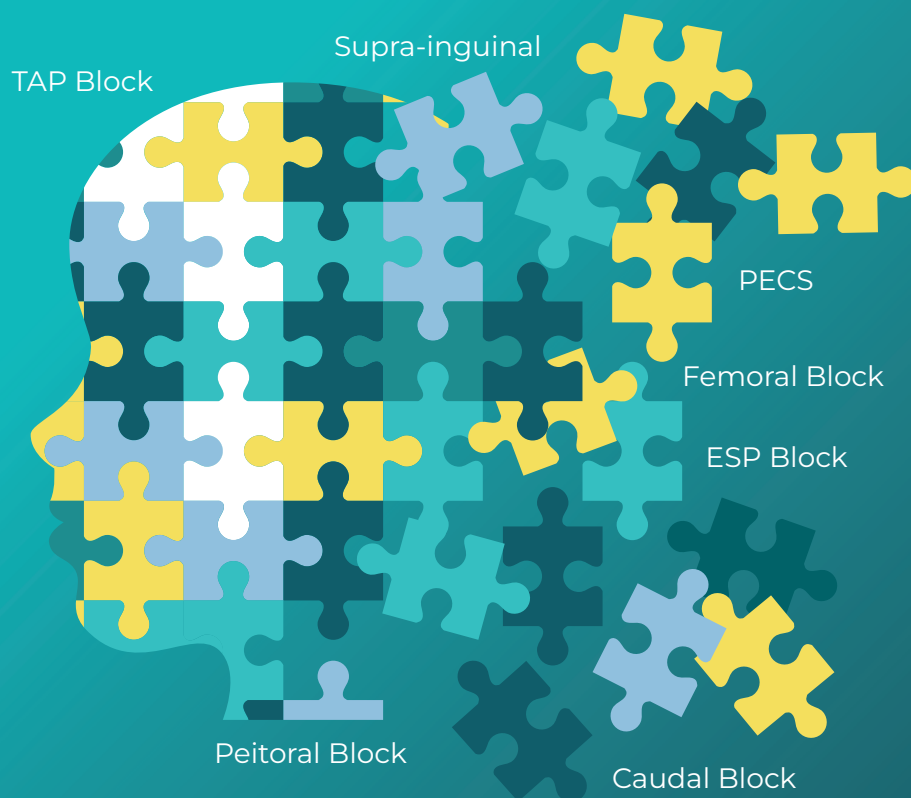




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EDITORIAL

Optimizing pediatric surgical analgesia: recent trends in regional anesthesia



Regional anesthesia increasingly occupies a central role in pediatric anesthesia. Most children undergoing surgical procedures can benefit from a regional technique.^{1,2} Assessing and managing pain in childhood remains a constant challenge, particularly in preverbal or nonverbal children. An agitated emergence may reflect pain, emergence delirium, anxiety, hunger, or discomfort. Therefore, implementing effective, long-lasting analgesic strategies with minimal side effects is essential for safe and smooth postoperative recovery.

Clinical experience and scientific evidence consistently highlight the clear advantages of regional anesthesia in pediatric patients: reduced intraoperative opioid use, smoother emergence, shorter recovery room stays, prolonged analgesia, and a lower incidence of postoperative complications such as paralytic ileus and atelectasis. Beyond these direct clinical benefits, greater satisfaction is also observed among the child, family members, and the multidisciplinary perioperative care team.³⁻⁵

Over the past decades, one of the most remarkable advances has undoubtedly been the incorporation of ultrasonography into regional anesthesia practice. Ultrasound has transformed the landscape of pediatric anesthesia by enabling real-time visualization of anatomical structures — such as nerves, vessels, and fascial planes — and monitoring of local anesthetic spread. This approach has enhanced safety, reduced the risk of inadvertent punctures, minimized the need for large volumes, and expanded the repertoire of available blocks, particularly fascial plane blocks. As a result, technical success rates have significantly increased, with fewer needle passes, faster onset, and longer-lasting analgesia.^{6,7}

This technological progress has been accompanied by robust evidence demonstrating the safety of regional anesthesia in children. For many years, it was believed that performing blocks under general anesthesia might mask early signs of neural injury. However, prospective multicenter studies — such as the Pediatric Regional Anesthesia Network (PRAN) and the Association des Anesthésistes Réanimateurs

Pédiatriques d'Expression Française (ADARPEF) — have consistently documented the safety of regional anesthesia in children, including almost 160,000 blocks without evidence of permanent neurologic sequelae.^{4,5,8} In addition, a recent study using magnetic resonance imaging to measure the distances between neural structures and the epidural canal demonstrated substantial safety margins for thoracic and lumbar punctures in pediatric patients, strengthening the anatomic evidence for the safety of these techniques.⁹

Expanding from safety to efficacy, abdominal wall blocks have become integral to modern pediatric anesthesia. The most commonly used include the transversus abdominis plane (TAP), quadratus lumborum (QL), and rectus sheath blocks, with several technical variations. These techniques have become routine in surgeries such as herniorrhaphies, appendectomies, and urological procedures.

Recent studies comparing the analgesic efficacy of TAP and QL blocks suggest that QL may be superior in reducing intraoperative opioid consumption and postoperative pain scores.^{10,11} In a double-blind clinical trial, Mutlu and colleagues observed that children receiving QL blocks had lower pain scores and reduced remifentanyl requirements compared with the TAP group.¹²

The QL block can be performed using different approaches — lateral (QL1), posterior (QL2), and anterior or transmuscular (QL3) — which vary in complexity and patterns of anesthetic spread. In a randomized study of 120 children, Arun et al. compared the three approaches and demonstrated that the anterior approach resulted in lower fentanyl consumption, longer analgesic duration, and greater parental satisfaction.¹³ These findings emphasize that approach selection should be individualized, taking into account the surgical procedure, operator experience, and patient profile.

Beyond the abdominal wall, thoracic approaches such as the erector spinae plane (ESP) block has emerged as a versatile and safe alternative applicable to abdominal, thoracic, and cardiac procedures. When performed under ultrasound guidance, ESP is relatively straightforward, and its

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anatomical target lies distant from critical structures such as the pleura and spinal cord.

A recent meta-analysis including nine clinical trials and 507 patients showed that the ESP block provides analgesia comparable to caudal block, with a lower incidence of urinary retention.¹⁴ This finding is particularly relevant in short procedures and ambulatory patients, in whom early mobilization and discharge are desirable.

In a broader context, a network meta-analysis by Wegner et al. on pediatric cardiac surgery demonstrated that the transversus thoracic muscle plane block (TTPB) and thoracic paravertebral block are among the most effective techniques for post-sternotomy analgesia, significantly reducing opioid consumption and extubation time.¹⁵ These results expand the concept of regional anesthesia beyond the abdominal wall, integrating thoracic and paravertebral blocks as key components of pediatric enhanced recovery after surgery (ERAS) protocols.

For upper-limb procedures, the infraclavicular block has become the technique of choice for forearm, wrist, and hand surgeries. Recently, Yayik et al. compared the lateral sagittal and costoclavicular approaches, finding significantly shorter procedure times with the latter, without differences in analgesic efficacy or safety.¹⁶ This is particularly relevant in pediatric practice, where procedural agility and predictability directly influence anesthetic workflow efficiency and patient stability.

In addition to perineural and fascial plane blocks, other analgesic strategies are gaining ground in modern pediatric anesthesia. Intraperitoneal instillation of local anesthetic is a simple, quick, and low-risk technique. Moen and colleagues compared bupivacaine combined with dexmedetomidine or magnesium sulfate in pediatric laparoscopic surgeries, and found lower pain scores and fewer rescue analgesic requirements with adjuvant use, without an increase in adverse effects.¹⁷ These findings reinforce the role of multimodal strategies and rational adjuvant use to optimize analgesia and accelerate post-operative recovery.

The advances described in these studies — from MRI-validated safety margins to novel block comparisons — represent significant progress in pediatric regional anesthesia. However, translating this evidence into practice requires thoughtful educational frameworks.

Recent international consensus work by Hagen et al. identified core pediatric regional anesthesia techniques that balance clinical effectiveness with accessibility, providing a structured, consensus-driven model for training programs.¹⁸ This framework builds on earlier conceptual work advocating for simplified, high-value blocks to improve adoption rates. Importantly, these guidelines should be viewed as structured starting points rather than rigid doctrine — encouraging practitioners to progress beyond foundational techniques as their skills and institutional capabilities evolve.

While the quadratus lumborum and erector spinae plane blocks featured prominently in these studies were not selected as core techniques — reflecting ongoing debates about reliability, complexity and standardization — their growing evidence base suggests they may represent a natural progression for practitioners who have mastered foundational blocks.

Facilitating this journey from foundational to advanced techniques, educational platforms like Baby Blocks (www.baby-blocks.com) exemplify how modern resources can bridge the gap between research and practice, offering structured learning pathways from basic to advanced techniques.¹⁹ These initiatives, combined with the growing evidence base summarized here, support the editorial's central message: optimizing pediatric surgical analgesia requires not only advancing techniques but also ensuring their thoughtful implementation through structured education that adapts to local contexts and evolves with emerging evidence.

In summary, pediatric regional anesthesia has evolved rapidly over the past two decades, driven by ultrasound incorporation, standardized multicenter registries, and a growing body of safety and efficacy evidence. The field is now entering a new era in which block selection is guided not only by anatomy but also by integration within multimodal enhanced recovery protocols.

Training in pediatric anesthesiology should therefore include mastery of these techniques, safe ultrasound use, and understanding of emerging evidence — such as that from recent studies on QL, ESP, and thoracic blocks. Optimizing surgical analgesia in children goes beyond pain reduction: it means improving outcomes, reducing opioid use, and humanizing anesthetic care.

Conflicts of interest

JH serves as Editor-in-Chief of Baby Blocks. VCQ serves as contributor to Baby Blocks. No financial compensation interest is involved. All other authors declare no conflicts of interest.

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EDITORIAL

Clinical application of CNS injury biomarkers in anesthesia and intensive care



Introduction

Central nervous system (CNS) injury as a consequence of trauma, ischemia, hemorrhage, or critical illness is a significant medical problem affecting millions of patients worldwide. Furthermore, all intensive care and surgical patients are at risk of neurological sequelae, including not only organic brain damage such as stroke or hemorrhage, but also postoperative delirium (POD) or postoperative cognitive disorders (POCD). Despite recent progress in neuroimaging and clinical management, CNS injuries remain the leading cause of mortality and disability in all age groups.¹ We are still lacking refined laboratory measures that can be implemented in everyday practice to facilitate diagnostic workups, prognostication, and monitoring for reversible sequelae that cause secondary injury.

The ideal biomarker of CNS injury should possess similar characteristics to other diagnostic markers, such as cardiac troponins. The biomarker should be CNS-specific, have high sensitivity and specificity for diagnostic and prognostic purposes, yield rapid results, and be widely accessible – this includes easily obtainable sampling material as well as economic efficiency of the measurements. Biomarkers may enable the monitoring of CNS-related complications and the prediction of future outcomes after brain injury and critical illness. They could also facilitate preoperative evaluation of patients who are potentially susceptible to postoperative neurological dysfunction, such as POD and POCD. Recently, several agents have been proposed as potential biomarker candidates for assessing CNS injury. These markers reflect pathological processes following brain tissue injury, such as neuronal and glial damage, axonal injury, neuroinflammation, and increased blood-brain barrier (BBB) permeability. This article provides an overview of available research data on the clinical utility of potential CNS biomarkers in anesthesia and intensive care.

Possible clinical application of CNS biomarkers in anesthesiology and intensive care

Perioperative Assessment

Preoperative assessment and postoperative monitoring for neurological complications are essential for optimal patient outcomes. In the perioperative setting, CNS biomarkers could facilitate rapid detection and evaluation of patients presenting with postoperative neurological dysfunction. Neurological sequelae are common in the postoperative period, and specific patient groups may be at higher risk of developing them. Biomarkers can supplement other diagnostic modalities, such as neuroimaging, EEG, or transcranial Doppler, in monitoring for potential neurological complications following surgical procedures. Numerous potential biomarker candidates were identified that may provide insights into neuronal damage, neuroinflammation, or secondary brain ischemia following operative treatment. Furthermore, there is data on the potential clinical utility of biomarkers in monitoring the neurological consequences of anesthesia.

During the acute postoperative phase, surgery-induced tissue injury results in the release of cytokines and chemokines, which increase the permeability of the BBB and lead to further vascular and neuronal damage.² Numerous studies have proven that this process is associated with elevated levels of CNS-derived proteins, including glial fibrillary acidic protein (GFAP), neurofilament light (NfL), tau protein, and S100B protein, in both blood and CSF samples of patients following different types of invasive procedures.³ Some groups of patients may be more prone to surgery-induced CNS injury. Postoperative levels of S100B were reported to be higher in elderly patients and ApoE 4 carriers, suggesting that age and genetic susceptibility may influence the serum concentrations of S100B in cases of Alzheimer's Disease (AD), intracerebral hemorrhage, head trauma, and brain hypoperfusion during surgeries with cardiopulmonary bypass. Research on POD and its relationship with CNS

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biomarkers has reported that higher serum levels of IL-6, CRP, S100B, and NfL, as well as altered serum expression of selected miRNAs, are associated with POD.^{4,5} Perioperative biomarker assessment may enable the identification of patients at risk of delirium and POCD, along with predicting long-term patient outcomes.

Neurological complications of critical illness

Intensive care patients are particularly vulnerable to neurological complications such as delirium, cognitive dysfunction, seizures, encephalopathy, or delayed cerebral ischemia. There are reports on the prognostic value of selected CNS-derived proteins in critical care patients. GFAP, S100B, NfL, neuron-specific enolase (NSE), and Ubiquitin Carboxyl-terminal Hydrolase L1 (UCHL-1) have been investigated as prognostic markers for critically ill patients with various comorbidities.

The potential prognostic utility of CNS biomarkers has been confirmed in several studies involving both adult and pediatric patients after cardiac arrest. Elevated CNS protein levels following cardiac arrest can result from multiple mechanisms, including neuronal apoptosis and BBB disruption. NSE has been confirmed to show an ability to discriminate between survivors and non-survivors of cardiac arrest, and levels of NSE at 48 h post-admission or 72 h post-cardiac arrest are associated with a 90-day outcome. Guidelines recommend NSE level assessment as part of post-cardiac arrest care.⁶ The latest meta-analysis on the utility of brain biomarkers in predicting survival and neurological outcomes in pediatric patients confirmed that NSE is correlated with prognosis and neurological outcomes in this population.

Furthermore, UCHL-1 and GFAP demonstrated promising potential for stratifying early outcomes.⁷ Studies on NfL have similarly shown promising data on prognostication in out-of-hospital cardiac arrest (OHCA). In a prospective study, serum NfL levels 1–3 days after OHCA were correlated with worse neurological outcomes at 6 months, and this prognostic performance exceeded that of standardized neuromonitoring techniques and other biomarkers.⁸ Biomarker studies analyzing their potential prognostic utility were performed in patients undergoing Extracorporeal Membrane Oxygenation (ECMO). It is reported that higher serum levels of selected biomarkers (GFAP, NSE, S100B) are correlated with the extent of brain injury and mortality. They were also independently associated with survival and functional outcomes in ECMO patients.⁹

Research data indicate that assessing CNS injury biomarkers may help predict cognitive disorders in the course of critical illness. A prospective study of a large group of patients with respiratory failure on mechanical ventilation found that NfL concentration, measured early in the course of hospitalization, was associated with a clinical diagnosis of delirium.⁴ On the other hand, some CNS-derived proteins may play a protective role; studies have shown that elevated levels of brain-derived neurotrophic factor (BDNF) and UCHL-1 early after ICU admission are associated with a decreased risk of delirium in critical care patients.^{4,10} Some pharmaceuticals may enhance this effect. Dexmedetomidine, which exerts neuroprotective properties mediated by BDNF, was proven to reduce the incidence rate of POD in neurosurgery patients.¹¹

Traumatic brain injury assessment and prognostication

Primary brain injuries account for a significant portion of patients hospitalized in the ICU. CNS biomarker assessment can assist in prognostication and crucial therapeutic decisions. The CNS biomarkers have been extensively studied in traumatic brain injury (TBI) patients for use in diagnostic workups, monitoring, and prognostication of long-term outcomes. GFAP, UCHL-1, and S100B are already established in clinical practice to exclude the presence of lesions in CT scans in case of mild to moderate head trauma.^{12,13} These biomarkers are available for quick, bedside assessments, helping to reduce the need for high-risk transportation, imaging, and radiation in this patient group. Recently, more agents have been investigated for use as both diagnostic and prognostic markers of brain damage, mainly in correlation with clinical grading scales. Studies reported that S100B and NSE levels in conjunction with the APACHE II calculation are efficient predictors of compromised outcome among critically ill patients with primary brain injuries.¹⁴ Another study by Ito et al. suggests that in TBI patients, levels of growth differentiation factor 15 (GDF-15) are correlated with Sequential Organ Failure Assessment scores.¹⁵

Recent studies have demonstrated the diagnostic and prognostic potential of miRNA profiling in TBI patients. Researchers have reported altered expression of selected miRNAs following TBI.¹⁶ Data prove that combining the use of miRNAs, CNS-derived proteins, and markers of inflammation can enhance the specificity and sensitivity of prognostic assessments.¹⁷ New reports highlight the potential utility of urine and saliva samples for detecting biomarkers of CNS injury. UCHL-1 has been suggested as a promising diagnostic marker in urine samples of patients with TBI,¹⁸ and miRNA profiling of saliva demonstrated elevated expression of specific miRNAs in a population of pediatric patients following brain concussion.¹⁹

Stroke

Stroke, including acute ischemia, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), is a CNS injury that often results in a critical state. It remains one of the most important causes of disability and mortality in adult patients. Despite ongoing progress in neuroimaging and reperfusion treatment, a universal biomarker for ischemic or hemorrhagic brain injury remains elusive. CNS-derived proteins, miRNA, and inflammatory agents proposed as potential acute ischemic stroke (AIS) biomarkers are reported to be associated with specific pathological features in the course of stroke – neuronal death, increased BBB permeability, neuroinflammation, delayed cerebral ischemia, or secondary hemorrhagic transformation. Research suggests that serum GFAP may be used to differentiate between AIS and ICH, provide insights into the time from symptom onset, and the extent of the ischemic lesion.²⁰ There is data on the correlation of other CNS-derived proteins and the clinical severity of AIS. It is reported that elevated levels of β -synuclein, NfL, and GFAP are associated with higher NIHSS scores and lower Alberta Stroke Program CT Score on admission.²¹

There is growing interest in the potential application of miRNA profiling in stroke diagnostics and prognostication.

Research brings interesting data on the correlation between the expression of selected miRNAs (miR-125b-5p, miR-143, miR-146b, miR-218, miR-21, miR-93, miR-29b, miR-126, and miR-130) and critical clinical features of stroke, such as the volume of the ischemic lesion, systemic inflammation, or neurological deficit.²² It is also suggested that miRNA assessment may bring insights into the evaluation of the efficacy of reperfusion treatment of AIS patients with large vessel occlusion.²³ Possible use of miRNA biomarkers was also confirmed for hemorrhagic stroke. A systematic review on miRNA signatures in ICH patients revealed a potential role for miRNAs as biomarkers for the early detection and differentiation of ICH.²⁴ Assessment of miRNA expression in aneurysmal SAH patients revealed an upregulation of miRNAs during vasospasm, suggesting a potential for early detection and monitoring for delayed cerebral ischemia in this patient group.²⁵

The future consequences of stroke may be strongly correlated not only with complications and comorbidities, but also with medical procedures that may affect the perfusion, oxygenation, and metabolism of brain tissue. Growing interest in biomarkers of reperfusion after endovascular treatment highlights the importance of selecting the optimal anesthetic method for mechanical thrombectomy in AIS and improving perioperative care to reduce the extent of brain injury and enhance patient outcomes.^{26,27}

Limitations and Challenges

The implementation of blood biomarkers for CNS injury still presents considerable challenges, including pre-analytical and analytical standardization, comorbidities, and the diverse demographics of the studied population.

One of the main confounding factors is the fact that most agents proposed as biomarkers for CNS injury are not specific to the nervous system. S100B can be found in non-nervous tissues, such as skin, muscle, and bone, and its elevated level in blood samples may result from extracranial injuries like burns or fractures.²⁸ GFAP serum concentration can also be higher in the course of inflammatory and degenerative diseases, such as inflammatory bowel disease, hepatic fibrosis, Parkinson's disease, or following complicated surgical procedures.²⁹ Moreover, the correlation between CNS and blood concentration of many biomarkers remains unclear. In the case of S100B, studies demonstrate that CSF levels may be more predictive of outcome than serum or plasma levels. An increase in GFAP blood level has been well-documented in ABI with transient blood-brain barrier disruptions. This aspect suggests that the release of these biomarkers during CNS injury may be more closely correlated with impaired BBB function than with intraparenchymal pathology. Emerging research suggests that miRNAs have high specificity for tissue or cell types, and their expression may also vary according to disease progression or therapy responsiveness. Data indicate that miRNA can cross the BBB and are remarkably stable in peripheral biofluids, even under extreme conditions, which makes them potentially interesting biomarker candidates.³⁰

The standardization of CNS injury biomarker measurements may additionally be affected by demographic factors and comorbidities. Research indicates that CSF levels of S100B are significantly correlated with age and gender, with

higher levels observed in women and older individuals.³¹ Even in the case of the most standardized tests, such as chemiluminescence ELISA for GFAP/UCHL-1 tandem assessment, there is a significant variability influenced by age, genetic ethnicity, and systemic trauma. This fact underscores the need for age-stratified reference ranges and recalibration across diverse ethnic populations to ensure the accurate interpretation of results.³²

Validated and standardized tests for detecting CNS injury biomarkers are crucial for the widespread adoption and implementation in clinical practice. To acquire objective data, not only assessment methods, but also sample collection timing and indications for sample handling need to be systematized. Only reproducible and consistent results obtained across laboratories and assay kits can increase the confidence of both users and regulatory agencies in the future widespread use of blood biomarkers in ABI management.³³

Conclusions and future perspectives

Biomarkers have the potential to play a crucial role in the diagnosis, prognosis, and treatment of neurocritical patients. They may provide an objective and measurable assessment of CNS pathology. Clinical applications in various areas of anesthesia and intensive care, such as preoperative assessment, monitoring postoperative neurological complications, and early detection of brain pathologies, could significantly improve management. Despite multiple studies on possible indicative agents, the translation of biomarkers from laboratory findings to clinical practice is not always feasible. Before CNS biomarkers can be successfully implemented into routine clinical evaluation, further research is needed to develop standardized assessment methods and address the clinical challenges associated with their use. Furthermore, it is necessary to assess the implementation costs, potential budget impacts, and long-term effectiveness of biomarkers in everyday clinical practice. Future randomized validation trials with precisely designed protocols are crucial for determining the diagnostic and prognostic accuracy of proposed brain injury biomarkers and evaluating their potential role in the medical management of patients with CNS disorders.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

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ORIGINAL INVESTIGATION

Comparison of three quadratus lumborum block approaches for pediatric lower abdominal surgeries: a randomized controlled trial

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KEYWORDS

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Abstract

Background: Lower abdominal surgeries in the pediatric population are associated with significant post-operative pain. Regional anesthesia techniques including ilioinguinal nerve block, Transversus Abdominis Plane (TAP) block, and Quadratus Lumborum (QL) block have been explored for lower abdominal surgeries. This study compares the analgesic effect of three different approaches to quadratus lumborum block in pediatric patients undergoing lower abdominal surgeries.

Methods: This randomized controlled trial included 120 pediatric patients aged between 1 and 7 years, scheduled for lower abdominal surgery under general anesthesia. Patients were randomized into 3 groups. Patients of Group A received QL block via anterior approach, Group L received QL block via lateral approach, and Group P received QL block via posterior approach. A volume of 0.5 mL.kg⁻¹ of 0.375% ropivacaine was injected unilaterally for QL block in all patients. The primary outcome was 24hr postoperative fentanyl consumption. Secondary outcomes included intraoperative fentanyl use, postoperative pain scores, time to rescue analgesia and parental satisfaction.

Results: Postoperative mean fentanyl consumption was significantly lower in Group A as compared to Group L ($p < 0.001$) and Group P ($p < 0.011$). Postoperative median FLACC scores were significantly lower ($p < 0.05$) in Group A in comparison to Group L and Group P in the early post-operative period. The parent satisfaction score was significantly higher ($p < 0.05$) in Group A.

Conclusion: Anterior approach to QL block reduces postoperative analgesic consumption and provides longer duration analgesia with better parental satisfaction scores in comparison to lateral and posterior approaches in pediatric patients undergoing lower abdominal surgeries.

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Introduction

Lower abdominal surgeries in the pediatric population are among the most performed procedures and are associated with significant postoperative pain. Effective postoperative analgesia is therefore essential to ensure patient comfort. The current trend in pediatric pain management in anesthesia is moving beyond traditional opioid use, focusing instead on multimodal strategies to alleviate pain.¹

Newer regional nerve blocks are being increasingly utilized, either to avoid the risks associated with neuraxial anesthesia or to minimize the side effects of opioids, such as hypotension, respiratory depression, pruritus, nausea, and vomiting.²⁻⁵ Due to the potential complications of caudal blocks, including hypotension and urinary retention, alternative regional anesthesia techniques – such as the Erector Spinae Plane (ESP) block, posterior Transversus Abdominis Plane (TAP) block, and Quadratus Lumborum (QL) block – have been explored.²⁻⁵ These blocks are typically performed under Ultrasound (US) guidance, which has enhanced their safety and utility in pediatric patients.^{2,3,5}

The QL block is a posterior abdominal wall block first described by Blanco et al.⁶ It allows the spread of injected local anesthetic to the paravertebral space and has been used for abdominopelvic surgeries in pediatric and adult patients with good results.⁷⁻⁹ Earlier studies revealed that the quadratus lumborum block potentially results in extensive sensory blockade (T7–L2), with beneficial effects on both somatic and visceral pain.¹⁰ Various techniques of this block have been described, leading to differential spread of local anesthetic, and varied sensory and motor blockade. The QL muscle is surrounded by the Thoracolumbar Fascia (TLF), which consists of three distinct layers. The anterior layer blends laterally with the transversalis fascia and medially with the fascia of the psoas major. The middle layer lies between the QL and the erector spinae muscles, while the posterior layer is located posterior to the erector spinae. In the posterior approach, LA is deposited between the posterior surface of the QL and the TLF. In the lateral approach, LA is deposited between the muscle aponeurosis and the fascia at the lateral border of the QL. In the anterior (transmuscular) approach, LA is deposited between the anterior border of the QL and the psoas major (PM).¹¹

Cadaver studies have shown that the anterior approach is characterized by cephalad migration into the Thoracic Paravertebral Space (TPVS) along the QL and PM muscles via a pathway posterior to arcuate ligaments.¹² While previous studies have compared different regional anesthesia techniques, limited evidence exists on the comparative efficacy of anterior, lateral and posterior QL block approaches in pediatric patients. However, Kumar et al. compared three different approaches to QL block in adult patients who underwent inguinal hernia surgery.¹³ They found better postoperative analgesia in the anterior approach in comparison to the posterior or lateral approaches to the QL block. This is the first randomized controlled trial aimed at determining the optimal approach by assessing opioid consumption, pain scores and parental satisfaction.

We hypothesized that a pre-incisional anterior QL block would provide better postoperative analgesia, reduce 24-hour analgesic consumption and result in higher parental satisfaction compared to other approaches (posterior and

lateral) in pediatric patients undergoing lower abdominal surgeries.

The primary objective of this study was to compare 24-hour postoperative fentanyl requirement among US guided anterior, posterior, and lateral approaches of the QL block in pediatric patients undergoing elective lower abdominal surgery. The secondary objectives included postoperative pain scores using the Faces, Leg, Activity, Cry, Consolability (FLACC) scale, duration of analgesia, intraoperative fentanyl consumption, parental satisfaction, and adverse effects like hematoma, vomiting, hypotension and others.

Method

This double-blinded, randomized controlled trial was conducted at our tertiary care institute after obtaining Ethical committee clearance and registration with the Clinical Trial Registry of India (CTRI: 2020/02/023623) registration. This study was conducted prospectively over three years (April 2020 to February 2023). A total of 120 pediatric patients, aged 1 to 7 years with American Society of Anesthesiologists (ASA) physical status I and II, undergoing elective open lower abdominal surgery (orchidopexy, hernia repair, pyeloplasty) were included in this study. Patients whose parents refused to give consent, infection at the site of infection, and those suffering from coagulopathy, liver or kidney disorder were excluded from this study. Patients meeting the inclusion criteria were randomized into 3 groups (40 patients each). Simple randomization was done by the co-PI (CS) using the online software (Open Epi software version 3.01, Atlanta, GA, USA). The allocation sequence was concealed in sequentially numbered opaque, sealed envelopes that were opened by the primary surgeon on the day of surgery.

Patients in Group A received QL block via the anterior approach, Group L via the lateral approach, and Group P via the posterior approach. A volume of 0.5 mL.kg⁻¹ of 0.375% ropivacaine was injected unilaterally for QL block in all patients. Written and informed consent for publication was obtained from the parents of every patient. This study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients received oral midazolam (0.5 mg.kg⁻¹) one hour before shifting to the Operating Room (OR). Upon arrival in the OR, standard monitors including Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), Electrocardiogram (ECG), Oxygen Saturation (SpO₂) were applied and recorded. Anesthesia was induced with an injection of fentanyl 2 mcg.kg⁻¹, propofol 2 mg.kg⁻¹, and atracurium 0.5 mg.kg⁻¹. This was followed by trachea intubation with an appropriate-size endotracheal tube. Anesthesia was maintained with 2% sevoflurane in 50% oxygen. Hemodynamic parameters (HR and Mean Arterial Pressure (MAP) were recorded every 5 minutes till the end of surgery. Ultrasound-guided QL block was performed after induction of anesthesia with patients placed in the lateral decubitus position. All blocks were performed by trained anesthesiologists with over 7 years of experience in administering US-guided blocks. These anesthesiologists were not involved in data collection, which was performed by Operating Room (OR) residents. Postoperative assessments were conducted by trained pain nurses blinded to the intraoperative interventions.

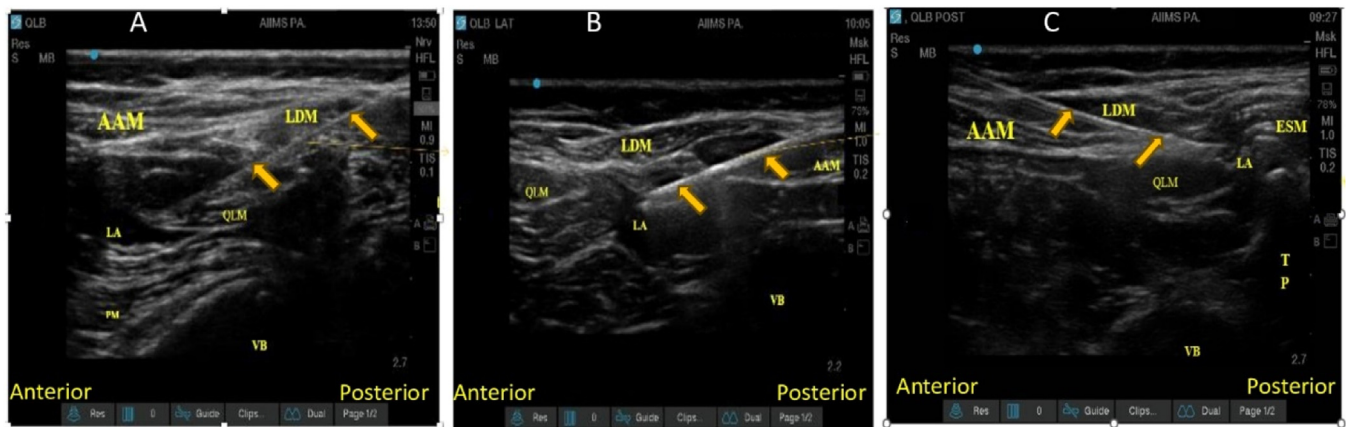


Figure 1 Sonoanatomy of QL block, Panel A: Anterior approach; Panel B: Lateral approach; Panel C: Posterior approach. AAM, Anterior Abdominal Muscle; ESM, Erector Spinae Muscle; LA, Local Anesthetic; LDM, Latissimus Dorsi Muscle; QLM, Quadratus Lumborum Muscle; VB, Vertebral Body.

Technique of QL block: All QL blocks were performed in the lateral position. A high-frequency linear probe (Ultra-sound machine Edge II, Fujifilm Sonosite, Inc., Bothell, WA, United States) was used to visualize the structures and a 22G, 80 mm echogenic needle (Sonoplex needles, Pajunk, Germany) was inserted to deposit the drug.

Anterior QL block: The probe was placed above the iliac crest, and Petit's triangle was identified. The three abdominal muscles (i.e., the external oblique, internal oblique, and transversus abdominis muscles) were identified and followed posteriorly until the layers of the Thoracolumbar Fascia (TLF) appeared as a bright hyper-echogenic line. The needle was inserted in-plane along the posterior edge of the probe in anteromedial direction (Fig. 1, panel A) targeting the plane between the quadratus lumborum and psoas major muscle. After confirming the correct needle tip position and negative aspiration for blood, ropivacaine was injected.

Lateral QL block: The probe was placed in the axial plane in the mid-axillary line, and moved posteriorly until the posterior aponeurosis of the transversus abdominis muscle became visible. The needle was inserted from the anterior and advanced until the needle tip just penetrated the posterior aponeurosis of the transversus abdominis muscle (Fig. 1, panel B). Local anesthetic was injected between the aponeurosis and the fascia at the lateral margin of the QL muscle. **Posterior QL block:** With the patient in the lateral position, the probe was again placed in the axial plane at the mid-axillary line and moved posteriorly to identify the posterior border of the QL muscle. The needle tip was placed between QL and the erector spinae muscle (Fig. 1, panel C).

At the end of surgery, all patients received a diclofenac suppository (1 mg.kg^{-1}) and intravenous paracetamol (15 mg.kg^{-1}) every 8 hours during the postoperative period. Fentanyl (1 mcg.kg^{-1}) was administered intraoperatively and postoperatively in response to a 20% increase in HR or MAP from baseline or if the FLACC score exceeded 4.

Complications like postoperative nausea and vomiting, motor weakness, or block site occurring during the procedure were documented. Patients were extubated after they were awake and generating adequate tidal volume. Postoperative pain was assessed using a FLACC (Face, Legs, Activity, Cry, Consolability) scale at 30 minutes, 2, 4, 8, 12,

and 24 hours. IV Fentanyl 1 mcg.kg^{-1} was administered till 24 hours if the FLACC was more than 4. The time to first rescue analgesic requirements in the postoperative period was documented. Parental satisfaction with pain management was rated on a 10-point Likert scale (where 0 represented the lowest and 10 the highest level of satisfaction).¹⁴

An online calculator (www.clinicalcalc.com) was used to calculate the sample size and power analysis using the Neyman-Pearson approach based on a pilot study done on 18 pediatric patients receiving anterior, lateral, and posterior approaches of QL block. The 24-hour postoperative fentanyl requirement was found to be ($17 \pm 9 \text{ mcg}$), ($25 \pm 12 \text{ mcg}$), and ($22 \pm 12 \text{ mcg}$), respectively, in the anterior, lateral, and posterior approaches of the QL block. Assuming a mean fentanyl difference of 8 mcg between the groups, a standard deviation of 12, a power of 80% and alpha as 0.05, the sample size came out to be 35 in each group. Considering 15% dropouts, we included a total of 120 patients (40 in each group).

Data were entered into Microsoft Excel and analyzed in IBM SPSS software version 23. The normality of the data was tested using the Shapiro-Wilk test. Normalcy of data was checked using the Shapiro-Wilk test. Continuous quantitative variables are presented as mean $\pm$ Standard Deviation (SD) and the intergroup comparisons between the three groups were analyzed by Analysis of Variance (ANOVA) with post-hoc analysis. Quantitative discrete data like FLACC score, time required for first rescue analgesia, and total analgesic consumption were presented as median (IQR) as all the data were not normally distributed when tested using the Shapiro-Wilk test. The Kruskal-Wallis test with pairwise comparisons was applied for comparisons between anterior, lateral, and posterior blocks for the pain scores, time required for first rescue analgesia, and total opioid consumption. Bonferroni corrections were applied for multiple pairwise comparisons between the groups and p-values < 0.0167 were taken as significant. All other comparison levels of p-value < 0.05 were taken as significant.

Results

A total of 130 patients were assessed for eligibility, of whom 10 were excluded (4 did not meet the inclusion criteria and

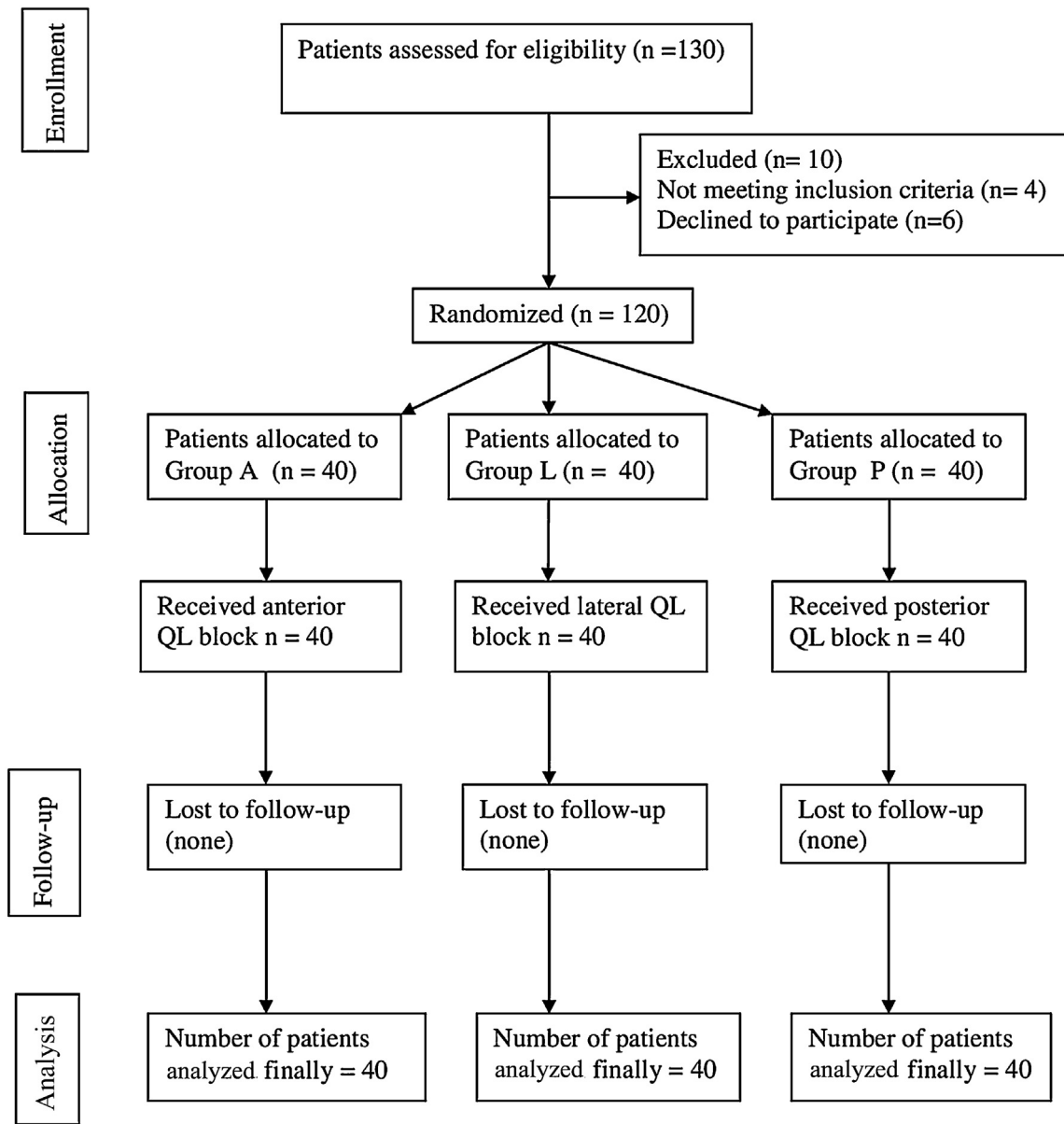


Figure 2 Consort flow diagram of study population.

6 declined to participate). The remaining 120 patients were randomly assigned to three groups and completed the study protocol (Fig. 2). The surgical and demographic characteristics were similar in all 3 groups (Table 1). Postoperative mean fentanyl requirements were lower in Group A (15.0 ± 7.47), than in Group L (23.80 ± 9.56), and in Group P (20.15 ± 9.59) (Table 2). Post-hoc analysis showed significant differences when Group A was compared with Group L and Group P, while differences were insignificant between Group L and Group P (Table 3). Intraoperative mean fentanyl requirement was also lower in Group A (18.48 ± 6.46), in comparison to Group L and Group P (20.0 ± 5.20 and 20.0 ± 8.98 respectively), although differences among groups were insignificant ($p > 0.05$) (Table 2). Post-hoc analysis also showed insignificant differences among groups (Table 3).

Median time to first rescue analgesic requirements was significantly prolonged in Group A in comparison to Group L

and Group P ($p < 0.05$) (Table 2). Post-hoc analysis showed significant differences when Group A was compared with Group L and Group P, while differences were insignificant between Group L and Group P (Table 3).

Median FLACC scores showed variable results among the groups at different time points. It was significantly lower in Group A in comparison to Group L and Group P during the early postoperative period (at 4 hours $p < 0.05$), while the differences were insignificant at 8 hours, at 12 hours and at 24 hours after surgery ($p > 0.05$) (Table 4).

The parent satisfaction score was significantly higher in Group A (8.5 ± 0.55) compared to the other two groups, Group L and Group P, (7.43 ± 0.64 and 8.0 ± 1.01 , respectively; $p < 0.05$) (Table 2). Post-hoc analysis also showed significant differences among groups (Table 3). There were no complications in any of the groups.

Table 1 Demographic and surgical characteristics.

Characteristics	Group A (n = 40)	Group L (n = 40)	Group P (n = 40)	p-value
Age (years) ^a	3.73 ± 1.48	3.30 ± 1.45	2.98 ± 1.49	0.086
Weight (Kg) ^a	16.65 ± 4.28	17.65 ± 5.56	16.10 ± 5.81	0.413
Duration of surgical procedure (mins) ^a	55.0 ± 19.35	55.50 ± 19.93	61.50 ± 18.12	0.244
Types of surgery ^b : Hernia / Orchidopexy / Pyeloplasty	13/13/14	10/14/16	16/10/14	0.690

^a Analysis of Variance (ANOVA), data expressed as mean and Standard Deviation (SD).^b Chi-Square test, data expressed as frequency.**Table 2** Comparison of intraoperative and postoperative opioid consumption, time to first rescue analgesia and postoperative parental satisfaction.

Parameter	Group A (n = 40)	Group L (n = 40)	Group P (n = 40)	p
Intraoperative fentanyl requirements (mcg) ^a	18.48 ± 6.46	20.00 ± 5.20	20.00 ± 8.98	0.538
Postoperative fentanyl consumption (mcg) ^a	15.00 ± 7.47	23.80 ± 9.56	20.15 ± 9.59	0.001
Time to 1 st rescue analgesia (hrs) ^b	20 (16–24)	13 (10–16)	8 (7–16)	0.001
Parental satisfaction score ^a	8.50 ± 0.55	7.43 ± 0.64	8.00 ± 1.01	0.001

^a Analysis of Variance (ANOVA), data expressed as mean and Standard Deviation (SD).^b Kruskal-Wallis test, data expressed as median and interquartile range (IQR), p < 0.05: significant.**Table 3** Post-hoc analysis of intraoperative and postoperative opioid consumption, time to 1st rescue analgesia and postoperative parental satisfaction between the groups.

Variables	Intergroup comparison	Mean difference	95% CI	p-value
Intraoperative fentanyl requirements (mcg)	Group A & Group L	-1.52	-4.65 to 1.60	0.336
	Group A & Group P	-1.52	-4.65 to 1.60	0.336
	Group L & Group P	0.00	-3.13 to 3.13	1.000
Postoperative fentanyl consumed (mcg)	Group A & Group L	-8.80	-12.75 to -4.85	0.001 ^a
	Group A & Group P	-5.15	-9.10 to -1.20	0.011 ^a
	Group L & Group P	3.65	-0.30 to 7.60	0.070
Time to 1 st rescue analgesia (hrs)	Group A & Group L	5.17	2.79 to 7.56	0.001 ^a
	Group A & Group P	7.15	4.76 to 9.54	0.001 ^a
	Group L & Group P	1.975	-0.41 to 4.36	0.104
Parental satisfaction score	Group A & Group L	1.07	0.74 to 1.41	0.001 ^a
	Group A & Group P	0.50	0.16 to 0.84	0.004 ^a
	Group L & Group P	-0.57	-0.91 to -0.24	0.001 ^a

CI, Confidence Interval.

^a p-value < 0.0167 is taken as statistically significant.**Table 4** Comparison of median FLACC “Scores”.

FLACC score (rest)	Group A (n = 40)	Group L (n = 40)	Group P (n = 40)	p-value
30 mins	3 (2–4)	4 (3–5)	4 (3–6)	0.001
2h	3 (2–4)	4 (2–4)	4 (4–5)	0.001
4h	3 (1–5)	3 (2–4)	4 (3–6)	0.003
8h	3 (1–4)	3 (3–4)	3 (1–5)	0.320
12h	1.5 (0–3)	2 (2–3)	3 (2–4)	0.065
24h	1 (0–3)	1 (0–2)	2 (1–2)	0.800

Kruskal-Wallis test, data expressed as median and Interquartile Range (IQR), p < 0.05: significant, FLACC, Faces, Leg, Activity, Cry, “Consolability”.

Discussion

Our findings indicate that the anterior QL block is superior to the lateral and posterior approaches in terms of postoperative analgesic outcomes. Post-hoc analysis also showed a significantly prolonged duration of analgesia, decreased requirement for postoperative fentanyl, and higher parent satisfaction in the anterior QL block group. FLACC scores were significantly lower in Group A compared to Group L and Group P during the early postoperative period, up to 4 hours. However, the difference in median FLACC scores may not be clinically significant, as the difference in medians was not more than 2 points. This discrepancy might be attributed to the rescue dose of fentanyl administered during the postoperative period, which could have influenced the FLACC scores. The median duration of analgesia in Group A was significantly longer compared to Group L and Group P (20 hours vs. 13 hours vs. 8 hours, respectively), which appears to be clinically significant as well.

