allowing for convenient once-weekly dosing.[2] These drugs have revolutionized the treatment of type 2 Diabetes by effectively controlling glycemia with minimal risk of hypoglycemia. Prescription rates have increased further due to their adoption for obesity management, given the significant weight loss observed with the continuous use.[3] GLP-1RAs confer multisystem organ protection by reducing inflammation, improving endothelial function, lowering lipid levels, enhancing cardiovascular outcomes, and slowing the progression of renal dysfunction in patients with diabetes.[2,4]

GLP-1RAs dosages are variable and usually titrated gradually due to gastrointestinal side effects. The most common side effects are related to reduced gastric emptying and peristalsis, causing nausea and vomiting, abdominal pain, diarrhea, or constipation. These effects typically occur during the initiation or dose-escalation phase and are self-limited, manifesting across all preparations, short- or long-acting, subcutaneous or oral.[2,3] Residual gastric content increases the risk of pulmonary aspiration during general anesthesia/sedation and can result in aspiration pneumonia or chemical pneumonitis.[1]

A clinical practice guideline jointly developed by several American societies, including the American Society of Anesthesiologists, recommends that the decision to continue or withhold GLP-1RA therapy in the perioperative period should be guided by shared decision-making among the patient, anesthesiologist, and prescribing team, with an individualized risk-benefit assessment. The care team should consider variables known to increase the risk of delayed gastric emptying, including dose escalation, higher or weekly dosing regimens, the presence of gastrointestinal symptoms, and medical conditions associated with impaired gastric motility. If the decision is made to withhold GLP-1RA therapy, the optimal suspension interval remains uncertain. However, current recommendations suggest withholding daily formulations on the day of surgery and weekly formulations should be withheld one week prior to surgery. Regardless, all patients should still be assessed on the day of the procedure for gastrointestinal symptoms. Additionally, in patients with suspected delayed gastric emptying, a preoperative liquid diet for at least 24 hours is recommended, similar to bowel preparation used in colonoscopy or bariatric surgery. When clinical concern about retained gastric content exists on the day of the procedure the point-of-care gastric ultrasound can be used to assess aspiration risk.[5]

According to the Brazilian Society of Diabetes, GLP-1RAs should be withheld before a procedure involving general anesthesia or sedation and a specialist should adjust the treatment. Oral or subcutaneous semaglutide should be withheld for 21 days prior to the procedure, and tirzepatide (Mounjaro®) for 15 days, based on the pharmacokinetic principle of three elimination half-lives.[6]

The 2025 consensus of British societies, including Association of Anaesthesists and Royal College of Anaesthesists, recommends continuing GIP/GLP-1 agonists or GLP-1RAs throughout the perioperative period. Their approach emphasizes that the risk of pulmonary aspiration and mitigation strategies should be discussed with the patient using a shared decision-making.[7]

Maselli et al. conducted a retrospective evaluation of 57 patients undergoing Endoscopic Sleeve Gastroplasty without GLP-1RAs discontinuation and found no instances of retained gastric solids on endoscopy. All patients followed a liquid diet on the day prior the procedure and 12 h fasting, emphasizing the potential benefit of preoperative dietary modifications in reducing retained gastric content.[8]

https://doi.org/10.1016/j.bjane.2025.844668

Clinical recommendations from Australian and New Zealand societies emphasize the importance of inquiring patients about the use of GLP-1RAs. For endoscopic procedures, the patients should follow a fluid diet 24 h prior to endoscopy and continue the use of GLP-1RAs. For non-endoscopic procedures the focus remains on patient engagement in risk assessment and procedural planning. All patients taking these drugs should be considered non-fasted. The point-of-care gastric ultrasound should be considered for risk stratification to determine the qualitative and quantitative content of stomach before the anesthesia. Extending the fasting time is not recommended given the current lack of evidence and the absence of gastrointestinal symptoms does not exclude retained gastric content, but the presence of gastrointestinal symptoms may be associated to retained gastric content.[9]

Pharmacokinetic and clinical data indicate that short interruptions of long-acting GLP-1RAs (one half-life) may not be sufficient to complete drug clearance. Currently, no data available on gastric emptying from residual GLP-1RAs levels and prolonged interruptions (four or five half-lives) could be impractical, clinically harmful, and inconsistent with a patient-centered approach.[3]

Tracheal intubation using cuffed tubes is the best method for airway protection against the aspiration, however, it is not foolproof. Accumulated secretions may bypass the cuff into the trachea, especially in cases of large-volume regurgitation, in patients positioned in Trendelenburg during the procedure or other reflux-facilitating conditions, such obesity or laparoscopic procedures. Point-of-care gastric ultrasound has emerged as a critical tool for aspiration risk stratification in this context. As discussed above, there is insufficient data on the residual effects of GLP-1RAs on gastric emptying, so it would be unsafe to assume that standard fasting protocols ensure gastric emptying, regardless of the drug suspension time. Even if regurgitation does not occur at the time of anesthetic induction, it may still occur during the procedure, patient positioning, extubation or in the post-anesthesia recovery room, sometimes without the medical team's awareness, leading to postoperative pulmonary complications and delaying the suspicion of aspiration pneumonia.

The current literature increasingly supports the continuation of GLP-1RAs due to their clinical benefits. However, there remains a lack of robust data on the optimal preoperative dietary strategy to ensure complete gastric emptying. Until further evidence becomes available, two key practices should be integrated into perioperative protocols: implementation of an institutional protocol aimed at systematically screening patients for GLP-1RA use, and incorporation of gastric ultrasound. These tools enable individualized risk stratification and management, prioritizing patient safety in the perioperative setting, independent of drug discontinuation status.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 21 April 2025; accepted 28 May 2025
Available online 5 August 2025

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