Lower abdominal surgeries are common in pediatric patients, and inadequate pain control can lead to complications such as delayed recovery, poor patient satisfaction, and the development of chronic pain syndromes. The Quadratus Lumborum (QL) block provides sensory analgesia to the inguinal region by consistently blocking both the iliohypogastric and ilioinguinal nerves (root values L1 and L2), owing to its wide dermatomal coverage (T7–L2).¹⁰

The proposed hypothesis for superior analgesia with the anterior QL block is that it allows a more extensive spread of Local Anesthetic (LA) to the lumbar nerve roots and their branches, as well as to the thoracic paravertebral space, thereby providing both somatic and visceral analgesia.^{15,16} In contrast, the posterior QL block limits drug spread primarily to the middle thoracolumbar fascia and intertransverse area.⁶ The lateral QL block achieves its effect via spread along the transversus abdominis plane and into the subcutaneous tissue.¹⁷

These findings are supported by a cadaveric dye study conducted by Elsharkawy et al.,¹⁸ in which dye spread widely into the thoracic paravertebral space (T9–T12), staining the iliohypogastric and ilioinguinal nerves (L1), and the subcostal nerve in the anterior approach, thereby providing broader coverage and more effective sensory blockade.

Sato et al., in a study involving pediatric patients, reported that the QL block was superior to both the Transversus Abdominis Plane (TAP) block and caudal blocks in terms of pain scores, patient satisfaction, and the number of patients requiring rescue analgesia.¹⁹ Similarly, Aksu and Gurkan demonstrated that the QL block was effective for pediatric day-care hernia surgeries and outperformed the TAP block in terms of analgesic efficacy.²⁰

Since its initial description in 2007, the QL block has evolved, with three commonly practiced approaches. Ahmed et al. compared the anterior and posterior approaches in patients undergoing unilateral inguinal hernia repair.²¹ They found that patients receiving the anterior approach had significantly longer-lasting analgesia compared to those who received the posterior approach.

Despite these findings, literature describing the use of QL blocks in children for postoperative analgesia across various surgeries remains limited.^{22–24} To the best of our knowledge,

no randomized studies have compared all three approaches – anterior, posterior, and lateral – in the pediatric population. However, El Malla et al.²⁵ compared the anterior and posterior approaches and found that the anterior QL block provided a better analgesic profile, with significantly reduced postoperative morphine consumption, longer analgesic duration, and lower pain scores, without any adverse effects, in pediatric patients undergoing laparoscopic inguinal hernia repair.

Our findings align with these results, showing reduced requirements for rescue analgesia during both intraoperative and postoperative periods, improved pain scores, and prolonged analgesia with the anterior approach. This approach also yielded higher parental satisfaction compared to the lateral and posterior approaches.

In contrast, a study by Ahuja et al.²⁶ found that a single-shot anterior QL block offered no significant advantage over no block in pediatric patients undergoing unilateral inguinal hernia surgery under Subarachnoid Block (SAB). This may be due to various factors affecting the spread of local anesthetic, including anatomical variations, the path of least resistance, injection speed, and the volume of anesthetic administered.

The anterior approach was first described by Borglum et al. An MRI study conducted one-hour post-injection demonstrated that the LA had spread cephalad to reach the thoracic paravertebral space. This spread was attributed to the shared embryological origin and insertion of the psoas major and quadratus lumborum muscles within the thoracic cage. These findings were later confirmed by additional cadaveric studies.

There have been reports of lower limb weakness due to the spread of LA to the lumbar plexus. Although we did not specifically assess muscle strength due to the young age of our participants, we did not observe any visible signs of lower limb weakness.²⁷ Additionally, no complications related to QL block were encountered in our study. Despite being a deep block, which can be associated with risks such as retroperitoneal hematoma, organ injury, or local anesthetic toxicity,²⁸ no adverse events occurred. However, spread to the paravertebral space can, in some cases, lead to hypotension and bradycardia.

This study has several limitations. First, the inclusion of heterogeneous surgical procedures with distinct pain profiles could have influenced analgesic consumption and parental satisfaction outcomes. A stratified randomization or subgroup analysis may have mitigated this issue. Second, although experienced anesthesiologists performed the blocks, subtle visual or tactile clues may have compromised blinding. Third, due to the pediatric population, no objective assessment of motor weakness was conducted, despite potential lumbar plexus spread, especially with the anterior approach. Lastly, this study employed a single-shot block; continuous catheter techniques may yield different analgesic profiles and warrant further investigation.

Conclusion

In this randomized controlled trial, the anterior approach to the quadratus lumborum block was associated with lower postoperative opioid consumption, longer duration of analgesia, and higher parental satisfaction compared to lateral and posterior approaches in pediatric patients undergoing

lower abdominal surgery. Despite these findings, further multicenter studies with larger and more homogeneous populations are warranted to confirm these results and refine clinical guidelines for QL block in pediatrics.

Data availability statement

The datasets generated and/or analyzed during the current study are available in the SciELO Data repository - <https://doi.org/10.48331/SCIELODATA.Q22LU0>. Any additional data are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contribution

Arun SK: This author helped in writing-original draft; data curation.

Ajeet Kumar: This author helped in conceptualization; writing-review & editing.

Amarjeet Kumar: This author helped in writing-review & editing; supervision.

Chandni Sinha: This author helped in writing-review & editing; data curation.

Abhyuday Kumar: This author helped in writing-review & editing.

Poonam Kumari: This author helped in writing-review & editing.

Bindey Kumar: This author helped in supervision; data curation.

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Guilherme Antonio Moreira de Barros

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ORIGINAL INVESTIGATION

Lateral versus posterior quadratus lumborum block in children undergoing open orchiopexy: a double-blind randomized clinical trial



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KEYWORDS

Acute pain;
Analgesia;
Nerve block;
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Abstract

Background: Quadratus Lumborum Block (QLB) has recently become an effective analgesic regional technique frequently used in abdominal surgeries. However, due to the heterogeneity in studies regarding block approaches, a direct comparison of QLB types is needed. In this double-blind prospective randomized trial, we aimed to compare the effects of lateral and posterior approaches of QLB on pain and analgesic use in children undergoing orchiopexy.

Methods: Patients aged 6 months – 12 years undergoing elective unilateral open orchiopexy were included in the study. Patients were randomized into two groups using the closed-envelope method. Lateral or posterior QLB was applied under ultrasonography with 0.4 mL/kg 0.25% bupivacaine for both groups before the surgery. The primary outcome was the assessment of postoperative pain for 24 hours. Analgesic usage, parental satisfaction, and complications were recorded as secondary outcomes.

Results: Analyses were conducted on 80 patients. Both study groups achieved clinically adequate analgesia, and no significant pain score distinctions were observed within 24 hours (Total mean scores: FLACC [lateral QLB: 2.86 ± 4.69 vs. posterior QLB: 2.87 ± 3.71 , $p = 0.466$], Wong-Baker [lateral QLB: 0.86 ± 2.03 vs. posterior QLB: 1.24 ± 1.85 , $p = 0.151$]). No significant interaction effect between groups and postoperative time intervals on pain scores was observed (FLACC score p-interaction: 0.425, Wong-Baker score p-interaction: 0.451). There were no statistical differences in the number of patients necessitating intraoperative and postoperative analgesics. Parental satisfaction exhibited similarity between the groups, and no perioperative complications were observed in either group.

Conclusion: Lateral and posterior QLB provided similar perioperative analgesia in pediatric patients undergoing orchiopexy.

Clinical trial registration number: NCT05056038.

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Introduction

Pediatric patients exhibit a heightened response to pain stimulation, and potential barriers exist in managing pain, often resulting in undertreatment.¹ Postoperative pain is associated with complications, delayed recovery, diminished patient satisfaction, and chronic pain.² Hence, prioritizing effective pain management is crucial in children. Orchiopexy, a commonly performed surgical procedure, targets an anatomical region characterized by extensive and complex innervation, posing challenges for pain control.^{3,4}

Quadratus Lumborum Block (QLB) is a recently described fascial plane block that has been shown to be an effective and reliable analgesic method for lower abdominal surgeries and orchiopexy in pediatric patients.^{2,4,5} Numerous studies have demonstrated that QLB is more effective and longer-lasting compared to the caudal block.⁶

The concept of QLB was initially introduced by Blanco, and since then, different variations of QLB have been defined by administering injections on various sides of the Quadratus Lumborum Muscle (QLM).^{7,8} The mechanisms and analgesic efficacy of various QLB approaches remain controversial in the current literature.^{2,7-10} As of now, no conclusive evidence supporting one QLB type over the other.⁹

The aim of the study was to assess and compare the analgesic effectiveness of ultrasound-guided lateral and posterior QLB approaches in pediatric patients undergoing orchiopexy. We hypothesized that posterior QLB could provide better analgesia with a more extensive spread compared to lateral QLB.^{7,11,12}

Methods

This prospective study, designed as a randomized, double-blind trial, was approved by the Istanbul University-Cerrahpasa, Institutional Review Board (IRB #90211). Written informed consent was obtained from the parents or legal guardians of all patients who participated in the trial. The study was registered on clinicaltrials.gov (NCT05056038, date of registration: June 2021) before enrolling patients, and the manuscript adheres to the CONSORT guidelines, employing a flow diagram for patient enrollment and allocation.

The study included pediatric patients with the American Society of Anesthesiologists (ASA) class I–III, aged between 6 months and 12 years, undergoing elective unilateral orchiopexy between July 2021 and July 2022. Exclusion criteria encompassed patients with contraindications for regional anesthesia, declined to provide consent, scheduled for a laparoscopic approach, ASA class IV, and requiring postoperative admission to the intensive care unit. The primary outcome was the assessment of postoperative pain for 24 hours. Analgesic usage, parental satisfaction, and complications were the secondary outcomes.

Patients were premedicated with intravenous 0.05 mg/kg midazolam and 0.5 mg/kg ketamine. Following standard monitorization, induction of anesthesia was achieved using 5 mg/kg thiopental, 1 µg/kg fentanyl, 0.6 mg/kg rocuronium, and subsequent orotracheal intubation was performed. Anesthesia was maintained with 2% sevoflurane. The duration of surgical procedures was recorded.

All blocks were performed by two highly experienced pediatric anesthesiologists (A.C.T and P.K) after endotracheal intubation and prior to the surgical procedure. The specific type of block – either lateral or posterior QLB – was determined using a sealed envelope technique. Each patient was assigned a study number to ensure anonymized tracking. Perioperative follow-up and data collection were conducted by a third anesthesiologist, who was blinded to group allocation, along with nursing staff. The anesthesiologists performing the blocks were aware of the group assignments solely to perform the correct intervention; however, they were not involved in any aspect of data collection. Furthermore, both patients and their parents remained blinded to group allocation throughout the study period.

Both techniques were performed in a supine or semi-lateral position under sterile conditions, utilizing 18, 20, or 22-gauge intravenous cannulas (Bicakcilar Cooperation, Istanbul, Turkey) selected based on the patient's age. The needle was guided using the linear probe of the ultrasound system (GE Logiq-E Ultrasound System with 9L Linear Transducer, Illinois, USA), and the 'in-plane' technique was employed. After the probe was positioned at the umbilical level, advanced until the terminal of the Transversus Abdominis Muscle (TAM) and QLM were visualized. The needle was directed anteroposteriorly. Following the confirmation of correct needle placement, ascertained by the absence of blood aspiration and injecting small aliquots of 1 mL 0.9% saline, both blocks were initiated with the administration of 0.4 mL/kg of 0.25% bupivacaine.

Lateral QLB (QLB-1): Local Anesthetic (LA) is injected into the anterolateral aspect of the QLM, specifically at the junction with the posterior aponeurosis of the TAM and the transversalis fascia. The transversalis fascia merges with the QLM fascia to form the anterior Thoracolumbar Fascia (TLF) (Fig. 1A).^{7,8,13}

Posterior QLB (QLB-2): LA is injected on the posterior surface of the QLM. This injection site is located between the QLM, erector spinae, and latissimus dorsi muscles, targeting a specific anatomical region called the Lateral Interfascial Triangle (LIFT). The LIFT represents a triangular structure located at the juncture of the middle TLF and the deep lamina of the posterior TLF (paraspinal retinacular sheath) (Fig. 1B).^{7,8,13}

Following the administration of the block, the Mean Arterial Pressure (MAP) and Heart Rate (HR) were recorded before the surgical incision and at the 5, 10, 20, 30, 45, and 60 minutes after the incision. The surgery started at least 10 minutes after the performance of the block. In the event of a 20% increase in HR and MAP from the baseline, remifentanyl infusion was initiated in accordance with current guideline recommendations.¹⁴ The dose of remifentanyl was adjusted based on HR and MAP measurements (within ± 20% of the baseline), and the infusion was terminated as soon as possible.

Following surgery, all patients received standard postoperative care in the pediatric post-anesthesia care unit for 2 hours before being transferred to the pediatric surgery inpatient ward. Pain assessments were conducted by attending nurses using the Face, Legs, Activity, Cry, Consolability (FLACC) score at 10, 20, and 30 minutes, and at 1, 2, and 6 hours postoperatively.¹⁵ Analgesia was not routinely

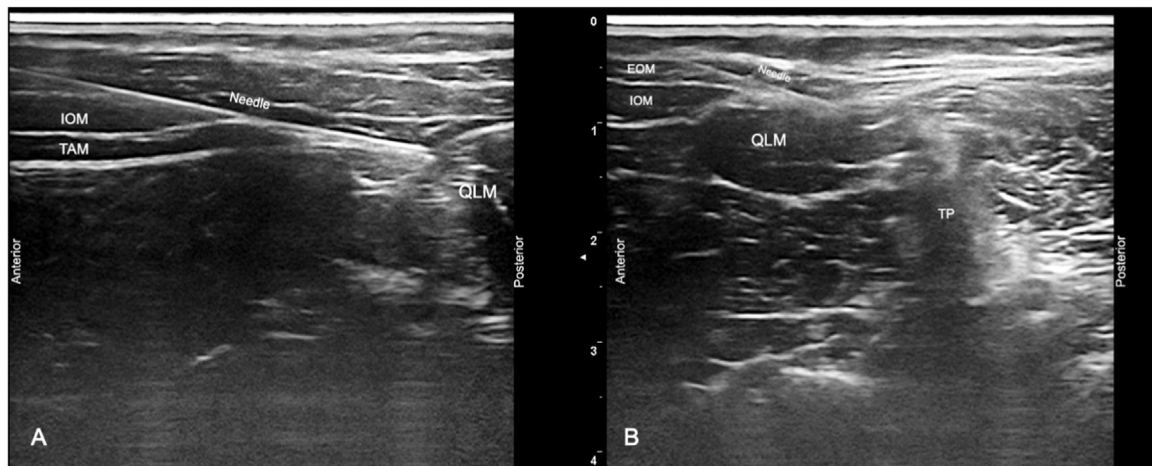


Figure 1 (A) USG imaging of the lateral QLB, (B) USG imaging of the posterior QLB. EOM, External Oblique Muscle; IOM, Internal Oblique Muscle; QLM, Quadratus Lumborum Muscle; TAM, Transversus Abdominis Muscle; TP, Transverse Process; USG, Ultrasonography.

administered to all patients. Instead, if a patient's FLACC score was ≥ 4 , indicating inadequate analgesia, 1 mg/kg intravenous tramadol was administered as the first-line rescue analgesic.^{14,16} If the pain score remained ≥ 4 following tramadol administration, 15 mg/kg intravenous paracetamol was given as a second-line intervention.

Prior to discharge, parents were educated on the use of the Wong-Baker Pain Scale and provided with a printed copy of the scale to use at home.¹⁵ They were instructed to assess their child's pain and, if the Wong-Baker score was 4 or higher, to administer 10 mg/kg oral ibuprofen.

Follow-up phone calls were conducted at 16 and 24 hours postoperatively to inquire about Wong-Baker pain scores, any use of analgesics, and overall patient comfort. During the 24-hour follow-up, parental satisfaction regarding postoperative pain management was recorded using a 3-point scale: not satisfied (1), partially satisfied (2), and very satisfied (3).

Patients were monitored for any complications related to the QLB both during their hospital stay and throughout the 24-hour postoperative follow-up period, and any adverse events were recorded.

Sample size calculation

A pilot study involving five patients per group was conducted to estimate the effect size using the Confidence Interval (CI) approach described by Cocks et al.¹⁷ The sample size was calculated using the G*Power program, version 3.1 (Heinrich-Heine University, Duesseldorf, Germany), for a two-way repeated measures within-between interaction multivariate analysis of variance test, with $\alpha = 0.05$, and power $(1 - \beta) = 0.80$. The outcomes considered for sample size estimation were the FLACC score, measured at six postoperative time points, and the Wong-Baker score, measured at two time points. The effect size $f(V)$ was determined to be 0.44 based on the pilot study. A sample size of 36 per group was calculated, and accounting for a 20% loss to follow-up, the total number of participants required was determined as 86 patients.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean (SD) or median (Interquartile Range [IQR]). Normality of distribution was assessed using both visual methods (histograms, Q-Q plots) and analytical methods (Shapiro-Wilk test). Independent samples *t*-test or Mann-Whitney *U* test was utilized to compare continuous variables. Chi-Squared and Fisher's Exact test were employed to analyze categorical variables, as appropriate. Odds ratios were derived from contingency tables.

A non-parametric rank-based analysis of variance test type statistic for factorial longitudinal data was used to assess the interaction effect between time points and scores within the two groups with "nparLD" package version 2.2.^{18,19} Relative Treatment Effects (RTE) were calculated for each group at each time point. An RTE reflects the probability that a randomly chosen score from that group and time point is higher than a randomly chosen score from the entire sample. An RTE of 0.5 indicates no deviation from the overall average. For pain scores, RTE < 0.5 indicates lower scores, and RTE > 0.5 indicates higher scores.

Effect sizes were also calculated using Cliff's Delta, which quantifies the probability that a randomly selected observation from one group is higher than one from the other group. Effect sizes were interpreted as negligible (< 0.15), small ($0.15 - 0.33$), medium ($0.33 - 0.47$), or large (> 0.47). Due to the non-normal distribution of the data, Cliff's Delta was chosen over Cohen's *d* as a more robust measure for non-parametric data.²⁰

Post hoc pairwise comparisons were performed using the Wilcoxon signed-rank test, with Bonferroni correction applied to adjust for multiple comparisons among all condition pairs where significant overall differences were observed. These analyses were exploratory and aimed at identifying specific group differences. Additionally, postoperative time without analgesics and time to first analgesic requirement (any rescue analgesia) were compared between the two groups using Kaplan-Meier analysis and the log-rank

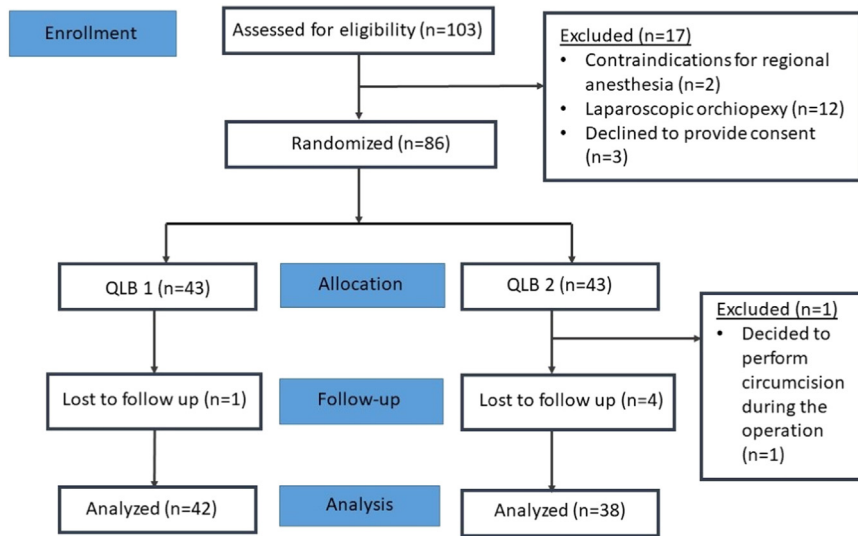


Figure 2 CONSORT diagram.

test. All statistical analyses were performed using R Statistical Software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages “survival”, “nparLD”, “ggplot2”, and “effsize”. The p-value of < 0.05 indicated statistical significance and all p-values were two-sided.

Results

Figure 2 demonstrates the CONSORT diagram for the enrollment process of the study. Analyses were conducted on 80 patients, with 42 allocated to the lateral group (QLB-1) and 38 to the posterior group (QLB-2).

Baseline characteristics, the time between block and incision, the duration of surgery, and intraoperative hemodynamic parameters were similar between the two groups (Table 1, Supplementary Table 1). No significant interaction effect on intraoperative hemodynamic parameters was observed between the two QLB techniques across time intervals (Supplementary Fig. 1 and 2). Regarding the intraoperative usage of remifentanyl, no statistically significant differences were observed in both groups (Supplementary Table 2).

FLACC and Wong-Baker scores were comparable between two groups at any recorded time interval ($p > 0.05$) (Table 2). Relative treatment effects were calculated for each group

and the interaction effects between groups and postoperative time intervals measurements were not statistically significant (FLACC score p-interaction: 0.425, Wong-Baker score p-interaction: 0.451) (Fig. 3A–3B; Supplementary Table 3). Clinically adequate analgesia, as indicated by total mean FLACC and Wong-Baker scores below four, was achieved in both study groups. Mean total FLACC ([QLB-1] 2.86 ± 4.69 vs. [QLB-2] 2.87 ± 3.71 , $p = 0.466$; Cliff’s delta = -0.086, 95% CI: -0.313 to 0.150) and Wong-Baker ([QLB-1] 0.86 ± 2.03 vs. [QLB-2] 1.24 ± 1.85 , $p = 0.151$; Cliff’s delta = -0.149, 95% CI: -0.345 to 0.060) scores were similar between two groups. Furthermore, parental satisfaction scores were similar between the groups ($p = 0.400$) (Table 2). In post-hoc pairwise comparisons, no statistically significant difference was observed at each time interval for either group (Supplementary Table 4 and 5). In the subgroup of patients older than 7 years, there were no significant differences in FLACC scores compared to patients younger than 7 years (Supplementary Table 6).

During postoperative follow-up, it was noted that 14 patients from the QLB-1 group and 16 patients from the QLB-2 group required additional analgesics ($p = 0.563$). No statistically significant differences were observed in the number of patients requiring postoperative analgesics between the two groups at any time in 24 hours ($p > 0.05$) (Fig. 4A, Supplementary Table 7). Moreover, the durations of

Table 1 Demographic and clinical data.

	QLB1 (n = 42)	QLB2 (n = 38)	p-value
Median age (IQR) in months	42 (22–69)	48 (36–82)	0.078 ^a
Median weight (IQR) in kilograms	17 (12–22)	19 (13–24)	0.347 ^a
Mean height (SD) in centimeters	101 ± 16	107 ± 18	0.130 ^b
Median body surface area (IQR) in m ²	0.70 (0.56–0.83)	0.75 (0.55–0.88)	0.312 ^a
Median start time between block and incision (IQR) in minutes	15 (13–18)	15 (12–20)	0.794 ^a
Median surgery duration (IQR) in minutes	94.5 (89.0–100.5)	96.0 (92.5–100.7)	0.130 ^a

IQR, Interquartile Range; SD, Standard Deviation; QLB, Quadratus Lumborum Block.

^a Mann-Whitney-*U* test.

^b Independent Samples *t*-test.

Table 2 Postoperative pain and parent satisfaction scores.

	QLB1 (n = 42)		QLB2 (n = 38)		p-value ^a	Cliff's delta (95% CI)
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]		
Total FLACC score	2.86 (4.69)	1 [1–5]	2.87 (3.71)	2 [1–5]	0.466	–0.086 (–0.313, 0.150)
10 th min	1.38 (2.87)	0 [0–0]	1.55 (2.29)	0 [0–3]	0.214	–0.131 (–0.333, 0.082)
20 th min	0.52 (1.47)	0 [0–0]	0.45 (1.43)	0 [0–0]	0.657	0.033 (–0.115, 0.180)
30 th min	0.50 (1.44)	0 [0–0]	0.55 (1.50)	0 [0–0]	0.846	–0.016 (–0.175, 0.145)
60 th min	0.45 (1.21)	0 [0–0]	0.32 (0.90)	0 [0–0]	0.822	0.018 (–0.136, 0.171)
2 nd hour	0.36 (1.62)	0 [0–0]	0.21 (1.14)	0 [0–0]	0.949	–0.003 (–0.101, 0.095)
6 th hour	0.69 (1.81)	0 [0–0]	0.55 (1.61)	0 [0–0]	0.841	0.016 (–0.138, 0.169)
Total Wong Baker score	0.86 (2.03)	0 [0–0]	1.24 (1.85)	0 [0–3]	0.151	–0.149 (–0.345, 0.060)
16 th hour	0.67 (1.51)	0 [0–0]	0.79 (1.60)	0 [0–0]	0.642	–0.043 (–0.225, 0.141)
24 th hour	0.19 (0.74)	0 [0–0]	0.45 (1.01)	0 [0–0]	0.084	–0.135 (–0.286, 0.023)
Parent satisfaction score	2.90 (0.30)	3 [3–3]	2.84 (0.37)	3 [3–3]	0.400	0.063 (–0.087, 0.210)

Data are displayed as mean (SD), median [IQR], or n/total n (%).

CI, Confidence Interval; IQR, Interquartile Range; P, Percentile; SD, Standard Deviation; min, Minute.

^a Mann-Whitney-U test.

analgesic-free interval were similar in both groups ($p = 0.421$) (Fig. 4B, Supplementary Table 8). No hemodynamic abnormalities, complications, or side effects were observed in either group throughout the perioperative period.

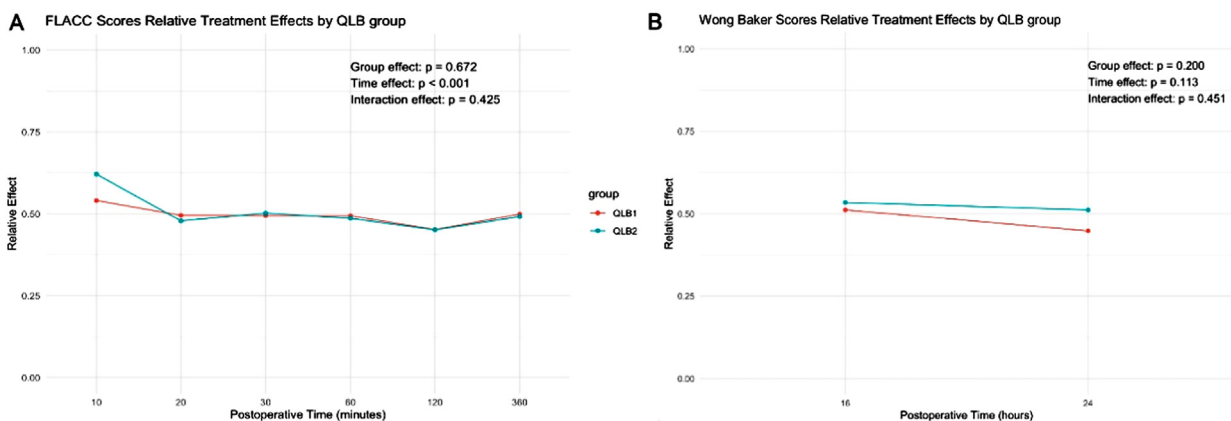
Discussion

This study compared the clinical effectiveness of lateral and posterior QLB. The main findings of our study were as follows: there was no statistically significant difference in (1) Postoperative pain scores in 24 hours, (2) Perioperative analgesic requirements, and (3) Parental satisfaction between the two blocks, demonstrating comparable postoperative analgesia in pediatric patients undergoing open orchiopexy.

To our knowledge, this is the first double-blind, prospective, randomized study comparing perioperative analgesic efficacy of lateral and posterior QLB in children. QLB is an effective fascial plane block for lower abdominal surgeries and orchiopexy in pediatric patients.^{2,4-6} However, in the literature, QLB techniques vary across studies, highlighting the need for direct comparative evaluations of different QLB approaches.^{2,9}

The lateral QLB is performed at the anterolateral border of the QLM, specifically at its junction with the transversalis fascia.¹³ The mechanism of action is thought to involve the spread of injectate into the Transversus Abdominis Plane (TAP) and potentially further through the anterior TLF into the paravertebral space.^{7,8,11} In contrast, the posterior QLB targets the posterior aspect of the QLM, aiming at the LIFT, and is proposed to spread via the middle TLF.^{11,13} In addition, the TLF, which has a high-density network of sympathetic fibers and mechanoreceptors, is considered to be a contributing factor in the effects of QLB.^{7,8}

An imaging study with Computed Tomography (CT) demonstrated that, in both lateral and posterior QLB, the injected solution was consistently observed in the TAP and intercostal planes, particularly around the 10th and 11th ribs.¹¹ These regions correspond to the pathways of the ilioinguinal, iliohypogastric, subcostal, and lower intercostal nerves.¹¹ This observation aligns with the findings of anatomical studies and suggests a plausible mechanism of action for these blocks in patients undergoing abdominal surgery.^{8,21,22} We hypothesized that posterior QLB could provide better analgesia due to its potentially broader spread, as demonstrated by imaging studies using CT and contrast-enhanced MRI.^{11,12} However, these studies primarily focused

**Figure 3** Changes in relative treatment effects of QLB groups over postoperative time for (A) FLACC, and (B) Wong-Baker scores.

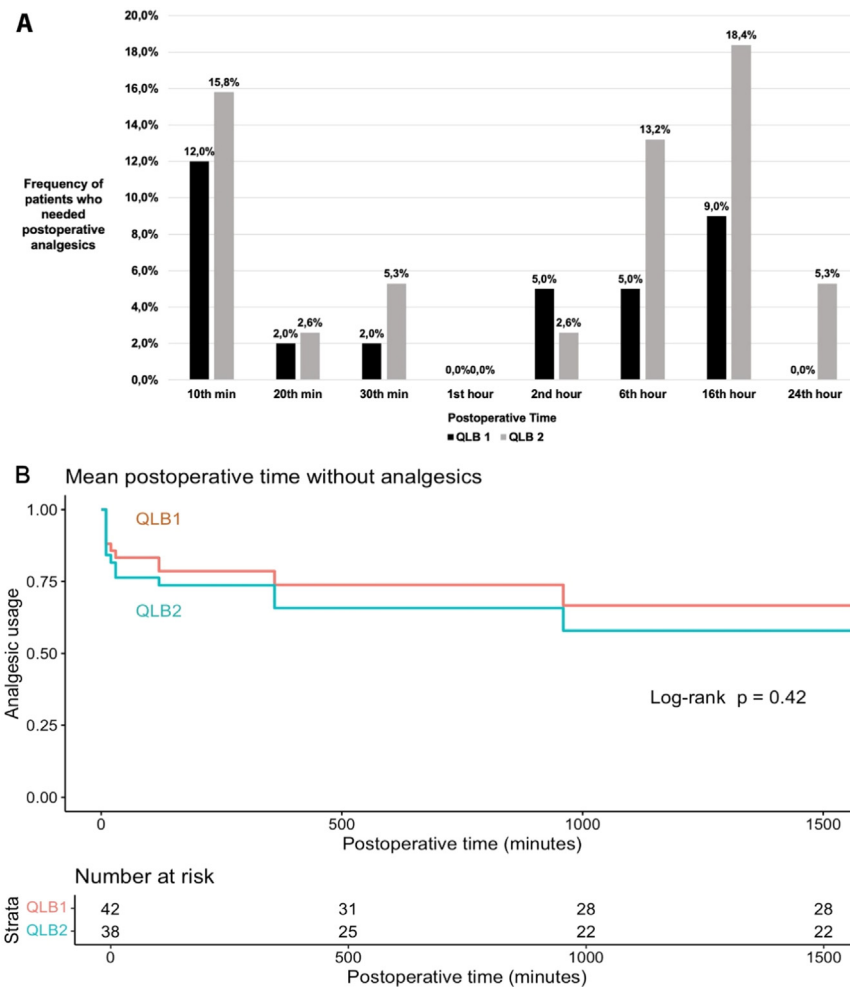


Figure 4 (A) Postoperative analgesic utility, (B) Kaplan-Meier plot for mean postoperative time without analgesics.

on the anatomical distribution of the injectate rather than comparing clinical analgesic outcomes.^{11,12} In contrast to our expectations, our findings did not demonstrate a significant analgesic advantage of posterior over lateral QLB in pediatric patients undergoing orchiopexy.

Our previous study compared the posterior TAP block and lateral QLB, showed that lateral QLB is clinically more effective than the TAP block in children undergoing open orchiopexy.⁵ In the current study, the comparable efficacy observed between lateral and posterior QLB further reinforces the clinical value of QLB techniques overall and highlights their potential advantage over the TAP block for orchiopexy. In line with these findings, a recent meta-analysis demonstrated that QLB reduces postoperative pain scores and the need for rescue analgesia compared to caudal block and other peripheral nerve blocks, without increasing side effects after lower abdominal surgery in children.² However, in the subgroup analysis, there was no consistent difference between the QLB techniques due to notable study heterogeneity.²

There are limited number of clinical studies comparing the analgesic efficacy of posterior and lateral QLB in adults, no data in children exists.^{9,23,24} Li et al. compared lateral and posterior QLB with a control group, including 32 patients

in each group aged 18–70 years, undergoing laparoscopic renal surgery. Unlike our study, all patients received routine flurbiprofen and a basal sufentanil infusion (1.25 mcg/mL at 0.5 mL/h) via a Patient-Controlled Analgesia (PCA) pump. Both QLB approaches provided a decrease in somatic and visceral pain intensity for up to 24 hours after surgery compared to the control group; however, they did not lead to a reduction in total opioid consumption, which was attributed to the continuous PCA basal infusion administered across all groups. Furthermore, there was no statistically significant difference in analgesic efficacy between the lateral and posterior QLB techniques.²³

In another study, lateral and posterior QLB approaches were compared in overall 57 patients aged 20–60 undergoing laparoscopic cholecystectomy. Tenoxicam was routinely administered before the end of surgery. Postoperative analgesia was managed with intravenous PCA tramadol, and paracetamol was used as rescue medication. The blocks did not result in any significant differences in pain scores at any postoperative time point, nor in intraoperative or postoperative analgesic consumption.²⁴ Our findings align with those reported in adult studies, showing that lateral and posterior QLB techniques yield comparable outcomes.^{23,24} Therefore, these results may extend across different age groups and

surgical settings. However, direct comparison of effect sizes is limited by differences in patient demographics, surgical procedures, and analgesic protocols.

On the other hand, differences between pediatric and adult regional anesthesia should be considered. Pediatric regional anesthesia is generally more technically challenging than in adults, although ultrasound image interpretation and needle visualization tend to be easier. Specifically regarding QLB, the spread of LA may differ due to variations in muscle and fascial planes compared to adults.²⁵ The recommended LA concentration and volume for pediatric QLB is 0.2–0.5 mL/kg of 0.25% bupivacaine, 0.25% levobupivacaine, or 0.2% ropivacaine in accordance with the current guideline.¹⁶ Additionally, only a limited correlation has been demonstrated between the postoperative pain scores and the volume of LA administered.²⁶

In children undergoing orchiopexy, previous data indicated that the most intense period of postoperative pain occurs within the initial 24 hours following the procedure.²⁷ Consequently, our primary objective centered on evaluating perioperative pain and analgesic usage within critical 24-hour timeframe. In our study, both approaches demonstrated clinically effective for analgesia, with no significant disparities observed in pain scores between the two groups. The fact that both blocks provided sufficient analgesia to minimize postoperative distress and reduce the overall need for additional analgesics highlights their practical value in pediatric patients, where undertreated pain is known to have lasting effects on pain perception and long-term outcomes.²⁸

Nevertheless, it is worth noting that 14 patients in the lateral QLB group and 16 in the posterior QLB group required additional analgesic intervention, although there were no statistically significant distinctions in any time or duration of analgesic-free intervals within these two groups. We postulate that the primary reason for the demand for supplemental analgesics can be attributed to anatomical variations in the dispersion of LA within the TLF.^{8,11} Secondary factors may include disparities in the intensity of surgical stimuli and areas of uncovered innervation, which may arise due to the intricate innervation of the testis, spermatic duct, and scrotum.^{3,29}

Innervation of the spermatic cord is supplied by three main sources: the superior spermatic nerves from the renal and intermesenteric plexus, the median spermatic nerves from the superior hypogastric plexus, and the inferior spermatic nerves from the pelvic plexus. Innervation of the testis and scrotum includes: (1) Somatic and sensory innervation through the iliohypogastric, ilioinguinal, genitofemoral, and pudendal nerves (from the L1–L2 and S2–S4 roots); (2) Parasympathetic innervation from the S2–S4 segments; (3) Sympathetic innervation from the T10–L1 roots, which embryologically share innervation with the kidney.^{29,30} However, both lateral and posterior QLB predominantly provide analgesia by involving dermatomes from T7 to L1.^{7,26,31} This may not be sufficient for scrotal incision due to the complex scrotal innervation from the genitofemoral, pudendal, posterior femoral cutaneous, and ilioinguinal nerves originating from L1–S3.²⁹

QLB is generally recognized as a reliable regional technique,^{2,26} and no complications or side effects were observed in our study. Nevertheless, it is crucial to be aware

of potential complications. Hemodynamic side effects and motor block can occur due to the dispersion of LA into paravertebral spaces and the lumbar plexus.^{2,9} The risks of retroperitoneal hematoma and solid organ damage, such as liver, kidney, and intestine, should not be overlooked.^{7,9} LA toxicity should be considered, especially after the bilateral block performance.^{2,8} Lastly, postoperative nausea/vomiting and urinary retention can also manifest. A recent meta-analysis has shown comparable results in postoperative nausea/vomiting and urinary retention between QLB or non-QLB in children.¹⁰

The limitations of our study were as follows: (1) We could not assess the level of sensory block during intraoperative and postoperative periods. (2) Pain assessment and analgesic administration after the 6th hour were determined by parents, as the orchiopexy procedure was performed on an outpatient basis. Using the Wong-Baker score for post-discharge pain evaluation was necessitated because the FLACC score was deemed unsuitable for parental assessment. (3) While the FLACC score is typically more appropriate for children under seven, we employed it across all age groups to maintain a consistent approach to pain assessment. The mean age of the patients included in our study was 51 months; therefore, we believe that using the FLACC score in older age groups did not significantly impact the study's results. Additionally, we performed a subgroup analysis comparing children older than seven years with those younger than seven, and the results indicated no significant differences in FLACC scores between the two groups. (4) The sample size for this study was initially determined based on a pilot study, aiming to assess both between-group differences and within-group changes. Final study calculations confirmed that sufficient statistical power was achieved for detecting between-group differences; however, the power to detect within-group changes may have been limited.

Conclusion

This study demonstrated that both lateral and posterior QLB provide effective postoperative analgesia in pediatric patients undergoing orchiopexy, with no significant differences between them in terms of 24-hour postoperative pain scores, rescue analgesic requirements, parental satisfaction, or complications. Consequently, either technique may be considered based on the patient's clinical condition, without the need to reposition the patient after anesthesia induction. The lateral QLB may be preferred for orchiopexy due to its relative technical simplicity, whereas the posterior approach requires greater expertise. Nonetheless, it is noteworthy that there is limited research directly comparing these two techniques. Therefore, further studies are needed to better understand their comparative efficacy and safety profiles.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Ozgecan P. Zambak Mutlu made substantial contributions to the conception and design of the study, data collection, interpretation, and drafting of the manuscript. She also critically revised the work for important intellectual content and provided final approval of the version to be published. Pinar Kendigelen contributed significantly to the implementation of blocks. Ayse C. Tutuncu played a key role in the study's conception and design, implementation of blocks, and critical revision of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.bjane.2025.844661](https://doi.org/10.1016/j.bjane.2025.844661).

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ORIGINAL INVESTIGATION

Retrospective review of spinal magnetic resonance images to determine the margin of safety for epidural analgesia in pediatric patients



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Abstract

Background: Deeply sedated children cannot provide feedback if an epidural needle traumatizes the Spinal Cord (SC). Knowing relevant structure depths may, therefore, improve safety. We aimed to determine the epidural margin of safety, i.e., distances from the Ligamentum Flavum (LF) and from the dura mater to the SC in pediatric patients measured (i) Perpendicular to the SC and (ii) Parallel to the spinous process (to approximate needle trajectory).

Methods: Retrospective review of pediatric (0–12 years-old) T2-weighted sagittal MRI spine scans without spinal pathology. Three investigators independently measured distances from the ventral edge of the LF, and from the ventral edge of the dura mater to the SC at T5/T6, T9/T10, and L1/L2. All measurements were taken perpendicular to the SC and parallel to the angle of the spinous process of the inferior vertebra.

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Results: 111 MRI scans [52 females, 0.08–12 (median 7) years-old] were analyzed. The conus medullaris was identified superior to the L1 vertebra in 47 scans, requiring L1/L2 measurement exclusion. When all ages were combined, the largest median (range) depth [dura-mater–SC = 4.87 (2.30–10.30) mm, LF–SC = 8.10 (4.57–12.53) mm, measured perpendicular to the SC; and dura-mater–SC = 8.20 (3.75–19.57) mm; LF–SC = 13.40 (5.50–39.77) mm, measured at the angle parallel to the inferior spinous process] was at T5/T6.

Conclusion: Our results suggest that the margin of safety (dura-mater–SC distance and LF–SC distance) for performing epidurals in children may be greatest at the mid-thoracic spinal region. The measured ranges were very wide. Further studies are warranted to validate these findings in pediatric patients with other relevant “epidural placement” positions.

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Introduction

Perioperative epidural analgesia is an important option for pediatric patients.^{1–3} Despite very low rates of undetected/inadvertent catheterization of the subarachnoid space and needle/catheter trauma to the Spinal Cord (SC), the potentially catastrophic consequences of such occurrences warrant attention.³ The challenges of pediatric epidural placement include patient size, smaller distances between critical anatomic structures, increased compliance of the rib cage, reduced rigidity of the Ligamentum Flavum (LF), and asleep insertion with lack of patient feedback.⁴

It has been suggested that knowledge of the distances from the skin to the dura mater (or simply, “dura”) and from the dura to the SC may improve safety while performing epidural analgesia.⁵ Four studies have examined this topic in adults^{6–9} and three in children.^{5,10,11} These studies have reported distances from the skin to the epidural space and from the dura to the SC. However, to our knowledge, no studies have examined the distance from dura to SC in children or the distance from LF to SC in adults or children, both of which we believe are relevant to the safe placement of all epidurals. Additionally, previous pediatric studies^{5,10,11} limited the measurements of thoracic spine anatomy to ≤ 8 years of age. To address these knowledge gaps, and recognizing that children > 8 years-old also undergo major truncal surgeries that could benefit from epidural analgesia, we aimed to determine the margins of safety for neuraxial anesthesia techniques in pediatric patients aged 0–12 years by measuring the distances at thoracic (T5/T6 and T9/T10) and lumbar (L1/L2) levels on Magnetic Resonance Image (MRI) scans from (i) The ventral edge of the LF to the dorsal edge of the SC, and from (ii) The ventral edge of the dura to the dorsal edge of the SC. T5/T6 is an appropriate level for thoracotomies and chest tubes and may also encompass chest trauma-related rib fractures, while T9/T10 and L1/L2 are suitable levels for upper and lower abdominal surgeries as well as threading the epidural catheter to higher (thoracic) levels. In previous adult studies, the dura-SC distances were found to vary widely. For instance, at T6/T7, the range in 19 patients (supine position) was 2.1–7.5 mm¹² and the range in nine volunteers (supine position) was 4.3–15.8 mm.⁹ Similarly, we hypothesized that wide distance ranges would be found at certain spinal levels in children. As the study was not comparative, no power analysis was performed and only a convenience sample was used.

Materials and methods

Following institutional research ethics board approval (Queen’s University Research Ethics Board protocol 6029558, Hospital das Clínicas HCFMUSP CAAE 65178522.1.0000.0068, Rede D’Or CAAE 83100824.5.0000.0087), we retrospectively reviewed T2-weighted sagittal MRI spine images from 111 patients (0–12 years-old) from three institutions (Kingston Health Sciences Centre, Kingston, Canada; São Luiz Hospital, São Paulo, Brazil; Hospital das Clínicas HCFMUSP, São Paulo, Brazil) who had suspected spine pathologies but whose MRI scans were within normal limits. The convenience-based sample size consisted of all eligible patients undergoing MRI scans between January/2013 and January/2023. No statistical power calculation was performed prior to data collection. Images were de-identified and accessed through the institutional clinical databases. All MRI scans were performed with patients in the supine position. As damage to the SC during epidural catheterization was our main concern, we focused on the spine levels where the SC is theoretically at the highest risk of direct needle trauma. Three investigators from the Canadian center (N.L., D.A., A.H.), as well as three investigators from each of the Brazilian centers (V.C.Q., F.B.C., R.V.C. and L.M.S., F.N.B., S.Q.S.) independently collected the following four measurements/distances at levels T5/T6, T9/T10, and L1/L2 (Fig. 1) in a standardized fashion: from the ventral edge of the LF to the dorsal edge of the SC both (1) Perpendicular to the SC as well as (2) At an angle parallel to the inferior spinous process; and from the ventral edge of the dura to the dorsal edge of the SC both (3) Perpendicular to the SC as well as (4) At an angle parallel to the inferior spinous process. All investigators participating in data collection were blinded to each other’s measurements. Notably, measurements at an angle parallel to the inferior spinous process aimed to mimic the epidural needle trajectory. In equivocal scans where the conus medullaris was located in close proximity to L1/L2, all 3 investigators met to review the images and ultimately reach a consensus as to whether the conus medullaris could be reached by a needle traversing the L1/L2 interspace. The mean measurements collected by the 3 independent investigators at each center were used in data analysis, and the Intraclass Correlation Coefficient (ICC) was calculated to assess Inter-Rater Reliability (IRR). Normality of the distribution of each measurement was assessed using the Shapiro-Wilk test and visually inspected using histograms. Given the non-normal distribution observed across the analyzed variables, descriptive statistics are presented as

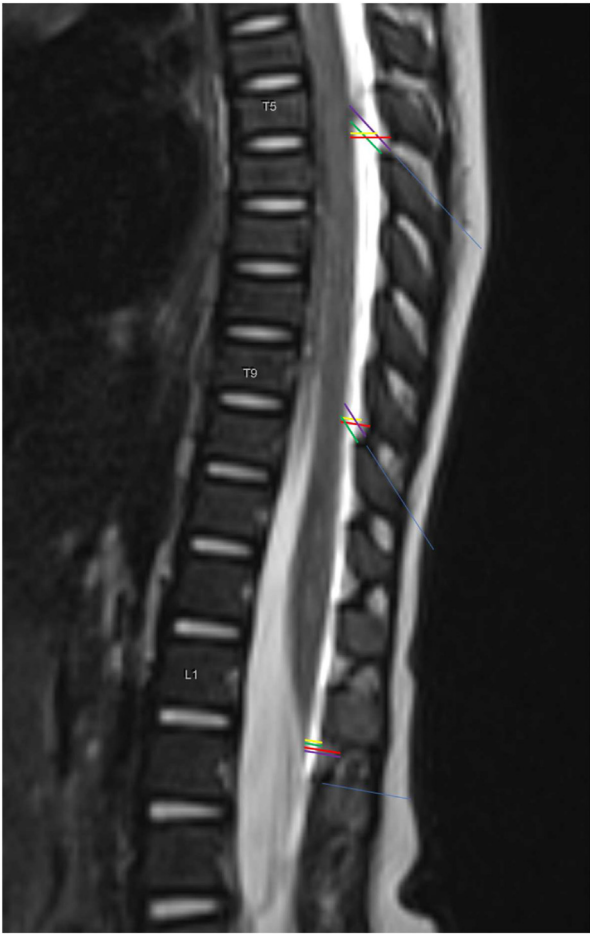


Figure 1 T2-weighted sagittal MRI spine image demonstrating 4 measurements/distances measured at levels T5/T6, T9/T10, and L1/L2: (1) dura-SC perpendicular to the SC (yellow line); (2) LF-SC perpendicular to the SC (red line); (3) dura-SC parallel to spinous process (green line); and (4) LF-dura parallel to spinous process (purple line). The long/blue line represents the line parallel to the inferior spinous process used as reference for measurements (3) and (4). Dura, Dura mater; SC, Spinal Cord; LF, Ligamentum Flavum.

medians and ranges. ICC estimates and their 95% Confident Intervals (95% CIs) were calculated using SPSS statistical package version 23 (SPSS Inc, Chicago, IL, USA) based on a mean-rating ($k = 3$), absolute-agreement, 2-way mixed-effects model. Notably, ICC values < 0.5 , between 0.5 - 0.75 , between 0.75 - 0.9 , and > 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.¹² The MRI resolution is approximately 0.1 mm. For production of graphs, Microsoft Excel Version 2016 (Microsoft Inc, Redmond, WA, USA) was used. This was a retrospective descriptive imaging study which adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

The demographic characteristics associated with the MRI scans reviewed are shown in Table 1. All scans were within normal limits as reported by certified radiologists. In total,

Table 1 Demographic characteristics of pediatric patients whose MRI images were retrospectively reviewed. Data presented as n (%) or median (IQR).

	Age (years)									
	All ages (n = 111, 100%)	< 1 (n = 8, 7%)	1-2 (n = 13, 12%)	3-4 (n = 21, 19%)	5-6 (n = 13, 12%)	7-8 (n = 16, 14%)	9-10 (n = 21, 19%)	11-12 (n = 19, 17%)		
Median (IQR) age (years)	7 (3-10)	0.2 (0.15-0.44)	1.9 (1.6-2)	4 (3-4)	6 (5-6)	7 (7-8)	10 (9-10)	11 (11-12)		
Male	59 (53%)	4 (50%)	5 (38%)	9 (43%)	9 (69%)	7 (44%)	12 (57%)	13 (68%)		
Female	52 (47%)	4 (50%)	8 (62%)	12 (57%)	4 (31%)	9 (56%)	9 (43%)	6 (32%)		
Conus Medullaris above L1/L2	47 (42%)	4 (50%)	5 (38%)	12 (57%)	2 (15%)	4 (25%)	10 (48%)	10 (53%)		
Conus Medullaris at or below L1/L2	64 (58%)	4 (50%)	8 (62%)	9 (43%)	11 (85%)	12 (75%)	11 (52%)	9 (47%)		

L1/L2, Lumbar 1/Lumbar 2; MRI, Magnetic Resonance Imaging.

there were 52 females, and the cohort's median age was 7 years old. ICC was estimated at 0.929 (95% CI 0.916–0.940) for the raters at the Canadian center, and 0.920 (95% CI 0.898–0.939) at the Brazilian centers, indicating excellent IRR.¹² Male and female data were analyzed together as previous data have shown that there were no significant differences between sexes in our measurements of interest.⁹

The conus medullaris was superior to the L1/L2 vertebral interspace in 47 patients, requiring exclusion of their L1/L2 measurements. There were nine patients in which L1/L2 images were available and included in measurements; however, images were not accessible for T5/T6 or T9/T10, and there was one patient with all but T5/6 measurements available. Given the limited nature of data on our topic of investigation, we attempted to include all measurements. When data were not available at all vertebral levels for participants, the remaining data were included with no imputations for missing values. The age distribution among these 111 children is shown in Table 1. Investigators met to review nine equivocal scans where the conus medullaris was in close proximity to L1/L2. Of these, three scans were in the < 1 year-old cohort (of which two were excluded from the L1/L2 measurements), two scans in the 3–4 year-old cohort (one excluded), one scan in the 5–6 year-old cohort (not excluded), one scan in the 7–8 year-old cohort (excluded), and two scans in the 11–12 year-old cohort (both excluded).

Tables 2 and 3 and Figures 2 and 3 present our distance results (please note the different y-axis scales in the figures). When measured perpendicular to the SC, the greatest distances (i.e., dura-SC distance and LF-SC distance) for our entire cohort were at T5/T6, as seen in Figures 2A and 3A. Specifically, the median dura-SC distance (measured perpendicular to the SC) in our cohort was 4.87 mm at T5/T6, compared to 4.03 mm at T9/T10 and 2.31 mm at L1/L2; whereas, the median LF-SC distance was 8.10 mm at T5/T6, compared to 6.65 mm at T9/T10 and 5.82 mm at L1/L2.

As expected, the distances were greater when measured at the angle parallel to the inferior spinous process. When considering these particular measurements, the greatest distances (i.e., dura-SC distance and LF-SC distance) in all the age groups were also at the T5/T6 interspace as seen in Figures 2B and 3B. Specifically, the median dura-SC distance (measured at the angle parallel to the inferior spinous process) in our entire cohort was 8.20 mm at T5/T6, compared to 5.86 mm at T9/T10 and 2.80 mm at L1/L2, whereas the median LF-SC distance was 13.40 mm at T5/T6, compared to 9.00 mm at T9/T10 and 6.56 mm at L1/L2.

While the various distances are expected to increase with age, once the subjects reach the ages 3–4 years, the measured differences from there on to ages 11–12 years were small and not necessarily linear. This is especially true of the ventral dura to dorsal SC distance, which remains within a small range even as children grow.

Discussion

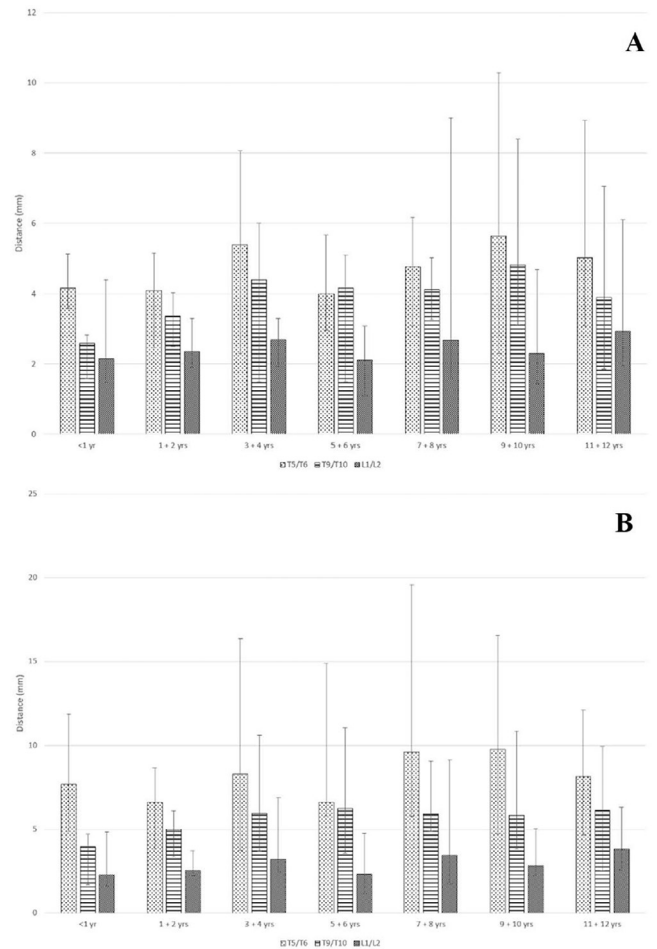
The greatest depth of the SC at all ages was at T5/T6, regardless of whether it was measured perpendicular to the SC or parallel to the spinous process,^{5-7,9} which is clinically more relevant. The difference between the perpendicular and parallel distances is greatest at T5/T6 because of the

Table 2 Distances (median, range) (mm) from the ventral dura-mater to the dorsal spinal cord measured perpendicular to the spinal cord (A) and parallel to the inferior spinous process (B) at the T5/T6, T9/T10, and L1/L2 interspaces across age groups.

A									
Vertebral Interspace		Age (years)							
All ages		< 1	1–2	3–4	5–6	7–8	9–10	11–12	
T5/T6	4.87 (2.30–10.30)	4.16 (3.60–5.13)	4.10 (2.46–5.16)	5.40 (2.30–8.07)	4.01 (2.96–5.67)	4.76 (3.10–6.17)	5.63 (2.30–10.30)	5.03 (3.10–8.92)	
T9/T10	4.03 (1.50–8.40)	2.60 (1.58–2.83)	3.37 (2.50–4.03)	4.40 (1.50–6.00)	4.16 (1.51–5.10)	4.12 (3.27–5.03)	4.83 (3.13–8.40)	3.90 (1.86–7.05)	
L1/L2	2.31 (1.10–9.00)	2.15 (1.48–4.40)	2.36 (1.90–3.30)	2.70 (1.93–3.30)	2.11 (1.10–3.07)	2.68 (1.60–9.00)	2.30 (1.43–4.70)	2.93 (1.93–6.10)	

B									
Vertebral Interspace		Age (years)							
All ages		< 1	1–2	3–4	5–6	7–8	9–10	11–12	
T5/T6	8.20 (3.75–19.57)	7.68 (4.87–11.83)	6.60 (3.80–8.67)	8.30 (3.75–16.36)	6.60 (5.80–14.87)	9.62 (5.78–19.57)	9.76 (4.73–16.53)	8.15 (4.66–12.07)	
T9/T10	5.86 (1.69–11.07)	3.95 (1.69–4.70)	5.00 (3.37–6.10)	5.96 (3.70–10.63)	6.24 (3.57–11.07)	5.91 (4.87–9.07)	5.83 (3.83–10.86)	6.13 (2.53–9.93)	
L1/L2	2.80 (1.16–9.13)	2.28 (1.61–4.85)	2.53 (2.23–3.73)	3.20 (2.43–6.90)	2.33 (1.16–4.76)	3.47 (1.77–9.13)	2.83 (2.23–5.03)	3.81 (2.60–6.30)	

A								
Vertebral Interspace	Age (years)							
	All ages	< 1	1–2	3–4	5–6	7–8	9–10	11–12
T5/T6	8.10 (4.57–12.53)	5.60 (4.97–6.43)	6.90 (4.57–8.23)	8.70 (4.70–10.46)	7.23 (5.69–9.06)	8.17 (6.89–10.50)	9.33 (5.90–12.53)	8.70 (6.81–11.93)
T9/T10	6.65 (2.20–11.30)	3.60 (2.43–5.10)	5.63 (3.90–7.70)	6.67 (5.03–9.33)	5.94 (2.20–7.73)	6.48 (5.13–8.03)	7.96 (5.40–11.30)	6.70 (5.66–10.32)
L1/L2	5.82 (2.96–12.16)	4.53 (3.47–5.80)	4.56 (3.60–5.06)	5.76 (2.96–7.36)	5.10 (3.22–6.85)	6.38 (3.77–12.16)	6.23 (4.33–9.00)	6.94 (4.20–11.60)
B								
Vertebral Interspace	Age (years)							
	All ages	< 1	1–2	3–4	5–6	7–8	9–10	11–12
T5/T6	13.40 (5.50–39.77)	12.22 (7.53–14.80)	10.80 (7.16–13.30)	14.33 (5.50–21.03)	12.00 (7.57–21.57)	16.42 (8.06–39.77)	14.63 (12.16–20.70)	12.76 (9.02–17.30)
T9/T10	9.00 (3.03–15.20)	6.13 (3.03–7.33)	7.63 (5.67–9.43)	8.90 (7.23–14.53)	8.73 (4.87–15.20)	9.21 (6.57–12.47)	10.00 (8.60–14.13)	9.70 (7.79–13.38)
L1/L2	6.56 (3.27–12.36)	4.78 (4.43–8.30)	4.90 (3.76–5.43)	7.63 (5.00–8.83)	5.83 (3.27–7.76)	6.82 (5.99–12.36)	7.23 (5.07–9.90)	6.77 (4.33–11.80)



steep angle of the spinous processes. Our results confirm previously reported findings in pediatric patients both at thoracic and lumbar levels.^{5,9,10}

The mid-thoracic region is at the apex of the thoracic spine curvature, where the SC is located most ventral due to tethering of the dentate ligaments, creating the largest space ventral to the dura and dorsal to the SC at this level.⁶ The epidural space is also largest in the mid-thoracic region. In contrast, the SC at the lower thoracic and lumbar levels are more dorsal because of normal lumbar SC enlargement which generally starts at T11 and ends at L2.⁹ Taken together, this means that the greatest safety margin for epidural needle/catheter placement is in the T5/T6 region. However, this advantage needs to be balanced against the potential damage at a higher SC level, should one occur. Furthermore, the pediatric rib cage being more compliant at the mid-thoracic level may increase the chance of accidentally inserting the needle too far during a recoil.

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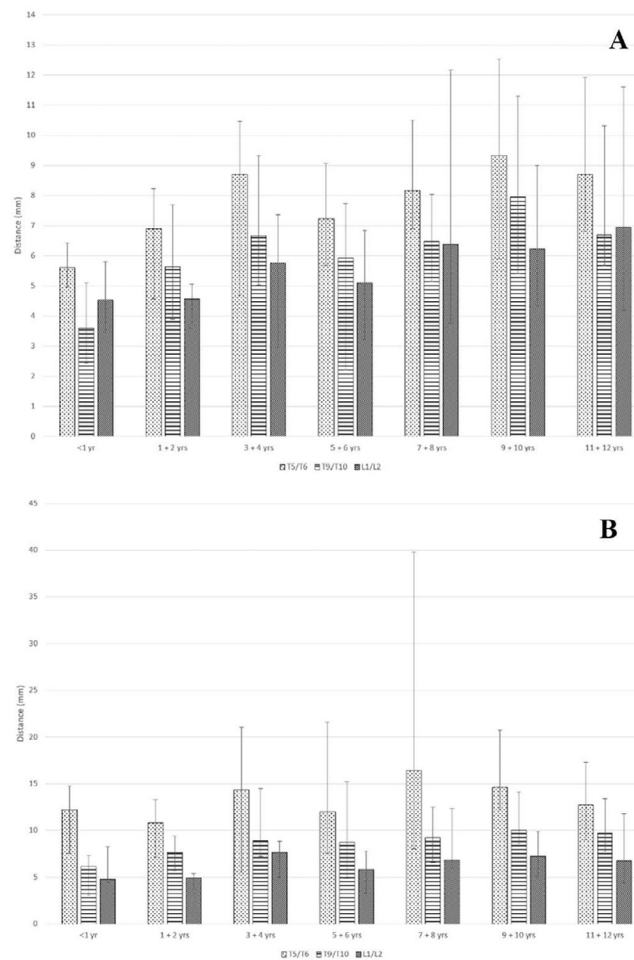


Figure 3 Distances (Median, Range) from the ventral ligamentum flavum to the dorsal spinal cord measured perpendicular to the spinal cord (A) and parallel to the inferior spinous process (B) at the T5/T6, T9/T10, and L1/L2 interspaces across age groups.

performing an epidural, namely that mean distances should not be relied upon to expect when important anatomic structures are reached. Rather, a relatively unpredictable wide distance range is to be expected.

The largest mean differences in the various measured distances between the youngest and the oldest in our cohort are only a mere ~2–4 mm, depending on the spinal level and the needle trajectory, in agreement with a previous study that measured dura to SC in children,⁹ suggesting that older children are not significantly less susceptible to inadvertent injury to the SC than very young children.

Our study is the first of its kind to measure the dura-SC and the LF-SC distances in children. Our results complement those in children that measured the skin-dura^{5,11} and dura-SC¹⁰ distances. Awareness of the approximate distances between these important structures and their high variability may improve safety.

There is always a risk of inadvertent dural puncture (and ultimately SC injury depending on how far the needle is advanced) during epidural access regardless of the thoracic level. The Pediatric Regional Anesthetic Network reported two dural punctures out of 103 lumbar epidurals and one dural puncture out of 13 thoracic epidurals.¹³ Giaufre et al. recorded two dural punctures in a total of 2,396 pediatric lumbar epidurals.¹⁴ In a follow-up study, four dural taps

were recorded in 1,547 epidurals (ages from 1-month to 13 years), three at the lumbar level (with one catheterization of the subarachnoid space), and one at the thoracic level.¹ An audit from the U.K. (10,633 pediatric epidurals) reported permanent residual neurologic deficits in a 3-month-old child (at 1-year follow-up) and one post-dural puncture headache.³ Direct SC needle trauma¹⁵⁻¹⁷ and inadvertent catheterization of the subarachnoid space¹⁸ resulting in permanent neurologic deficits have also been reported. Knowing the dura and SC depths may be particularly helpful for novices, who have less experience with tactile sensation. Accordingly, SC injury has been reported in a pediatric patient after a practitioner with 3 years of clinical experience attempted epidural placement.¹⁵

With Loss of Resistance (LOR), the epidural needle can be advanced continuously or incrementally. If while utilizing intermittent LOR, the incremental distance is larger than the distance between the ventral aspect of the LF and the dura, the first LOR encountered may be after the dura has been breached (if the needle tip during the resistance check prior to the dural puncture had been just before emerging from the LF). Likewise, if the incremental distance is larger than the LF-SC distance, a needle that had been on the verge of emerging from the LF may reach the SC with the next increment. As such, there may not be the LOR expected

in the epidural space or the CSF feedback when dural puncture or SC contact occurs. Although theoretical, this may encourage clinicians to consider using the continuous rather than intermittent LOR technique or reduce their incremental advancing distance in pediatric patients.

The length of the needle bevel opening also deserves consideration. At the study centers, it measured approximately 1.2 millimeters in pediatric Tuohy needles, which may result in an increased safety profile, particularly for the smaller patients. If any portion of this opening is in the epidural space, the operator would expectedly encounter LOR and not advance the needle further.

One limitation of our study is the small sample size due to the low number of apparently normal pediatric spinal MRI scans taken at our centers. This may be particularly important at the L1/L2 interspace, where measurements were performed in 63/111 scans, due to the conus medullaris ending superior to L1 in the remaining ones. Additionally, the studied population (i.e., patients undergoing MRI scan for suspected spine pathology) may not be fully representative of the general pediatric population. Another limitation is patient positioning. All MRI scans were performed with patients in the supine rather than in the lateral position or, less commonly, sitting position, all used for neuraxial blocks. The supine position causes the SC to migrate dorsally with gravity⁶ and may cause compression of subcutaneous tissues, suggesting that the distances measured in our study, including the safety margins, may actually underestimate the distances an operator encounters (and those previously reported)^{5-8,10,11} once the patient assumes an ideal epidural placement position. Furthermore, during neuraxial block, the spine is arched to maximize the inter-spinous process space whereas, during MRI, the spine is not. In adults, there are indeed significant differences in the dura-SC distances between the sitting (slightly hunched back), supine, and lateral recumbent (relatively neutral and not decubitus) positions.⁹ We did not collect data on MRI machine specifications (specifically, resolutions) over the studied period; there was likely lack of standardization of MRI machines among participating centers, thereby resulting in image quality/resolution variation. Lastly, because of the wide distance ranges found and the intrinsic resolution of MRI images, our study does not provide the answer to whether LOR should be sought with incremental vs. continuous advancement of the Tuohy needle in children. In simulation, overshoot of the Tuohy needle is worse (thus theoretically threatening the SC) with the incremental approach.¹⁹ If an incremental approach is the preferred technique, small increments must be used with each check of LOR.

Conclusion

Our findings suggest that the margin of safety (i.e., dura-SC distance and LF-SC distance) for performing epidurals in children may be greatest at the mid-thoracic spinal region, regardless of whether it was measured perpendicular to the SC or parallel to the spinous process. Additionally, mean distances should not be relied upon while performing an epidural, given the observed wide distance ranges. Further studies are warranted to validate these findings in pediatric

patients with other relevant “epidural placement” positions.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors conceived, drafted and critically revised the manuscript, and approved the final version submitted for publication in the Brazilian Journal of Anesthesiology.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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ORIGINAL INVESTIGATION

Efficacy of pectoserratus plane block versus erector spinae plane block on acute and chronic pain after mastectomy: randomized clinical trial



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Abstract

Objectives: To compare Pectoserratus Plane Block (PSPB) and Erector Spinae Plane (ESP) block regarding perioperative opioid consumption and chronic pain risk among women undergoing elective mastectomy.

Methods: Single-blind (patients), randomized (1:1) trial. The primary outcome was the composite measure defined as the use of fentanyl intraoperatively or tramadol postoperatively. Secondary outcomes encompassed intraoperative hemodynamics, short (24h), medium (3 months) and long-term (6 months) postoperative pain intensity and complications.

Results: 99 patients were randomized (50 in the PSPB group and 49 in the ESP block group). Of these, 93 patients had complete data for the primary outcome. Use of either fentanyl or tramadol was required for 20 of 47 patients (43%) in the PSPB group and 28 of 46 patients (61%) in the ESP block group (Relative Risk [RR] 0.70, 95% Confidence interval [95% CI] 0.47–1.05, $p = 0.09$). PSPB-treated patients had a lower risk of tramadol (RR = 0.31, 95% CI 0.12–0.77, $p = 0.01$) and dipyrone (RR = 0.60, 95% CI 0.39–0.92, $p = 0.02$) consumption than ESP block-treated patients. PSPB lowered chronic pain risk at 3 months (RR = 0.66, 95% CI 0.47–0.92, $p = 0.02$), with lower scores for the Short-Form McGill Pain Questionnaire (Mean Difference [MD] -2.55, 95% CI -4.31 to -0.78, $p = 0.005$) and the Douleur Neuropathique 4 Questions questionnaire (MD = -1.08, 95% CI -2.05 to -0.11, $p = 0.03$). By 6 months, pain outcomes were statistically comparable between groups. Hemodynamic variables and complications were comparable between groups.

All of the co-authors have contributed meaningfully to the study and manuscript.

The trial was approved by the local ethics committee (Fundação de Ensino e Pesquisa em Ciências da Saúde, FEPECS, ID: CAAE 38892320.8.0000.0025) and registered on Plataforma Brasil (<http://application.saude.gov.br/plataformabrasil>). The study was prospectively registered on ClinicalTrials.gov (Identifier: NCT05069805; Date of registration: September 25, 2021. URL: <https://clinicaltrials.gov/study/NCT05069805>).

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Conclusion: PSPB and ESP block resulted in similar overall opioid consumption among women undergoing mastectomy. However, PSPB was associated with lower postoperative tramadol consumption.

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Introduction

Breast cancer remains the most prevalent cancer affecting women worldwide.¹ Modified radical mastectomy is a surgical procedure commonly employed in breast cancer treatment with high success rates.² The procedure removes the entire breast with axillary evacuation and a substantial portion of skin, resulting in a sizeable wound area. Multiple nerves are present in the breast area.² Thus, the procedure can often injure the sensory system surrounding the surgical site.³ As a result, a large proportion of breast cancer patients experience moderate or severe acute postoperative pain that cannot be effectively relieved by the diversified analgesic armamentarium available.⁴ The pain greatly hinders early postoperative recovery. In the medium to long-term following surgery, 2% to 78% of the patients suffer from Post-Mastectomy Pain Syndrome (PMPS),⁵ a complex condition characterized by significant and persistent pain lasting for several months.⁶ This condition can restrict normal function, diminishing the patient's overall quality of life and worsening clinical outcomes.⁷

Among the different characteristics potentially associated with the incidence of PMPS, the presence of moderate to severe acute pain in the postoperative period has been a consistent risk factor.⁸ In fact, unresolved acute pain can activate several mechanisms not only at the periphery (primary hyperalgesia) but also within the central nervous system with sensitization of nociceptive neurons (secondary hyperalgesia), inflammation, defective inhibition of nociceptive inputs and higher expression of transmitters, receptors, and ion channels, all of which favor the transition from acute to chronic pain.⁹

In recent years, regional anesthesia techniques have gained prominence for their potential to provide superior pain relief while minimizing opioid consumption and associated adverse effects. Among these techniques, the Pectoratus Plane Block (PSPB)¹⁰ and Erector Spinae Plane (ESP)¹¹ block have emerged as promising options for thoracic analgesia in breast surgery. Despite increasing use of these regional anesthesia techniques, robust comparative evidence regarding their efficacy and safety for mastectomy remains limited. Previous research has predominantly focused on immediate postoperative outcomes,¹² limiting the ability to draw comprehensive conclusions regarding long-term pain management and complications. Thus, there is a critical need for additional randomized controlled trials to determine the comparative effectiveness of PSPB and ESP block in this patient population.

To address this gap in existing research, we conducted a single-center, single-blind randomized trial to evaluate the perioperative and long-term outcomes of PSPB versus ESP block in elective mastectomy. Our study aimed to provide comprehensive insights into perioperative opioid consumption, pain intensity, hemodynamic variables, and complication rates, and

long-term pain outcomes up to 6 months postoperatively. We hypothesized that PSPB would reduce perioperative opioid consumption and lower chronic pain scores at 3 and 6 months compared to ESP block.

Material and methods

Trial registration and design

This was an investigator-initiated, single-center, single-blind, superiority randomized trial with a 1:1 allocation ratio conducted at the Hospital de Base, a tertiary teaching hospital in the Distrito Federal, Brazil. The trial was approved by the local ethics committee (Fundação de Ensino e Pesquisa em Ciências da Saúde, FEPECS, ID: CAAE 38892320.8.0000.0025) and was registered on clinicaltrials.gov (NCT05069805). All patients provided informed consent, and the trial followed the ethical standards of the Declaration of Helsinki.

Participants

We enrolled female patients aged between 18 and 70 years submitted to elective mastectomy. Patients had to have an American Society of Anesthesiology (ASA) status between I and III. Patients with a previous history of chronic pain, severe cardiac, hepatic, renal diseases, or neurological disorders were excluded. We also excluded pregnant participants, those using psychoactive medications, those taking any medication investigated in the study or patients with known allergies to any of the study drugs.

Interventions

All procedures and blocks were performed by the study investigators, who were second- and third year anesthesiology residents, under direct supervision of consultant anesthesiologists with established expertise in thoracic wall regional anesthesia. Investigators received structured, hands-on training in both block techniques prior to study commencement. No blocks were performed by clinicians other than the designated study team.

Standard procedures for both interventions

Before receiving the interventions (PSPB or ESP block), all patients received standard monitoring, including electrocardiography, pulse oximetry, Non-Invasive Blood Pressure (NIBP), and body temperature. After venous catheterization in the upper limb contralateral to the surgery using an 18G or 20G needle catheter, all patients received intravenous (IV) midazolam 0.03 mg.kg⁻¹ and IV fentanyl 1 mcg.kg⁻¹ for anxiolysis, along with 4 mg of IV dexamethasone. All patients underwent general anesthesia, initiated with induction with

IV fentanyl 3 mcg.kg⁻¹, lidocaine 2 mg.kg⁻¹, propofol 2 mg.kg⁻¹, cisatracurium 0.15 mg.kg⁻¹, or rocuronium 0.6 mg.kg⁻¹ at the discretion of the anesthesiologist. Induction was followed by direct laryngoscopy using a Macintosh blade number 3 or 4, and insertion of a 7.0 or 7.5 endotracheal tube with a cuff. Tube position was confirmed by auscultation of lung fields and capnography. Anesthesia was maintained with sevoflurane (approximately 1 to 1.5 Minimum Alveolar Concentration [MAC] of expired fraction) and neuromuscular blockade at the discretion of the anesthesiologist. Increases in Systolic Blood Pressure (SBP) exceeding 20% of the baseline values, measured post-anxiolysis, were interpreted as pain, and increments of 1 mcg.kg⁻¹ of fentanyl were administered for each episode, a decision endorsed by two clinical investigators. Reductions in SBP over 20% of baseline or below 90 mmHg were managed with ephedrine 5 to 10 mg. Heart Rate (HR) reductions below 50 bpm associated with a concurrent decrease in SBP were managed with atropine 0.5 to 1 mg. After receiving sedoanalgesia, patients allocated to the ESP block underwent antisepsis with 70% ethanol at the puncture site on the ipsilateral side to be operated on.

Pectoserratus plane block (PSPB)

PSPB involves two injections: the first between the pectoralis major and minor muscles (priorly known as PECS I), and the second (priorly known as PECS II) between the pectoralis minor and serratus anterior muscles at the level of the third rib. This technique targets the medial and lateral pectoral nerves, the intercostobrachial nerve, the long thoracic nerve, and the thoracodorsal nerve, providing analgesia to the anterolateral chest wall and axilla. Anatomical studies have shown that the conventional PECS II block produces extensive spread to the axillary region, reliably staining the intercostobrachial, thoracodorsal, long thoracic, and both pectoral nerves, which is particularly advantageous for mastectomy with axillary dissection. In contrast, a subserratus approach, where local anesthetic is deposited deep to the serratus anterior, results in limited axillary spread and incomplete blockade of the pectoral nerves, reducing its effectiveness for axillary procedures.

Patients were positioned in the supine position with the arm abducted at 90 degrees. A high-frequency linear ultrasound probe (SonoSite M-Turbo®), protected with a sterile plastic cover, was applied. The probe was positioned in the region below the clavicle, in the deltopectoral groove, identifying the pectoral muscles along with the axillary artery and vein at the level of the first rib. Subsequently, the probe was displaced distally to the space between the 2nd and 3rd ribs, identifying the structures of the pectoralis major, pectoralis minor, and serratus anterior muscles, arranged in sonoanatomy in that order from superficial to deep. A UniPlex NanoLine® 22G × 50 mm needle was introduced in-plane. The entire needle trajectory was visualized during the puncture. A 10 mL injection of 0.5% ropivacaine was administered between the pectoralis major and minor muscles. Needle progression continued to the interfascial plane of the pectoralis minor and serratus anterior muscles with an injection of 20 mL of 0.5% ropivacaine.

Erector spinae plane (ESP) block

The ESP block is performed by injecting local anesthetic deep into the erector spinae muscle at the level of the transverse process, typically at T4–T5 for breast surgery. The injectate spreads cranio-caudally along the fascial plane, with potential extension into the paravertebral and epidural spaces, as well as lateral spread into the intercostal spaces. This results in a multidermatomal sensory block involving the dorsal and ventral rami of the thoracic spinal nerves, providing analgesia to the hemithorax, including the breast and, to a lesser extent, the axilla. Imaging and cadaver studies confirm that the ESP block produces extensive craniocaudal spread (spanning 5–9 thoracic levels) and may reach the paravertebral and neural foraminal spaces; however, the degree of anterior and lateral spread to the axilla and pectoral nerves is less consistent when compared to the PECS II block.

Patients were positioned in a seated position with the support of assistants. A high-frequency linear ultrasound probe (SonoSite M-Turbo®) was applied and protected with a sterile plastic cover. The probe was positioned in the paravertebral region for the identification of the transverse process of the T5 vertebra, the structures of the trapezius, rhomboid, and erector spinal muscles, arranged in sonoanatomy from superficial to deep. A UniPlex NanoLine® 22G × 50 mm needle was introduced in-plane, directed toward the transverse process of the vertebra. The entire needle trajectory was visualized during the puncture. A 30 mL injection of 0.5% ropivacaine was administered between the transverse process and the erector spinal muscles, with the observation of the dispersion of the local anesthetic in this plane.

Rescue analgesia

In both groups, during the initial 24 hours postoperatively, patients reporting moderate pain (above 2 on a 0-to-10 numeric rating scale) received intravenous paracetamol (acetaminophen) (1 g) as the first analgesic drug every 6 hours. In the case of persistent pain, intravenous tramadol (100 mg) was administered every 6 hours. Patients exhibiting nausea and/or vomiting received intravenous ondansetron (8 mg) every 8 hours. Clinicians responsible for rescue analgesia decisions were blinded to group treatment.

Block failure

Block failure was defined as the inability of regional anesthesia to provide adequate surgical anesthesia, attributable to either technical errors during administration or patient-specific anatomical variability. Clinically, block failure manifested as nociceptive response at the surgical incision site. The primary hemodynamic correlates of block failure were intraoperative tachycardia and hypertension, operationally defined as a ≥ 20% increase in heart rate and arterial blood pressure relative to pre-induction baseline values.

Outcomes

The primary outcome was a composite outcome, defined as any use of opioids either during the surgery (fentanyl) or

postoperatively (tramadol). Secondary short-term efficacy outcomes included overall pain intensity at rest and incidental pain (pain during movement). Pain intensity was assessed at arrival to and discharge from the post-anesthetic care unit (PACU), and 12 and 24 hours postoperatively. Pain intensity was captured on a 0-to-10 numeric rating scale, with 0 indicating “no pain at all” and 10 representing the “worst possible pain”.

Perioperative hemodynamics and surgery-related outcomes included mean arterial pressure (mmHg), and heart rate (in beats per minute). Additionally, we estimated the expired fraction of sevoflurane intraoperatively, consumption of fentanyl, ephedrine or atropine during surgery, and the use of analgesics (tramadol or dipyrone) and antiemetics (ondansetron) up to 24 hours postoperatively. We assessed the degree of bleeding in the surgical field, which was scored by the surgical team, using a 6-point scale (0 = no bleeding; 1 = slight bleeding with no suction required; 2 = slight bleeding not treating the surgical site but requiring occasional suction; 3 = slight bleeding that improves for several seconds once suction has occurred; 4 = moderate bleeding hampering visualization and requiring frequent suctioning; and 5 = severe bleeding requiring constant suctioning). We graded the level of satisfaction of the surgical team with the surgical procedure and the patient’s level of overall satisfaction with perioperative care using a 5-point Likert scale (1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat satisfied, 4 = satisfied, or 5 = very satisfied).

Long-term pain outcomes included the validated, Brazilian Portuguese version of the Douleur Neuropathique en 4 Questions (DN4q), ranging from 0 to 10, with scores ≥ 4 denoting suggestive neuropathic pain.¹³ We also assessed the Short-Form McGill Pain Questionnaire (global, sensory and affective) to capture the quality of pain in the long term using the validated, Brazilian Portuguese version (0 to 45, with higher scores meaning greater pain intensity and unpleasantness).¹⁴ Chronic pain at the surgical site or adjacent areas was defined as persistent/recurrent pain lasting ≥ 3 months.¹⁵ Secondary safety outcomes included nausea and vomiting up to 24 hours after surgery.

Randomization and allocation concealment

Participants were randomly allocated to PSPB or ESP block groups using simple randomization according to a computer-generated random sequence (1:1) (<https://www.randomizer.org>). The randomization schedule remained concealed from all investigators until the beginning of surgical procedures. The allocation group was communicated to the surgical team just before starting the surgery. Sealed, sequentially numbered opaque envelopes were provided to the operating room. The surgical team opened the envelope at the time of the procedure and implemented the intervention as allocated.

Blinding

The trial was single blinded at the participant level, with the nerve block performed under sedation. Given the different characteristics of the interventions, blinding of clinical investigators was not possible. To mitigate performance bias, we ensured that all procedures related to general

anesthesia and surgery were meticulously followed according to protocol to ensure standardized procedures. We also reduced the risk of detection bias by employing blinded outcome assessors during follow-up assessments.

Sample size

Based on our prior clinical trial,¹⁵ and additional local data, we estimated that the primary outcome would be observed in 30% of patients in the PSPB group. We expected the ESP group to be associated with a higher risk of any opioid consumption during and after surgery, with a relative risk of approximately 2.0, resulting in an estimated 60% of participants in the ESP group requiring fentanyl during surgery and/or tramadol postoperatively. Using a two-sample proportions Z-test (without continuity correction)¹⁶ with a 5% alpha level, we calculated that 84 participants (42 per group) would be required to give the trial 80% statistical power (see [Supplementary Material for details](#)). To account for attrition (estimated to be approximately 14%), we increased the number to 98 participants (49 per group).

Statistical analysis

We summarized continuous variables with an approximately normal distribution using means (Standard Deviation, SD). Continuous variables with non-normal distribution were presented as median (Interquartile Range, IQR). Categorical variables were summarized as numbers (percentages). For continuous variables measured at a single time point, we employed Student’s *t*-tests for independent groups. In cases where the variables exhibited non-normal distributions, we used a bootstrap *t*-test with 5000 simulations.

Continuous outcomes with repeated measurements were analyzed via linear mixed-effects models using the restricted maximum likelihood estimator for the variance components. Missing data were assumed to be missing at random. In the fixed-effect part of the model, we included treatment, time, and the interaction term between time and treatment. Time was treated as a categorical variable. The random-effects component involved a random intercept, which accounted for the repeated measurements and correlation between time points. Within-group effects were presented as means (95% Confidence Intervals) and treatment effects as Mean Differences (MD) with 95% CI. MDs < 0 favor of the PSPB group.

For binary outcomes evaluated at a single time point, we assessed treatment effects using a generalized linear model with Poisson distribution, log link and robust standard errors. Results were presented as relative risks (95% CI), with RRs < 1 favoring the PSPB group. For binary outcomes with repeated measurements, we used mixed-effects logistic regression using the same predictors as described above for the continuous case. In the mixed-effects models, we evaluated statistical differences at each relevant time point and examined the overall difference between groups (joint test). Categorical outcomes were assessed via Fisher’s exact test for 2xk tables. No corrections for multiple testing were applied because all secondary outcomes were considered exploratory. Statistical analyses were performed using Stata 18 (StataCorp, TX, USA). A *p*-value < 0.05 (two-tailed) was considered statistically significant.

Results

Characteristics of the participants

From October 1, 2021, to August 30, 2023, we enrolled 102 patients, of which 99 met all eligibility criteria and were randomized to PSPB ($n = 50$) or ESP block ($n = 49$) groups (Fig. 1). Baseline data were evaluated for 97 participants (50 in the PSPB group and 47 in the ESP block group). A total of 93 patients (91%) had complete data regarding the primary outcome (47 in the PSPB group and 46 in the ESP block group). After 3 months of follow-up, 42 patients in the PSPB group and 34 patients in the ESP group had complete data, and after 6 months, 41 patients in the PSPB group and 31 patients in the ESPB group had complete data; patients lost to follow-up were those who did not respond to the telephone call. Throughout the entire study follow-up period, one patient died in each group (see Fig. 1 for details).

The mean (SD) age of the participants was 55.7 (12) years, and the mean (SD) BMI (kg.m^{-2}) was 27.4 (4.3). Sector resection was the most common procedure, performed on 57 (59%) patients. Table 1 presents additional baseline sociodemographic and clinical characteristics, indicating comparable groups at baseline. Both groups had similar anesthesia or

surgery durations. However, we observed clinically important differences in the proportion of axillary dissections between the PSPB and ESP block groups (23/47, 48.9% vs. 10/46, 21.7%, respectively).

Primary outcome: use of opioids during surgery and postoperatively

Use of either fentanyl intraoperatively or tramadol postoperatively was necessary for 20 of 47 patients (43%) in the PSPB group and 28 of 46 patients (61%) in the ESP block group (RR = 0.70, 95% CI 0.47 to 1.05, $p = 0.09$).

Secondary outcomes (intraoperative)

Use of fentanyl intraoperatively

Use of fentanyl intraoperatively was necessary for 18 of 47 patients (38%) in the PSPB group and 15 of 46 patients (33%) in the ESP block group (RR = 1.17, 95% CI 0.67 to 2.04, $p = 0.57$). Among participants who received fentanyl, the mean (SD) dose of fentanyl was statistically significantly lower in the PSPB group than in the ESP block group (mean difference: $-28.3 \mu\text{g}$, 95% CI -46.6 to $-10.1 \mu\text{g}$, $p = 0.003$) (Table 2).

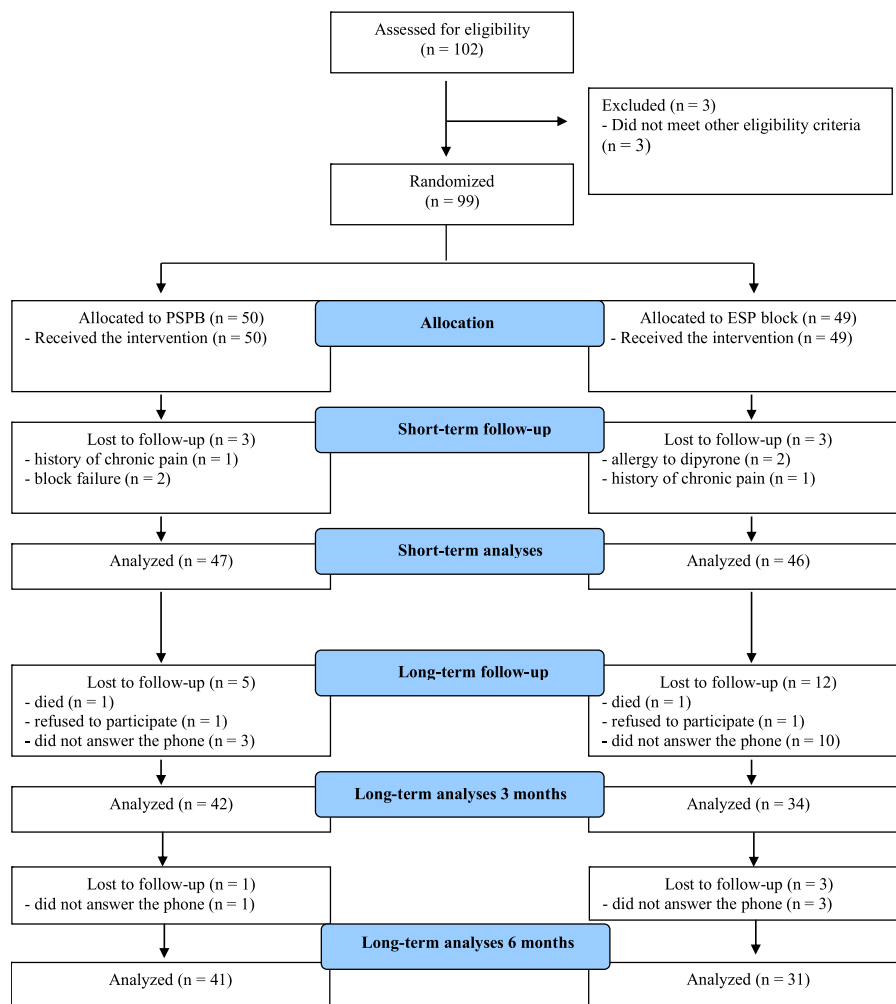


Figure 1 Flowchart summarizing the participant selection process. PSPB, Denotes Pectoserratus Plane Block. ESP, Denotes Erector Spinae Plane Block.

Table 1 Baseline characteristics of the study population.

	PSPB (n = 47)	ESP block (n = 46)
Sociodemographics		
Age (years), mean (SD)	55.5 (11.7)	55.8 (12.5)
Weight (kg), mean (SD)	69.6 (12.5)	69.8 (12.0)
BMI (kg.m ⁻²), mean (SD)	27.2 (4.3)	27.4 (4.4)
Clinical characteristics		
ASA status, n (%)		
I	1 (2)	1 (2)
II	42 (89)	39 (84.7)
III	4 (8.5)	6 (13)
Type-II diabetes, n (%)	9 (19)	11 (23.9)
Obesity, n (%)	16 (34)	13 (28)
Depression or anxiety, n (%)	12 (25.5)	10 (21.7)
Smoking, n (%)	3 (6.5)	5 (10.8)
Surgery-related characteristics		
Type of surgery, n (%)		
Mastectomy	3 (6.4)	1 (2)
Radical mastectomy	16 (34)	17 (37)
Sectorectomy	28 (59.5)	28 (61)
Reconstruction, n. (%)	5 (10.6)	2 (4.3)
Axillary dissection, n (%)	23 (48.9)	10 (21.7) ^a
Chemotherapy, n (%)	26 (55.3)	14 (30.4)
Radiotherapy, n (%)	17 (36.1)	22 (47.8)
Surgical time (min), median (IQR)	125 (95–160)	110 (90–140)
Anesthesia duration (minutes), median (IQR)	150 (135–200)	150 (135–180)

^a p-value < 0.05 (two-tailed) was considered statistically significant.

BMI, Body Mass Index; ASA status, American Society of Anesthesiologists physical status; ESP, Erector Spinae Plane block; PSPB, Pector serratus Plane Block; SD, Standard Deviation; IQR, Interquartile Range. Obesity was as a Body Mass Index (BMI) above 30 kg.m⁻².

Intraoperative mean arterial pressure and heart rate

Figure 2 (panel A) shows the variations in mean arterial pressure between the PSPB and ESP block groups throughout the surgical procedures. Although statistical differences occasionally emerged between the two groups at certain specific time intervals, no consistent pattern was observed. The joint test indicated that the two groups were not statistically different overall ($p = 0.27$). Similar results were observed for heart rate ($p = 0.20$) (Fig. 2, panel B).

Sevoflurane consumption

Figure 2 (panel C) shows a significant difference in sevoflurane consumption between groups (joint test, $p = 0.003$), particularly between minutes 75 and 180 during surgery, with the PSPB group consuming more sevoflurane than the ESP block group.

Use of ephedrine and atropine

Use of ephedrine intraoperatively was necessary for 24 of 47 patients (51%) in the PSPB group and 27 of 46 patients (59%)

in the ESP block group (RR = 0.87, 95% CI 0.60 to 1.26, $p = 0.46$). Among participants who received ephedrine, the mean (SD) dose of ephedrine was not statistically different between the groups (mean difference: -1.7 mg, 95% CI -6.04 to 2.66 mg, $p = 0.44$) (Table 2). None of the patients required atropine in our study.

Blood volume loss

No statistical differences were observed between the groups regarding blood volume loss (Table S1, $p = 0.65$).

Surgeon satisfaction

The surgical approach was associated with surgeon satisfaction ($p < 0.001$), with surgeons in the ESP block group choosing higher satisfaction categories than those from the PSPB group (Table S1).

Secondary outcomes – postoperatively (short-term)

Use of tramadol postoperatively

Use of tramadol for pain control after surgery was necessary for 5 of 47 patients (11%) in the PSPB group and 16 of 46 patients (35%) in the ESP block group (RR = 0.31, 95% CI 0.12 to 0.77, $p = 0.01$). Among patients requiring tramadol postoperatively, there was no difference in the mean (SD) dose between the PSPB and ESP block groups (120 [44.8] vs. 125 [57.7] mg, respectively; $p = 0.86$), with a median (IQR) dose of 100 (100 to 100) mg for both groups.

Use of dipyrone postoperatively

Use of dipyrone postoperatively was necessary for 18 of 47 patients (38%) in the PSPB group and 28 of 44 patients (64%) in the ESP block group (RR = 0.60, 95% CI 0.39 to 0.92, $p = 0.02$). Among patients receiving dipyrone postoperatively, there was no difference in the mean (SD) dose between the PSPB and ESP block groups (1382 [740] mg vs. 1429 [825] mg, respectively; $p = 0.85$), with a median (IQR) dose of 1000 (1000 to 2000) mg for both groups.

Time to request analgesics postoperatively

There was no statistically significant difference in time to request for analgesics between the groups, regardless of whether tramadol or dipyrone was used (Table 2).

Use of antiemetics

Use of ondansetron postoperatively was necessary for 7 of 47 patients (15%) in the PSPB group and 10 of 46 patients (22%) in the ESP block group (RR = 0.69, 95% CI 0.28 to 1.65, $p = 0.40$). Among participants who received ondansetron, the mean (SD) dose of ondansetron was statistically significantly higher in the PSPB group than in the ESP block group (mean difference: +4.9 mg, 95% CI 0.40 to 9.42 mg, $p = 0.03$), but the clinical relevance of this difference is unclear (Table 2). There was no statistical difference in the risk of developing postoperative nausea and vomiting between the groups (RR = 0.73, 95% CI 0.27 to 1.96, $p = 0.54$).

Pain intensity – short-term

Figure 3 (panels A and B) shows the trajectory of pain intensities from PACU arrival to 24 hours post-discharge. Pain at rest (panel A) or incidental pain (panel B) did not differ statistically between the two groups.

Table 2 Short-term clinical and resource utilization outcomes.

Outcome	PSPB (n = 47)	ESP block (n = 46)	Mean difference or relative risk (95% CI)	p
Primary outcome				
Use of fentanyl intraoperatively and/or tramadol postoperatively, n (%)	20 (43)	28 (61)	0.70 (0.47 to 1.05)	0.09
Secondary outcomes – intraoperative				
Use of fentanyl intraoperatively, n (%)	18 (38)	15 (33)	1.17 (0.67 to 2.04)	0.57
Dose of fentanyl (μ g), mean (SD)	41.7 (19.2)	70 (31.6)	-28.3 (-46.6 to -10.1)	0.003 ^a
Use of ephedrine, n (%)	24 (51)	27 (59%)	0.87 (0.60 to 1.26)	0.46
Dose of ephedrine (mg), mean (SD)	13.5 (7.2)	15.2 (8.3)	-1.7 (-6.04 to 2.66)	0.44
Use of atropine, n (%)	0	0	–	–
Secondary outcomes – postoperatively				
Use of tramadol	5 (11)	16 (35)	0.31 (0.12 to 0.77)	0.01 ^a
Dose of tramadol (mg), mean (SD)	120 (44.8)	125 (57.7)	-5 (-64.2 to 54)	0.86 ^b
Time to require tramadol (min), mean (SD)	204 (131.5)	247.8 (154.1)	-43.8 (-204 to 117)	0.57 ^b
Use of dipyrone	18 (38)	28 (64)	0.60 (0.39 to 0.92)	0.02 ^a
Dose of dipyrone (mg), mean (SD)	1382.4 (740)	1428.6 (825)	-46.2 (-501 to 408)	0.85 ^b
Time to require dipyrone (min), mean (SD)	434.1 (278.7)	305 (260)	129.1 (-33.7 to 292)	0.12 ^b
Use of ondansetron	7 (15)	10 (22)	0.69 (0.28 to 1.65)	0.40
Dose of ondansetron (mg), mean (SD)	13.7 (6.05)	8.8 (2.53)	4.9 (0.40 to 9.42)	0.03 ^a
PONV, n (%)	6 (13)	8 (17)	0.73 (0.27 to 1.96)	0.54
Time in the PACU (minutes), mean (SD)	143.1 (51.5)	111.9 (60.8)	31.1 (6.9 to 55.1)	0.01 ^{a,b}
Length of hospital stay (hours), mean (SD)	21.8 (3.6)	22.8 (4.0)	-0.94 (-2.52 to 0.63)	0.24 ^b
Complication, n (%) ^c	1 (2.1)	1 (2.2)	0.98 (0.06 to 15.4)	0.99

^a p-value < 0.05 (two-tailed) was considered statistically significant.

^b Bootstrapped t-test for independent samples.

^c One patient of each group developed an early hematoma, with was managed conservatively without additional interventions.

ASA, Status denotes the American Society of Anesthesiologists physical status; ESP, denotes Erector Spinae Plane, PSPB, denotes Pectorseratus Plane Block; PACU, denotes Post-Anesthetic Care Unit; SD, denotes Standard Deviation; SF-MPQ, denotes Short-form McGill Pain Questionnaire.

Time in the PACU and length of hospital stay

The time in the PACU was statistically significantly higher for the PSPB group than for the ESP block group (mean difference: 31.1 minutes, 95% CI 6.9 to 55.0, $p = 0.01$). However, there was no statistical difference between the average length of hospital stay for the groups (mean difference: -0.94 hours, 95% CI -2.52 to 0.63, $p = 0.24$) (Table 2).

Patient satisfaction and complications

Patients in the PSPB group were associated with higher levels of satisfaction compared to their ESP-treated counterparts ($p = 0.04$) (Table S2). However, the overall satisfaction rates were high in both groups, indicating that these differences are unlikely to have clinical significance. In each group, one patient experienced a complication, with no statistically significant difference between the groups (Table 2).

Secondary outcomes – long-term

Pain intensity and global chronic pain – long-term

Figure 4 shows the trajectory of pain intensity from the immediate postoperative period to 6 months after surgery. Pain intensity was statistically significantly lower for the PSPB group than for the ESP block group from the immediate postoperative period to two months after surgery. However, when considering all time points together, there were no significant statistical differences between the groups (joint

test, $p = 0.24$). Based on responses regarding the duration of pain, 22 of 42 patients (52%) in the PSPB group and 27 of 34 patients (79%) in the ESP block group were classified as experiencing chronic pain at 3 months (RR = 0.66, 95% CI 0.47 to 0.92, $p = 0.02$). However, at 6 months, the groups were statistically similar regarding the proportion of patients classified as experiencing chronic pain (20 of 41 [49%] vs. 18 of 31 [58%] for the PSPB and ESP block groups, respectively, RR = 0.84, 95% CI 0.54 to 1.30, $p = 0.43$) (Table 3).

Rescue medications and chronic pain-related questionnaires

The PSPB and ESP block groups showed no difference in the proportions of patients requiring rescue medication for pain at either 3 or 6 months after surgery (Table 2). Similar conclusions were drawn regarding DN4q scores and the proportion of patients classified as having neuropathic pain. At 3 months postoperatively, SF-MPQ (global) ratings were significantly lower in the PSPB group compared to the ESP block group (mean difference: -2.55, 95% CI -4.31 to -0.78, $p = 0.005$). However, at 6 months postoperatively, no significant difference was observed between the groups for this outcome (mean difference: -1.27, 95% CI -3.07 to 0.53, $p = 0.17$). Results for the subcomponents (sensory and affective) followed similar trends (Table 2).

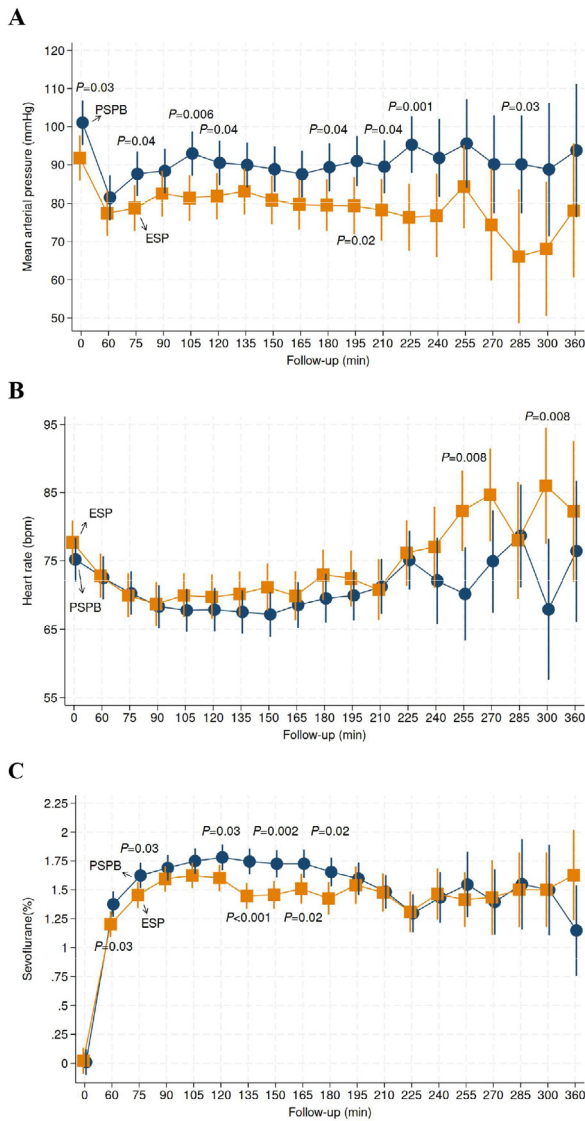


Figure 2 Intraoperative trajectories of mean arterial blood pressure (mmHg) (panel A), heart rate (bpm) (panel B) and sevoflurane consumption (%) (panel C). PSPB denotes pectoroserratus plane block (blue disks). ESP denotes erector spinae plane block (orange squares). Results are presented as means (95% Confidence Intervals) and were obtained via mixed-effects linear regression models.

Discussion

Principal findings

This randomized controlled trial showed that PSPB and ESP blocks were comparable in terms of intraoperative and post-operative opioid consumption in patients undergoing elective mastectomy. Both anesthetic blocks were associated with a similar and low risk of complications. However, statistically and clinically important differences emerged 3 months after surgery, with PSPB-treated patients exhibiting a reduced risk of chronic pain, lower DN4q scores, and lower pain intensity scores than their ESP block-treated counterparts. Nonetheless, at 6 months after surgery there were no noticeable differences in pain intensity or pain quality

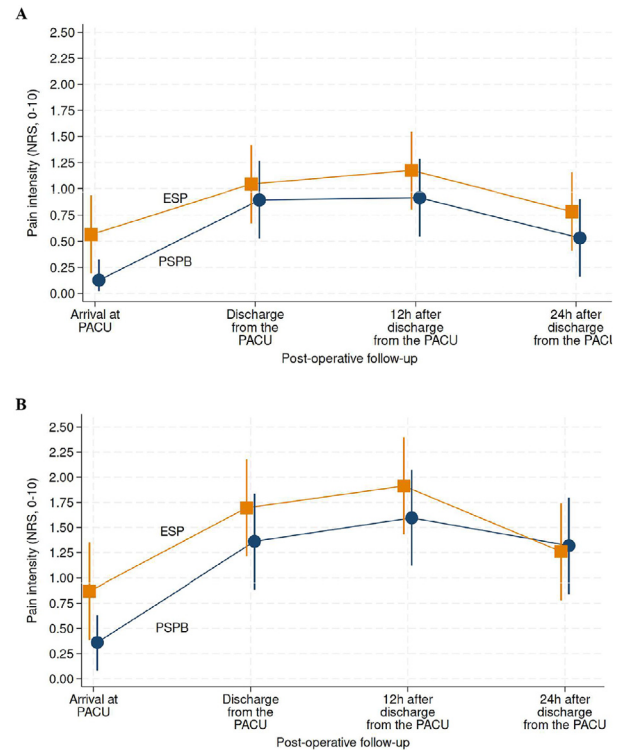


Figure 3 Trajectories of short-term pain intensity. In panel A, pain intensity at rest (panel A). In panel B, incidental pain (pain intensity under stress/movement). NRS denotes numeric rating scale. PSPB denotes Pectoroserratus Plane Block (blue disks). ESP denotes Erector Spinae Plane block (orange squares). There was not statistically significant between-group difference observed at any time point, either in terms of pain at rest or pain under stress (movement). The joint test resulted in a p-value of 0.55 for pain at rest, and a p-value of 0.50 for incidental pain.

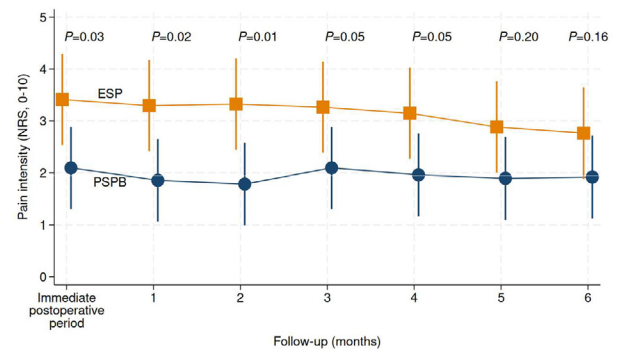


Figure 4 Trajectories of long-term pain intensity. PSPB denotes Pectoroserratus Plane Block (blue disks). ESP denotes Erector Spinae Plane block (orange squares). The immediate postoperative period refers to the assessment of pain intensity within a few days following surgery, typically ranging from 1 to 2 days after the procedure. The joint test resulted in a p-value of 0.24 (linear mixed-effects model).

Table 3 Secondary medium- and long-term outcomes (pain-related).

Outcome	PSPB	ESP block	Mean difference or relative risk (95% CI)	p
Secondary outcomes – pain-related				
Chronic pain, n (%)				
3 months ^b	22 (52)	27 (79)	0.66 (0.47 to 0.92)	0.02 ^a
6 months ^c	20 (49)	18 (58)	0.84 (0.54 to 1.30)	0.43
Use of rescue medications, n (%)				
3 months ^b	13 (31)	17 (51.5)	0.61 (0.35 to 1.07)	0.09
6 months ^c	10 (24)	13 (41)	0.59 (0.31 to 1.15)	0.12
DN4q scores, mean (SD)				
3 months ^b	2.30 (2.37)	3.38 (2.40)	-1.08 (-2.05 to -0.11)	0.03 ^a
6 months ^c	1.80 (1.87)	2.30 (2.10)	-0.47 (-1.46 to 0.52)	0.35
Neuropathic pain, n (%)				
3 months ^b	15 (36)	18 (53)	0.68 (0.41 to 1.15)	0.15
6 months ^c	11 (27)	12 (39)	0.66 (0.34 to 1.27)	0.21
SF-MPQ, mean (SD)				
Global				
3 months ^b	3.2 (3.6)	5.8 (5.3)	-2.55 (-4.32 to 0.78)	0.005 ^a
6 months ^c	2.4 (3.0)	3.4 (3.7)	-1.27 (-3.07 to 0.53)	0.17
Sensory				
3 months ^b	2.8 (3.18)	4.97 (4.34)	-2.16 (-3.70 to -0.62)	0.006 ^a
6 months ^c	2.34 (2.84)	3.35 (3.52)	-1.09 (-2.66 to 0.48)	0.18
Affective				
3 months ^b	0.40 (0.86)	0.79 (1.91)	-0.39 (-0.94 to 0.16)	0.17
6 months ^c	0.1 (0.37)	0.06 (0.36)	-0.21 (-0.77 to 0.35)	0.46

^a p-value < 0.05 (two-tailed) was considered statistically significant.

^b Based on 42 participants with complete data in the PSPB group and 34 in the ESP.

^c Based on 41 participants with complete data in the PSPB group and 31 in the ESP.

DN4q, Douleur Neuropathique 4 Questions; ESP, denotes Erector Spinae Plane block; PSPB, Pectoserratus Plane Block; SD, Standard Deviation; SF-MPQ, Short-form McGill Pain Questionnaire.

between women treated with PSPB and those treated with ESP block.

In principle, both techniques are capable of providing good anesthetic conditions for breast surgery, and therefore, similar general anesthetic consumption would be expected. However, individual patient variations, anesthesiologist preference for sevoflurane dosing, and differences in surgical procedures (such as more axillary dissections in the PSPB group, as observed in this study) may have contributed to the statistically significant reduction in sevoflurane consumption in the ESP group. Nevertheless, this reduction was not deemed clinically significant. Notably, most studies have primarily evaluated outcomes related to postoperative analgesia, opioid consumption, and quality of recovery, rather than intraoperative consumption of volatile anesthetics like sevoflurane.

Despite higher reported pain scores and increased postoperative opioid requirements in the ESP block cohort, we observed that ESP block patients were associated with a reduced duration of stay in the PACU. However, the observed difference of approximately 30 minutes in PACU length of stay was not deemed clinically significant, as discharge timing is influenced by multiple variables, including staffing schedules, PACU census, and the circadian timing of patient admission (morning, afternoon, or evening), among other operational factors.

We observed that patient satisfaction was higher in the PSPB group, while surgeon satisfaction was greater with ESP block. Patients reported greater satisfaction with PSPB,

likely due to superior analgesic efficacy and reduced opioid consumption. Conversely, from the surgeon's perspective, local anesthetic spread into the axilla during PSPB can complicate axillary dissection, hinder the use of electrocautery, and particularly impede identification of the sentinel lymph node, which could explain, at least partially, the surgical team's concerns.

Comparison with previous studies

We are not aware of previous or ongoing randomized trials of PSPB versus ESP block specifically designed to evaluate the composite use of intraoperative fentanyl and/or tramadol postoperatively as the primary outcome, or their efficacy regarding long-term pain intensity after elective mastectomy. Wong et al. (2021) conducted a comprehensive network meta-analysis and used direct and indirect evidence from 66 randomized trials in breast surgery.¹⁷ The authors found no evidence of a difference in postoperative pain intensity between the PSPB and the ESP block. However, this analysis focused on immediate postoperative outcomes, such as pain intensity at rest within 0–2 hours and 8–12 hours after surgery. Our findings for the short-term pain score were consistent with the results reported by Wong et al. (2021).¹⁷

A few head-to-head trials corroborate our findings, but they used different local anesthetics for local anesthetic infiltration. For example, Altıparmak et al. (2019) assessed total postoperative tramadol consumption in the first

24 hours after radical mastectomy surgery as the primary outcome.¹² The authors used 0.25% levobupivacaine for the blocks. This trial demonstrated a statistically significant reduction in tramadol consumption and a lower need for rescue analgesia in the first 24 postoperative hours in the PSPB group compared to the ESP block.¹² In terms of fentanyl consumption, there were no discernible differences in intraoperative fentanyl usage between the groups.¹²

In another 2019 randomized trial, Sinha et al. used 0.2% ropivacaine in both groups and also demonstrated the analgesic superiority of PSPB over ESP block.¹⁸ The authors reported a decrease in morphine consumption during the first 24 hours after surgery in the PSPB group compared to the ESP block group, and a 23% longer analgesia duration with the PSPB compared to the ESP block.

In our trial, patients who received PSPB exhibited lower mean scores on the SF-MPQ global scale at 3 months, with a greater reduction in sensory domain scores than for the ESP block, indicating that regional anesthesia techniques may play a more crucial role in modulating nociceptive pain. Previous evidence suggests that the superiority of PSPB, when compared to the ESP block, in managing nociceptive pain could be attributed, at least partially, to its more complete blockade of sensory innervation in the breast.¹⁹⁻²³ This blockade includes branches from the brachial plexus, lateral cutaneous branches of the intercostal nerve at the mid-axillary line, the long thoracic nerve, and the thoracodorsal nerve, covering the C5–T4 dermatomes.¹⁹⁻²³ In contrast, ESP block primarily targets intercostal nerves and, when performed at the level of the fifth vertebral transverse process, extends sensory blockade to the T2–T9 dermatomes.¹⁹⁻²³ Notably, PSPB has been associated with decreased levels of stress hormones like cortisol and prolactin postoperatively compared to the ESP block.²⁴

Strengths and limitations

Our study has several strengths, including a comprehensive assessment of resource utilization and clinical outcomes spanning perioperative, short-term, and long-term periods. However, several limitations are worth discussing. First, we did not adjust our results for multiple tests. We considered all secondary outcomes exploratory, which needs further assessment in confirmatory trials.²⁵ Second, our sample size was relatively modest, and we cannot rule out small to moderate differences in treatment effects between PSPB and ESP block concerning intraoperative and postoperative opioid consumption. Third, while our results have high internal validity for elective mastectomies, they may not generalize to other non-mastectomy-related surgical procedures. Fourth, our attrition rates were higher than anticipated, particularly 6 months after surgery, which may have reduced our statistical power to detect differences between the groups. Patients were often lost to follow-up due to lack of contact and non-responsiveness. Future trials examining long-term pain after mastectomy should anticipate high attrition rates and incorporate retention strategies to mitigate these challenges. Fifth, participants in the PSPB group more frequently underwent axillary lymph node dissection and immediate breast reconstruction, procedures that could increase intraoperative requirements for sevoflurane, perioperative opioid consumption, and the risk of both acute and persistent postoperative pain. Nonetheless, these anticipated effects

were only partially observed. Specifically, sevoflurane consumption was higher intraoperatively in the PSPB group than in the ESP block group, while opioid consumption was lower in the PSPB group. These results suggest that the increased surgical burden did not compromise, but rather reinforced, our confidence in the postoperative analgesic efficacy of PSPB. Sixth, although chronic pain rates estimated in our study were relatively high in both groups when considering the broader definition of chronic pain, the incidence of neuropathic pain, which is of greater clinical concern due to its substantial impact on patients, fell within the range reported in the existing literature on chronic pain following breast cancer surgery.^{5,26}

Conclusion

We can conclude that both ESP and PSPB blocks are safe, effective, and comparable for oncologic mastectomy. However, PSPB presents a slight advantage in outcomes related to acute and chronic pain, including reduced postoperative opioid consumption and lower incidence of chronic pain. The choice between the two techniques may be based on the type of breast surgery, surgical team experience, and anesthesiology team's technique preference.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Presentation

Preliminary data for this study were presented at the Brazilian Anesthesiology Congress in November 2022.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.bjane.2025.844691](https://doi.org/10.1016/j.bjane.2025.844691).

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ORIGINAL INVESTIGATION

Effect of intravenous dexmedetomidine on sensory block duration in spinal anesthesia for lower limb surgery: a randomized controlled trial



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KEYWORDS

Dexmedetomidine;
Postoperative
analgesia;
Sensory block;
Spinal anaesthesia

Abstract

Study objective: To study the effect of Intravenous (IV) dexmedetomidine during spinal anesthesia on duration of sensory block and postoperative analgesia in patients undergoing lower limb orthopedic surgery.

Design: Prospective randomized double blind controlled trial.

Intervention: Patients in intervention (DX) group received 0.5 mcg.kg⁻¹ IV dexmedetomidine over 10 min. Spinal anesthesia was administered and an infusion of dexmedetomidine 0.5 mcg.kg⁻¹.h⁻¹ was given throughout surgery.

Measurements: Onset time of sensory and motor block, maximum height of sensory block and duration of sensory and motor block were assessed. Intraoperative Heart Rate (HR), Blood Pressure (BP), Peripheral Oxygen Saturation (SpO₂), sedation scores, postoperative pain scores, time to requirement of first analgesic and analgesic consumption over first 24h were noted.

Results: Data of 58 ASA I/II adults was analyzed. Duration of sensory block, defined as time to two-dermatome regression, was 137.03 ± 25.02 min in DX group and 79.45 ± 11.27 min in the NS group (p = 0.000). Onset of sensory and motor block and maximum height of sensory block were similar. Postoperative VAS scores were lower in the DX group at 4h and 24h (p = 0.001, p = 0.0001) and comparable at 0h, 8h and 12h. Time to requirement of postoperative analgesia was longer in the DX group (p < 0.001) and requirement of postoperative analgesics was higher in the NS group. Sedation scores and incidence of bradycardia were higher in the DX group, but hypotension was similar.

Conclusion: IV dexmedetomidine (0.5 mcg.kg⁻¹ followed by 0.5 mcg.kg⁻¹.h⁻¹) resulted in extended sensory and motor block, prolonged postoperative analgesia and reduced postoperative analgesic consumption with minimal side effects.

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Introduction

Lower limb orthopedic surgeries encompass a wide range of procedures which can be performed under neuraxial or regional anesthesia. Various modalities have been used to manage postoperative pain after lower limb orthopedic surgery. Opioids like fentanyl, morphine and tramadol have great analgesic potential and are commonly used for intraoperative and postoperative analgesia. IV administration of non-steroidal anti-inflammatory drugs is also utilized for the same purpose. Epidural analgesia provides effective pain relief and the option for continuous postoperative analgesia. Lower limb nerve blocks enhance pain management, facilitate early mobilization and improve patient satisfaction during recovery. However, all these modalities are associated with their own specific set of advantages and disadvantages.

Spinal anesthesia is commonly used for lower limb surgeries as it is easy to administer, has a rapid onset of action, and avoids the difficulties associated with airway management. When local anesthetic agents are used alone for spinal anesthesia, they provide a finite duration of analgesia. The duration of spinal analgesia and anesthesia can be prolonged by the addition of adjuvant drugs such as opioids, alpha-2 agonists, adrenaline, etc. to the local anesthetic or by placing a catheter.^{1,2}

The synergistic effect of local anesthetics and alpha-2 agonists may be due to their differing sites of action. While local anesthetics block voltage-gated sodium channels which are necessary for nerve impulse transmission, alpha-2 agonists provide analgesia by several mechanisms at spinal and supraspinal sites. By binding to alpha-2 receptors in the spinal cord and brainstem, they inhibit transmission of nociceptive impulses through the posterior horn of the spinal cord, inhibit the release of norepinephrine, which is a neurotransmitter involved in transmitting pain signals, activate descending pain control pathways and promote the release of acetylcholine from spinal interneurons, resulting in increased synthesis and release of nitric oxide which may be involved in regulation of analgesia. They also modulate pain processing in the brain, making pain appear less intense and unpleasant, and the sedation and anxiety provided further help reduce the perception of pain.^{3,4} All these effects may contribute to prolonging the sensory block of spinal anesthesia. The prolongation of motor block of spinal anesthesia may be due to binding of these drugs to motor neurons in the dorsal horn.⁵ However, potential adverse effects like hypotension and bradycardia must be taken into consideration when these drugs are administered.

When administered IV, dexmedetomidine provides excellent analgesia without respiratory depression and has been safely utilized as a preoperative sedative or medication for patients undergoing surgery under regional anesthesia.⁶ A few earlier studies have reported a prolongation of the sensory block of spinal anesthesia by pre-administration of IV dexmedetomidine. The target site of IV administered alpha-2 agonists is also the alpha-2 receptors and a similar potentiation of spinal anesthesia may be achieved by administering the drug by the IV route. As most spinal additives have not obtained approval for intrathecal administration from regulatory bodies, it seems safer to opt for IV administration if a similar benefit can be obtained.

Kaya et al.⁶ found a significant increase in the duration of the sensory blockade of spinal anesthesia when patients received 0.5 mcg.kg⁻¹ IV dexmedetomidine before spinal anesthesia with 0.5% heavy bupivacaine. Kavya et al.⁷ administered 0.5 mcg.kg⁻¹ IV dexmedetomidine as a pre-spinal bolus, followed by a continuous infusion of 0.5 mcg.kg⁻¹ for 1h and found a prolongation of both the sensory and motor blockade of spinal anesthesia.

While Harsoor S et al.⁸ and Bhurud PH et al.⁹ studied the characteristics of spinal anesthesia after the administration of 0.5 mcg.kg⁻¹ IV dexmedetomidine before spinal anesthesia followed by an IV infusion of 0.5 mcg.kg⁻¹.h⁻¹ through the entire duration of surgery, they did not study the postoperative pain scores and analgesic requirements. It has been suggested that the use of IV dexmedetomidine intraoperatively may result in lower postoperative pain and reduced opioid consumption,¹⁰ and improvement in the quality of recovery and chronic pain after surgery.¹¹

We hypothesized that the administration of 0.5 mcg.kg⁻¹ IV dexmedetomidine before spinal anesthesia followed by an IV infusion of 0.5 mcg.kg⁻¹.h⁻¹ throughout surgery should result in prolongation of the sensory block of spinal anesthesia, prolonged postoperative analgesia and reduced postoperative analgesic consumption with minimal side effects. Our primary objective was to compare the duration of sensory blockade of spinal anesthesia with and without IV dexmedetomidine bolus and infusion in patients undergoing lower limb orthopedic surgery. Secondary objectives were to compare the other characteristics of spinal anesthesia and postoperative pain and analgesic requirements.

Methods

Ethics approval

This prospective, randomized, double-blind controlled trial was conducted between July 2023 and August 2024. The study protocol was approved by the Institutional Ethics Committee on 19/04/2023 and the trial was prospectively registered under the Clinical Trials Registry of India (CTRI/2023/06/054571) on 30/06/2023. The trial adheres to the principles of the Declaration of Helsinki. Written and informed consent was obtained from all participating patients. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized controlled trials. The full trial protocol and statistical analysis plan are available on request.

Inclusion and exclusion criteria

We studied adults of American Society of Anesthesiologists (ASA) physical status I/II of ages 18–65 years of either sex scheduled to undergo elective lower limb surgery of an anticipated duration of 1–2h under spinal anesthesia. Patients with contraindications to spinal anesthesia or previous failed spinal anesthesia, long-standing diabetes mellitus, cardiac or neurological disease, neuropsychiatric disorders, hypersensitivity to study drug, chronic treatment with opioids/sedatives and pregnant women were excluded from the study. Obese patients (BMI > 30 kg.m⁻²) were also excluded due to their higher risks of underlying

cardiovascular comorbidities and consequent hemodynamic instability and altered drug pharmacokinetics.

Randomization and Group allocation

Prospective patients were screened for eligibility and included in the study on the morning of surgery. Randomization was done by computer-generated numbers and allocation into groups by opening a sealed opaque envelope before surgery by an anesthesiologist not involved in the study protocol. Patients were randomly allocated in 1:1 to either Group DX (Dexmedetomidine) to receive IV dexmedetomidine bolus followed by dexmedetomidine infusion or Group NS (Normal Saline) to receive IV normal saline bolus followed by NS infusion through the duration of surgery.

Blinding

Patients were blinded to their group allocation. All study drugs were prepared by an independent anesthesiologist who was not involved in the subsequent conduct of the study. Intraoperative and postoperative assessments, including pain scoring, were performed by a separate anesthesiologist who remained blinded to group allocation throughout the study.

Anesthesia technique

A detailed pre-anesthetic check-up including history, physical examination, and investigations as indicated was carried out in all patients and the anesthetic procedure was explained. During the preoperative visit, patients were taught how to grade their pain using the Visual Analogue Scale (VAS).¹² All patients were fasted as per ASA guidelines. Premedication in the form of tablet alprazolam 0.25 mg was given at night and at 6 am on the day of surgery.

In the operating room, the patients were placed in the supine position, and standard ASA monitoring consisting of ECG, non-invasive Blood Pressure (BP), pulse oximetry and temperature monitoring was instituted. Baseline Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR), and Peripheral Oxygen Saturation (SpO₂) were recorded. IV access was secured with a 16 G/18 G IV cannula and ringer lactate infusion was commenced at 20 mL.kg⁻¹.h⁻¹.

Patients in Group DX received 0.5 mcg.kg⁻¹ IV dexmedetomidine in 20 mL of NS over 10 min (bolus dose). Spinal anesthesia was then administered and an IV infusion of dexmedetomidine 0.5 mcg.kg⁻¹ in 20 mL of NS was given at 20 mL.h⁻¹ through the duration of surgery. Patients in Group NS received 20 mL of NS IV over 10 min (bolus dose). Spinal anesthesia was then administered and an IV infusion of NS at 20 mL.h⁻¹ was continued through the duration of surgery.

After receiving the bolus dose of the study drug in a volume of 20 mL over 10 min, the patient was assisted into the sitting or lateral position and using full asepsis, subcutaneous infiltration with 1 mL of 2% xylocaine was done at the L3–L4 space. A subarachnoid block was performed using a 25-gauge spinal needle through the midline approach. After attaining free flow of CSF, 2.5 mL of 0.5% hyperbaric bupivacaine was administered intrathecally and following this, the patient was returned to the supine position immediately

with the table maintained horizontally. Infusion of the study drug was then commenced in all patients as per group allocation at the rate of 20 mL.h⁻¹ and was continued up to the last skin suture. All patients were given oxygen at the rate of 5 lpm via a face mask throughout the procedure.

At the end of the surgery, the patients were shifted to the Post Anesthesia Care Unit (PACU). On arrival in PACU, they received injection Paracetamol 1g IV and then henceforth every 8 hours. Pain scores using VAS were assessed at rest at 0h, 4h, 8h, 12h, and 24h. Patients with a VAS score > 3 received injection diclofenac 75 mg IV and if the patients were not relieved of pain within 30 min, they were given injection tramadol 1–2 mg.kg⁻¹ IV along with injection ondansetron 4 mg. If the patient was sleeping comfortably, the VAS score was considered to be zero. The duration of analgesia was taken to be the time from administration of subarachnoid block to the request of first additional post-operative analgesia or VAS > 3, whichever was earlier. The duration of analgesia and total additional analgesic consumption in 24h postoperatively was noted. Both the patient and the anesthesiologist following up the patient were blinded to the patient's group allocation.

During the study period, hypotension, defined as a decrease in MAP below 20% of baseline or systolic pressure < 90 mmHg was treated with lactated ringer's solution 200 mL over a 5 min period and then intravenous ephedrine 5 mg if the hypotension persisted. Bradycardia (HR < 50 bpm) was treated with intravenous atropine 0.5 mg. Only if the bradycardia and hypotension persisted or worsened, the study drug infusion would be interrupted until the vital signs stabilized.

Measurements and data handling

The time of intrathecal injection was recorded. Sensory blockade was assessed using pinprick in the mid axillary line on both sides. The motor block was assessed immediately after sensory block assessment using a Modified Bromage Scale. Sensory and motor block were assessed every 2 min till the maximum height of the sensory block was attained and a Modified Bromage scale score of 3 was attained and thereafter every 10 min.

The onset time of sensory blockade was defined as the interval between intrathecal administration and the attainment of T10 sensory dermatome blockade. The maximum height of the sensory block achieved was noted. The duration of the sensory blockade was defined as the interval from intrathecal administration to the point of a two-dermatome regression of sensory block from the maximum level. The onset time of motor blockade was defined as the time from intrathecal injection to Modified Bromage score of 3. Motor block duration was defined as the time from intrathecal administration to the point at which the Modified Bromage score was back to zero. After administration of the subarachnoid block, HR, SBP, DBP, MAP and SpO₂ were recorded every 5 min for the initial 30 min, and then every 10 min for the duration of surgery. The Ramsay Sedation Score¹³ was used to score sedation every 10 min intra-operatively and upon arrival in the PACU. Excessive sedation was defined as a score greater than 4/6. The presence of any other complications in the perioperative period like nausea or vomiting and headache were also noted. At the end of the

study, participants were asked to guess their group allocation (intervention, control, or unsure) as part of the blinding assessment.

Primary and secondary outcomes

The primary outcome measure was the time for two-segment regression of sensory blockade of spinal anesthesia. Secondary outcomes were onset time of sensory block, onset time and duration of motor block, maximum level of sensory block achieved, postoperative pain scores, time to requirement of first additional postoperative analgesic and additional analgesic consumption over the first 24h.

Sample size calculation

The primary outcome variable was the duration of the sensory block, defined as the time (in mins) required for two-segment regression following spinal anesthesia. Based on a previous study,⁷ the mean ($\pm$ SD) regression time was 166.2 ± 26.7 min in the IV dexmedetomidine (bolus plus infusion) group and 133.2 ± 28.2 min in the normal saline group. Accordingly, an expected mean difference of 33 min and a pooled standard deviation of 28 min were used for sample size estimation. The sample size was calculated using the formula for comparing two independent means, assuming a Type I error (α) of 0.05 and a power ($1 - \beta$) of 80%, which yielded a requirement of approximately 22 participants per group. To account for a potential 30% dropout rate, the total sample size was increased, and 58 patients were enrolled. This calculation assumed a continuous, normally distributed outcome variable and was based on the referenced study.⁷

Statistical analysis

Data was collected and analyzed using Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp., Armonk, NY, USA). A total of 58 patients were included in the final analysis. Continuous variables, including duration of sensory block and time to regression, were summarized as mean $\pm$ standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of data distribution, and the data were found to be normally distributed. Group comparisons for continuous variables were performed using the independent samples *t*-test. Categorical variables were expressed as frequencies and percentages, and comparisons between groups were made using the Pearson Chi-Square test. Pain and sedation scores, expressed as median [Interquartile Range, IQR], were compared between groups using the Mann-Whitney *U* test. For secondary endpoints, adjustment for multiple comparisons was applied to control the family-wise error rate, using the Bonferroni correction. A *p*-value < 0.05 was considered statistically significant.

Results

Sixty-two patients were assessed for eligibility. Four patients did not meet the inclusion criteria. Fifty-eight patients were included in the study and their data analyzed (Fig. 1).

No differences in baseline patient characteristics were observed between the study groups (Table 1).

The time for two-segment regression of sensory blockade was significantly prolonged in the DX group (137.03 ± 25.02 min) compared to the NS group (79.45 ± 11.27 min). An independent sample Student's *t*-test showed that this difference was statistically significant ($p < 0.001$). The calculated effect size (Cohen's $d \approx 2.97$) indicated a very large treatment effect, suggesting not only statistical but also strong clinical relevance (Fig. 2, Table 2).

The onset of sensory blockade was 3.24 ± 1.12 min in the DX group and 3.59 ± 1.12 min in NS group ($p = 0.246$). The onset of motor blockade was 4.28 ± 0.88 min in the DX group and 4.55 ± 1.06 min in the NS group ($p = 0.285$). The duration of motor blockade was longer in the DX group (236.34 ± 37.16 min) as compared to the NS group (158.69 ± 23.64 min) ($p < 0.001$). The maximum height of the sensory block attained was similar in both groups ($p = 0.239$) (Table 2). The block level was assessed bilaterally and was similar on both sides.

The postoperative VAS scores were comparable at 0h, 8h and 12h in both groups. However, at 4h and 24h, the DX group demonstrated significantly lower pain scores compared to the NS group ($p = 0.001$, $p = 0.0001$ respectively). The mean duration of analgesia or time to the requirement of first additional postoperative analgesia in both groups could not be calculated, as 10 patients (34.4%) in the DX group and 2 patients (6.89%) in the NS group did not require any additional postoperative analgesia in the first 24h after surgery. However, the time to requirement of first additional postoperative analgesia was significantly longer in the DX group. The requirements of additional analgesia with both diclofenac and tramadol were higher in the NS group (Table 2). To adjust for multiple comparisons and control the Family-Wise Error Rate (FWER) in the secondary endpoints (onset time of sensory and motor block, duration of motor block, maximum level of sensory block achieved, postoperative pain scores at 24h, time to requirement of first additional postoperative analgesic, diclofenac consumption over the first 24h and tramadol consumption over the first 24h), Bonferroni correction was applied. The Bonferroni correction ($\alpha = 0.00625$) revealed that only 4 of the 8 secondary outcomes remained statistically significant i.e., the duration of motor block, postoperative pain scores at 24h, time to first postoperative analgesic and diclofenac consumption over 24h. The rest, including tramadol consumption ($p = 0.027$), were not significant after adjustment, even though they may have appeared so at the unadjusted $\alpha = 0.05$ level.

The RSS values observed were found to be significantly higher in Group DX from 20 min after the beginning of surgery up to arrival in the PACU (Fig. 3). However, no patient had a RSS $> 4/6$ indicating excessive sedation.

HR during surgery was significantly lower in the DX group from 20 to 90 min following administration of spinal anesthesia ($p < 0.05$) (Fig. 4). The mean HR during surgery was 70.32 ± 8.81 bpm in the DX group and 80.41 ± 12.55 bpm in the NS group ($p = 0.001$). The Mean Arterial Pressure (MAP) measured during the surgery was also significantly lower in the DX group from 50 to 100 min following administration of spinal anesthesia ($p < 0.05$) (Fig. 5). The mean value of intraoperative MAP was 81.52 ± 7.08 mmHg in the DX group and 86.04 ± 7.89 mmHg in the NS group ($p = 0.026$). SpO₂ showed no significant differences between the groups.

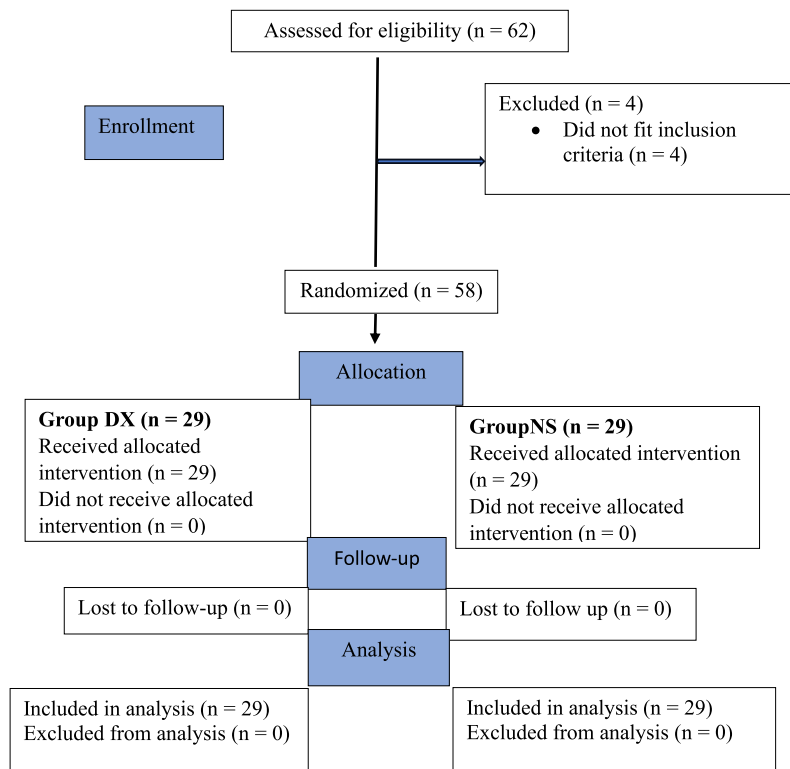


Figure 1 CONSORT flowchart of subject enrollment. CONSORT, Consolidated Standards of Reporting Trials.

The incidence of bradycardia was significantly higher in the DX group as compared to the NS group. Four (13.79%) patients in the DX group developed bradycardia and received IV atropine 0.5 mg, while no patient in the NS group had bradycardia ($p = 0.038$). Three patients in the DX group had hypotension as compared to two patients in the NS group ($p = 0.640$). The hypotension in most cases responded to IV fluids and only one patient in both the groups required a vasopressor. Also, the study drug infusion did not require interruption in any patient. There was no statistically significant difference observed between the groups regarding other side effects such as nausea and vomiting, headache, and excessive sedation. Furthermore, none of the patients needed assistance with ventilation using a bag-mask or endotracheal intubation (Table 3). When asked to guess their group

allocation (intervention, control, or unsure) as part of the blinding assessment, we found that the distribution of responses did not differ significantly from chance, with most participants choosing “unsure”. These findings suggest that blinding was successfully maintained throughout the study.

Discussion

We found that the time to two-segment regression of sensory block was significantly longer in the DX group (137.03 ± 25.02 min) as compared to the NS group (79.45 ± 11.27 min). The duration of motor blockade was also significantly prolonged in the DX group as compared to NS group (236.34 ± 37.16 min vs. 158.69 ± 23.64 min). The onset time of

Table 1 Demographic data.

Parameter	Group DX	Group NS	p-value
Age (yrs)	35.00 ± 10.76	36.24 ± 13.18	0.696 ^b
Sex – Male/Female	22/7	24/5	0.517 ^a
Height (cm)	162.72 ± 7.61	164.90 ± 7.39	0.275 ^b
Weight (kg)	64.69 ± 10.20	69.00 ± 10.23	0.114 ^b
BMI ($\text{kg} \cdot \text{m}^{-2}$)	24.30 ± 2.60	25.37 ± 2.85	0.140 ^b
ASA grade I/II	21/8	16/13	0.172 ^a
Duration of surgery (min)	80.34 ± 23.37	73.10 ± 20.76	0.217 ^b
Duration of anesthesia (min)	117.93 ± 24.11	112.07 ± 21.77	0.335 ^b

Data is expressed as Mean $\pm$ SD or as number of patients.

SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists.

^a Using χ^2 test.

^b Using t -test.

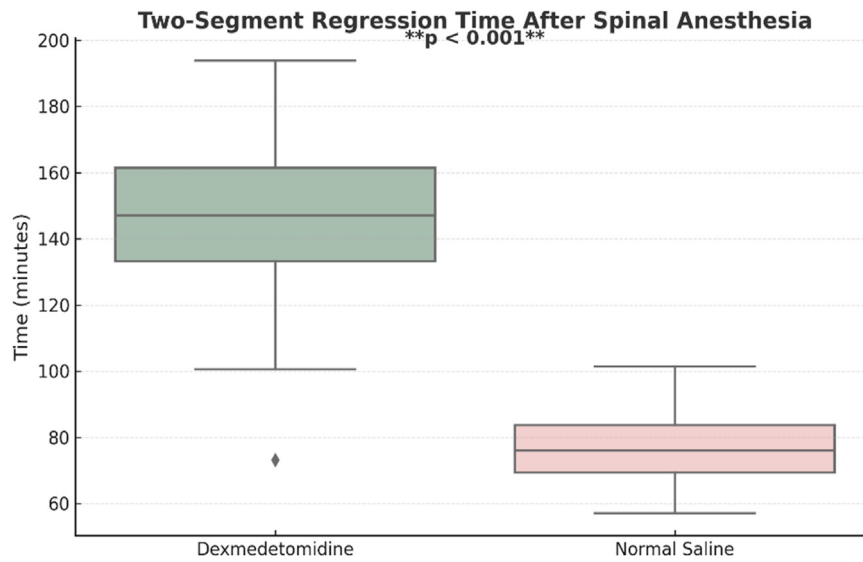


Figure 2 Boxplot showing two-segment regression time in the DX and NS groups.

Table 2 Primary and secondary outcomes.

Parameter	Group DX (n = 29)	Group NS (n = 29)	p-value
Onset time of sensory block (min)	3.24 ± 1.12	3.59 ± 1.12	0.246 ^a
Onset time of motor block (min)	4.28 ± 0.88	4.55 ± 1.06	0.285 ^a
Duration of sensory blockade (min)	137.03 ± 25.02	79.45 ± 11.27	< 0.001 ^a
Duration of motor blockade (min)	236.34 ± 37.16	158.69 ± 23.64	< 0.001 ^a
Maximum height of block achieved			
T6 dermatome	20	14	
T8 dermatome	8	12	0.239 ^b
T10 dermatome	1	3	
VAS Scores			
VAS (0h/arrival in PACU)	0 (0–0)	0 (1–0)	0.102 ^c
VAS (4h)	1 (2–0)	2 (2–1)	0.001 ^c
VAS (8h)	1 (2–1)	2 (2–1)	0.051 ^c
VAS (12h)	2 (2–1)	2 (2–1)	0.333 ^c
VAS (24h)	0 (1–0)	1 (2–1)	0.0001 ^c
Time to requirement of first postoperative analgesic			
≤ 4h	1	6	
> 4h to ≤ 8h	2	18	< 0.001 ^b
> 8h to ≤ 12h	8	3	
> 12h to ≤ 24h	8	0	
> 24h	10	2	
Postoperative Diclofenac requirement			
0 dose	10	2	
1 dose	15	4	< 0.001 ^b
2 doses	4	15	
3 doses	0	8	
Postoperative Tramadol requirement			
0 dose	26	19	0.027 ^b
1 dose	3	10	

Data is expressed as Mean ± SD, Median (IQR) or numbers.

VAS, Visual Analogue Scale, T6, 6th thoracic sensory dermatome, T8, 8th thoracic sensory dermatome, T10, 10th thoracic sensory dermatome.

^a Using *t*-test.

^b Using χ^2 test.

^c Using Mann-Whitney nonparametric test.

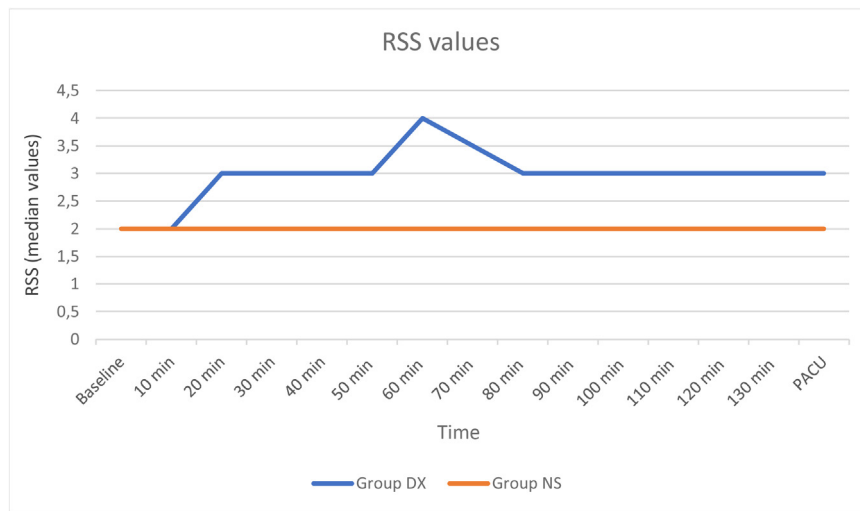


Figure 3 The RSS values were significantly higher in the DX group from 20 min onwards till PACU arrival. RSS, Ramsay Sedation Scores.

sensory and motor block and the maximum height of sensory blockade achieved was similar in both groups. Postoperative VAS scores were significantly lower at 4h and 24h after surgery and the requirement of additional diclofenac in the post-operative period was significantly reduced in the DX group.

Recent studies have explored the use of various adjuncts to spinal anesthesia aimed at prolonging the duration of sensory blockade. Dexmedetomidine is a highly selective alpha-2 agonist which acts on presynaptic alpha-2 receptors in the locus coeruleus in the brain stem resulting in sedation and analgesia. Postsynaptic activation in the central nervous system inhibits sympathetic activity, leading to a decrease in HR and BP. It is likely that a dexmedetomidine infusion will activate alpha-2 receptors in the spinal cord, resulting in inhibition of transmission of nociceptive impulses,⁷ thus enhancing the action of local anesthetic agents resulting in prolonged sensory blockade and better pain control after surgery.^{14,15}

Intrathecal dexmedetomidine has been used in several studies to prolong the duration of spinal anesthesia with

hyperbaric bupivacaine.¹⁶⁻¹⁸ Recent studies have found that the duration of spinal anesthesia can be similarly prolonged by the simultaneous administration of IV dexmedetomidine.^{6-9,19-34} These studies have used various different doses and dose combinations of dexmedetomidine. IV dexmedetomidine prolongs the duration of spinal block primarily by enhancing central analgesia by reducing sympathetic outflow and inhibiting nociceptive transmission. It seems to have a synergistic effect with local anesthetics by systemic absorption and indirect central pain modulation rather than direct action at the level of the spinal cord. By decreasing spinal cord blood flow, it may slow down the clearance of the local anesthetic from the subarachnoid space. The sedation and analgesia provided can mask the waning of the spinal block, thus giving the impression of longer duration.

Some studies have used a single bolus dose of 0.5 mcg.kg^{-1} ,^{6,18,25,30-32} while others have used a bolus of 1 mcg.kg^{-1} .^{7,19,25,33} However, a higher incidence of bradycardia and hypotension was observed in some of these studies.^{19,33} Subsequently investigators studied the use of a bolus followed by infusion of dexmedetomidine

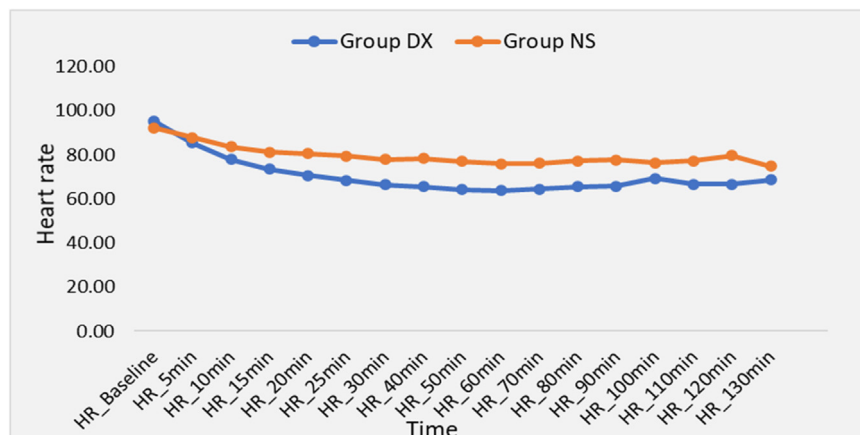


Figure 4 Intraoperative Heart Rate (HR).

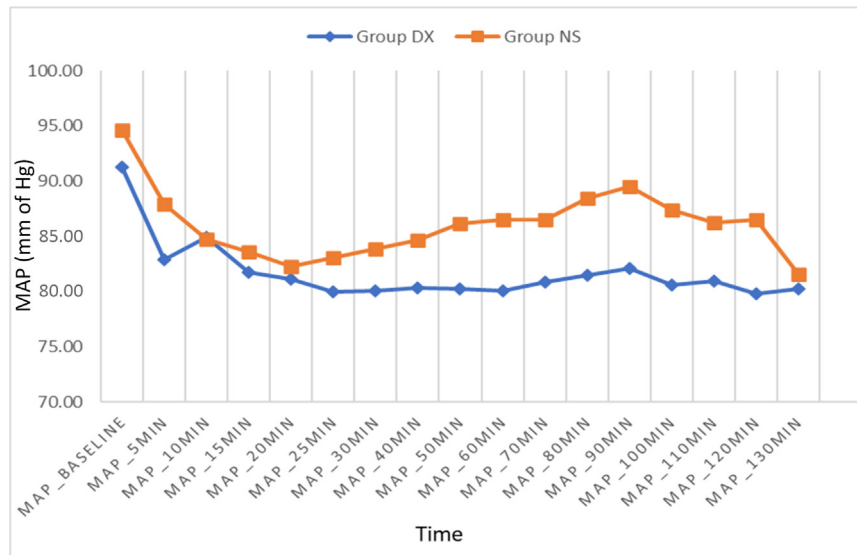


Figure 5 Intraoperative Mean Arterial Pressure (MAP).

to prolong the duration of sensory blockade of spinal anesthesia. The use of a 1 mcg.kg^{-1} bolus followed by an infusion of 0.2 to $0.6 \text{ mcg.kg}^{-1}.\text{h}^{-1}$ resulted in a similar prolongation of sensory blockade but a higher incidence of bradycardia and hypotension.²⁰⁻²³ There are very few studies on the effect of IV dexmedetomidine given as a 0.5 mcg.kg^{-1} bolus followed by a continuous infusion of $0.5 \text{ mcg.kg}^{-1}.\text{h}^{-1}$ throughout the surgery on prolongation of duration of sensory blockade of spinal anesthesia.⁷⁻⁹ The incidence of side effects has not been reported to be significant with this dose schedule.

We observed that the time to two-segment regression of sensory blockade was 137.03 ± 25.02 min in patients in the DX group and 79.45 ± 11.27 min in the NS group. Kavya et al.⁷ reported a two-segment regression time of sensory blockade of 166.2 ± 26.7 min compared to 133.2 ± 28.2 min in the control group when using an IV bolus of 0.5 mcg.kg^{-1} followed by an infusion of $0.5 \text{ mcg.kg}^{-1}.\text{h}^{-1}$ for 1h. Harsoor et al.⁸ reported time for two-segment regression as 111.52 ± 30.9 min (DX group) vs. 53.6 ± 18.22 min (NS group) when a bolus of IV dexmedetomidine 0.5 mcg.kg^{-1} over 10 min before subarachnoid block was followed by a continuous infusion of $0.5 \text{ mcg.kg}^{-1}.\text{h}^{-1}$ throughout the surgery. Using similar doses, Bhirud et al.⁹ reported a two-segment

regression time of sensory blockade of 152.3 ± 18.7 mins, which was similar to what we found.

In earlier studies, a 0.5 mcg.kg^{-1} IV bolus resulted in a time to two-segment regression ranging from 106.67 ± 45.5 min to 148.54 ± 20.66 min.^{6,18,30-32} A 1 mcg.kg^{-1} bolus of dexmedetomidine resulted in prolongation of two-segment regression time to 171.43 ± 22.89 min up to 178.2 ± 21.8 min,^{7,33,34} but with a significant incidence of bradycardia. The use of a 1 mcg.kg^{-1} bolus followed by an infusion resulted in a duration of 130.33 ± 14.49 min to 142.5 ± 2.32 min.^{20,21,23} But again, with a higher incidence of bradycardia.

We found that the duration of motor block also showed a significant difference between the two groups. Patients in the DX group had a prolonged duration of motor blockade compared to the NS group (236.34 ± 37.16 min vs. 158.69 ± 23.64 min). Investigators who used the same dosing schedule as ours reported similar findings.⁷⁻⁹ We observed that the onset time of sensory block and motor block was similar in both groups. This was similar to the observations made in several previous studies.^{7,19,23,26,31,32} In contrast, some studies^{8,22} have reported a faster onset of sensory block in the DX group. These conflicting results could be attributed to factors such as variations in study protocols or methodological differences in assessing the onset of sensory block.

Table 3 Incidence of any side effects.

Side effect	Group DX (n = 29)	Group NS (n = 29)	Pearson Chi Square	p-value
Hypotension	3 (10.34%)	2 (6.89%)	0.219	0.640 ^a
Bradycardia	4 (13.79%)	0 (-)	4.296	0.038 ^a
Nausea	2 (6.89%)	1(3.44%)	0.352	0.553 ^a
Vomiting	1(3.44%)	2 (6.89%)	0.352	0.553 ^a
Headache	0 (-)	0 (-)	NA	NA
Excessive sedation	0 (-)	0 (-)	NA	NA

Data is expressed as number of patients (percentage of patients).

NA, Not Applicable.

^a Using χ^2 test.

We observed that the maximum height of sensory blockade achieved was similar in both groups. This was again similar to several previous studies.^{8,25,26,31,32} A few investigators^{20,22} reported a significant difference in the maximum level of sensory block attained between the dexmedetomidine and the control groups. This may be because of the higher bolus dose of dexmedetomidine administered, i.e., 1 mcg.kg⁻¹ unlike the 0.5 mcg.kg⁻¹ dose in our study.

As both spinal anesthesia and use of dexmedetomidine reduce sympathetic outflow, the simultaneous administration of both may result in significant bradycardia and hypotension. We observed that MAP was significantly lower in the DX group from the 50th to 100th min and HR was significantly lower from the 20th to 90th min. The hemodynamic response to dexmedetomidine infusion is influenced by both the dosage and the infusion rate. Dexmedetomidine reduces HR and MAP due to a diminished central sympathetic outflow as well as the sedative and anxiolytic actions of dexmedetomidine. We found that the incidence of bradycardia was significantly higher in the DX group as compared to the NS group, which is similar to findings in earlier studies.^{19,20,22} However, an incidence of 13.79% is clinically significant, which suggests that dexmedetomidine infusion should be used cautiously in patients with baseline bradycardia or when high levels of neuraxial blockade with consequent sympathetic blockade are required. Although MAP was significantly lower in the DX group, the incidence of hypotension was similar in both groups which is again similar to previous studies.²⁶

Intraoperatively, and on arrival in the PACU, patients in the DX group were more sedated as compared to the control group. Dexmedetomidine induces sedation by binding to alpha-2 receptors in the locus coeruleus. This area, along with the dorsal raphe, comprises key central neural structures where it acts producing sedation and analgesia.³⁵ Dexmedetomidine is unique in its ability to cause conscious sedation. The fact that RSS scores did not exceed 3/6 in any patient at any time supports this.

We found that postoperative VAS scores were comparable at 0h, 8h and 12h. However, at 4h and 24h, the DX group demonstrated significantly lower pain scores compared to the NS group. The similar VAS scores on arrival in the PACU could be because surgeries were of < 2h duration and it is likely that there was a residual effect of spinal anesthesia. The similarity in VAS scores at 8h and 12h between the DX and NS groups can be attributed to the fact that most of the patients in the NS group had received their first dose of additional analgesic by then. The VAS scores at 24h were significantly lower in the DX group as perhaps, an overall better pain control had been achieved. Although a 1-point reduction (on a 10-point VAS) is usually not considered clinically meaningful,^{36,37} this should be interpreted keeping in mind that the NS group was also receiving more postoperative analgesics.

All patients in our study received injection Paracetamol 1g IV on arrival in PACU and then henceforth every 8h. Ten patients (34.4%) in the DX group and 2 patients (6.89%) in the NS group did not require any additional postoperative analgesia in the first 24h after surgery and the requirement of additional analgesics in the postoperative period was significantly reduced in the DX group as compared to the NS group. Reduced requirement of postoperative analgesia is beneficial as it

reduces the side effects associated with the use of both opioid and nonopioid analgesics.

With intravenous dexmedetomidine, we achieved a sensory block duration ranging from 102 to 184 min and a motor block duration of 174 to 316 min. This duration appears optimal for patients undergoing elective lower limb orthopedic procedures of approximately 1–2 hours under spinal anesthesia. The prolongation of both sensory and motor blockade obviates the need for intraoperative epidural catheterization, which is advantageous given the increasing use of peripheral nerve blocks for postoperative analgesia – techniques that offer several benefits over epidural analgesia in orthopedic settings.

An extended sensory block facilitates a smoother transition into the postoperative period by reducing early pain and enhancing patient comfort and satisfaction. This, in turn, lowers the immediate postoperative opioid requirement, decreases the need for rescue analgesics, and lessens the workload for recovery room staff – aligning well with Enhanced Recovery After Surgery (ERAS) protocols. Moreover, many lower limb orthopedic surgeries are associated with significant postoperative pain. In such cases, prolonged sensory blockade can delay or reduce the need for systemic opioids, minimizing opioid-related adverse effects such as nausea, sedation, and respiratory depression. These benefits are particularly relevant for elderly or opioid-sensitive patients, for whom opioid-sparing strategies are clinically advantageous.

In addition to improving patient outcomes, longer blocks may also enhance surgical team satisfaction by preventing early breakthrough pain in the Post-Anesthesia Care Unit (PACU). However, overly prolonged sensory or motor blockade may delay mobilization, voiding, and discharge – especially in frail or elderly patients – potentially increasing the risk of urinary retention, pressure ulcers, or falls. Early mobilization is critical in orthopedic surgery to minimize the risk of venous thromboembolism and to support functional recovery. If the motor block persists excessively, it may interfere with physiotherapy, hinder ambulation, and prolong hospital stay. Patients with residual motor weakness may also be unaware of limb instability, increasing fall risk during early mobilization.

Overall, intraoperative use of intravenous dexmedetomidine offers distinct clinical advantages in lower limb orthopedic surgeries by prolonging spinal anesthesia in a controlled and effective manner, provided careful consideration is given to the duration of motor block and its impact on postoperative recovery.

Limitations of the study

Only ASA I/II patients undergoing surgical procedures of < 2h duration were recruited in this study. Our results cannot be extrapolated to ASA III/IV patients undergoing prolonged surgical procedures under spinal anesthesia. The sample size of the study may not have been adequate to detect significant differences in the secondary outcomes. We assessed the effects of dexmedetomidine on spinal anesthesia with only a fixed dose of 2.5 mL of 0.5% hyperbaric bupivacaine in spinal anesthesia and one fixed loading (bolus) and maintenance dose of dexmedetomidine. Hence, the dose response relationship of dexmedetomidine and the duration of spinal

anesthesia could not be discussed. As there was no long-term patient follow-up, we cannot comment on rebound hyperalgesia or other delayed side effects.

Conclusion

Intravenous dexmedetomidine (0.5 mcg.kg⁻¹ bolus followed by 0.5 mcg.kg⁻¹.h⁻¹ infusion) prolonged the duration of sensory and motor blockade and improved postoperative analgesia in patients undergoing lower limb orthopedic surgery under spinal anesthesia, with minimal adverse effects. Further studies are warranted to evaluate optimal dosing strategies and safety in higher-risk populations.

Data availability statement

The datasets generated and/or analyzed during the current study are available in the SciELO Data repository - <https://doi.org/10.48331/SCIELODATA.N9KIZX>. Any additional data are available from the corresponding author upon reasonable request.

Authors' contributions

Simran Chahal: Conceptualization; Methodology; Software. Anju R. Bhalotra: Conceptualization; Methodology; Data curation; Writing-original draft preparation. Rahil Singh and Snigdha Singh: Methodology; Visualization; Investigation. Shweta Dhiman: Supervision; Software; Validation.

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Conflicts of interest

The authors declare no conflicts of interest.

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Associate Editor

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ORIGINAL INVESTIGATION

An anesthetic perspective on transoperative complications in open versus robot-assisted radical cystectomy: a five-year retrospective study

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Abstract

Background: Radical cystectomy remains the standard treatment for invasive bladder cancer, yet it carries significant anesthetic risks. While robot-assisted surgery has gained popularity, data comparing its anesthetic implications to those of open surgery are limited. This study aimed to compare the incidence of transoperative complications between the two techniques.

Methods: We retrospectively analyzed 44 patients who underwent open (n = 29) or robot-assisted (n = 15) radical cystectomy in a university hospital between 2019 and 2024. Data were collected on American Society of Anesthesiologists (ASA) physical status, intraoperative hemodynamic parameters, ventilatory complications, additional postoperative opioid requirements, Intensive Care Unit (ICU) stay, and total length of hospital stay. Correlations between blood loss, transfusion requirements, and hemodynamic variables were evaluated.

Results: The robotic cystectomy group experienced less intraoperative bleeding (mean of 410 ± 185 mL vs. 662.5 ± 210 mL; $p = 0.002$), but no significant reduction in transfusion requirements (95% CI not reported; $p = 0.110$) despite a strong correlation between bleeding volume and need for transfusion ($r = 0.78$; $p < 0.001$). Opioid consumption was significantly higher in the open cystectomy group (75.9% vs. 33.3%; $p = 0.004$). There was no significant difference in intraoperative hypotension, vasoactive drug use, ventilatory complications, in-hospital mortality, ICU stay, or total hospital stay ($p > 0.05$ for all). However, the small sample size limits the precision of these estimates.

Conclusion: While robot-assisted radical cystectomy was associated with reduced blood loss and lower additional postoperative opioid use, our small retrospective sample did not identify significant differences in intraoperative hemodynamic parameters or major complications. The surgical technique had no impact on in-hospital mortality.

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Introduction

The increasing life expectancy, especially in low- and middle-income countries, has contributed to a rise in bladder cancer incidence. In Brazil alone, an estimated 11,370 new cases are expected annually between 2023 and 2025.¹ Radical cystectomy remains the gold standard treatment for localized muscle-invasive tumors and non-muscle-invasive disease with a high risk of recurrence. While effective, this procedure carries significant morbidity and mortality risks.

Recent years have seen the emergence of Robot-Assisted Radical Cystectomy (RARC) as a minimally invasive alternative, associated with less intraoperative bleeding, faster recovery, and shorter hospital stay.² However, studies such as the RAZOR trial and Cochrane meta-analyses suggest that, despite these perioperative benefits, RARC does not significantly differ from Open Radical Cystectomy (ORC) in terms of major complications and positive surgical margins.³⁻⁵

RARC poses specific anesthetic challenges, including the need for deep neuromuscular blockade, precise fluid management, adjustments in pulmonary ventilation, hemodynamic control, and meticulous patient positioning. In contrast, ORC, while also complex, presents fewer anesthetic considerations and can be performed under regional anesthesia even in older patients.⁶⁻¹⁰

Anesthetic-surgical implications for ORC and RARC are still poorly described in the literature. Therefore, this study aimed to compare the incidence of transoperative complications in a university hospital over a five-year period, focused on anesthetic implications. We hypothesized that RARC would be associated with fewer transoperative complications than ORC.

Methods

This retrospective comparative cohort study was conducted in a tertiary care university hospital by analyzing data from electronic medical records of patients who underwent ORC or RARC between March 2019 and March 2024. The project was approved by the Institutional Review Board, and research and methods adhered to the provisions of the Declaration of Helsinki and the STROBE guidelines.

Eligible participants were all adult patients (aged ≥ 18 -years) undergoing radical cystectomy with an American Society of Anesthesiologists (ASA) physical status I, II, or III. Patients with ASA IV or V, patients undergoing emergency surgery, patients undergoing radical cystectomy exclusively under regional anesthesia (spinal + epidural), and those undergoing radical cystectomy combined with other surgical interventions were excluded from the study. Cases with incomplete information on critical variables were excluded in advance.

Radical cystectomy was indicated for muscle-invasive urothelial carcinoma of the bladder or non-muscle-invasive disease refractory to transurethral resection and/or intravesical therapy.

Both ORC and RARC used balanced general anesthesia with sevoflurane and remifentanyl. In cases of open surgery, general anesthesia was combined with epidural anesthesia using morphine and ropivacaine. Continuous epidural

analgesia was employed with intermittent boluses administered at the patient's request. The epidural catheter was maintained for up to 48 hours postoperatively and removed based on clinical outcomes.

Transoperative complications

For this study, transoperative complications were defined as anesthesia-related adverse events that occurred during or immediately after surgery. The following complications were analyzed:

- Arterial hypotension: defined as Mean Arterial Pressure (MAP) < 60 mmHg, sustained for more than one minute, based on continuous intraoperative monitoring;
- Need for vasoactive drugs;
- Ventilatory complications: hypoxemia – considered present when oxygen saturation as measured by pulse oxymetry (SpO_2) was $< 90\%$, sustained for more than five minutes during the procedure; and hypercarbia – defined as End-Tidal Carbon Dioxide ($ETCO_2$) > 45 mmHg with continuous capnography monitoring, sustained for more than two minutes during the procedure;
- Neurological complications, such as cognitive dysfunction;
- Neurological or dermatological events attributable to patient positioning;
- Need for additional opioid administration in the immediate postoperative period (as documented in the medical records);
- In-hospital mortality (deaths during hospitalization).

Outcomes

The following outcomes were assessed:

- Intraoperative outcomes – bleeding volume, need for blood transfusion, arterial hypotension, need for vasoactive drugs, ventilatory complications (hypoxemia and hypercarbia), and operating time;
- Postoperative outcomes – additional opioid requirements in the immediate postoperative period, neurological or dermatological injuries associated with patient positioning, neurological complications (e.g., cognitive dysfunction), major complications (Clavien-Dindo grade $\geq III$), and in-hospital mortality;
- Recovery times – length of stay in the Intensive Care Unit (ICU), time to resume oral intake, and total length of hospital stay.

Statistical analysis

The number of cases in the hospital during the study period determined the sample size. SPSS version 28.0 (IBM SPSS, Armonk, NY, USA) was used for statistical analysis. Descriptive statistics are presented as mean $\pm$ standard deviation or frequency and percentage. The Shapiro-Wilk test was used to assess the normality of data distribution. Continuous variables were compared using Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables were analyzed using the Chi-Square test or Fisher's exact test.

Ridge regression was employed to identify predictors of transoperative complications (defined as the presence of prolonged hypotension, need for vasopressors, or ventilatory complications). The following variables were included in the model: age, sex, body mass index, ASA classification, surgical approach (RARC vs. ORC), and operating time. Crude Odds Ratios (OR) were calculated to estimate the probability of outcome occurrence. Correlations between variables were also performed, with a correlation coefficient (r) of ≤ 0.39 considered weak, 0.40 – 0.59 considered moderate, and ≥ 0.60 considered strong. To strengthen the internal validity of our between-group comparisons, we conducted a 1:1 propensity score matching, using age and ASA classification as predictors of complications.

As all assessed outcomes were essential information on critical variables, there were no missing data in our study. The significance level was set at $p < 0.05$ for all analyses.

Results

Of 59 patients initially identified, 13 were excluded for undergoing radical cystectomy exclusively under regional anesthesia (spinal + epidural), and two were excluded for undergoing combined surgical procedures (one with a hysterectomy and another with a nephrectomy). Therefore, our sample consisted of 44 patients: 29 who underwent ORC, and 15 who underwent RARC. The groups did not differ significantly in age, sex, or ASA physical status, ensuring a homogeneous sample (Table 1).

The most prevalent comorbidities were hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (data not shown). Preoperative hemoglobin levels ranged from 9.9 to 15.1 g.dL⁻¹.

The Ridge regression model showed that ASA III classification tended to be associated with a higher risk of complications (positive coefficient), but without statistical significance ($p > 0.05$). None of the other variables showed a

significant association with anesthetic outcomes in the adjusted model. The discriminatory power of the model (Area Under the Curve [AUC]) was 0.64 , indicating modest predictive ability.

Propensity score matching revealed statistically significant differences in the need for blood transfusion ($p = 0.000004$) and vasoactive drug use ($p = 0.0003$), both of which were significantly lower in the RARC group. In addition, there was a trend toward lower opioid use ($p = 0.069$) and hypotension ($p = 0.082$) in this group, without reaching statistical significance, however.

Intraoperative outcomes

Intraoperative complications per group are shown in Table 2. There was no statistically significant difference between the groups in the incidence of hypotension (OR = 0.53 , $p = 0.492$), vasoactive drug use (OR = 0.56 , $p = 0.512$), or ventilatory complications ($p > 0.05$). Patients undergoing RARC experienced significantly less intraoperative bleeding (410.0 ± 185 mL) than those undergoing ORC (662.5 ± 210 mL) ($p = 0.002$). While the odds of requiring blood transfusion were lower in the RARC group (OR = 0.29), there was no significant difference in transfusion requirements between the groups ($p = 0.110$). The correlation between bleeding volume and need for transfusion was strong ($r = 0.78$; $p < 0.001$), whereas the correlation between blood loss and vasoactive drug use was weak ($r = 0.25$; $p = 0.130$).

The data indicate a significantly longer operating time for RARC (340 ± 60 min) than for ORC (270 ± 50 min) ($p < 0.0001$).

Postoperative outcomes

Postoperative complications per group are shown in Table 3. The data show a significantly higher need for additional postoperative opioid analgesia in the ORC group (OR = 0.12 , $p = 0.004$). There was no statistically significant difference

Table 1 Sample characteristics.

Variable	Open surgery (n = 29)	Robotic surgery (n = 15)	p
Age (years), mean $\pm$ SD [95% CI]	68.2 $\pm$ 7.4 [65.4 – 71.0]	66.8 $\pm$ 6.9 [63.0 – 70.6]	0.512
Male, n (%) [95% CI]	24 (82.8) [24.7 – 27.5]	12 (80.0) [23.5 – 27.3]	0.752
BMI (kg.m ⁻²), mean $\pm$ SD	26.1 $\pm$ 3.8	25.4 $\pm$ 3.5	0.601
ASA I–II, n (%)	13 (44.8)	8 (53.3)	0.435
ASA III, n (%)	16 (55.2)	7 (46.7)	0.518

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; CI, Confidence Interval; SD, Standard Deviation.

Table 2 Intraoperative outcomes.

Variable	Open surgery (n = 29)	Robotic surgery (n = 15)	p
Bleeding volume (mL), mean $\pm$ SD [95% CI]	662.5 $\pm$ 210 [582.6 – 742.4]	410.0 $\pm$ 185 [307.6 – 512.4]	0.002
Need for blood transfusion, n (%)	13 (44.8)	3 (20.0)	0.110
Arterial hypotension, n (%)	14 (48.3)	6 (40.0)	0.492
Use of vasoactive drugs, n (%)	13 (44.8)	5 (33.3)	0.512
Hypoxemia, n (%)	2 (6.9)	1 (6.7)	0.980
Hypercarbia, n (%)	3 (10.3)	2 (13.3)	0.722
Operating time (min) mean $\pm$ SD [95% CI]	270 $\pm$ 50 [251.0 – 289.0]	340 $\pm$ 60 [306.8 – 373.2]	< 0.0001

CI, Confidence Interval; SD, Standard Deviation.

Table 3 Postoperative outcomes.

Variable	Open surgery (n = 29)	Robotic surgery (n = 15)	p
Additional opioid use ^a , n (%)	22 (75.9)	5 (33.3)	0.004
Clavien-Dindo grade $\geq$ III, n (%)	8 (27.6)	5 (33.3)	0.742
In-hospital mortality, n (%)	7 (24.1)	3 (20.0)	1.00

^a Number of patients requiring at least one additional dose of opioid after the end of the surgical procedure.

Table 4 Recovery times.

Variable	Open surgery (n = 29)	Robotic surgery (n = 15)	p
Length of ICU stay (days) mean $\pm$ SD [95% CI]	2.1 $\pm$ 1.8 [1.4 – 2.8]	1.9 $\pm$ 1.5 [1.1 – 2.7]	0.351
Time to resume oral intake (days) mean $\pm$ SD [95% CI]	3.8 $\pm$ 1.5 [3.2 – 4.4]	3.6 $\pm$ 1.4 [2.8 – 4.4]	0.352
Total length of hospital stay (days) mean $\pm$ SD [95% CI]	10.2 $\pm$ 4.1 [8.6 – 11.8]	10.1 $\pm$ 3.9 [7.9 – 12.3]	0.980

CI, Confidence Interval; ICU, Intensive Care Unit; SD, Standard Deviation.

between the groups regarding the incidence of major complications (Clavien-Dindo grade $\geq$ III) (OR = 1.25, p = 0.742), or in-hospital mortality rates (24.1% in ORC vs. 20.0% in RARC; p = 1.00).

Neither group experienced neurological or dermatological injury due to patient positioning. None of the patients exhibited any neurological or cognitive dysfunction that could be detected without specialized evaluation.

Recovery times

Recovery times per group are shown in Table 4. There was no statistically significant difference between the groups in length of ICU stay (p = 0.351), time to resume oral intake (p = 0.352), or total length of hospital stay (p = 0.980). The correlation between operating time and total length of hospital stay was weak (r = 0.18; p < 0.21).

Discussion

Our results indicate that both surgical approaches are safe from an anesthetic perspective, ensuring hemodynamic stability and maintaining intraoperative ventilation. While the robotic approach resulted in less blood loss, potentially contributing to less hemodynamic instability, this did not significantly affect the need for blood transfusion. RARC also required less additional postoperative opioids.

Our findings are consistent with previous studies showing less blood loss in RARC, but with varying results regarding the need for transfusion.^{3,11} In a recent meta-analysis by Khetrapal et al., RARC was associated with a shorter length of hospital stay, less blood loss, fewer transfusions, and a lower incidence of thromboembolic events, although with longer operating time than ORC.¹² Despite a lower incidence of blood transfusions in our study, this finding did not achieve statistical significance. Our data also align with the observation of longer operating time for RARC.¹² At our center, we are in the early phase of the learning curve for RARC, which may have had an impact on operating times and, potentially, on complication rates.¹³ Additionally, more than one surgeon performed the procedures without controlling for individual experience, which could introduce variability

in the results. However, it is worth noting that most of our reference studies also involved procedures performed by multiple surgeons.

Both open and robotic approaches used balanced general anesthesia, with open surgery incorporating epidural anesthesia. Nevertheless, the ORC group still required more additional postoperative opioids than the RARC group. This suggests that open surgery may be associated with a more intense pain response, even with epidural analgesia. This finding aligns with current literature indicating that the minimally invasive nature of robotic surgery results in less surgical trauma, which lessens the endocrine-metabolic response and, consequently, decreases the need for opioid analgesia, contributing to a more comfortable recovery with fewer opioid-related adverse effects.^{14,15}

Our study found no hypoxemia or hypercarbia, suggesting that the ventilation strategies employed were sufficient to maintain adequate pulmonary ventilation in both surgical approaches. These findings align with those of Vejlgard et al., who concluded that the prolonged Trendelenburg position combined with pneumoperitoneum, while challenging for anesthesia management, can be used safely in robotic surgery with appropriate ventilation adjustments.¹⁶ Specifically, Pressure-Controlled Ventilation (PCV) has demonstrated superior efficacy over volume-controlled ventilation in robotic and laparoscopic surgery. PCV has been shown to improve lung compliance and oxygenation in procedures performed with pneumoperitoneum, which may facilitate the adoption of protective tidal volumes and reduce the risk of barotrauma and atelectasis.¹⁷ We routinely use the PCV with Volume-Guarantee (PCV-VG) mode intraoperatively for patients in the head-down position.¹⁸

No significant difference was observed in intraoperative arterial hypotension between ORC and RARC. This is noteworthy because open surgery is typically associated with increased bleeding and involves neuraxial blockade, both of which can lower blood pressure. Our findings suggest that intraoperative bleeding was not sufficient to cause such changes, and that the sympathetic blockade was well-managed to maintain hemodynamic stability. These results indicate that arterial hypotension is more closely related to factors such as anesthetic management and individual patient hemodynamic response than to the surgical

approach. While intraoperative hypotension can be linked to postoperative ischemic events, such as cerebral and myocardial ischemia, we found no documented cases of neurological or ischemic cardiac complications in our patients in the immediate postoperative period or during hospitalization. However, given the retrospective nature of our study, we did not systematically collect data from complementary tests (e.g., serial troponin measurements or neurological imaging) that would have detected these specific complications. Therefore, we lack sufficient data for a robust analysis on this matter and suggest that future prospective studies include more specific monitoring to address this issue.

Major complications and in-hospital mortality did not differ significantly between ORC and RARC. These findings align with previous research, including the RAZOR trial³ and Clement et al.'s meta-analysis.⁴ However, the mortality rate in both groups was high. This can be attributed to the complex patient profile at our institution. As a tertiary care university hospital, we predominantly treat patients with advanced disease and multiple comorbidities, often referred from other facilities after failure of initial therapy. This context differs substantially from centers that perform earlier interventions or treat lower-risk patients. Additionally, the still limited volume of cases per year at our center and our team's early phase of the learning curve with the robotic approach may have negatively influenced the results, especially in the RARC group. It is also important to note that the study period (March 2019 to March 2024) includes the COVID-19 pandemic, during which surgical procedures were curtailed to prioritize pandemic-related burdens.

Our study found no significant difference in ICU or total hospital stay between ORC and RARC. This aligns with the systematic review by Rahman et al., who concluded that robotic surgery does not significantly reduce total length of stay.¹⁹ However, the literature presents conflicting results. Some studies suggest that robotic surgery, when combined with the Enhanced Recovery After Surgery (ERAS) protocol, can reduce hospital stay. The meta-analysis by Williams et al. showed that rigorous ERAS implementation reduced average hospital stay by up to 4.5 days, regardless of surgical or anesthetic technique.²⁰ Conversely, Courboin et al. observed a significant reduction in hospital stay in the robotic surgery group, without any additional care.²¹ While we recognize the benefits of the ERAS protocol, it has not been systematically implemented at our institution. However, some of its components are routinely applied in our clinical practice, such as reduced fasting time, early oral liquid and solid re-feeding, early mobilization, multimodal analgesia with anesthetic blocks or wound infiltration, prevention of hypothermia, and opioid-sparing anesthesia.

Time to resume oral intake did not differ significantly between ORC and RARC. This suggests that gastrointestinal function recovery is similar regardless of the surgical technique.^{3,11,22} In contrast, a potential trend toward faster gastrointestinal function recovery has been observed in patients undergoing RARC.²³ Additionally, alvimopan, an opioid receptor antagonist acting selectively in the intestine without compromising central opioid analgesia, significantly reduces time to first bowel movement, especially when combined with the ERAS protocol.²⁴ Unfortunately, alvimopan is not currently available in Brazil.

While Ridge logistic regression helped address collinearity, the small number of events and limited sample size, particularly in the RARC group, compromised the statistical robustness of the model. The predictive ability was modest (AUC = 0.64), and no variables reached clear statistical significance. ASA III classification hinted at a possible association with increased complication risk. Propensity scores matching results suggest that the hemodynamic benefits of the robotic approach may persist even after controlling for important clinical confounders, supporting its potential as a less invasive and physiologically stable technique compared with the open approach. We recommend that future studies with larger sample sizes explore more robust predictive models to further investigate these associations.

Our study has limitations. First, all data included in the study were collected from electronic hospital records, and the variables used in our analysis were mandatory fields (e.g., age, sex, ASA, duration of surgery, anesthetic events). To ensure the integrity of our database, we performed a complementary manual check during data extraction, and cases with incomplete information on critical variables were excluded. However, we acknowledge that this methodology may introduce selection bias. Second, as a single-center study, the results may not be directly generalizable to settings with different characteristics. Third, a formal sample size calculation was not performed due to the exploratory and retrospective design of our study, which may have led to the study being underpowered to detect significant differences, particularly for low-incidence outcomes. Confidence intervals and clinical relevance should guide data interpretation, reinforcing the need for prospective studies with larger sample sizes. Fourth, the only statistically significant differences between groups were for intraoperative blood loss and opioid use, which were not adjusted for potential confounders such as baseline hemoglobin, institutional analgesic protocol, or individual anesthetic technique. Due to the retrospective nature and small sample size of our study, robust multivariate adjustments would have compromised statistical validity, especially in the RARC group. However, we noticed similar methodological limitations in previous studies we consulted, which also did not adjust for these specific variables. Further prospective studies with greater control over baseline clinical variables are needed to better address these issues. Fifth, we analyzed anesthetic complications individually to preserve the clinical specificity of each outcome, given the diverse pathophysiological mechanisms and multiple clinical implications associated with each event. We did not define a hierarchy of severity or a composite outcome because the frequency and clinical impact of these variables differ substantially. We recognize, however, that the lack of a consolidated index may limit integrated comparisons between groups. Future investigations may benefit from the development of clinically weighted severity scores or composite outcomes. Additionally, the administration of vasoactive drugs does not depend solely on the intensity of intraoperative hypotension. It is a multifactorial clinical decision influenced by several factors, including the patient's baseline hemodynamic status, existing cardiovascular comorbidities, response to fluid replacement, institutional protocols, and the anesthesiologist's preferences. Therefore, while the need for amines was analyzed as a marker of hemodynamic instability, the

specificities of this indication warrant a separate analysis. Finally, we did not differentiate between anesthetic techniques; however, our focus was on evaluating transoperative complications within the broader surgical context (surgery and anesthesia combined), rather than comparing specific anesthetic techniques.

Conclusion

While RARC was associated with reduced blood loss and lower additional postoperative opioid use, our small retrospective sample did not identify significant differences in intraoperative hemodynamic parameters or major complications. The surgical technique had no impact on in-hospital mortality. Further prospective controlled studies are needed to confirm these findings.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

The project was approved by the Institutional Review Board of Hospital Universitário Pedro Ernesto of Universidade do Estado do Rio de Janeiro (HUPE-UERJ) (approval n° 6.600.371), and all research and methods adhered to the provisions of the Declaration of Helsinki and the STROBE guidelines.

Authors' contribution

Sérgio Luiz do Logar Mattos: Conception and design of the study, analysis and interpretation of data; Drafting the article.

Ronaldo Damião: Conception and design of the study; revising the article critically for important intellectual content.

Fabício Borges Carrerette: Conception and design of the study; analysis and interpretation of data; drafting the article.

Aretha Paes de Lima Carneiro: Acquisition of data; analysis and interpretation of data; drafting the article.

Ian Maia Fontes: Acquisition of data; drafting the article.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Quality of recovery after laparoscopic cholecystectomy: a randomized trial of pneumoperitoneum pressure and neuromuscular blockade depth

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KEYWORDS

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Abstract

Introduction: Laparoscopic Cholecystectomy (LC) is a commonly performed surgical procedure. The pneumoperitoneum and the depth of Neuromuscular Blockade (NMB) may impact the occurrence of postoperative pain and the quality of recovery.

Methods: A randomized, double-blind, and prospective clinical trial with 124 patients undergoing LC, divided into 4 groups: SP/MB (Standard Pneumoperitoneum pressure and Moderate NMB); LP/MB (Low Pneumoperitoneum pressure and Moderate NMB); SP/DB (Standard Pneumoperitoneum pressure and Deep NMB); and LP/DB (Low Pneumoperitoneum pressure and Deep NMB). Recovery quality was assessed using the Quality of Recovery Questionnaire (QoR-40), and postoperative pain was evaluated using a Verbal Numerical Rating Scale (VNRS).

Results: No difference was observed between groups regarding the total QoR-40 score 24 hours after surgery ($p = 0.903$). Despite better surgical conditions (scored from 0 to 5) in the LP/DB group (4.7 ± 0.52) and lower in the LP/MB group (4.1 ± 0.95), the LP/DB group showed a longer stay in the Post-Anesthesia Care Unit (PACU), a higher need for rescue treatment for nausea and vomiting in the ward ($p = 0.044$), and greater resting pain at 24 hours ($p = 0.027$).

Conclusion: The use of different pneumoperitoneum pressures under moderate or deep neuromuscular blockade in patients undergoing Laparoscopic Cholecystectomy (LC) did not alter patients' perception of postoperative recovery quality. The combination of standard pneumoperitoneum pressure with deep neuromuscular blockade was associated with a better perception of surgical field quality as evaluated by the surgeon.

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Introduction

Laparoscopic Cholecystectomy (LC) is one of the most commonly performed surgical procedures worldwide.¹ Although it is a short-duration surgery, many patients still experience unexpectedly prolonged hospital stays or readmissions due to difficult-to-control postoperative pain.²

Several studies have sought to propose possible alternatives for preventing postoperative pain. One of the most researched interventions is the use of low-pressure pneumoperitoneum compared to standard pressure.³ However, the reduction of effective working space provided by lower intra-abdominal pressure can increase technical difficulty, the incidence of procedure-related injuries, and the duration of the surgery.⁴

Another variable to consider is the depth of Neuromuscular Blockade (NMB). Deep NMB can improve surgical conditions by facilitating visualization and manipulation of intra-abdominal structures. The limitation for the use of deep NMB in the past was the lack of agents capable of reversing the blockade quickly and predictably. However, this limitation was eliminated with the advent of sugammadex. Many studies have evaluated the benefits of deep NMB on patient's pain intensity and postoperative recovery in patients undergoing laparoscopic surgeries.⁵ However, it is unclear whether these positive effects result from lower pneumoperitoneum pressure, the depth of NMB, or both, further studies are needed to clarify aspects related to postoperative recovery.

Traditionally, perioperative studies have focused on postoperative outcomes such as time to wakening, hospital length of stay, nausea, vomiting and pain control. Measurements that assess quality of life from patients' perspective are increasingly recognized as important in clinical studies that aim to investigate the effect of anesthesia and surgery on patient recovery and satisfaction. One such tool is the Quality of Recovery Questionnaire (QoR-40) which is validated 40-item scoring system developed to assess many aspects of post-surgical recovery.⁶

The hypothesis of the present study was that low-pressure pneumoperitoneum combined with deep neuromuscular blockade, compared to standard-pressure pneumoperitoneum and moderate neuromuscular blockade, would be able to improve the quality of postoperative recovery as assessed by the Quality of Recovery-40 (QoR-40) questionnaire after laparoscopic cholecystectomy. Accordingly, this study aims to compare the quality of recovery in patients undergoing elective laparoscopic cholecystectomy under low-pressure pneumoperitoneum (10 mmHg) and standard pressure (14 mmHg) associated with either deep or moderate neuromuscular blockade. The following secondary outcomes were also considered: surgical conditions, occurrence of postoperative pain, nausea and vomiting, and analgesic consumption.

Methods

This double-blind, randomized, and prospective clinical trial was approved by the Research Ethics Committee (CAAE 42586621.9.3001.5447) and registered with the Brazilian Registry of Clinical Trials (ReBEC) under U1111-1265-2384. The informed consent was obtained voluntarily from each patient. A total of 132 participants aged between

18 and 65 years, classified as physical status according to the American Society of Anesthesiologists (ASA) I and II, were included and underwent general anesthesia for elective LC at the Regional Hospital of Jundiaí-SP. Data were collected during the period from May to October 2022.

The exclusion criteria before randomization were: (I) Patient refusal; (II) Altered consciousness level or inability to communicate; (III) Contraindications to the use of any agent described in the protocol; (IV) Alcohol or drug abuse; (V) Body Mass Index (BMI) ≥ 35 , which could impact the safety of surgeries under the low-pressure pneumoperitoneum protocol; (VI) Chronic pain or opioid use; (VII) Neuromuscular disease; (VIII) Complicated cholelithiasis. Exclusion criteria after randomization included: (I) Protocol violation; (II) Conversion to open surgery; and (III) Patient refusal in the postoperative period.

The participants were randomly allocated into four distinct groups using a random number generator (www.random.org): Group SP/MB (standard Pneumoperitoneum pressure and Moderate NMB); Group LP/MB (Low Pneumoperitoneum pressure and Moderate NMB); Group SP/DB (Standard Pneumoperitoneum pressure and Deep NMB); and Group LP/DB (Low Pneumoperitoneum pressure and Deep NMB). The randomization sequence was stored by a non-research participant and revealed only when all data were forwarded for statistical analysis. For each patient, two opaque envelopes were prepared (one containing the pneumoperitoneum pressure and the other describing the degree of NMB), sealed and sequentially numbered. The envelopes were opened at the time of surgery by an independent nurse who was not involved in patient care or data collection. Neither the patient, surgeon, nor anesthesiologist involved in data collection knew which group each patient belonged to. The degree of NMB was only known by the anesthesiologist responsible for anesthesia.

The study participants did not receive pre-anesthetic medication, as it could negatively influence completion of the Quality of Recovery-40 questionnaire prior to surgery. Age, sex, ASA physical status, and BMI were recorded. Anesthesia induction was performed with sufentanil ($0.5 \mu\text{g.kg}^{-1}$), propofol (2.0 mg.kg^{-1}), and rocuronium (0.45 mg.kg^{-1}), $1.5 \times \text{ED}_{95}$. Patients in the deep NMB groups (SP/DB and LP/DB) received an additional dose of rocuronium (0.45 mg.kg^{-1}) two minutes after intubation (total of $3 \times \text{ED}_{95}$). NMB was monitored using acceleromyography (TOF Watch SX®; Schering-Plough). The Train-Of-Four (TOF) was evaluated at 15-second intervals by analyzing the response to stimulation of the ulnar nerve, aiming to maintain 1–3 responses in the moderate NMB groups and no response (Post-Tetanic Count [PTC] of 1–3) in the deep NMB groups. Additional doses of 5 to 10 mg of rocuronium were used to maintain the TOF and PTC according to the depth of NMB previously determined. Anesthesia maintenance was performed with sevoflurane (1.5%–3%). After incision at each trocar insertion site, infiltration with 0.75% ropivacaine (total volume 20 mL) was performed by the surgical team. The abdomen was insufflated with carbon dioxide to maintain intra-abdominal pressure at 10 mmHg (LP group) or 14 mmHg (SP group), according to the group determined by randomization. The pneumoperitoneum pressure levels were determined based on previous studies^{3,4} and the participating surgeons agreed with the protocol. The display showing the insufflation pressure was obscured so that only the room nursing

staff had access to this information. All patients received dexamethasone (10 mg), ketoprofen (100 mg), dipyrone (2000 mg) and ondansetron (4 mg). After the procedure, atropine (0.01 mg.kg^{-1}) and neostigmine (0.04 mg.kg^{-1}) were administered for patients in the moderate NMB group and sugammadex 4 mg.kg^{-1} for those in the deep NMB group. After awakening, extubation was performed. The time from the end of surgery to awakening was recorded, as well as the surgical time. Surgical conditions were evaluated by surgeons according to an ordinal scale: 1 (extremely poor conditions), 2 (poor conditions), 3 (acceptable conditions), 4 (good conditions), and 5 (excellent conditions).

Pain intensity was assessed at rest and recorded every 15 minutes during the stay in the Post-Anesthesia Care Unit (PACU) using a Verbal Numeric Scale (VNRS) from 0 to 10. Morphine 1–2 mg intravenously was administered every 5 minutes to achieve a score below 4 (1 mg for pain < 7 and 2 mg for pain ≥ 7). After discharge from the recovery room, all patients received ketoprofen 100 mg every 12 hours and paracetamol 500 mg orally every 6 hours. Pain intensity was evaluated upon arrival at the ward, 4 h, 8 h, 12 h, and 24 hours after surgery using the VNRS. In cases of insufficient analgesia, tramadol (100 mg) was offered. Postoperative Nausea and Vomiting (PONV) were treated with dimenhydrinate (30 mg), which was considered as rescue medication. The use of rescue medications and the occurrence of postoperative nausea and vomiting were recorded. All patients remained in the hospital for at least 24 hours.

The primary outcome was the quality of recovery on the first day after surgery, assessed using the Quality of Recovery Questionnaire (QoR-40) in its version validated for Brazilian Portuguese. Interviews were conducted twice for each patient: before surgery and in the ward 24 hours after surgery, carried out by a member of the research team trained and knowledgeable in administering the questionnaire. It was not necessary to consider the Minimum Clinically Important Difference (MCID) in our study because, for the QoR-40 questionnaire, this value is 6.3.⁷ Our results did not reach this threshold.

Sample size calculation was based on a similar randomized clinical trial that assessed postoperative recovery quality using the QoR-40 questionnaire in patients undergoing abdominal hysterectomy with different anesthetic techniques,⁸ considering an alpha error of 0.05 and a power of 90% to detect a 10-point difference in QoR-40, requiring the inclusion of 31 patients per group. A 10-point difference represents a 15% improvement in recovery quality based on previously reported values in QoR-40. Considering potential losses, the final sample size included 132 patients.

Categorical variables were expressed as absolute values for frequency comparison (percentages) and analyzed using the Chi-Square test. Quantitative variables, whose results were not normally distributed according to the Kolmogorov-Smirnov test, were compared using the Kruskal-Wallis test to simultaneously compare all four groups. When a difference was found between groups, the Mann-Whitney test was used for pairwise comparisons to determine where the difference occurred. A post hoc analysis for multiple comparisons (Bonferroni correction) was performed to more accurately determine the differences between groups. Pre- and postoperative moments were compared separately for

all scores (paired data) using the Wilcoxon test. A significance level of 5% and a 95% Confidence Interval were considered for all tests. For this statistical analysis, the software SPSS version 20 and Minitab 16 were used.

Results

A total of 163 patients were considered eligible to participate in the study. Of these, 31 were excluded before randomization. One hundred thirty-two patients were randomly allocated into four groups and received the intervention. Eight patients were excluded from the study after randomization, resulting in 124 participants for analysis (Fig. 1).

The groups were considered homogeneous with respect to demographic and perioperative characteristics, except for the surgical field conditions as evaluated by the surgeons ($p = 0.039$). The mean score was significantly higher in the SP/DB group (4.71 ± 0.52) and lowest in the LP/MB group (4.12 ± 0.95), with values expressed as median and interquartile range in Table 1.

The data related to the scores obtained according to the QoR-40 are described in Table 2. Both the total score and those obtained for the different domains were similar across the groups.

The parameters obtained in the PACU and during the stay in the ward are described in Table 3. The patients' time in the PACU was significantly longer for those in the SP/DB group ($p = 0.010$) compared to the other groups. Pain intensity at rest 24 hours after surgery was significantly higher in the SP/DB group ($p = 0.027$).

Regarding the use of antiemetics in the ward, it was observed that the patients in the deep NMB groups had a greater need for rescue medication ($p = 0.04$).

Discussion

Patients subjected to lower pneumoperitoneum pressures appear to experience less postoperative pain intensity after laparoscopic surgeries. However, the decrease in the effective working space provided by lower intra-abdominal pressure may increase technical difficulty, the incidence of procedure-related injuries, and surgery duration.⁹ The appropriate relaxation of the diaphragm and abdominal muscles with deep NMB could mitigate this issue and even reduce postoperative pain intensity.¹⁰ To our knowledge, no author has yet investigated which variable (pneumoperitoneum pressure and/or NMB) could improve the recovery quality of patients undergoing Laparoscopic Cholecystectomy (LC) without compromising the quality of the surgical field visualization.

In the present study, patients subjected to 10 or 14 mmHg pneumoperitoneum pressure with or without deep NMB were compared. According to the scores obtained through the QoR-40 application, neither low pneumoperitoneum pressure, deep NMB, nor the combination of both variables were able to improve recovery quality (total score or each domain) within 24 hours after LC. Özdemir-van Brunschot et al.¹¹ evaluated recovery quality in patients undergoing laparoscopic nephrectomy with low pneumoperitoneum

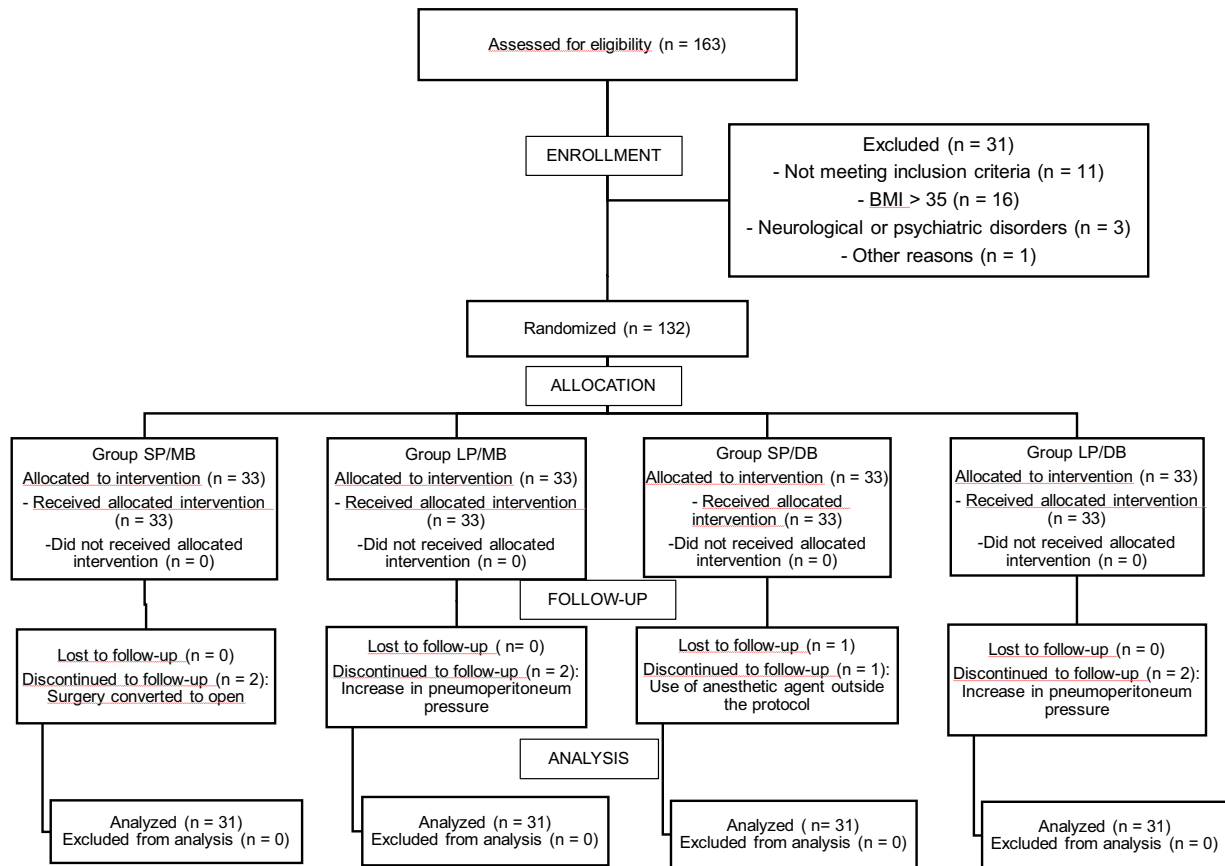


Figure 1 CONSORT flow diagram of patient selection and allocation.

pressure associated with deep NMB and concluded that this technique was unable to alter the QoR-40 score.

Regarding the use of deep Neuromuscular Blockade (NMB) to improve postoperative recovery in laparoscopic surgeries, Torensma et al.¹² evaluated patients undergoing laparoscopic bariatric surgery and observed that deep NMB was able to reduce postoperative pain intensity. Yang et al.¹³ applied the Quality of Recovery-15 questionnaire, a simplified version of the QoR-40, in patients undergoing laparoscopic bariatric surgery and found higher QoR-15 scores and lower pain intensity scores. On the other hand, two

other studies failed to demonstrate such benefit.^{14,15} In our study, deep neuromuscular blockade did not result in improved postoperative recovery quality as assessed by the QoR-40 questionnaire and did not reduce pain following laparoscopic cholecystectomy. According to a recent consensus published by the European Society of Anaesthesiology, there is insufficient evidence to support the use of deep NMB for the purpose of reducing postoperative pain.¹⁶

Pneumoperitoneum results in an acutely elevated intra-abdominal pressure. Patients with morbid obesity have chronically elevated abdominal pressures. During

Table 1 Demographic and perioperative characteristics.

	Group SP/MB (n = 31)	Group LP/MB (n = 31)	Group SP/DB (n = 31)	Group LP/DB (n = 31)	p-value
Age (years)	47 (34–53)	52 (42–57)	47 (38–55)	47 (38–57)	0.563
ASA					0.965
I	12 (38.7%)	12 (38.7%)	11 (35.5%)	13 (41.9%)	
II	19 (61.3%)	19 (61.3%)	20 (64.5%)	18 (58.1%)	
BMI (kg.m⁻²)	30.90 (27.00–32.07)	28.20 (24.62–30.06)	28.00 (26.15–30.38)	29.70 (26.09–31.30)	0.217
Female gender	25 (80.6%)	25 (80.6%)	28 (90.3%)	26 (83.9%)	0.698
PONV Risk	2 (1–2)	2 (1–2)	2 (2–2)	2 (2–2)	0.280
Wake up time (min)	10 (7–14)	12 (10–15)	10 (10–15)	10 (10–15)	0.167
Surgery time (min)	55 (45–64)	55 (50–73)	60 (50–65)	60 (50–71)	0.377
Surgical conditions	5.0 (4.0–5.0)	4.0 (3.5–5.0)	5.0 (4.5–5.0)	5.0 (4.0–5.0)	0.039
Adverse events	3 (9.7%)	1 (3.2%)	1 (3.2%)	3 (9.7%)	0.659

Results expressed in Median (interquartile range) or frequency of occurrence (%).

PONV, Postoperative Nausea and Vomiting; Risk (risk factors 0 to 4), Simplified Apfel Score.

Table 2 Dimensions of the Quality of Recovery-40 (QoR-40) Questionnaire by Study Groups before surgery and 24 hours after surgery.

	Group SP/MB (n = 31)	Group LP/MB (n = 31)	Group SP/DB (n = 31)	Group LP/DB (n = 31)	p-value
Before surgery					
Comfort	56 (55–58)	58 (56–60)	57 (55–59)	58 (58–60)	0.257
Emotional state	42 (38–43)	43 (40–44)	43 (42–44)	43 (41–44)	0.131
Physical independence	20 (19–20)	20 (20–20)	20 (20–20)	20 (20–20)	0.004
Psychological support	40 (39–40)	40 (40–40)	40 (39–40)	40 (40–40)	0.160
Pain	34 (32–35)	34 (33–35)	35 (34–35)	35 (35–35)	0.519
TOTAL	189 (186–194)	195 (189–197)	194 (189–198)	195 (191–198)	0.050
24 hours after surgery					
Comfort	58 (56–59)	58 (55–59)	58 (55–59)	58 (57–59)	0.928
Emotional state	43 (41–45)	44 (43–45)	44 (43–45)	44 (42–45)	0.297
Physical independence	20 (19–20)	20 (18–20)	20 (19–20)	20 (18–20)	0.725
Psychological support	40 (40–40)	40 (40–40)	40 (40–40)	40 (40–40)	0.669
Pain	33 (32–34)	33 (32–34)	33 (32–34)	33 (32–34)	0.903
TOTAL	194 (188–197)	193 (188–197)	194 (190–197)	193 (190–196)	0.938

Results expressed in median (interquartile range).

laparoscopy in morbidly obese patients, the pneumoperitoneum pressure should not be lower than 15 mmHg in order to provide adequate visualization and exposure of the operative field.¹⁷ Therefore, we excluded patients with a BMI $\geq$ 35. A systematic review found that low-pressure pneumoperitoneum in laparoscopic surgeries was associated with lower pain scores, assessed using the Numeric Rating Scale,

compared to standard pressure during the first two postoperative days.¹⁸ However, in the present study, low-pressure pneumoperitoneum did not improve the evaluated parameters of postoperative recovery quality compared to standard pressure. A Cochrane systematic review revealed a high risk of bias and low or very low quality of evidence in 20 out of 21 studies analyzed, providing no justification to support the

Table 3 Parameters in the Post-Anesthesia Care Unit (PACU) and in the ward.

	Group SP/MB (n = 31)	Group LP/MB (n = 31)	Group SP/DB (n = 31)	Group LP/DB (n = 31)	p-value
Pain PACU					
Arrival	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.472
15 min.	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	0.501
30 min.	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–0)	0.052
45 min.	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–0)	0.054
Morphine (mg) – PACU	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.219
PONV in PACU	2 (6.5%)	4 (12.9%)	2 (6.5%)	1 (3.2%)	0.676
PACU time (min.)	30 (30–45)	32 (30–45)	45 (41–60)	43 (30–45)	0.010
Pain Ward					
Arrival	0 (0–4.5)	0 (0–0)	0 (0–1)	0 (0–0)	0.216
4 hours	0 (0–1)	0 (0–0)	0 (0–3)	0 (0–1.5)	0.548
8 hours	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.779
12 hours	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.576
24 hours	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.027
Pain medication in Ward	5 (16.1%)	4 (12.9%)	6 (19.4%)	6 (19.4%)	0.919
PONV in Ward	2 (6.5%)	2 (6.5%)	8 (25.8%)	6 (19.4%)	0.092
PONV medications in Ward	1 (3.2%)	2 (6.5%)	8 (25.8%)	6 (19.4%)	0.044

Results expressed in Median (interquartile range) or number (percentage).

PONV, Postoperative Nausea and Vomiting.

use of low-pressure pneumoperitoneum in patients undergoing elective laparoscopic cholecystectomy.¹⁹

Pneumoperitoneum results in a state of acutely elevated intraabdominal pressure. Similar to nonobese subjects, the intraabdominal pressure during laparoscopy of the morbidly obese is set at 15 mmHg to provide adequate visualization and exposure of the operative field. The normal intraabdominal pressure of nonobese individuals is 5 mmHg or less. In contrast, morbidly obese patients have a chronically elevated intraabdominal pressure at 9 to 10 mmHg. This section discusses the physiologic effects in increased intraabdominal pressure during pneumoperitoneum on femoral venous flow and renal, hepatic and respiratory function.

In a meta-analysis, the authors concluded that reduced pneumoperitoneum pressure combined with deep NMB was not significantly more effective than moderate NMB to optimize the surgical space conditions and postoperative pain. This review did not evaluate recovery quality after laparoscopic surgery.²⁰ Another recent study comparing patients undergoing LC under different pneumoperitoneum pressures with deep NMB found no difference between groups regarding recovery quality.²¹ Although it did not improve recovery quality, deep NMB in patients with Standard Pneumoperitoneum pressure (SP/DB group) provided better surgical field visualization according to the surgeons' opinion. As expected, the combination of low pneumoperitoneum pressure with moderate NMB resulted in the opposite effect, i. e., worse surgical field quality. These findings are in line with previous studies that recommend deep neuromuscular blockade to optimize intraoperative conditions when visualization is suboptimal.^{5,12-14,16} Martini et al.¹¹ and Rosenberg et al.²⁰ also demonstrated that deep NMB improves the surgeon's perception of the surgical field quality compared to moderate NMB.

Other variables were assessed. Pain intensity in the first 24 hours postoperatively and the need for antiemetic rescue were greater among patients subjected to standard pneumoperitoneum pressure and deep NMB (SP/DB group). Although these findings are statistically significant, we do not consider them to have substantial clinical relevance. In the individualized evaluation of patients at the final postoperative assessment, two patients reported a pain intensity score of 2, which is considered mild, and this accounted for the observed statistical difference. Considering the assessment of the Minimum Clinically Important Difference (MCID) in postoperative pain studies, we know that it varies considerably, being influenced by patients' baseline pain, definitions of clinical pain improvement, and study design. In this context, the definition of an MCID value is highly individualized.²² In the present study, the MCID was based on the authors' consensual judgment. Regarding the increased use of rescue medication for PONV, we believe this finding lacks clinical significance, especially since the statistical result was close to the conventional threshold ($p = 0.044$). We were unable to find a plausible explanation for this statistical finding. The results observed in these two variables were not sufficient to reduce the overall quality of recovery in these patients.

This study has some limitations. First, the recovery quality was limited to the first 24 hours postoperatively, and it would be interesting to know the impact of the different interventions on the following days. Second, cases where

the protocol was violated were excluded, and the distribution of these patients according to the "intention-to-treat" principle was not applied. Third, the sample size was calculated to evaluate the primary outcome (recovery quality) but not for other outcomes, such as pain intensity or NVPO incidence. Fourth, this study was conducted at a single university hospital, and a multicenter evaluation is needed for these data to be safely extrapolated to the general population. Finally, the assessment of NMB depth was not blinded. However, as the primary outcome was evaluated by an independent researcher and on the following day, we believe this did not interfere with the results.

Conclusion

The use of pneumoperitoneum pressures of 10 or 14 mmHg under moderate or deep neuromuscular blockade did not significantly affect the quality of recovery in patients undergoing laparoscopic cholecystectomy, as assessed by the QoR-40 questionnaire. However, deep neuromuscular blockade under standard pneumoperitoneum pressure improved surgical field conditions as evaluated by the surgeons, although it was associated with increased postoperative pain and a greater need for antiemetics. Future studies are necessary to validate these findings and expand the available evidence.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Trial registration

Brazilian Registry of Clinical Trials (ReBEC) U1111-1265-2384. Date: 26/09/2024

<https://ensaiosclinicos.gov.br/observador/submissao/sumario/11131>.

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Authors' contributions

José Fernando Amaral Meletti: Study design, data collection, data interpretation, manuscript drafting, and final approval of the version to be published.

Marina Gasparotto Fernandes: Study design, data collection, data interpretation, manuscript review, and final approval of the version to be published.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Hypertonic saline versus mannitol for brain relaxation in supratentorial tumor surgery: a prospective randomized trial



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KEYWORDS

Craniotomy;
Glioblastoma;
Mannitol

Abstract

Background: Hypertonic saline and mannitol are widely used to improve brain relaxation during supratentorial mass surgeries. Although continuous administration of hypertonic saline is known to reduce intracranial pressure, it has not yet been evaluated in supratentorial mass surgeries.

Methods: After institutional ethical committee approval, 92 patients scheduled for supratentorial craniotomy with glioblastoma multiforme, metastasis and/or midline shift (> 0.5 cm) were enrolled into this prospective, randomized, and double-blind study. The patients received hypertonic saline 3 mL.kg^{-1} bolus, hypertonic saline infusion 20 mL.h^{-1} or 20 % mannitol 0.6 gr.kg^{-1} after head positioning. Brain relaxation score (1 = Perfectly relaxed, 2 = Satisfactorily relaxed, 3 = Firm brain and 4 = Bulging brain) was the primary outcome. Sodium and chlorine levels were the secondary outcomes. Postoperative brain edema and midline shift were assessed.

Results: After randomization, two patients were excluded from the study. Brain relaxation scores were higher with hypertonic saline bolus compared to mannitol ($p = 0.047$). The effect size between groups for brain relaxation score was 0.22. Hypertonic saline continuous infusion and mannitol were similar with respect to brain relaxation scores. Sodium and chlorine levels were lower in the mannitol group. Postoperative midline shift and edema were lower with continuous hypertonic saline compared to other groups ($p = 0.001$, $p = 0.006$).

Conclusion: Continuous infusion of 3 % hypertonic saline was associated with better relaxation scores in the intraoperative period and with lower incidences of edema/midline shift in the

The study registered to Clinical Trials.gov in 15 March 2020 (NCT 04,314,674).

The study procedures performed in this study were approved by the ethical committee of the University of Istanbul-Cerrahpasa (Ethical Committee n° 05712/2019-186156, chair Prof. Dr. Ozgur Kasapçopur).

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postoperative period of supratentorial mass surgeries with glioblastoma multiforme, metastasis and/or midline shift.

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Introduction

One of the main goals of neuroanesthesia is to ensure satisfactory relaxation of the brain during supratentorial mass surgery. Surgical retraction also contributes to vasogenic edema and increased intracranial pressure caused by the tumor.¹

Hyperosmolar therapy is frequently used in the perioperative period to increase brain elastance and decrease brain edema and intracranial pressure. While the efficacies of 3 % Hypertonic Saline (HS) and 20 % mannitol used for this purpose were found to be similar in some studies, other studies showed that hypertonic saline was more effective.^{2–4} As a result, no consensus has yet been reached regarding the dose and duration of administration of HS and more studies are needed on this subject.^{1,2,4,5}

Brain swelling has been reported more frequently after opening the dura during surgery of supratentorial masses diagnosed as glioblastoma multiforme, metastasis and/or with midline shift.⁶

Continuous administration of HS in traumatic brain injury patients with increased intracranial pressure has been studied and has been shown to increase survival.⁷ Moreover, expected electrolyte disturbances could be milder compared to bolus dosing of HS. Renal damage due to hyperchloremia and metabolic acidosis are the points to be considered in long-term use of HS. Continuous administration of HS has not been studied yet in supratentorial mass surgery. The primary aim of this prospective, randomized, double-blind study was to compare the effects of continuous infusion of HS with bolus administration of 3 % HS and 20 % mannitol on brain relaxation and the secondary aim was to compare the effects on serum electrolyte levels during supratentorial mass surgery with glioblastoma multiforme, metastasis and/or midline shift.

Materials and methods

The study was registered on Clinical Trials.gov on March 15, 2020 (NCT 04,314,674). The procedures performed in this study were approved by the ethical committee of the University of Istanbul-Cerrahpasa (Ethical Committee n° 05712/2019-186156) and adhere to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This prospective, randomized and double-blind study was performed from April 2020 to December 2022 on a total of 92 patients with glioblastoma multiforme, metastasis and/or intracranial midline shift (> 0.5 cm) scheduled for supratentorial mass resection, aged 18–70 years, Glasgow Coma Scale (GCS): ≥ 13 and ASA (American Society of Anesthesiologists) I–III class. The midline shift was measured in the axial plan of the cranial tomography at the level of the foramen of Monro, which is the channel connecting

the frontal horns of the lateral ventricles to the third ventricles, by first measuring the width of the intracranial space (“a”), followed by measuring the distance from the bone to the septum pellucidum (“b”), and then the midline shift determined by $(a/2) - b$. Written informed consent was obtained from all patients. Patients with renal failure, congestive heart failure and fluid-electrolyte imbalance (cerebral salt loss, diabetes insipidus, inappropriate antidiuretic hormone secretion) were excluded.

Patients were premedicated with 0.05 mg.kg^{-1} Intravenous (IV) midazolam and taken to the operating room. Electrocardiography, noninvasive arterial pressure, Peripheral Oxygen Saturation (SpO_2), Bispectral Index (BIS) and electroencephalographic Density Spectral Array (DSA) were monitored in the operating room. Propofol ($1\text{--}2 \text{ mg.kg}^{-1}$ IV), rocuronium (0.15 mg.kg^{-1} IV) and remifentanyl ($0.1 \mu\text{g.kg}^{-1}\text{min}^{-1}$) IV infusion were used for induction of anesthesia. Sevoflurane inhalation in an oxygen-air mixture with FiO_2 of 35 % was used for maintenance of anesthesia. Sevoflurane concentration was titrated between 0.5–1 MAC according to BIS and DSA. Remifentanyl maintenance began at a dose of $0.05\text{--}0.1 \mu\text{g.kg}^{-1}\text{min}^{-1}$ and titrated to maintain ± 20 % of the initial Mean Arterial Pressure (MAP). After orotracheal intubation patients were ventilated with volume-controlled mode, tidal volume 8 mL.kg^{-1} (ideal body weight), inspiration: expiration ratio of 1:2, Positive End-Expiratory Pressure (PEEP) $5 \text{ cm H}_2\text{O}$ and the respiratory rate ($10\text{--}12$ per minute) was adjusted to maintain PaCO_2 in the range of 35 to 38 mmHg. Each patient underwent invasive arterial pressure monitoring with a radial arterial cannula, end-tidal carbon dioxide pressure monitoring, and diuresis was monitored with a urinary catheter. Each patient received isoflurane solution $2\text{--}3 \text{ mL.kg}^{-1}\text{.h}^{-1}$ IV.

Each patient underwent scalp block with 0.5 % bupivacaine with a maximum dose of 2 mg.kg^{-1} . After the pin head holder application, the head was positioned with 30 degrees of elevation. Head rotation was maximum 45 degrees and recorded (Neutral, $0^\circ\text{--}30^\circ$, $30^\circ\text{--}45^\circ$). All patients were given 4 mg ondansetron IV as an antiemetic during bone flap placement. Patients were extubated after decarization with sugammadex (2 mg.kg^{-1}) at the end of surgery. All patients were followed up in the neurosurgical intensive care unit in the first 24 h postoperatively.

The study was performed in three groups: Group 1: 3 % NaCl (HS) 3 mL.kg^{-1} IV bolus; Group 2: 3 % NaCl (HS) Continuous infusion 20 mL.h^{-1} ; Group 3: 20 % mannitol 0.6 gr.kg^{-1} IV bolus.

Patient groups were determined by the closed envelope method. After head fixation, HS or mannitol infusions were started in all patients. In Groups 1 and 3, HS and mannitol infusions were administered in 20 min. In Group 2, HS infusion was continued until the end of surgery. HS and mannitol were prepared by the anesthesia nurse (the bags of the solutions were closed so that the writings were not visible). In

Groups 1 and 3, arterial blood gas samples were taken before HS and mannitol were administered (Baseline) and at the 30th minute after the end of infusion and then at the 2nd and 4th hour; in Group 2, arterial blood gas samples were taken before HS was administered and at the 30th minute after the infusion started and then at the 2nd and 4th hour. Sodium, chlorine, base excess, lactate levels and osmolarity (calculated) were recorded. Arterial blood gas analyzer (ABL800 FLEX, Radiometer®, Denmark) was used for sodium, chlorine, base excess, lactate and osmolarity levels.

When the dura was opened by the surgical team, brain relaxation was evaluated by the surgeon on a 4-point scale (1 = Perfectly relaxed, 2 = Satisfactorily relaxed, 3 = Firm brain and 4 = Bulging brain) by looking at the relationship between the brain and the dura. To minimize bias in BRS assessment, 2 neurosurgeons decided BRS without the knowledge of the other surgeon's decision. The neurosurgeons who decided BRS were blinded to group allocation.

Demographic data, preoperative steroid use, mass location, pathological diagnosis, the position in which the operation was performed, the degree of head rotation and the duration of the operation were recorded. Total urine output and fluid balance were recorded at the end of the operation. The presence or absence of a midline shift (> 0.5 cm) and edema on cranial CT in the first six hours postoperatively was recorded (0 = Absent, 1 = Exist). The midline shift was quantified using the same method of the preoperative measurement described above. Postoperative edema was decided as either existing (1) or absent (0) and it was considered existing when there were areas of low density and loss of gray/white matter differentiation, on an unenhanced image. The obliteration of the cisterns and sulcal spaces were also evaluated. In the study, the patient, the surgeon evaluating brain relaxation and the anesthesiologist evaluating the postoperative CT did not know which hyperosmolar agent was used.

If serum Na level reached 155 meq.L^{-1} and Cl^{-1} reached 110 mmol.L^{-1} , hypertonic saline administration was discontinued. Preoperative and postoperative urea and creatinine values were recorded.

The rules applied for stopping the study: Unconsciousness after surgery, serum sodium levels $> 155 \text{ meq.L}^{-1}$ and chlorine levels $> 110 \text{ mmol.L}^{-1}$.

The patients were closely monitored neurologically in the postoperative period for the possibility of central pontine myelinolysis as an adverse event. Postoperative cranial MR imaging findings were evaluated.

The data analysis of the study followed a per-protocol approach.

The primary endpoint of this study was to compare the effects of continuous infusion with bolus administration of 3 % HS and 20 % mannitol on brain relaxation and the secondary endpoint was to compare the effects on serum electrolyte (sodium, chlorine) levels in the surgery of supratentorial masses with glioblastoma multiforme, metastasis and/or midline shift.

Statistical analysis

A difference of 1-point in BRS between the groups was considered primary endpoint for the power analysis.² The power

analysis was performed with the G*Power statistical program (ver. 3.1.9.7). A total of 84 patients (28 subjects in each treatment group) was calculated for a Cohen's d effect size of 0.5 (expected mean difference of 1.0, SD in both groups of 1.2 for BRS) with a probability of error type I of 0.05 and power of 0.95. Sample size was increased to at least 30 patients per treatment group to compensate for potential dropouts and possible inaccuracy of predictions used for the power analysis. The conformity of the continuous variables in the study to normal distribution was evaluated graphically and by Shapiro-Wilks test. One-Way ANOVA test was used for comparisons between groups of parameters showing normal distribution. Kruskal Wallis non-parametric variance analysis was used for comparisons between groups of parameters not showing normal distribution. Bonferroni correction was applied in pairwise comparisons.

Mean $\pm$ Standard Deviation and median (minimum–maximum) values were used to represent descriptive statistics.

Cross tabulations were created. Number (n), percentage (%) and Chi-Square (χ^2) test statistics were given for the comparison of categorical variables according to groups such as gender, ASA scores, Body Mass Index (BMI), corticosteroid administration, site and pathology of the mass, preoperative presence of the midline shift, metastasis and GBM, head position, BRS and also postoperative midline shift and edema. Kruskal-Wallis non-parametric variance analysis was used for comparison of age between groups which did not show normal distribution.

One-Way ANOVA test was used for intergroup comparisons of normally distributed parameters such as baseline osmolarity levels. Kruskal-Wallis non-parametric analysis of variance was used for intergroup comparisons of parameters that did not show normal distribution such as sodium, chlorine, base excess, lactate and MAP levels at all time intervals, and osmolarity levels in the 30th min, 2nd and 4th hours, and also urine output and fluid balance. Bonferroni correction was used in pairwise comparisons, and the results of the analysis were given.

In order to examine whether the parameters in the study differed at the measurement times (baseline, 30th min, 2nd hour, 4th hour), repeated ANOVA measures were used for the parameters with normal distribution such as lactate levels in Groups 2 and 3, osmolarity levels in Groups 1 and 2 and MAP measurements in Group 2. Dependent sample Friedman's test was used for the parameters without normal distribution such as sodium, chlorine, base excess levels in all groups and lactate levels in Group 1, osmolarity levels in Group 3 and MAP measurements in Groups 1 and 3. Bonferroni correction was performed for pairwise comparisons and the results of the analysis were given.

Dependent sample *t*-test was used to compare preop-postop urea and creatinine values for normally distributed parameters and Wilcoxon Signed Rank test was used for non-normally distributed parameters.

The tests were two-sided. Data transformation was not required.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used. Statistical significance level was accepted as $p < 0.05$.

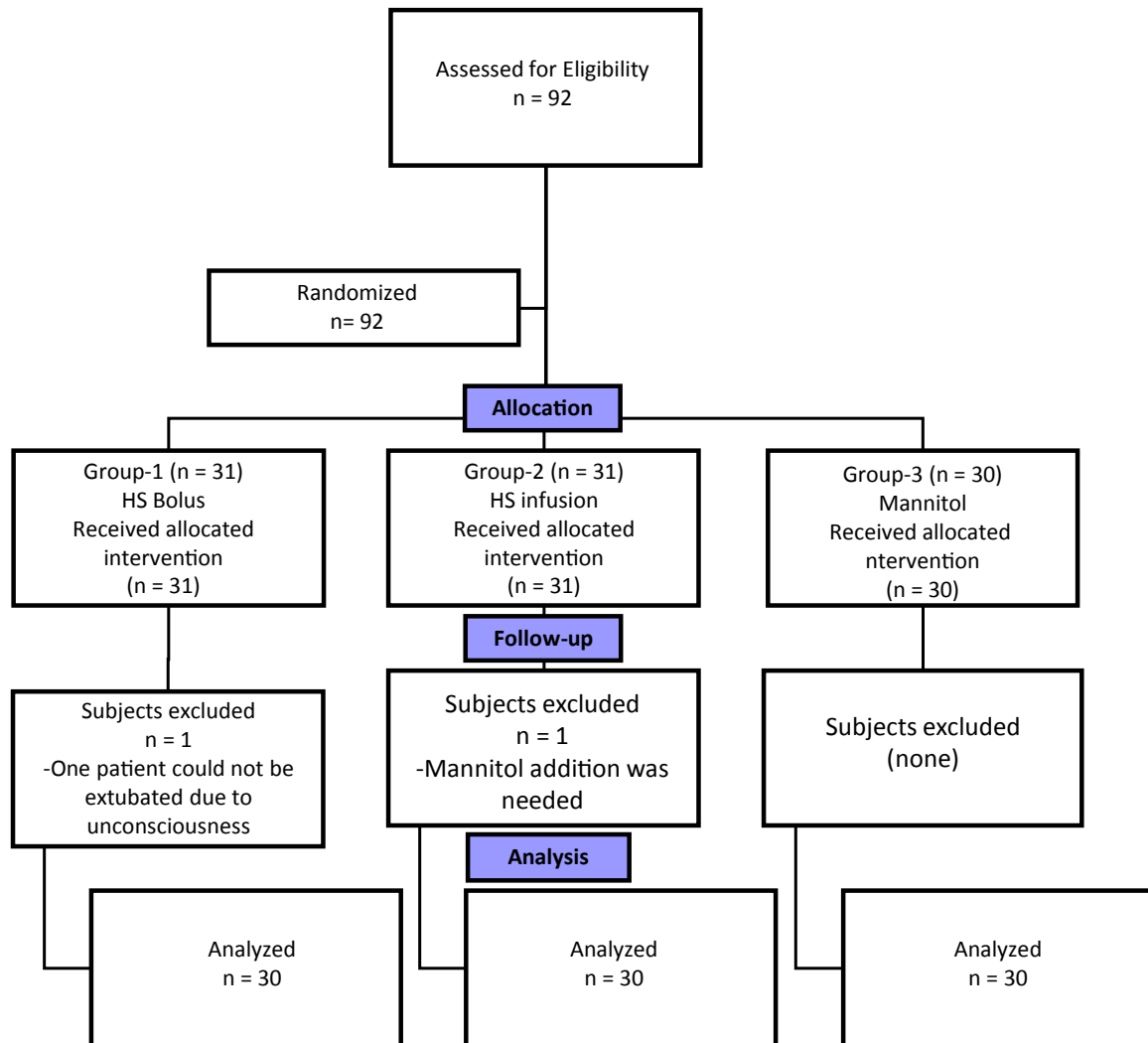


Figure 1 Study flowchart. HS, Hypertonic saline; n, Number.

Results

A total of 92 patients met the inclusion criteria. In 1 patient from Group 2, mannitol addition to HS infusion was needed, and 1 patient in Group 1 could not be extubated at end of the operation due to unconsciousness, therefore they were excluded from the study. Thus, the study included 90 patients (Figure 1).

The study groups were similar with respect to gender, ASA physical status scores, Body Mass Index (BMI) and corticosteroid administration preoperatively ($p > 0.05$). Patient ages were lower in Group 3 compared to Group 2 ($p = 0.042$) (Table 1). Although there was a statistically significant difference between two groups in terms of age, we consider that given all patients were adults, it did not have a confounding effect on the study and further adjustment was not needed.

The groups were similar with respect to site and pathological type of mass, surgical position, presence or not of the preoperative midline shift, metastasis and/or GBM and the duration of the operation ($p > 0.05$). The neutral head position was lower in Group 1 compared to the other groups ($p = 0.001$).

BRS3 was higher in Group 1 compared to Group 3 ($p = 0.047$) (Table 2).

Postoperative midline shift and edema were lower in Group 2 compared to Groups 1 and 3 ($p = 0.001$, $p = 0.006$) (Table 2).

Sodium levels in Group 3 were lower in the 30th min compared to Groups 1 and 2 (134.97 ± 3.46 vs. 140.03 ± 3.49 and 137.60 ± 3.64), and in the 2nd hour compared to Group 1 (136.33 ± 2.59 vs. 139.23 ± 4.01) ($p = 0.009$, $p = 0.001$ respectively). Baseline sodium levels were lower compared to the 30th min, 2nd and 4th hours in Group 1 (137.63 ± 3.97 vs. 140.03 ± 3.49 , 139.23 ± 4.01 and 137.93 ± 3.82) ($p < 0.001$, $p = 0.002$, $p = 0.042$ respectively). The 30th min sodium levels were lower compared to the 2nd and 4th h in Group 2 (137.60 ± 3.64 vs. 138.10 ± 3.49 and 138.67 ± 3.62) ($p = 0.001$, $p < 0.001$ respectively) and compared to baseline, the 2nd and 4th h in Group 3 (134.97 ± 3.46 vs. 136.33 ± 2.59 and 137.33 ± 2.52) ($p < 0.001$, $p = 0.012$ and $p < 0.001$ respectively). There was a linear increase in the sodium levels in time in Group 2 (Figure 2).

The chlorine levels were similar between groups. Baseline chlorine levels were lower compared to the 30th min,

Table 1 Demographic data.

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p	MD
Age ^b (years) (mean ± SD)	51.37 ± 13.25	55.50 ± 13.59	45.40 ± 16.57	0.042 ^c	Group 1 – Group 2 –4.13 (–13.09–4.82) Group 1 – Group 3 5.97 (–2.99–14.92) Group 2 – Group 3 10.10 (1.14–19.06)
Female Gender ^a n (%)	15 (50.0)	14 (46.7)	13 (43.3)	0.875	
ASA physical status ^a (I/II/III) (n)	8/19/3	5/21/4	11/17/2	0.492	
BMI ^a (kg.m ⁻²) (mean ± SD)	27.76 ± 4.44	30.37 ± 5.44	27.47 ± 3.96	0.105	Group 1 – Group 2 –2.61 (–5.48–0.26) Group 1 – Group 3 0.28 (–2.58–3.15) Group 2 – Group 3 2.89 (0.03–5.76)
Preoperative corticosteroid administration ^a , n (%)	19 (63.3)	21 (70.0)	24 (80.0)	0.358	

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; n, Number; SD, Standart Deviation; MD, Mean Differences.

^a χ^2 .

^b Kruskal-Wallis test.

^c The patients ages were lower in the Group 3 comparing to Group 2 ($p = 0.042$).

2nd and 4th h in Group 1 and Group 2 ($p < 0.001$). There was a linear increase in the chlorine levels in time in Group 2. The 30th min chlorine levels were lower compared to baseline, 2nd and 4th h in Group 3 ($p < 0.001$) (Figure 3).

The base excess levels were more negative in the 30th min in Group 1 compared to Group 2 ($p = 0.032$). Moreover, the base excess levels were more negative in the 30th min, 2nd and 4th h compared to baseline levels in all groups and tended to be less negative in time.

The lactate levels were similar between groups. The lactate levels were higher in the 30th min and 2nd h compared to baseline in Group 3 ($p = 0.009$, $p = 0.038$ respectively).

The group-by-time interaction effects of the parameters were for sodium $p < 0.001$, chlorine $p < 0.001$, lactate $p = 0.002$, base excess $p = 0.086$.

The osmolarity levels were lower in the 30th min in Group 3 compared to Groups 1 and 2 ($p = 0.001$, $p = 0.004$ respectively). Baseline osmolarity levels were lower compared to the 30th min, 2nd and 4th h in Group 1, and 2nd and 4th h in Group 2 ($p < 0.05$). The 30th min osmolarity levels were lower compared to baseline, 2nd and 4th h in Group 3

($p < 0.001$, $p = 0.042$, $p < 0.001$ respectively). The groups were similar with respect to MAP's.

The groups were similar with respect to urine output, fluid balance, preoperative and postoperative urea and creatinine levels. Postoperative creatinine levels were lower compared to preoperative ones in Groups 1 and 3 ($p = 0.004$ and $p = 0.013$ respectively) (Table 3).

Discussion

This study showed that 3 % HS infusion was effective as 20 % mannitol in providing brain relaxation and better provided brain relaxation as good as 20 % mannitol and better than 3 % HS bolus administration without electrolyte disturbance, hypovolemia, hemodynamic and renal dysfunction in supratentorial masses with GBM, metastases and/or midline shift. Moreover, postoperative midline shift and edema were less in the 3 % HS infusion group.

The effect of different concentrations of mannitol and HS on brain relaxation in supratentorial craniotomies has been

Table 2 The brain relaxation scores, postoperative midline shift and edema.

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p
BRS ^a I/II/III n	1/4/25	1/10/19	0/14/16	0.047 ^b
Postoperative midline shift ^a , n (%)	20 (66.7)	7 (23.3)	18 (60.0)	0.001 ^c
Postoperative edema ^a , n (%)	21 (70.0)	10 (33.3)	19 (67.9)	0.006 ^d

n, Number; BRS, Brain Relaxation Score.

^a χ^2 test.

^b The BRS III were higher in the Group 1 comparing to Group 3 ($p = 0.047$).

^c Postoperative midline shift was lower in the Group 2 compared to Group 1 and 3 ($p = 0.001$).

^d Postoperative edema was lower in the Group 2 compared to Group 1 and 3 ($p = 0.006$).

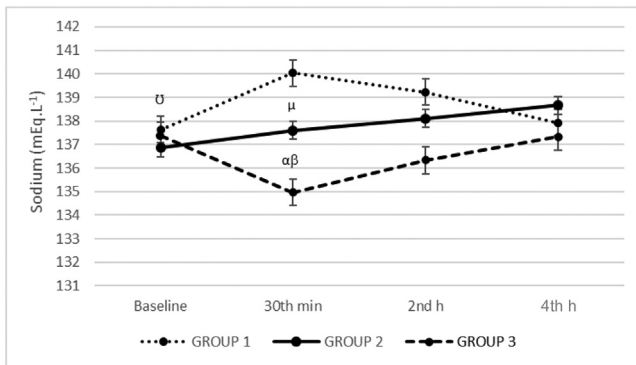


Figure 2 Sodium levels. (α) The sodium levels in the Group 3 were lower in the 30th min comparing to Group 1 and 2 (134.97 ± 3.46 vs. 140.03 ± 3.49 and 137.60 ± 3.64), and in the 2nd h comparing to Group 1 (136.33 ± 2.59 vs. 139.23 ± 4.01) ($p = 0.009$, $p = 0.001$ respectively). ($\bar{U}$) Baseline sodium levels were lower comparing to 30th min, 2nd and 4th h in Group 1 (137.63 ± 3.97 vs. 140.03 ± 3.49 , 139.23 ± 4.01 and 137.93 ± 3.82) ($p < 0.001$, $p = 0.002$, $p = 0.042$ respectively). (μ) The 30th min sodium levels were lower comparing to 2nd and 4th h in Group 2 (137.60 ± 3.64 vs. 138.10 ± 3.49 and 138.67 ± 3.62) ($p = 0.001$, $p < 0.001$ respectively). (β) The 30th min sodium levels were lower comparing to baseline, 2nd and 4th h in Group 3 (134.97 ± 3.46 vs. 136.33 ± 2.59 and 137.33 ± 2.52) ($p < 0.001$, $p = 0.012$ and $p < 0.001$ respectively). There was a linear increase in the sodium levels in time in the Group 2.

compared in several studies and no consensus has been reached on which is better in terms of brain relaxation.^{2–5,8–12} Better brain relaxation is essential during neurosurgery and neuroanesthesia practice to improve the quality of surgical exposure, to reduce brain retractor pressure and to reduce risk of ischemia due to raised ICP. Wu et al.⁴ reported better brain relaxation with HS compared to mannitol, while no difference was found in the studies

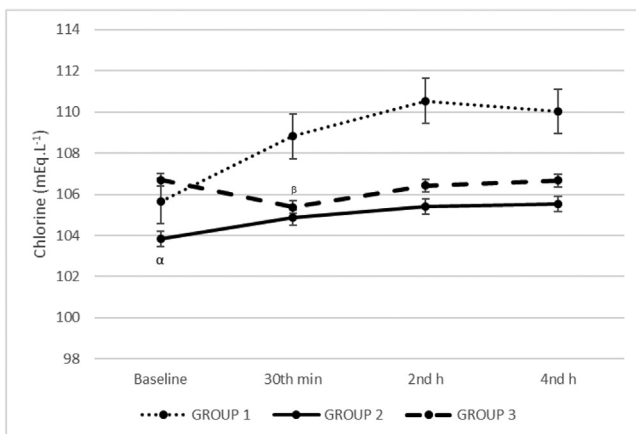


Figure 3 Chlorine levels. The chlorine levels were similar between groups. (α) Baseline chlorine levels were lower comparing to 30th min, 2nd and 4th h in Group 1 and Group 2 ($p < 0.001$). (β) The 30th min chlorine levels were lower comparing to baseline, 2nd and 4th h in Group 3 ($p < 0.001$). There was a linear increase in the chlorine levels in time in the Group 2.

conducted by Rozet et al.,⁵ Hernandez-Palazon et al.³ and Fang et al.¹³ Abdulhamid et al.^{14,14} reported statistically significant brain relaxation with HS in their meta-analysis and Mavrocordatos et al.¹⁵ reported better brain relaxation with HS, although not statistically significant.

In our study, we found that brain relaxation was better in the group given mannitol than in the group given echimolar HS bolus. The number of patients with neutral head position was lower in the group given HS bolus than in the other groups, but the literature has reported that the increasing effect of head rotation on intracranial pressure decreases with head elevation of 30 degrees. In addition, an increase in intracranial pressure has been reported with head rotation of more than 60 degrees or full rotation.^{16,17} All patients in this study were given a head position with 30 degrees of head elevation and a maximum rotation of 45 degrees.

When we administered HS continuously, we found that it provided brain relaxation at a level close to mannitol. Studies have been performed on continuous administration of HS in traumatic brain injury cases with increased intracranial pressure, and it has been shown to decrease intracranial pressure and increase survival.⁷ With the hypothesis that the sudden increase in sodium and metabolic acidosis that may occur with HS bolus administration would be less with continuous administration, we applied HS continuously in supratentorial mass surgeries with high ICP. In sodium levels, we obtained the highest value at 30 minutes after HS bolus administration; although it decreased over time, it remained higher than baseline, while a gradual increase occurred over time in the infusion group. In the mannitol group, as expected, it was lower than in the other groups and other measurement times of the same group at 30 minutes after administration. Chlorine levels were similar to sodium. The changes in sodium and chlorine levels were consistent with other studies and within physiological limits.^{11,14}

In terms of metabolic acidosis, we observed that base excess levels were more negative at 30 min in the HS bolus group. In our study, unlike other studies, lactate increase in mannitol groups was not detected.^{5,11} We think that this is due to the absence of increased urine output, hypovolemia and impaired fluid balance in our study, which were observed in mannitol groups in other studies.¹⁵

We found that HS caused an increase in osmolality and mannitol caused a decrease in the early period. De Vivo et al.¹² and Rozet et al.⁵ found a similar increase in osmolality with HS and mannitol, whereas Briscoe et al.¹⁸ found lower osmolality in the mannitol group at the second hour. We can explain the decrease in osmolality with mannitol by the fact that sodium was also low during the study periods.

One of the most important side effects of HS is renal dysfunction.^{19,20} Acute kidney injury has been observed in patients with sodium levels above 155 mEq.L^{-1} and chlorine levels above 115 mEq.L^{-1} in intensive care unit patients receiving HS.^{20,21} Conversely, it has been found that continuous infusion of hypertonic saline was not associated with renal dysfunction in traumatic brain injury patients due to frequent increase in renal clearance in trauma patients, which could increase the tolerance of hypertonic saline.²² In our study, there was no increase in the postoperative urea and creatinine levels of patients, we think due to the fact

Table 3 Urine output, fluid balance, pre- and postoperative urea and creatinine levels.

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p
Urine output ^b (mL) (mean ± SD)	925.33 ± 673.80	770.00 ± 756.88	766.67 ± 456.06	0.312
Fluid balance ^b (mL) (mean ± SD)	988.33 ± 760.18	1028.00 ± 796.89	827.00 ± 443.06	0.713
Preoperative urea ^b (mg.dL ⁻¹) (mean ± SD)	38.23 ± 14.16	41.13 ± 16.89	37.17 ± 14.46	0.787
Postoperative urea ^b (mg.dL ⁻¹) (mean ± SD)	44.63 ± 17.43 ^c c = 1.430; p = 0.153	44.77 ± 14.09 ^c c = 0.957; p = 0.339	37.40 ± 15.29 ^d d = 0.139; p = 0.891	0.281
Preoperative creatinine ^b (mg.dL ⁻¹) (mean ± SD)	0.78 ± 0.14	0.80 ± 0.21	0.79 ± 0.21	0.867
Postoperative creatinine ^b (mg.dL ⁻¹)	0.72 ± 0.20 ^{c,e} c = 2.870; p = 0.004	0.76 ± 0.20 ^d d = 1.608; p = 0.119	0.73 ± 0.19 ^{c,e} c = 2.477; p = 0.013	0.366

SD, Standard Deviation.

^b Kruskal-Wallis test.^c Wilcoxon Signed Rank test.^d Dependent sample t-test.^e Postoperative creatinine levels were lower compared to preoperative ones in the Group 1 and 3 (p = 0.004 and p = 0.013 respectively).

that sodium and chlorine levels were not above the specified limit.

Postoperative peritumoral edema and midline shifting are outcomes affecting neurological outcome in supratentorial tumor resection surgery.¹² In our study, we found that HS continuous administration reduced postoperative edema and midline shift compared to mannitol and HS bolus in patients with GBM, metastases and midline shift, which constitute the risk group in this sense. Based on the results of this study, we continue to administer HS continuously for at least 24 h in the postoperative period in patients in this high-risk group.

During supratentorial craniotomies, satisfactory brain relaxation is a major challenge. Cerebral swelling has many detrimental effects resulting in poor surgical exposure, increased brain retractor pressure as a main cause of cerebral ischemia and poor neurological outcome with deficits postoperatively. In our study we achieved satisfactory brain relaxation with HS and mannitol, therefore we did not observe newly developing or worsening neurological deficits in our patients in the postoperative period.

This study has some limitations. We can suggest that ICP increases in patients with midline shift, but we could have had more objective results if ICP monitoring had been performed instead of BRS in this study. On the other hand, ICP is equivalent to the atmospheric pressure when the dura is opened. Therefore, we could not use ICP as an objective parameter to evaluate brain relaxation except before dura opening. Although BRS is a subjective scale for evaluation of brain relaxation, it is widely used in the studies investigating the effects of hyperosmolar therapy on brain bulging during craniotomies in neurosurgery and neurosurgical anesthesia fields and it is considered a significant valuation criterion for therapeutic decisions. Moreover, this scale is not validated and there could be inter-observer variability. To minimize bias in BRS assessment, two surgeons decided BRS without the knowledge of the other surgeon's decision. Another point is that when we evaluated the amount of urine, we did not take hourly measurements over the total amount of

urine, and especially the 30th minute urine amount results may have led to different results in the mannitol group. A relatively short follow-up period is another limitation of this study, the electrolyte level measurements could have been extended until the postoperative 24th hour.

Conclusion

In supratentorial craniotomies with GBM, metastases and/or midline shift, continuous infusion of 3 % HS provided satisfactory brain relaxation and also postoperative edema and midline shift were less common compared with mannitol and HS bolus administration. Moreover, electrolyte imbalance did not develop, and renal functions were preserved. More studies addressing the effects of continuous HS on postoperative neurological outcomes and to change clinical practice of hyperosmolar therapy are needed.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Association between family environment and emergence delirium in pediatric patients after tonsillectomy and adenoidectomy: an observational prospective study



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KEYWORDS

Child;
Emergence delirium;
Family
characteristics;
Risk factors

ABSTRACT

Background: Preoperative anxiety in children is a known risk factor for Emergence Delirium (ED). The family environment may indirectly influence ED by modulating anxiety levels, but its direct role in ED remains unclear. The purpose of this study is to explore the associations between the occurrence of ED and family environmental factors in children. Identifying such associations may support the use of preoperative screening and targeted interventions to reduce ED risk.

Methods: In this prospective observational study, 334 children (3~7 years) undergoing elective tonsillectomy/adenoidectomy were assessed. Preoperative visits recorded clinical data and used the Chinese Family Environment Scale (FES-CV) and State/Trait Anxiety Inventories (parental anxiety). Preoperative child anxiety was measured via modified Yale Preoperative Anxiety Scale (m-YPAS). ED was assessed postoperatively in PACU using the Pediatric Anesthesia Emergence Delirium scale (PAED ≥ 10).

Results: ED incidence was 21.9%. No significant association existed between overall home environment and ED. However, achievement orientation (FES-CV) negatively correlated with the m-YPAS score (m-YPAS; $r = -0.139$, $p = 0.011$). Independent ED risk factors identified: younger age (OR = 0.949, 95% CI 0.912~0.988), introverted personality (OR = 0.393, 95% CI 0.184~0.843), and higher postoperative pain (FLACC score; OR = 1.885, 95% CI 1.610~2.208).

Conclusion: While no direct link between home environment and ED was found, the negative correlation between achievement orientation and preoperative anxiety suggests an indirect influence. Identifying high-risk children using factors like age, personality, and pain levels remains important for ED prevention.

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Introduction

Tonsillectomy and Adenoidectomy (T&A) is one of the most common surgeries in otolaryngology and is widely performed to treat chronic tonsillitis and obstructive sleep apnea. The procedure is especially effective in preschool-aged children.¹ However, children often experience Emergence Delirium (ED) after T&A, which is an early behavioral change following general anesthesia, primarily characterized by perceptual disturbances and psychomotor agitation. This phenomenon is particularly common in preschool-aged children.² Previous studies have shown that the incidence of ED in pediatric patients following anesthesia ranges from 1.3% to 84.4%.³⁻⁵ The large variation in incidence reflects the individual variability in the occurrence of ED. Still, the consequences of ED should not be underestimated, as the condition may lead to self-harm, surgical site rupture, and displacement of indwelling catheters. Consequently, hospital stay may be extended, increasing medical costs and potentially having long-term effects on the psychological and physiological health of children.⁶

The occurrence of ED is influenced by various factors, including the child's age, temperament, preoperative anxiety levels, type of surgery, and postoperative pain.⁷ Recent studies have reported that children with high preoperative anxiety have a higher incidence of postoperative ED and experience a more painful, slower, and more complex recovery process.^{7,8} The family environment, as the child's earliest living environment, has a profound impact on psychological and social development. Factors such as emotional support provided by the family, lifestyle, and the quality of postoperative care may all be closely related to the occurrence and development of ED.^{9,10} The impact of the family environment on children's mental health is widely recognized. Nonetheless, no study to date has explored the effects of family environmental factors on the incidence of ED or whether these factors affect the occurrence of ED by influencing preoperative anxiety levels.

Therefore, this study aims to explore the correlation between family environmental factors and the occurrence of postoperative ED in preschool children undergoing T&A,

as well as to investigate other potential risk factors affecting the occurrence of ED.

Methods

Study design

This prospective, single-center observational study was conducted in accordance with the principles outlined in the Declaration of Helsinki. This study was approved by the Medical Research Ethics Review Committee of the General Hospital of Ningxia Medical University (KYL-2024-0008) (<http://www.nyfy.com.cn/>) and registered at the Chinese Clinical Trial Registry on July 15, 2024 (ChiCTR2400086958) (<http://www.chictr.org.cn>). The study period spanned from January 2024 to September 2024. One day before surgery, trained researchers conducted preoperative visits, explaining the purpose, methods, and confidentiality principles of the study to the parents. The anesthesia process and risks were explained, and informed consent was obtained. Moreover, the children's general clinical data were recorded; the Family Environment Scale-Chinese Version (FES-CV) was used to assess the family environment, and the State Anxiety Inventory (SAI) and Trait Anxiety Inventory (TAI) were employed to investigate the parents' anxiety levels.¹¹ The occurrence of ED in children was evaluated using the Pediatric Anesthesia Emergence Delirium (PAED) scale after surgery.¹² The correlation between family environmental factors, other clinical data, and ED was analyzed (Fig. 1).

Sample size

Based on the literature review and clinical observations, this study intends to examine approximately four variables to analyze risk factors for ED. In unconditional logistic regression with a binary outcome, the sample size for the less frequent dependent variable should be at least 5~10 times the number of variables included. Furthermore, prior research indicated that the incidence of ED in pediatric patients undergoing T&A ranges from 13% to 28%.^{13,14} This study adopted the higher estimate of 13%. Consequently, the

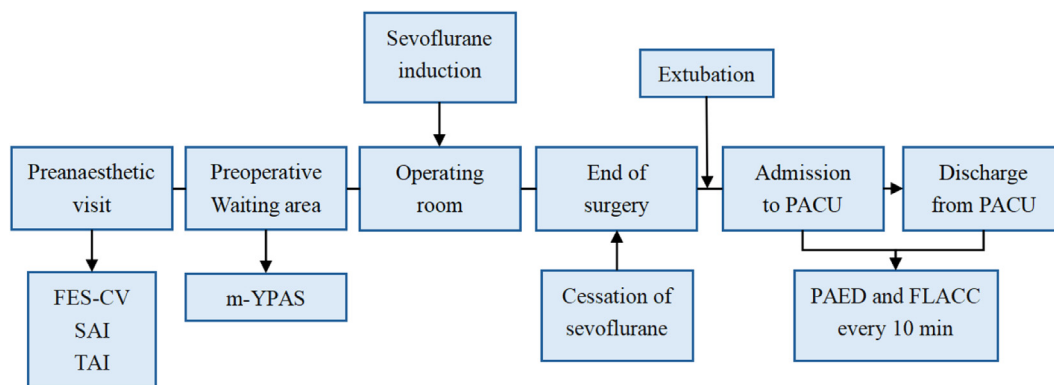


Figure 1 Flowchart of assessment according to the timeline. FES-CV, Family Environment Scale-Chinese Version; SAI, State Anxiety Inventory; TAI, Trait Anxiety Inventory; m-YPAS, modified Yale Preoperative Anxiety Scale; PACU, Post-anesthesia Care Unit; PAED, Pediatric Emergence Delirium; FLACC, Face, Legs, Activity, Crying, Consolability.

minimum sample size required was approximately 308, calculated as $4 \times 10 \div 0.13$. Accounting for a 5% attrition rate, the final sample size was determined to be 334 patients.

Study population and inclusion, and exclusion criteria

Inclusion criteria for this study: 1) Age 3~7 years; 2) American Society of Anesthesiologists (ASA) classification I~II; 3) Scheduled for elective T&A under general anesthesia, performed by the same surgeon; 4) Expected surgical duration not exceeding 2 hours; 5) Parents of the child could communicate normally and showed normal cognitive abilities, and independently completed the relevant questionnaires; 6) Parents of the child agreed to participate in this study and provided signed informed consent form. Exclusion criteria: 1) Refusal to participate in the study; 2) Congenital or other genetic diseases affecting brain development; 3) Either parent of the child had psychological issues such as mental abnormalities; 4) Either parent was not able to complete the relevant questionnaire due to other reasons; 5) Unanticipated cessation of surgery; 6) Incomplete data affecting judgment; 7) Observers actively withdrew from the study.

Anesthesia

All children fasted for 6 hours and avoided clear liquids for 2 hours. In the preoperative waiting area, the researchers assessed the children's preoperative anxiety levels using the Modified Yale Preoperative Anxiety Scale (m-YPAS).¹⁵ Anesthesia was managed by a designated anesthetist according to a unified inhalation and intravenous anesthesia plan. Upon arrival in the operating room, standard monitoring was initiated, including non-invasive blood pressure, pulse oximetry, electrocardiogram, and heart rate. Subsequently, 8% sevoflurane was administered with an oxygen flow rate of 6 L/min. Once the child lost consciousness and spontaneous movement ceased, a peripheral venous access was established. Midazolam $0.05 \text{ mg} \cdot \text{kg}^{-1}$, sufentanil $0.03 \mu\text{g} \cdot \text{kg}^{-1}$, etomidate $0.5 \text{ mg} \cdot \text{kg}^{-1}$, propofol $2 \text{ mg} \cdot \text{kg}^{-1}$, and rocuronium $0.6 \text{ mg} \cdot \text{kg}^{-1}$ were administered intravenously, and an appropriately sized endotracheal tube was inserted. Propofol was continuously infused at $4\sim 6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and remifentanyl at $0.1\sim 0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, while $0.3\%\sim 0.5\%$ sevoflurane was continuously inhaled. Heart rate or blood pressure fluctuations of more than 20% above baseline were corrected by adjustments to the infusion rates of propofol and remifentanyl and to the inhalation concentration of sevoflurane. During the surgery, intermittent doses of rocuronium $0.15 \text{ mg} \cdot \text{kg}^{-1}$ were administered according to the metabolism time of rocuronium and the needs of the procedure. The anesthesia machine was set to volume control ventilation, with an airway pressure of $10\sim 20 \text{ cmH}_2\text{O}$, tidal volume of $6\sim 10 \text{ mL} \cdot \text{kg}^{-1}$, and a respiratory rate of $20\sim 25 \text{ breaths} \cdot \text{min}^{-1}$. The tidal volume and respiratory rate were adjusted to maintain PETCO_2 at $35\sim 45 \text{ mmHg}$. At the end of the surgery, the infusions of propofol, remifentanyl, and inhaled sevoflurane were stopped. Oral secretions were fully suctioned, and sugammadex $2\sim 4 \text{ mg}^{-1}$ and flumazenil 0.01 mg^{-1} were administered. After stabilization of hemodynamics and restoration of consciousness, the endotracheal tube was

removed, and vital signs were closely monitored. After confirming that the child's vital signs were stable, the patient was transferred to the Post-Anesthesia Care Unit (PACU) for further observation (Fig. 1).

Predictive assessment tool

The Family Environment Scale (FES),¹⁶ developed by American psychologists Moss et al., was revised and adapted by LP Fei et al. in 1991 into its Chinese version. The assessment of the family environment utilizes the FES-CV, which comprises ten dimensions: cohesion, expressiveness, conflict, independence, achievement orientation, intellectual-cultural orientation, active-recreational orientation, moral-religious emphasis, organization, and control, each dimension containing nine items.

Study outcomes

The primary outcome is the correlation between family environmental factors and ED. The secondary outcomes include the incidence of ED, the general condition of children before surgery, anesthesia, operation time, and the correlation between postoperative pain and ED.

Flowchart of assessment according to the timeline is shown in Figure 1.

Statistical analysis

Software SPSS 26.0 (SPSS Inc., Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Inc., California, USA) were used for data analysis. The normality of quantitative data was evaluated using the Kolmogorov-Smirnov (K-S) test, with $p \geq 0.05$ indicating normal distribution. Quantitative variables conforming to a normal distribution were presented as mean $\pm$ Standard Deviation (SD), and comparisons between groups were conducted using the independent samples *t*-test. Non-normally distributed quantitative data were presented as medians with Interquartile Ranges (IQR), and comparisons between groups were conducted using the Mann-Whitney *U* test. Categorical data were presented as the number of cases (%) and compared using the Chi-Square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify the risk factors affecting the occurrence of ED. Variables showing $p < 0.05$ in the univariate analysis were incorporated into the multivariate binary logistic regression equation for further analysis. Additionally, R language was used to create forest plots and correlation heatmaps for data visualization.

Results

In this study, a total of 352 children were initially selected. Figure 2 displays the study flow diagram. Among them, four were excluded for not meeting the inclusion criteria; one was excluded due to developmental delay; five were excluded as their parents failed to complete the relevant questionnaires; and eight were excluded due to unplanned surgical termination. After these screenings, a total of 334 children were included for analysis. Ultimately, 73 cases of

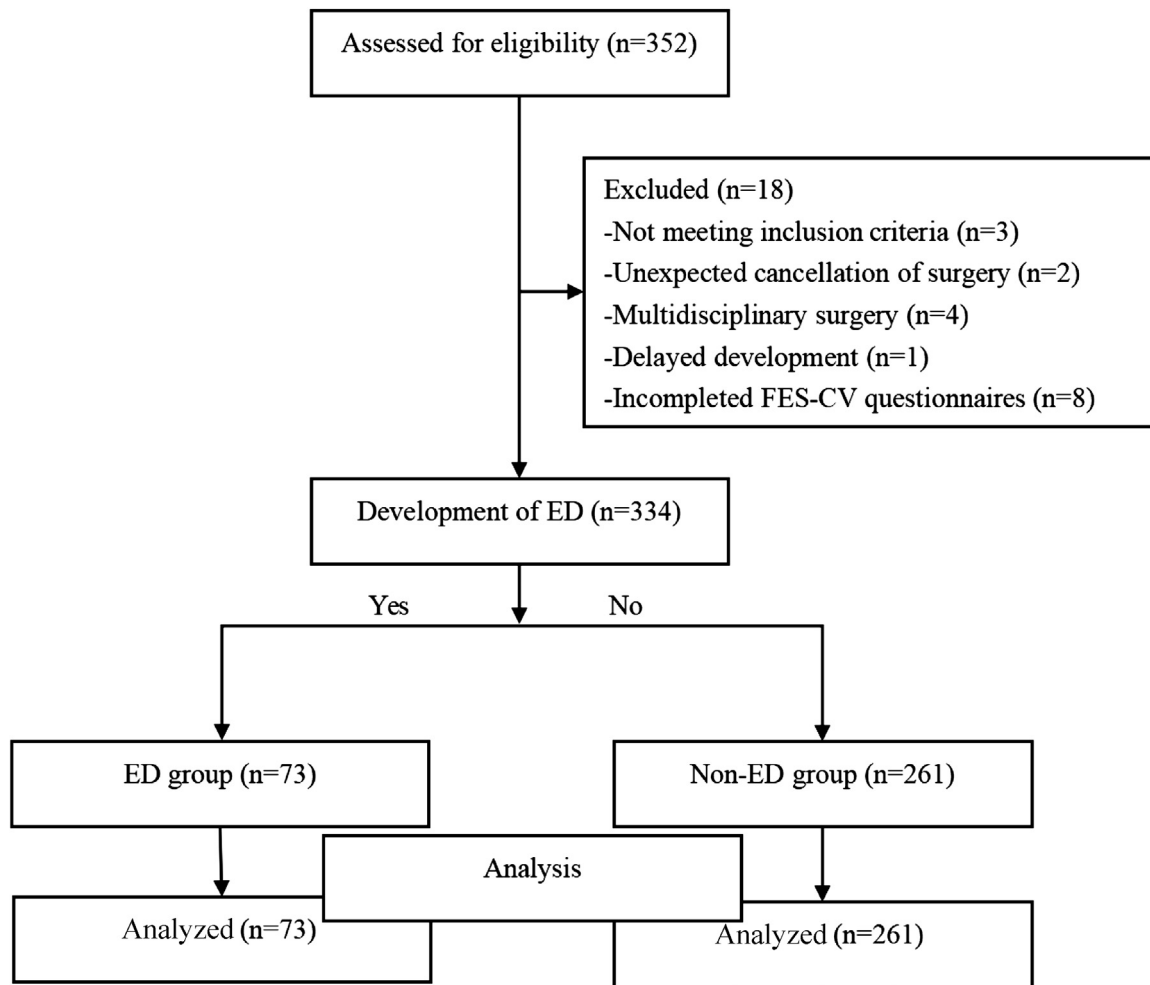


Figure 2 Study flow diagram. Patients involved in the study and the respective groups analyzed. ED, Emergence Delirium; FES-CV, Family Environment Scale-Chinese Version.

ED were detected, corresponding to an incidence rate of 21.9% (Fig. 2).

Patient demographics

Table 1 shows the perioperative demographic and clinical data of the patient population.

Compared to the non-ED group, the children in the ED group were significantly younger and had a lower level of schooling ($p < 0.05$). Children with introverted personalities were more likely to experience ED ($p = 0.022$), with higher m-YPAS and FLACC scores ($p < 0.05$) and longer anesthesia and surgery times ($p < 0.05$) (Table 1).

Primary and secondary outcomes

Table 2 summarizes the key outcomes. No significant differences were observed in the dimensions of FES-CV between the ED group and the non-ED group in terms of cohesion, expressiveness, conflict, independence, achievement orientation, intellectual-cultural orientation, active-recreational orientation, moral-religious emphasis, organization, and control ($p > 0.05$). Nonetheless, the measures of cohesion,

achievement orientation, intellectual-cultural orientation, and control in the ED group were slightly lower than those in the non-ED group. Conversely, the levels of expressiveness, conflict, independence, active-recreational orientation, moral-religious emphasis, and organization showed a higher trend in the ED group compared to the non-ED group (Table 2).

Table 3 displays the correlation between each dimension of the FES-CV scale and the m-YPAS scores of the children. This study revealed that the achievement orientation scores in the family environment scale were significantly negatively correlated with the m-YPAS scores ($r = -0.139$, $p = 0.011$). A correlation heatmap was generated using the corrplot package in R, with red indicating a positive correlation, blue indicating a negative correlation, and darker colors representing stronger correlations (Fig. 3).

Table 4 presents the multifactor binary logistic regression analysis predicting ED. Indicators with statistically significant differences between the two groups were included in the binary logistic regression model for analysis. The occurrence of ED post-T&A in preschool children was set as the dependent variable and was assigned a value of 1 for occurrence or 0 for non-occurrence. A multifactor binary logistic

Table 1 Demographic and clinical characteristics of study participants.

	ED group (n = 73)	Non-ED group (n = 261)	χ^2/t	p-value
Sex, n (%)			0.157	0.692
Male	46 (63.01)	171 (65.52)		
Female	27 (36.99)	90 (34.48)		
Age (month), mean $\pm$ SD	61.52 $\pm$ 14.56	71.78 $\pm$ 15.03	5.189	< 0.001 ^b
BMI (kg.m⁻²), mean $\pm$ SD	16.15 $\pm$ 3.15	15.80 $\pm$ 2.54	-0.980	0.328
ASA physical status, n (%)			0.018	0.893
I	52 (71.23)	188 (72.03)		
II	21 (28.77)	73 (27.97)		
History of surgery, n (%)			0.043	0.834
Yes	4 (5.48)	16 (6.13)		
No	69 (94.52)	245 (93.87)		
Only child status, n (%)			0.059	0.808
Yes	26 (35.62)	97 (37.16)		
No	47 (64.38)	164 (62.84)		
Single-parent child, n (%)			0.405	0.535
Yes	6 (8.22)	16 (6.13)		
No	67 (91.78)	245 (93.87)		
Children personality, n (%)			5.219	0.022 ^a
Introversion	30 (41.10)	71 (27.20)		
Extroversion	43 (58.90)	190 (72.80)		
Educational experience, n (%)			10.714	0.003 ^a
No educational experience	6 (8.22)	12 (4.60)		
Kindergarten	58 (79.45)	168 (64.37)		
Primary school	9 (12.33)	81 (31.03)		
Mother's education level, n (%)			0.546	0.460
Below college level	36 (49.32)	116 (44.44)		
College diploma or above	37 (50.68)	145 (55.56)		
Father's education level, n (%)			0.658	0.417
Below college level	33 (45.21)	132 (50.57)		
College diploma or above	40 (54.79)	129 (49.43)		
Residence, n (%)			0.006	0.941
County town	30 (41.10)	106 (40.61)		
City	43 (58.90)	155 (59.39)		
Anesthesia time (min), mean $\pm$ SD	65.68 $\pm$ 16.00	60.30 $\pm$ 18.29	-2.285	0.023 ^a
Surgical time (min), mean $\pm$ SD	47.79 $\pm$ 16.02	41.67 $\pm$ 17.12	-2.740	0.006 ^a
Total hospitalization duration (day), mean $\pm$ SD	2.88 $\pm$ 1.68	2.87 $\pm$ 1.79	-0.013	0.989
Postoperative hospitalization duration (day), mean $\pm$ SD	1.55 $\pm$ 0.88	1.72 $\pm$ 1.01	1.325	0.186
SAI score, mean $\pm$ SD	43.40 $\pm$ 8.93	43.51 $\pm$ 9.19	0.090	0.929
TAI score, mean $\pm$ SD	43.60 $\pm$ 8.69	43.51 $\pm$ 8.77	-0.077	0.939
m-YPAS score, mean $\pm$ SD	41.29 $\pm$ 19.50	35.45 $\pm$ 16.13	-2.346	0.021 ^a
FLACC score, mean $\pm$ SD	5.01 $\pm$ 3.08	1.13 $\pm$ 1.49	-10.447	< 0.001 ^b

ED, Emergence Delirium; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; m-YPAS, Modified Yale Preoperative Anxiety Scale; FLACC, Face, Legs, Activity, Cry, Consolability; SAI, State Anxiety Inventory; TAI, Trait Anxiety Inventory.

^a $p < 0.05$.

^b $p < 0.001$.

regression analysis was performed to identify the risk factors. The results indicated that younger age, higher FLACC scores, and an introverted personality in children were independent risk factors for the occurrence of ED after T&A in preschool children ($p < 0.05$). A forest plot was drawn using the forestploter in R language, revealing that child age (OR = 0.949, 95% CI 0.912~0.988), personality (OR = 0.393, 95% CI 0.184~0.843), and FLACC score (OR = 1.885, 95% CI 1.610~2.208) were independent risk factors for the occurrence of ED after T&A (Fig. 4).

Discussion

The incidence of ED in children aged 3 to 7 years undergoing T&A in this study was 21.9%. The results revealed that younger age, introverted personality, and postoperative pain are independent risk factors for ED in children undergoing T&A. However, this study found no direct evidence of an association between family environment and ED.

The family environment is the first environment that children come into contact with, playing a decisive role in their

Table 2 Family environmental factors associated with ED.

	ED group (n = 73)	Non-ED group (n = 261)	t	p-value
Cohesion (score), mean $\pm$ SD	8.11 $\pm$ 1.24	8.15 $\pm$ 1.37	0.224	0.823
Expressiveness (score), mean $\pm$ SD	5.86 $\pm$ 1.34	5.62 $\pm$ 1.38	-1.312	0.190
Conflict (score), mean $\pm$ SD	2.66 $\pm$ 1.62	2.46 $\pm$ 1.69	-0.910	0.363
Independence (score), mean $\pm$ SD	5.75 $\pm$ 1.40	5.65 $\pm$ 1.36	-0.565	0.573
Achievement orientation (score), mean $\pm$ SD	6.18 $\pm$ 1.23	6.29 $\pm$ 1.78	0.624	0.534
Intellectual-cultural orientation (score), mean $\pm$ SD	4.77 $\pm$ 1.93	4.96 $\pm$ 1.91	0.768	0.443
Active-recreational orientation (score), mean $\pm$ SD	6.45 $\pm$ 1.86	6.38 $\pm$ 2.10	-0.283	0.778
Moral-religious emphasis (score), mean $\pm$ SD	5.74 $\pm$ 1.34	5.61 $\pm$ 1.42	-0.683	0.495
Organization (score), mean $\pm$ SD	6.90 $\pm$ 1.40	6.83 $\pm$ 1.69	-0.375	0.708
Control (score), mean $\pm$ SD	4.32 $\pm$ 2.05	4.43 $\pm$ 1.92	0.428	0.669

ED, Emergence Delirium.

growth and development.^{9,10} In terms of psychological development, a warm and loving family gives children a sense of security and belonging, which promotes positive emotions and good character in children.¹⁷ In contrast, a poor family environment may lead to negative emotions, such as anxiety, fear, and inferiority.¹⁸ Research has shown that anxiety in children is largely influenced by environmental factors.¹⁹ Furthermore, studies have found that the family environment is an early risk factor for emotional disorders in children.^{20,21}

This study employed the FES-CV scale to evaluate family environment. Notably, the dimension of achievement orientation was significantly negatively correlated with preoperative anxiety in children. Families with higher achievement orientation tend to emphasize effort and progress, set positive examples for their children, and provide stable psychological support.²² This family environment may help reduce preoperative anxiety levels in children, thereby playing a preventive role in the occurrence of ED. Children with preoperative anxiety are more susceptible to stress responses both physiologically and psychologically, which increases the risk of postoperative ED.⁷ For every 10-point increase in the children's m-YPAS score, the risk of developing ED increases by 10%.¹⁵ Interactive videos can alleviate children's preoperative anxiety, thereby reducing the incidence of ED.¹⁵

Table 3 The correlation between the dimensions of the FES-CV scale and the children's m-YPAS scores.

	m-YPAS	
	r	p-value
m-YPAS	1	
Cohesion	0.009	0.870
Expressiveness	0.033	0.551
Conflict	0.077	0.158
Independence	-0.078	0.156
Achievement orientation	-0.139	0.011 ^a
Intellectual-cultural Orientation	-0.062	0.261
Active-recreational Orientation	0.076	0.164
Moral-religious emphasis	-0.025	0.647
Organization	-0.015	0.784
Control	-0.050	0.364

m-YPAS, Modified Yale Preoperative Anxiety Scale.

^a p < 0.05, ^b p < 0.001.

Therefore, families with a higher achievement orientation environment may be indirectly associated with a lower incidence of postoperative ED by lowering children's preoperative anxiety.

Although this study did not find a direct association between the various dimensions of the family environment scale and post-operative ED, a close connection was observed between achievement orientation and pre-operative anxiety. This finding provides a new perspective on the relationship between the family environment and children's post-operative recovery and offers potential directions for clinical intervention. Future research could further explore how improving the achievement orientation of the family environment can reduce pre-operative anxiety in children, providing a potential method for reducing the occurrence of post-operative ED.

Age is considered an important factor influencing the occurrence of ED.²³ This may be due to the incomplete brain development in younger children, who are more sensitive to external stimuli. During the brain development process, the hippocampus and cholinergic system are key neural structures that play important roles in cognitive and behavioral

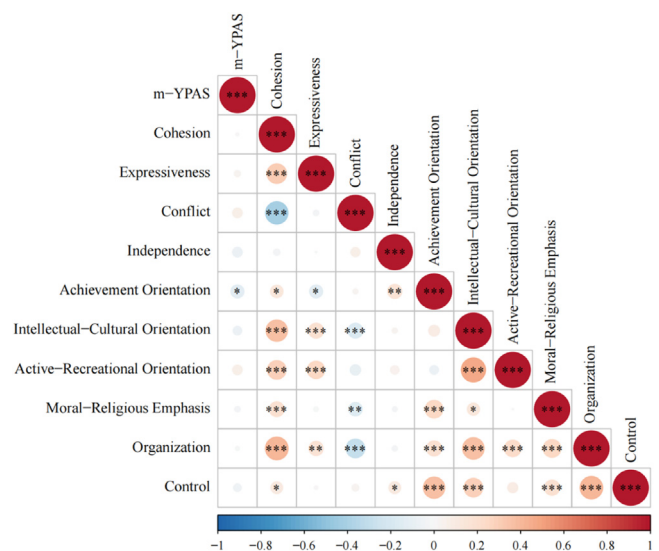
**Figure 3** Association of family environmental factors with preoperative anxiety in children. m-YPAS, modified Yale Preoperative Anxiety Scale.

Table 4 Multifactor binary logistic regression analysis predicting ED.

	β	SE	Wald χ^2	p-value	OR value	95% CI
Age (month)	-0.052	0.020	6.591	0.010 ^a	0.949	0.912~0.988
Outgoing child, n (%)	-0.933	0.389	5.760	0.016 ^a	0.393	0.184~0.843
Kindergarten, n (%)	0.698	0.782	0.796	0.372	2.009	0.434~9.297
Primary school, n (%)	1.181	1.154	1.047	0.306	3.257	0.339~31.260
Anesthesia time (min)	0.000	0.026	0.941	0.332	0.975	0.927~1.026
Surgical time (min)	0.040	0.027	2.095	0.148	1.040	0.986~1.098
m-YPAS (score)	0.001	0.010	0.006	0.937	1.001	0.981~1.021
FLACC (score)	0.634	0.081	62.020	< 0.001 ^b	1.885	1.610~2.208

ED, Emergence Delirium; m-YPAS, Modified Yale Preoperative Anxiety Scale; FLACC, Face, Legs, Activity, Cry, Consolability; CI, Confidence Interval; OR, Odds Ratio.

^a $p < 0.05$,

^b $p < 0.001$.

regulation. A reduction in the number of neurons in the locus coeruleus and gray matter can lead to decreased levels of neurotransmitters such as norepinephrine, acetylcholine, dopamine, and gamma-aminobutyric acid. This reduction in neurotransmitters may affect the cognitive function of children, leading to a higher incidence of ED.²⁴ Low effort control in children may be associated with ED (OR = 2.12, 95% CI 0.88~5.10).²⁵ The unique temperament of children influences their responses to stimuli, which is a result of the interaction between children and their environment. The results of this study reveal that children with an extroverted personality are better communicators and have a lower incidence of ED. Postoperative pain is one of the main risk factors for ED in children.²⁶ Pain can cause changes in brain wave patterns, specifically an increase in δ and γ wave activity, which in turn leads to the occurrence of ED.²⁷ Once pain is effectively controlled, the incidence of ED in children can be significantly reduced.²⁶

Limitations

Firstly, the family environment factors included are not comprehensive enough, which may affect the accuracy of the results. Secondly, the FES-CV scale includes many items, which may lead to respondent fatigue, leading to random answers and affecting the accuracy of the family

environment assessment. Finally, this research is a single-center study that only includes children undergoing T&A. Therefore, larger-scale, multi-center studies are needed to further validate and expand these findings.

Conclusion

This study found that the achievement orientation rate in the FES-CV scale is significantly negatively correlated with the preoperative anxiety level of children, while introverted personality, younger age, and higher postoperative FLACC scores are independent risk factors for the occurrence of ED. Although no direct association was found between family environment and ED, achievement orientation may indirectly affect ED by influencing the psychological state of children. Therefore, optimizing the family environment and conducting preoperative screening and psychological intervention for high-risk children may help reduce the incidence of ED.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

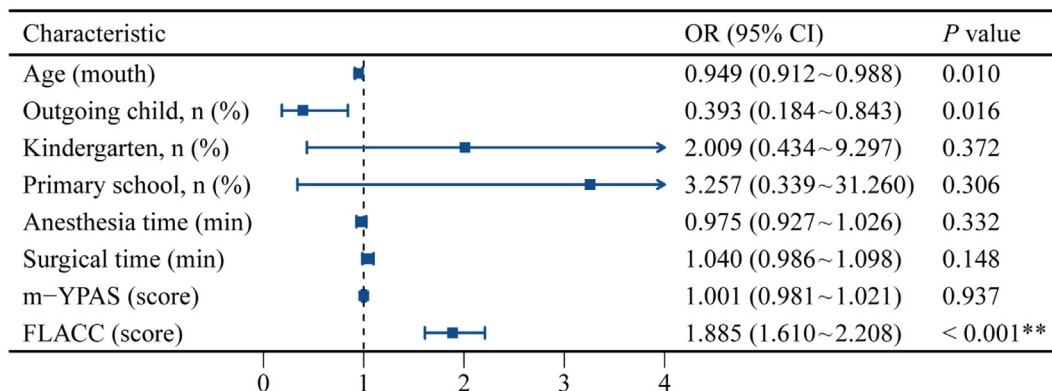


Figure 4 Forest plot of the binary variable predicting the occurrence of ED. ED, emergence delirium; m-YPAS, Modified Yale Preoperative Anxiety Scale; FLACC, Face, Legs, Activity, Cry, Consolability; CI, Confidence Interval; OR, Odds Ratio. * $p < 0.05$, ** $p < 0.001$.

Authors' contributions

XN contributed to the conception and design of the review. YG and HP contributed the case collection and manuscript writing. ZL and YB contributed equally to the overall text and figures. JL helped the statistical analysis of data. All authors contributed to the article and approved the final version.

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Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

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Associate Editor

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REVIEW ARTICLE

The use of ketamine on emergence agitation in children: a systematic review and meta-analysis

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KEYWORDS

Emergence agitation;
Emergence delirium;
Ketamine;
Meta-analysis;
Pain;
Systematic review

Abstract

Background: Ketamine is believed to reduce the incidence of emergence agitation in children after surgery. However, recent studies reported contradictory findings. Thus, the primary objective of this review and meta-analysis was to investigate the use of ketamine in the reduction of emergence agitation in children undergoing surgery or procedure.

Methods: MEDLINE, EMBASE and CENTRAL were systematically searched from their inception date until March 2024. Randomized controlled trials comparing intravenous ketamine and placebo in children were sought. Observational studies, editorial letters or case reports were excluded.

Results: Seventeen studies (1515 patients) were included. Children who received ketamine were reported to have a significantly lower incidence of emergence agitation (OR = 0.27, 95% Confidence Interval: 0.16 to 0.45, $p < 0.00001$, $I^2 = 61\%$, certainty of evidence: very low). As compared to placebo, the ketamine group had a significantly lower postoperative pain score (MD = -2.28, 95% Confidence Interval -3.68 to -0.87, $p = 0.001$, $I^2 = 91\%$, certainty of evidence: very low). However, no significant differences were observed in the incidence of postoperative nausea and vomiting, desaturation, and laryngospasm.

Conclusion: This meta-analysis highlights the potential benefits of ketamine in the reduction of emergence agitation in children undergoing surgery or diagnostic procedures. However, high degrees of heterogeneity and low certainty of evidence limit the recommendations of the rou-

Presentations: The project was shortlisted and presented as an oral presentation at the 20th Asian Society of Paediatric Anaesthesiologists (ASPA) and Malaysian Society of Paediatric Anaesthesiologists (MSPA) conference on 11th–14th July 2024.

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tine use of ketamine in the prevention of emergence agitation in children. Further high-quality randomized controlled trials are warranted before routine use can be recommended.

PROSPERO registration: CRD42024523680.

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Introduction

Emergence agitation, also known as emergence delirium, is a temporary state of psychomotor agitation and perceptual disruption that occurs after the emergence from general anesthesia.¹ First described by Eckenhoﬀ and colleagues in 1961, it presents a significant clinical challenge, particularly in pediatric patients.² Its incidence in the general population varies from 5 % to 30 %, but it could be reported from 20 % to 80 % in the pediatric population.³ Though it is often self-limiting and reversible, it poses great risks to healthcare staﬀs, family members and patients as it could impose harm to patients and surroundings, such as pulling out catheters, drains and intravenous lines, which may disrupt patient care and compromise patient safety.⁴

There are various possible risk factors for emergence agitation in children, mainly patient-related (preschool age, high pre-operation patient/caretaker anxiety level), surgery-related (type of surgery), and anesthesia-related (pain level, lack of premedication, choice of anesthetic).⁵ The management of pain in children undergoing surgery or diagnostic procedures are crucial as studies show patients with moderate and severe postoperative pain often associated with emergence agitation.⁶ One of the most common tools being used to assess the severity of emergence agitation, the Pediatric Anesthesia Emergence Delirium (PAED) scale, allows clinicians to differentiate between pain-related agitation and post-operative delirium based on five behavioral indicators namely eye contact, purposeful actions, awareness of surroundings, restlessness and inconsolability.^{7,8} Several studies have also demonstrated the positive correlation of lower rate of emergence agitation and satisfactory pain relief.^{8–10}

Ketamine is a N-Methyl-D-Aspartate (NMDA) receptor antagonist.¹¹ One of its enantiomers (S-ketamine) has been one of the main choices as general anesthetic in short procedures due to its wide margin of safety, analgesic, sedative and sympathomimetic effect.¹² Its use in prevention of emergence agitation has been described in numerous adults, and pediatric studies have demonstrated positive effects of ketamine in the reduction of emergence agitation in children.^{12–14} To the best of our knowledge, there has not been an up-to-date and relevant review since 2019, which previously advised caution due to substantial heterogeneity and potential for type I error.¹⁵ New clinical studies with more robust methodologies have since emerged to provide more clarity into the potential of ketamine in reducing emergence agitation. Thus, they underscore the need for an up-to-date meta-analysis to re-examine and consolidate all the available evidence.

We hypothesized that intravenous ketamine reduces the incidence of emergence agitation in children. Therefore, the primary objective of this meta-analysis was to re-investigate the evidence on use of ketamine in the incidence of emergence agitation in the pediatric population. Secondary objectives included the effect of ketamine on recovery time

(defined as time required to reach Aldrete score of ≥ 9), pain score at the arrival of recovery unit, incidence of nausea/vomiting, desaturation, and laryngospasm.

Material and methods

Study design

This review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions.¹⁶ It is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) reporting guideline.¹⁷ Our review protocol was registered and published in the PROSPERO database (CRD42024523680).

Search strategy

Literature search for relevant articles published in CENTRAL, EMBASE and MEDLINE was conducted in March 2024. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were thoroughly searched for any ongoing trials. Search strategy for this review is shown in the Online Supplementary Material (named [Supplementary Table S1](#)).

Inclusion and exclusion criteria

Inclusion criteria were: (a) Parallel arm Randomized Controlled Trials (RCTs); (b) Pediatric population less than 18 years old; (c) Comparison between intravenous ketamine and placebo/saline. No language restrictions were applied.

Exclusion criteria for this study were: (a) Non-human studies, observational studies, case reports, case reviews, cross-over RCTs; (b) Adult population age 18 and above; (c) Parent refusal, subject with mental health conditions or developmental delay; (d) Other forms of ketamine being used (oral, intranasal, epidural). Cross-over trials were excluded from our review to minimize potential bias of the pharmacokinetics of ketamine in the cross-over patients.

Study selection and data extraction

Both authors (JCH, WYT) screened titles and abstracts against the eligibility criteria for this meta-analysis with the Mendeley Reference Software. Full text articles which fulfilled the criteria were obtained for further screening by two authors (JCH, WYT). Any discrepancies were then resolved by the third author (KTN). Data extraction was then performed by two authors (JCH and WYT) independently using a standardized online data extraction form which was designed by the third author (KTN). The following data were extracted: Author name, publication year, study design, country, sample size, mean population age, clinical setting and the dosage of ketamine used.

Quality assessment

The Risk of Bias (RoB) assessment tool is developed by the Cochrane to assess the risk of bias for randomized controlled trials based on five domains, namely randomization process; any deviations from the intended interventions; any missing outcome data; the measurement of the outcome and the selection of the reported result.¹⁸ The RoB1 tool was utilized in this review by two authors (JCH and WYT) independently, with a third author (KTN) consulted to resolve any conflicts.

Measured outcomes

The primary outcome for this review was the incidence of emergence agitation in pediatric patients. In studies where the Pediatric Anesthesia Emergence Delirium (PAED) score of ≥ 10 , ≥ 12 and ≥ 15 was available, a PAED score of ≥ 10 was used to determine the incidence of emergence agitation due to its high diagnostic sensitivity and specificity.^{19–22} Other secondary outcomes were recovery time (defined as time required to reach Aldrete score of ≥ 9), pain score (the Children's Hospital of Eastern Ontario Pain [CHEOP] or modified Children's Hospital of Eastern Ontario Pain [mCHEOP] tools) at PACU arrival, incidence of nausea/vomiting, desaturation and laryngospasm.

Data analysis

Review Manager version 5.3 was used for data pooling in order to generate forest plots.²³ A p-value of less than 0.05 (two-tail) indicated that the test result was statistically significant. All the reported findings were described as Mean Difference (MD) and Odds Ratio (OR) with 95 % Confidence Interval (95 % CI) for continuous and binary outcomes respectively. The degree of heterogeneity in all measured outcomes was assessed with the I-square (I^2) test. I^2 -values of $< 40\%$, 40% – 60% , and $> 60\%$ indicated low, moderate and high heterogeneity respectively. If a high heterogeneity degree were present, a random-effect model would be used for data analysis. Otherwise, a fixed-effect model would be applied to all the measured outcomes. As there were different scoring systems on the severity of emergence agitation, a subgroup analysis was performed on the primary outcome of this study.

The GRADE approach was used to assess the quality of evidence for each outcome of the meta-analysis, with the aid of GRADEpro GDT.²⁴ The quality of evidence was assessed based on five domains: risk of bias, inconsistency of results, indirectness of evidence, imprecision, publication bias.²⁵ Any uncertainty was resolved by third author (KN).

Results

The PRISMA flow diagram illustrates the process of study selection and literature search (Figure 1). A total of 824 articles were retrieved for the title and abstract screening. Among all, thirty-two articles were selected for full text screening. Fifteen studies were excluded from the review (Supplementary Table S2). Seventeen articles with a total of 1515 patients were included in this review. Notable to

mention that one relevant ongoing clinical trial was identified during the literature search (TCTR20221024001), which was scheduled to be completed by June 1, 2025 (Supplementary Table S3).

The clinical characteristics of all the included studies are outlined in Table 1. All the 17 studies are single-centered RCTs. Fourteen of these trials were conducted in operating theatres,^{9,10,12,14,26–35} whereas the other three studies were in imaging scan rooms.^{36–38} In terms of comparators, the majority used ketamine or s-ketamine as comparators, with the exception of three studies that compared patients receiving ketamine-propofol versus propofol only.^{30,32,38} Most of the studies administered intravenous ketamine in bolus injection, whereas only two studies gave it bolus followed by infusion.^{9,32} The dosage used across all the included studies varied from 0.20 mg.kg^{-1} to 1.0 mg.kg^{-1} . The main choice of general anesthesia was sevoflurane in the 14 studies.^{9,12,14,27–31,33–38} In terms of the emergence agitation assessment tools, the PAED score was used in seven of the studies.^{9,12,28,31,32,37,38} Emergence Agitation Score (EAS) in three studies,^{29,33,36} Aono's Four-point Scale in six studies,^{10,14,26,27,30,34} and Richmond Agitation-Sedation Scale (RASS) in one study.³⁵ The overview of data analysis of primary and secondary outcomes is outlined in Table 2. Summary of findings and certainty of evidence using GradePRO is illustrated in Table 3.

The summary of risk of bias assessment using the RoB1 tool was illustrated in Online Supplementary Table S4. Of the overall risk of bias, seven out of 17 studies displayed low risk,^{9,12,27,34,35,37,38} while the remaining ten studies were deemed unclear.^{10,14,26,28–33,36} Both authors completed this review in accordance with the PRISMA checklist (Supplementary Table S5).

Primary outcome: incidence of emergence agitation

By summarizing the data of 15 studies ($n = 1319$), the incidence of emergence agitation in pediatric patients was 16.7% in the ketamine group and 34.9% in the control group. Children who received intravenous ketamine experienced a lower incidence of emergence agitation, with an OR of 0.27 ($p < 0.00001$, 95 % CI 0.16 to 0.45, $I^2 = 61\%$) (Figure 2). The certainty of evidence was deemed to be very low due to considerable risk of bias, result inconsistency and imprecision. This finding should be interpreted with great caution given the high substantiality, which might be due to differences in patient age and doses of intravenous ketamine applied across studies.

Subgroup analysis of three main scoring systems for emergence agitation (PAED score, Aono's four-point scale, EAS) demonstrated a similar result of ketamine's role in reducing emergence agitation (pooled OR = 0.27, 95 % CI 0.16 to 0.45, $p < 0.00001$) with significant heterogeneity (61 %) (eFigure 1). Chi-Squared test for subgroup differences produced a p-value of 0.09, which indicated no statistically significant differences in results between these scoring systems ($I^2 = 57.8\%$). Among the three measuring tools, Aono's four-point scale has the highest sensitivity as it yielded the most pronounced effect of ketamine in reduction of emergence agitation (pooled OR = 0.14, 95 % CI 0.06 to 0.33, $p = 0.02$, $I^2 = 64\%$). The funnel plot did not show evidence of publication bias graphically.

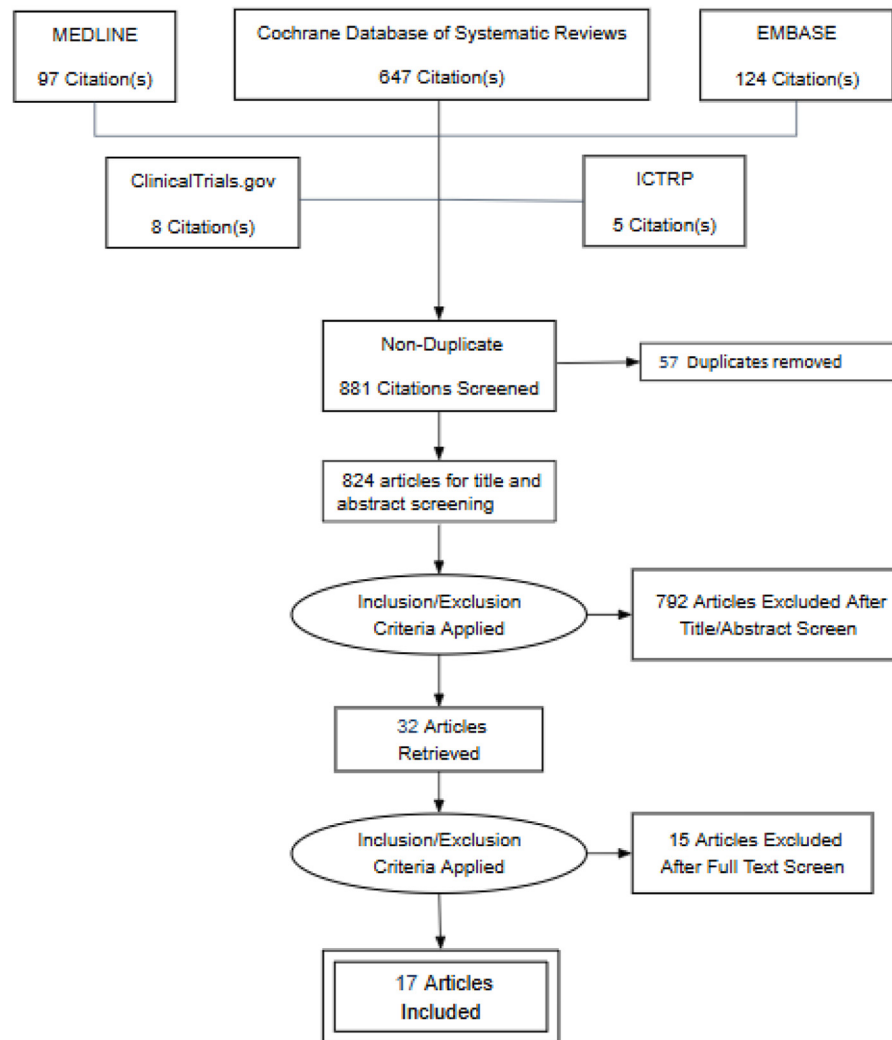


Figure 1 PRISMA flow diagram.

Secondary outcomes: postoperative pain, recovery time, nausea/vomiting, desaturation, laryngospasm

Six studies have examined the effect of intravenous ketamine on postoperative pain in pediatric patients. The pain score upon arrival at the PACU in the ketamine group was significantly lower than in the control group ($n = 429$, $p = 0.001$, MD = -2.28 , 95 % CI -3.68 to -0.87) (Figure 3). High degree of heterogeneity was found with an I^2 -value of 94 %. Sensitivity analysis was then performed by removing studies with high or unclear risk of bias, which showed the significance of pain reduction with the intravenous ketamine group (studies = 3, $n = 239$, $p = 0.03$, MD = -0.86 , 95 % CI 1.65 to -0.08 , $I^2 = 74$ %) (eFigure 2). Ketamine did not reduce the duration of recovery time (studies = 12, $n = 1108$, $p = 0.44$, MD = -0.77 , 95 % CI -2.76 to 1.21 , $I^2 = 91$ %) (eFigure 3), although this should also be interpreted with caution due to high heterogeneity.

The pooled result of 12 studies ($n = 1201$) did not find any significant effect of postoperative nausea and vomiting in both the ketamine and control group ($p = 0.36$, OR = 1.20, 95 % CI 0.81 to 1.75) (eFigure 4). No significant effects were observed in the incidence of desaturation (studies = 7,

$n = 817$, OR = 0.95, 95 % CI 0.58 to 1.56, $p = 0.84$) (eFigure 5) and laryngospasm (studies = 4, $n = 267$, OR = 0.82, 95 % CI 0.24 to 2.75, $p = 0.75$) (eFigure 6), with low degree of heterogeneity across the three measured outcomes ($I^2 = 0$ %). These findings demonstrate that intravenous ketamine in these populations did not result in significant adverse effects, such as desaturation or laryngospasm.

Discussion

This meta-analysis demonstrated the potential of intravenous ketamine in minimizing the occurrence of emergence agitation and severity of pain following procedures in the pediatric group, although there is considerable degree of heterogeneity and low certainty of evidence in the GRADE framework. Though it did not shorten the duration of recovery, the short-term use of ketamine in the study group also demonstrated a favorable safety profile among children in the reduction of emergence agitation. Clinicians should interpret these results with caution, recognizing that the low certainty of evidence indicates a need for further trials with more robust methodologies to confirm the findings.

Table 1 Clinical characteristics of included studies.

Author	Year	Design	Age (Mean $\pm$ S.D.) [Year]	Comparator	Ketamine Dose	Regime of ketamine	Timing of ketamine	Control	Choice of Anesthesia	Type of EA scale	% of EA (ketamine/placebo)	Type of procedure	Setting	Country	n
Dalens ¹⁶	2006	Single-center RCT	K: 36.8 $\pm$ 17.9 mo; C: 29.1 $\pm$ 20.2 mo	Ketamine	0.25 mg.kg ⁻¹	Bolus	At the end of procedure	Saline	Sevoflurane	Emergence agitation scale ≥ 4	0 % / 10.7 %	Elective MRI	MRI room	Canada	61
Abu-Shahwan ¹²	2007	Single-center RCT	K: 5.3 $\pm$ 0.9; C: 5.4 $\pm$ 0.8	Ketamine	0.25 mg.kg ⁻¹	Bolus	10 min before the end of surgery	Saline	Sevoflurane	PAED ≥ 15	16.6 % / 34.2 %	Dental repair with no extraction	Operation Theatre	Canada	80
Lee ¹⁴	2010	Single-center RCT	K0.25: 5.0 $\pm$ 0.4; K0.5: 5.0 $\pm$ 0.4; C: 4.8 $\pm$ 0	Ketamine	K0.25: 0.25 mg.kg ⁻¹ ; K0.5: 0.5 mg.kg ⁻¹	Bolus	Before the end of the surgery	Saline	Sevoflurane	Aono's four-point scale > 2	20 % / 80 %	Adenotonsillectomy	Operation Theatre	Korea	90
Jeong ²⁶	2012	Single-center RCT	K1.0: 5.0 $\pm$ 0.4; K0.5: 5.0 $\pm$ 0.4; C: 4.8 $\pm$ 0.4	Ketamine	K0.5: 0.5 mg.kg ⁻¹ ; K1.0: 1.0 mg.kg ⁻¹	Bolus	Before entering OT; 10 min before completion of surgery	Saline	Desflurane	Aono's four-point scale > 2	25 % / 85 %	Ophthalmic surgery	Operation Theatre	Korea	60
Abdelhalim ²⁷	2013	Single-center RCT	K: 5.1 $\pm$ 1.6; C: 4.8 $\pm$ 1.9	Ketamine	0.5 mg.kg ⁻¹	Bolus	10 min before the end of surgery	Saline	Sevoflurane	Aono's four-point scale > 2	15 % / 42.5 %	Tonsillectomy $\pm$ Adenoidectomy	Operation Theatre	Saudi Arabia	80
Chen ⁹	2013	Single-center RCT	K: 4.2 $\pm$ 1.2; C: 4.3 $\pm$ 1.1	Ketamine	1.0 mg.kg ⁻¹	Bolus + infusion	After induction	Saline	Sevoflurane	PAED ≥ 10	29.6 % / 70.8 %	Strabismus surgery	Operation Theatre	China	51
Eghbal ¹⁰	2013	Single-center RCT	K: 9.1 $\pm$ 3.3; C: 8.2 $\pm$ 3.1	Ketamine	0.25 mg.kg ⁻¹	Bolus	Before the end of the surgery	Saline	Isoflurane	Aono's four-point scale > 2	30.3 % / 90.9 %	Adenotonsillectomy	Operation Theatre	Iran	66
Ozcan ²⁸	2014	Single-center RCT	K: 4.0 $\pm$ 1.6; C: 4.8 $\pm$ 3	Ketamine	0.25 mg.kg ⁻¹	Bolus	10 min before the end of surgery	Saline	Sevoflurane	PAED ≥ 10	30 % / 55 %	Inguinal hernia repair, circumcision or orchiopexy	Operation Theatre	Turkey	40
Rashad ²⁹	2014	Single-center RCT	K: 26.9 $\pm$ 9.1 mo; C: 24.6 $\pm$ 10.2 mo	Ketamine	0.25 mg.kg ⁻¹	Bolus	Before the end of the surgery	Saline	Sevoflurane	Emergence agitation scale ≥ 4	20 % / 40 %	Hypospadias repair	Operation Theatre	Egypt	40
Rizk ³⁰	2014	Single-center RCT	K: 4.3 $\pm$ 1.5; C: 4.1 $\pm$ 1.3	Ketamine - Propofol	0.25 mg.kg ⁻¹	Bolus	Before the end of the surgery	Usual treatment (propofol)	Sevoflurane / Propofol	Aono's four-point scale > 2	16.7 % / 23.3 %	Tonsillectomy $\pm$ Adenoidectomy	Operation Theatre	Egypt	60
Moawad ²⁷	2015	Single-center RCT	K0.25: 4.3 $\pm$ 1.4; K1.0: 4.2 $\pm$ 1.5; C: 4.6 $\pm$ 1.4	Ketamine	K0.25: 0.25 mg.kg ⁻¹ ; K1.0: 1.0 mg.kg ⁻¹	Bolus	Before induction; 10 min prior to the end of procedure	Saline	Sevoflurane	PAED ≥ 10	–	Elective MRI	MRI room	Egypt	120
Ozturk ³¹	2016	Single-center RCT	K: 4.3 $\pm$ 1.3; C: 4.0 $\pm$ 1.6	Ketamine	0.5 mg.kg ⁻¹	Bolus	Post-extubation	Saline	Sevoflurane	PAED ≥ 15	–	Fiberoptic bronchoscopy	Operation Theatre	Turkey	46
Schmitz ³⁸	2018	Single-center RCT	K: 4.1 $\pm$ 0.8; C: 3.7 $\pm$ 0.8	Ketamine - Propofol	1.0 mg.kg ⁻¹	Bolus	Before the procedure	Usual treatment (propofol)	Sevoflurane / Propofol	PAED ≥ 10	4.3 % / 1.8 %	Elective MRI	MRI room	Switzerland	331
Jalili ³²	2019	Single-center RCT	K: 7.3 $\pm$ 2.1; P: 7 $\pm$ 2.1	Ketamine - Propofol	25 mg.kg ⁻¹ .min ⁻¹	Infusion	During operation (maintenance of anesthesia)	Usual treatment (propofol)	Sodium thiopental + Atracurium	PAED ≥ 12	20.9 % / 27.3 %	Tonsillectomy	Operation Theatre	Iran	87
Ibrahim ¹³	2023	Single-center RCT	K: 5.6 $\pm$ 1.32; C: 5.7 $\pm$ 1.3	Ketamine	0.25 mg.kg ⁻¹	Bolus	Post-extubation	Saline	Sevoflurane	5 step EA scale > 5 for > 3 mins	10 % / 16.6 %	Tonsillectomy $\pm$ Adenoidectomy	Operation Theatre	Egypt	90
Chen ³⁴	2023	Single-center RCT	K: 5.0 $\pm$ 1.4; C: 5.4 $\pm$ 1.4	S-ketamine	0.2 mg.kg ⁻¹	Bolus	Upon completion of surgery	Saline	Sevoflurane	Aono's four-point scale ≥ 3	7.4 % / 22.2 %	Tonsillectomy $\pm$ Adenoidectomy	Operation Theatre	China	108
Qiu ³⁵	2023	Single-center RCT	K: 35.6 $\pm$ 29.3 mo; C: 40.3 $\pm$ 35.8 mo	S-ketamine	0.5 mg.kg ⁻¹	Bolus	During induction	Saline	Sevoflurane	RASS > 0 [EA]	45.3 % / 78.9 %	Laparoscopic hernia repair	Operation Theatre	China	105

Table 2 Meta-analytic findings of primary and secondary outcomes.

	Outcomes	Trials	n	I ² (%)	MD/OR (95 % CI)	p
1	Incidence rate of emergence agitation	15	1319	61	0.27 [0.16, 0.45]	< 0.00001
1.1	Subgroup analysis by three different scoring systems					
	PAED	5	589	56	0.51 [0.23, 1.13]	0.10
	Aono's four-point scale	6	464	64	0.14 [0.06, 0.33]	< 0.00001
	Emergence agitation scale	4	266	0	0.28 [0.15, 0.54]	0.0001
2	Pain score upon arrival of PACU	6	429	94	-2.28 [-3.68, -0.87]	0.001
3	Recovery time (time required to reach Aldrete Score of ≥ 9)	12	1108	91	-0.77 [-2.76, 1.21]	0.44
4	Nausea/Vomiting	12	1201	0	1.20 [0.81, 1.75]	0.36
5	Desaturation	7	817	0	0.95 [0.58, 1.56]	0.84
6	Laryngospasm	4	267	0	0.82 [0.24, 2.75]	0.75

PAED, Pediatric Anesthesia Emergence Delirium; PACU, Post-Anesthesia Care Unit; n, Sample size; MD, Mean Difference; OR, Odds Ratio; CI, Confidence Interval; p, p-value.

Until more evidence is available, clinicians should incorporate these findings as part of a broader, evidence-based decision-making process rather than as a definitive recommendation for routine use.

Ketamine's non-competitive NMDA receptor antagonism reduces excitatory neurotransmission and prevents hyperexcitability after surgery.³⁹ It also provides analgesia by acting on opioid receptors and HCN channels.⁴⁰ This review highlights ketamine's dual role as both an anesthetic and analgesic, which is consistent with several studies in similar settings.^{41–43} However, given the considerable heterogeneity across the evidence, clinicians should interpret these results with caution. Our review also emphasizes the need to address study-level sources of heterogeneity that affect the interpretation of ketamine's clinical utility. While most studies utilized ketamine as monotherapy, there were two recent studies that chose S-ketamine,^{34,35} and three studies with ketamine-propofol.^{30,32,38} S-ketamine, the more potent enantiomer, has higher affinity for NMDA receptors and offers enhanced analgesic and sedation effects. Meanwhile, ketamine-propofol combinations provide more balanced sedation and pain relief as compared to ketamine alone, with propofol contributing antiemetic and sedative profiles, which may reduce the incidence of emergence agitation. These differences in formulation further introduce variability in efficacy and safety outcomes, complicating direct comparisons across studies.

Diagnostic and surgical procedures, ranging from minor diagnostic interventions to major surgeries may have a varied degree of pain and agitation potentials. This variability likely influences the baseline risk of emergence agitation and analgesic requirements, making direct comparisons challenging. While the majority of the studies utilized sevoflurane as maintenance agent, two studies used desflurane²⁶ and isoflurane.¹⁰ The differences in anesthetic agents may contribute to heterogeneity in the incidence of emergence agitation due to their distinct pharmacological profiles.

All included studies used different tools to measure emergence agitation, mainly PAED score, the 5-step EAS, and Aono's four-point score. This variation across studies reflects the lack of universal agreement on the most appropriate or sensitive tool for evaluating emergence agitation.

To address the divergence in findings, we conducted a subgroup analysis to examine whether ketamine's efficacy remains consistent across different assessment tools. This approach ensures the robustness of evidence and demonstrates the generalizability of ketamine's effect across varied clinical practices. By accounting for these methodological differences, the analysis helps contextualize our results within the broader clinical landscape, strengthening the recommendations of this review, and providing suggestions for future research and standardized assessment. The subgroup analysis has shown that the effect of ketamine in the reduction of emergence agitation among children was consistent across the three assessment tools, suggesting robustness across differing measurement methods. Our review found that ketamine did not significantly shorten the duration of recovery, with all studies universally agreeing on discharging patients only after an Aldrete score of at least 9 was reached. However, other variabilities, such as differences in patient population, procedural complexities, the use of other adjunct medications, may have prolonged sedation or recovery time, which contributed to inconsistencies in the result.

All trials included in this review administered intravenous ketamine with doses ranging between 0.20 mg.kg⁻¹ and 1.0 mg.kg⁻¹ before the end of the procedure, which were proven to be adequate for pain control and prevention of emergence agitation without experiencing any noticeable adverse event. Other studies have also acknowledged that a subanesthetic dose between 0.15 and 0.25 mg.kg⁻¹ could achieve sufficient analgesic control.^{44–47} While higher doses in some animal studies (as high as 30 mg.kg⁻¹ per day in rats) or chronic exposure of ketamine have raised concerns about ketamine's potential neurotoxicity,⁴⁸ no research data in a human study has yet conclusively demonstrated any potential clinical risk of a single low dose administration of ketamine in children.⁴⁹ The safety profile is further reinforced by the low incidence of adverse events, such as nausea, vomiting, desaturation and laryngospasm, in the included trials. However, the broad range of study groups (3-months to 15-years) may have contributed to variability in the findings, as younger children metabolize ketamine more

Table 3 Summary of findings table.

N° of studies	Study design	Certainty assessment					N° of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
15	Randomized trials	Very serious ^a	Serious ^b	Serious ^c	Not serious	Dose response gradient	115/689 (16.7 %)	220/630 (34.9 %)	OR 0.27 (0.16 to 0.45)	223 fewer per 1000 (from 270 fewer to 155 fewer)	⊕○○○ Very low ^{a,b,c}	
4	Randomized trials	Serious ^d	Not serious	Serious ^c	Not serious	Dose response gradient	112	105	—	MD 3.99 lower (5.03 lower to 2.95 lower)	⊕⊕⊕○ Moderate ^{c,d}	
6	Randomized trials	Serious ^d	Very serious ^e	Serious ^c	Not serious	Publication bias strongly suspected dose response gradient ^f	243	186	—	MD 2.28 lower (3.68 lower to 0.87 lower)	⊕○○○ Very low ^{c,d,e,f}	
12	Randomized trials	Serious ^d	Very serious ^e	Not serious	Not serious	Publication bias strongly suspected dose response gradient ^f	566	542	—	MD 0.77 lower (2.76 lower to 1.21 higher)	⊕○○○ Very low ^{d,e,f}	
12	Randomized trials	Serious ^d	Not serious ^e	Not serious	Not serious	Publication bias strongly suspected dose response gradient ^f	69/649 (10.6 %)	50/552 (9.1 %)	OR 1.20 (0.81 to 1.75)	16 more per 1000 (from 16 fewer to 58 more)	⊕⊕⊕○ Moderate ^{d,e,f}	
7	Randomized trials	Not serious	Not serious	Not serious ^c	Not serious	Publication bias strongly suspected dose response gradient ^f	36/406 (8.9 %)	40/411 (9.7 %)	OR 0.95 (0.58 to 1.56)	4 fewer per 1000 (from 38 fewer to 47 more)	⊕⊕⊕⊕ High ^{c,f}	
4	Randomized trials	Very serious ^a	Not serious	Serious ^c	Not serious	Publication bias strongly suspected dose response gradient ^f	5/135 (3.7 %)	6/132 (4.5 %)	OR 0.82 (0.24 to 2.75)	8 fewer per 1000 (from 34 fewer to 70 more)	⊕○○○ Very low ^{a,c,f}	

CI, Confidence Interval; MD, Mean Difference; OR, Odds Ratio.

Explanations.

^a The majority of included trials were high risk/unclear risk of bias.^b Heterogeneity > 50 %.^c The sample size of each group was < 300.^d Half of studies were unclear risk of bias.^e Heterogeneity > 80 %.^f Funnel plot showed asymmetrical graphically.

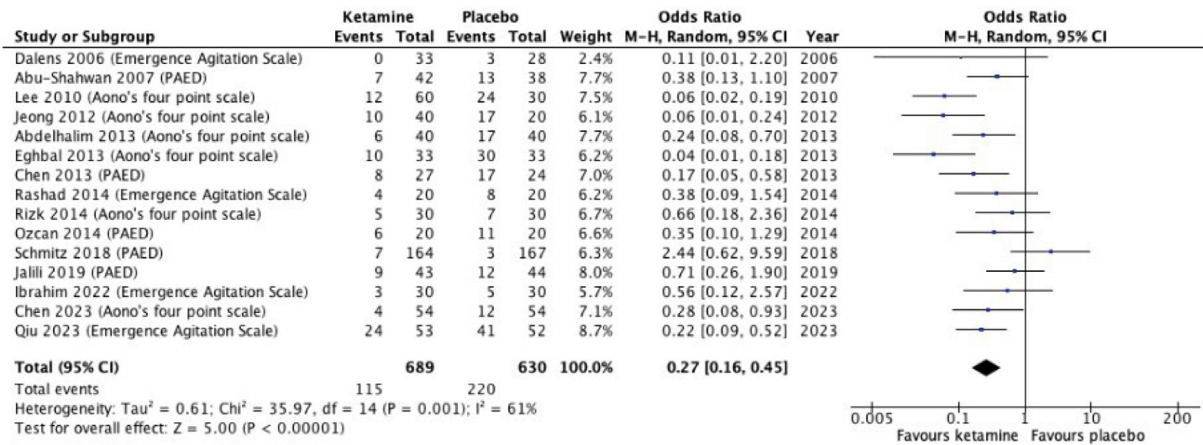


Figure 2 Incidence rate of emergence agitation.

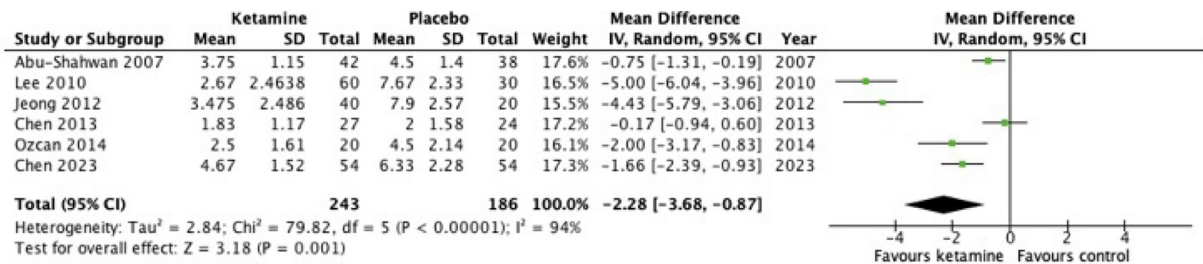


Figure 3 Pain score upon arrival of PACU.

rapidly compared to older children,⁵⁰ potentially requiring different dosing regimens.

While ketamine has shown potential in reducing emergence agitation, other anesthetic agents have also been reported to have similar effects in clinical practice, such as midazolam and dexmedetomidine. As an imidazole benzodiazepine, midazolam is widely used for preoperative sedation and lowering anxiety level,⁵¹ which contributes to lower risk of emergence agitation.⁵² However, it does not possess a significant analgesic property,⁵³ making it a less suitable candidate for postoperative pain control. Dexmedetomidine, a selective alpha 2-adrenergic receptor agonist,⁵⁴ displayed both sedative and pain relief characteristics with fewer neurocognitive concerns compared to ketamine.⁵⁵ However, two meta-analyses on dexmedetomidine have revealed that the treatment group significantly prolonged time to extubation, eye-opening, and discharge from the recovery room.^{56,57} Regardless, further large-scale studies and meta-analyses are warranted to compare these agents and establish whether ketamine's unique analgesic and sedation abilities hold a clinical advantage against other anesthetic medications in the pediatric population.

Several limitations must be acknowledged in this review: 1) Inconsistencies in variables such as age of subjects, dose of intravenous ketamine used, choice of anesthetic, and scoring tools were used to measure the degree of emergence agitation. 2) The inclusion of smaller sample size clinical trials, which may amplify the effects of intervention and cause false positive findings. 3) We did not evaluate time to extubation or PACU discharge as independent outcomes. 4) Other

patient-related risk factors of emergence agitation, such as the preoperative anxiety level of patients and guardians, may have influenced the study findings but were not consistently measured across the included studies. 5) Lack of long-term follow-up data to evaluate potential neurocognitive risks and provide clarity on safety of ketamine use in pediatric populations.

Conclusion

This systematic review and meta-analysis suggests that intravenous ketamine reduces the incidence of emergence agitation and postoperative pain in children undergoing surgery or diagnostic procedures. However, due to considerable heterogeneity and overall low certainty of evidence, further high-quality randomized controlled trials are required before routine use can be recommended.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844675.

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REVIEW ARTICLE

Respiratory outcomes of adrenergic beta-antagonists in patients undergoing tracheal extubation: a systematic review and meta-analysis of randomized controlled trials



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Abstract

Background: Tracheal extubation after general anesthesia may cause hemodynamic and respiratory complications, with no established strategies to prevent them. We conducted a meta-analysis to evaluate the safety and efficacy of beta-blockers in patients undergoing tracheal extubation.

Methods: We searched the MEDLINE, EMBASE and CENTRAL databases for randomized controlled trials up to 2024 comparing beta-blockers to placebo in patients undergoing tracheal extubation. Primary outcome: cough intensity; secondary: bronchospasm, bucking, hypertension. Risk Ratios (RR) with 95% Confidence Intervals (95% CI) were computed. Leave-one-out sensitivity and meta-regression analyses were performed for outcomes with high heterogeneity.

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Results: We included 31 randomized studies, comprising 1,803 patients, of whom 965 received beta-blockers. The risk of moderate/severe cough (RR = 0.21; 95% CI 0.13 to 0.34; $p < 0.001$; $I^2 = 0\%$) and hypertension (RR = 0.28; 95% CI 0.13 to 0.58; $p < 0.001$; $I^2 = 45\%$) was significantly lower in the beta-blockers group compared with the placebo group. There were no statistically significant differences between groups in the risk of bronchospasm (RR = 0.58; 95% CI 0.17 to 1.94; $p = 0.375$; $I^2 = 0\%$) or bucking (RR = 0.47; 95% CI 0.20 to 1.13; $p = 0.093$; $I^2 = 72\%$). Sensitivity analysis identified Mendonça (2023) as the main heterogeneity source in bucking.

Conclusion: Our study demonstrates that beta-blockers reduced moderate/severe cough and hypertension in patients undergoing tracheal extubation compared with placebo with no significant difference in the risk of bronchospasm and bucking. These findings suggest beta-blockers may be a valuable strategy for preventing peri-extubation hemodynamic instability and airway hyperresponsiveness.

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Introduction

Extubation is a procedure frequently used in surgeries performed under general anesthesia. Complications from this procedure may affect more than one-third of patients. Cough is a common complication, mainly due to the activation of irritant receptors in the tracheal mucosa, causing a contraction of the smooth muscle in the airways and consequently triggering the cough reflex and bronchospasm.^{1,2} As a result, there may be an exacerbated hemodynamic responses, leading to cardiovascular and respiratory decompensations.^{3–5} This occurs due to the stimulation of the sympathoadrenal reflex, with a concomitant increase in plasma catecholamine levels and activation of alpha and beta-adrenergic receptors.⁶ The development of this response necessitates immediate interventions to reduce the risk of potentially fatal complications such as acute myocardial infarction, arrhythmias, congestive heart failure, and other target organ damage.^{6,7}

Despite these concerns, pharmacological guidelines to control cardiovascular and respiratory decompensations during the peri-extubation period have not yet been developed. In this context, recent studies are investigating the potential use of prophylactic beta-blockers to reduce cardiovascular and respiratory responses and the risk of complications after the procedure.⁸ By counteracting sympathetic activation during acute stress through their antagonistic action on beta-1 receptors, these medications may prevent a hyperdynamic state throughout the tracheal extubation phase without prolonging the recovery phases.^{9–12}

The efficacy and safety of beta-blockers during tracheal extubation remain uncertain.^{12–42} Individual trials lack sufficient power to detect significant differences in outcomes and adverse events. To address these limitations, this meta-analysis pools data from multiple Randomized Controlled Trials (RCTs) to enhance statistical power and provide robust conclusions on the efficacy and safety of beta-blockers in tracheal extubation.

Material and methods

This systematic review and meta-analysis were conducted in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-

Analysis (PRISMA) statement guidelines and followed the methodological recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions.^{43,44} The protocol of this study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024542103).

Search strategy and data extraction

We systematically searched in databases of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to April 25th, 2024, with the search terms presented in [Supplementary Table 1](#). The titles and abstracts were first reviewed. Studies that did not satisfy the inclusion criteria were excluded, and all abstracts deemed potentially eligible were obtained in full text and assessed to confirm their inclusion. The entire screening process was conducted independently by two authors (L.B. and A.N.), followed by a comparison of decisions. Any discrepancies in decisions were resolved by a third independent author. Four authors (A.F., M.C., H.F. and C.F.) independently organized and extracted the data, using standardized tables for accuracy, following predefined search criteria and quality assessment. Disagreements were resolved by consensus between the authors.

Eligibility criteria

We included studies that fulfilled the following eligibility criteria: (1) Randomized Controlled Trials (RCTs) published in the indexed databases; (2) Studies comparing adrenergic beta-antagonists with placebo; (3) trials involving patients undergoing tracheal extubation; and (4) Studies assessing extubation-related complications using validated clinical scales or predefined hemodynamic parameters. We excluded studies based on the following criteria: (1) Lack of a control group; (2) Overlapping patient populations; (3) Trials not involving patients undergoing tracheal extubation; and (4) Administration of the drug solely during anesthetic induction, with no relevance to tracheal extubation outcomes.

Outcomes and subgroups

Primary outcomes were the incidence of cough and its severity, classified as no/mild cough, and moderate/severe

cough. Secondary outcomes included Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Mean Heart Rate (MHR), risk of bronchospasm, hypertension, hypotension, tachycardia, bradycardia, postoperative nausea or vomiting, and bucking, defined as a situation in which a patient is trying to cough and strain on an endotracheal tube and has violent expiratory contraction of skeletal muscles secondary to endotracheal tube stimulation of the tracheal mucosa.

Sub-analyses included data restricted to the time of outcome measurement after extubation (at extubation, 1-minute, 2 minutes, 5 minutes, 10 minutes, and 15 minutes or more).

Quality assessment

Quality assessment of RCTs was performed using the Cochrane Collaboration's tool for assessing the risk of Bias in Randomized trials (RoB-2). Studies were scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases.⁴⁵ Bias risk assessment was conducted independently by two authors (A.N and O.G.). Discrepancies were resolved through consensus among the authors. Publication bias was assessed with contour-enhanced funnel plot analysis⁴⁶ and Egger's test⁴⁷ of efficacy endpoints and evaluation for symmetrical distribution of trials with similar weights, using the Pustejovsky and Rodgers⁴⁸ approach when the standardized mean difference was used for the outcome of interest.

Statistical analysis

Treatment effects were compared for binary outcomes using Risk Ratios (RR) with 95% Confidence Intervals (95% CI). Mean Differences (MD) with 95% CI were used to compare the treatment effects for continuous endpoints. Given the expected heterogeneity between studies, we adopted the DerSimonian and Laird random-effects model for all outcomes reported. We used the Cochrane Q test and I^2 statistics to assess heterogeneity; p-values inferior to 0.1 and $I^2 > 40\%$ were considered significant for heterogeneity.⁴³ The p-values inferior to 0.05 were considered statistically significant. Funnel Plots with Egger's test was used to address publication bias in every outcome and subgroup that had at least 10 studies. R version 4.4.0 and the "meta" extension package was used for all analyses.⁴⁹

Sensitivity analysis

We performed a pre-specified sensitivity analysis for primary endpoints with (1) A leave-one-out approach to ensure that results were not dependent on a single study and to evaluate studies that had high contributions to the heterogeneity on primary endpoints when $I^2 \geq 40$; (2) Several univariable meta-regression analyses to assess any interactions with some covariates (time of drug administration; type of adrenergic beta-antagonist; age; American Society of Anesthesiologists physical status classification; type of surgery; preanesthetic medication; type of general anesthesia; baseline SBP, DBP, MAP, and MHR; duration of surgery and anesthesia) for the continuous outcomes reported by at least 9 studies. A multivariable meta-regression was not

conducted to assess the robustness and validity of the findings due to the limited number of included studies and lack of statistical significance of multiple covariates. Current methodological guidelines recommend a minimum of 10 studies per covariate to ensure reliable estimates in multivariable meta-regression analyses.⁴³

Results

Study selection and characteristics

As outlined in Figure 1, this study included 31 RCTs with a total of 1,803 patients, of whom 965 (53.5%) were assigned to the beta-blockers group and 838 (46.5%) to the placebo group.¹²⁻⁴² Among the interventions, 21 studies used esmolol, 4 labetalol, 3 used metoprolol, 1 landiolol, 1 atenolol, and 1 propranolol. The mean age of patients across studies ranged from 31.2 to 69 years, and the percentage of female patients ranged from 14.28% to 100%. At baseline, MAP ranged from 30.05 to 124.20 and MHR ranged from 52.74 to 98.76. Detailed baseline characteristics of the included studies can be found in Table 1. Given the heterogeneity in pharmacologic properties and clinical application of these agents, we present in Supplementary Table 2 a descriptive summary of their key characteristics and relevance in the context of tracheal extubation based on the studies included in this meta-analysis.

Pooled analysis

Primary outcomes

Beta-blockers significantly reduced the incidence of cough (RR = 0.55; 95% CI 0.36 to 0.83; $p < 0.01$; $I^2 = 73\%$; Fig. 2). Also, beta-blockers significantly altered the distribution of cough severity during tracheal extubation, shifting the severity distribution from moderate/severe to none/mild. Specifically, they significantly reduced the incidence of moderate/severe cough (RR = 0.21; 95% CI 0.13 to 0.34; $p < 0.01$; $I^2 = 0\%$; Fig. 3), while simultaneously increasing the incidence of patients experiencing no/mild cough (RR = 1.34; 95% CI 1.05 to 1.70; $p = 0.017$; $I^2 = 86\%$; Fig. 4).

Secondary outcomes

There was no difference between groups in bronchospasm (RR = 0.58; 95% CI 0.17 to 1.94; $p = 0.375$; $I^2 = 0\%$; Fig. 5), bucking (RR = 0.47; 95% CI 0.20 to 1.13; $p = 0.093$; $I^2 = 72\%$; Fig. 6), hypotension (RR = 1.43; 95% CI 0.87 to 2.38; $p = 0.161$; $I^2 = 0\%$; Supplementary Fig. 1) and bradycardia (RR = 1.24; 95% CI 0.31 to 4.97; $p = 0.759$; $I^2 = 0\%$; Supplementary Fig. 2).

The risk of hypertension (RR = 0.28; 95% CI 0.13 to 0.58; $p < 0.001$; $I^2 = 45\%$; Supplementary Fig. 3), tachycardia (RR = 0.20; 95% CI 0.08 to 0.51; $p < 0.001$; $I^2 = 71\%$; Supplementary Fig. 4), and nausea or vomiting (RR = 0.60; 95% CI 0.50 to 0.72; $p < 0.001$; $I^2 = 2\%$; Supplementary Fig. 5) was significantly reduced in the beta-blocker group compared with the placebo group in patients undergoing tracheal extubation.

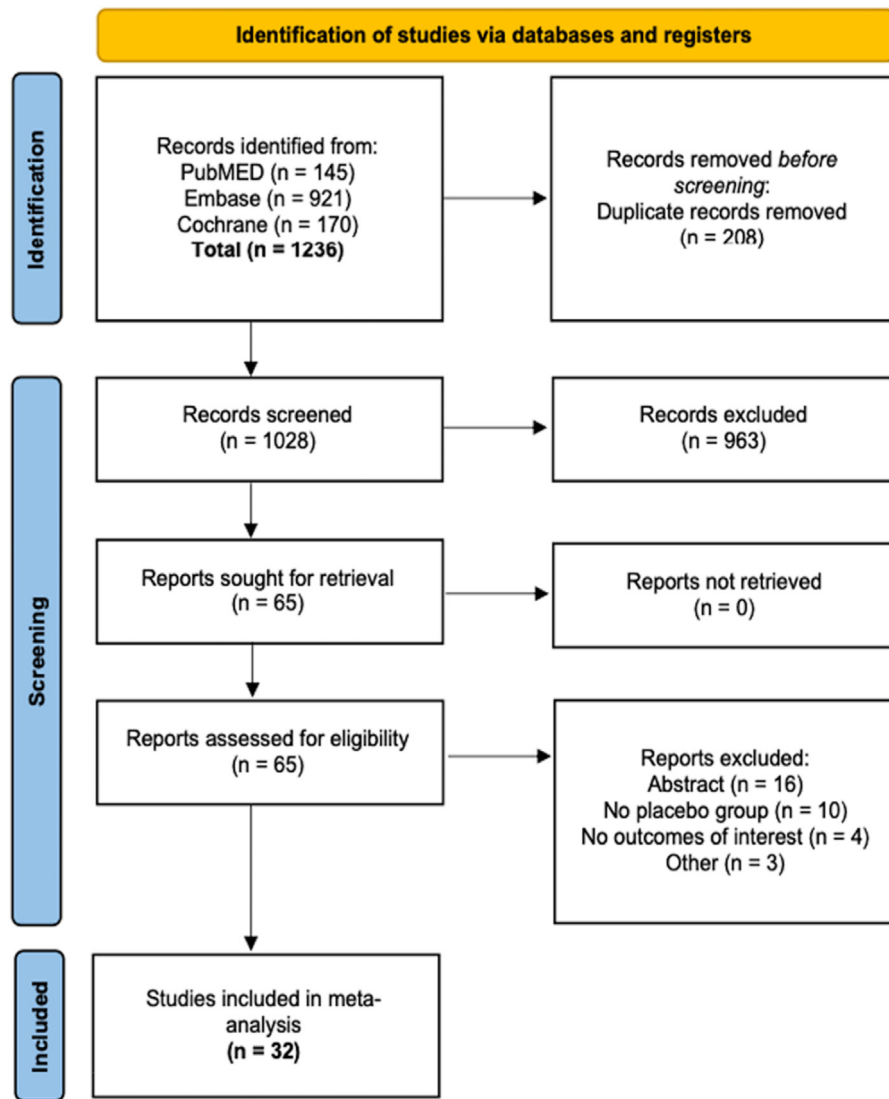


Figure 1 PRISMA flow diagram of study screening and selection.

Hemodynamic variables

SBP, DBP, MAP, and MHR were significantly lower in the beta-blockers group compared with the placebo group at tracheal extubation after 1, 2, 5, 10, and 15 or more minutes (Supplementary Table 2). However, there was no significant difference between groups for MAP and MHR at tracheal extubation after 15 minutes or more.

Sensitivity analyses

We conducted leave-one-out sensitivity analyses for the outcomes of bucking, hypertension, cough, no/mild cough, moderate/severe cough, and tachycardia due to high heterogeneity. The leave-one-out analysis of the outcome of bucking showed that omitting Mendonça (2023)¹² led to a significantly lower incidence of bucking in the beta-blockers group compared with the placebo group, with no heterogeneity observed ($I^2 = 0\%$; Supplementary Fig. 6). For the outcome of hypertension, cough, and no/mild cough, no study was identified as driving the heterogeneity, all omissions remained with high heterogeneity, favoring beta-blockers

(Supplementary Fig. 7; Supplementary Fig. 8; Supplementary Fig. 9). The leave-one-out sensitivity analysis for the outcome of tachycardia showed similar results in all scenarios with a lower heterogeneity when Shetabi (2023)³⁵ is omitted ($I^2 = 18\%$; Supplementary Fig. 10).

Additionally, we performed a meta-regression analysis for the following outcomes: SBP, DBP, MAP, and MHR using the mean age and the mean values at baseline of SBP, DBP, MAP, and MHR as predictors. Results are presented in Supplementary Table 4. Our results showed that age was a significant predictor ($Q_{mp} < 0.05$) for MHR at tracheal extubation, with higher baseline age values resulting in more positive mean differences, favoring placebo over beta-blockers. SBP, DBP, MAP, and MHR were not significant predictors of any outcome. Significant heterogeneity remained after accounting for the moderator effects of the selected predictors.

Quality assessment

The individual RCT appraisal is reported in Supplementary Table 5. Sixteen studies [12–22,25,32,34,39,41,50] were

Table 1 Baseline characteristics of included studies.

Study	Country	Intervention	Patients, n (I/C)	Female, % (I/C)	Age ^a , Y (I/C)	Follow-up	ASA classification	Preanesthetic medication	Weight. Kg ^b (I/C)
Queiroz 2024	Brazil	Metoprolol (5 mg/20 mL)	102/105	52 / 58	43.6 (15.1) / 47.1 (17)	120 min after extubation	I, II or III	Intravenous midazolam (0.05 mg.kg ⁻¹)	72.6 (14.6) / 69.8 (12.8)
Mendonça 2023	Brazil	Esmolol (2 mg.kg ⁻¹)	45/45	53.3 / 64.4	49.2 (12.8) / 44.2 (15.1)	10 min after extubation	I, II or III	Intravenous midazolam (0.05 mg.kg ⁻¹)	68.9 (10.3) / 68.7 (9.7)
Alkaya 2014	USA	Esmolol (0.2 µg.kg ⁻¹ .min ⁻¹)	15/15	43.7 / 43.8	39.4 (10.7) / 45.0 (13.3)	10 min after extubation	I or II	Intravenous midazolam (0.05 mg.kg ⁻¹)	NA
Arar 2007	USA	Labetalol (0.15–0.3 mg.kg ⁻¹)	40/40	57.5 / 60	57.4 (8.0) / 59.2 (9.9)	NA	I	NA	70.0 (15.3) / 70.6 (10.2)
Hosseinzadeh 2013	Iran	Esmolol (infusion at 0.5 mg.kg ⁻¹ 4 min before the extubation. followed by an infusion at 0.15 mg.kg ⁻¹ .min ⁻¹ for 10 min after extubation)	30/30	50/70	46.0 (16.2) / 49.0 (17)	15 min after extubation	I or II	NA	73.2 (10.3) / 71.6 (12.0)
Chia 2004	Taiwan	Esmolol (0.2 µg.kg ⁻¹ .min ⁻¹)	49/48	NA	48.5 (30–79) / 49.8 (27–75) ^b	PO + 72 h	I or II	NA	57.4 (7.2) / 61.3 (10.6)
Grillo 2003	France	Esmolol (0.3 mg.kg ⁻¹ .min ⁻¹)	15/15	NA	52 (10) / 47 (15)	60 min after anesthesia with esmolol	I or II	NA	65 (10) / 68 (16)
O'Dwyer 1993	UK	Esmolol (500 ng.kg ⁻¹ over 1 min followed by 100 ng.kg ⁻¹ .min ⁻¹)	7/7	NA	59.7 (5) / 58.8 (3.5)	10 min after extubation	NA	Etomidate (fentanyl 5 µg.kg ⁻¹) and midazolam	74.4 (3) / 82.8 (5.6)
Kawaguchi. 2010	Japan	Landiolol (0.125 mg.kg ⁻¹ .min ⁻¹ followed by an infusion at 0.01–0.04 mg.kg ⁻¹ .min ⁻¹)	15/15	26.7/20	60 (10) / 59 (8)	10 min after extubation	NA	NA	58 (9) / 60 (9)
Elokda 2015	Arabi Saudita	Esmolol (1 mg.kg ⁻¹ over 30 s followed 100 µg.kg ⁻¹ .min ⁻¹)	50/50	55/60	60 (3) / 62 (4)	10 min after extubation	I or II	Bromazepam (3 mg) and ranitidine (150 mg)	82.6 (6) / 85 (10)
Kshama 2022	India	Esmolol (0.5 mg.kg ⁻¹ and 1 mg.kg ⁻¹)	40/20	15/40	39.3 (8.4) / 38.7 (11.9)	10 min after extubation	NA	NA	62.8 (9.3) / 61.3 (7.9)
Song 2021	China	Esmolol (0.5 mg.kg ⁻¹ and 1.0 mg.kg ⁻¹)	84/41	38/39	56 (10.9) / 56.9 (8.9)	5 min after extubation	I, II or III	NA	67.4 (9.7) / 70.9 (10.6)
Shetabi 2023	Iran	Labetalol (0.1 mg.kg ⁻¹ or 0.2 mg.kg ⁻¹)	48/24	58.3/79.2	31.8 (10.7) / 33 (14.7)	10 min after extubation	I or II	NA	72.0 (8.3) / 69.9 (9.8)
Dash 2023	India	Esmolol (1 mg.kg ⁻¹)	30/30	53.3/46.6	37.1 (12.0) / 38.9 (12.5)	30 min after extubation	I or II	NA	61.5 (11.4) / 65.4 (10.9)

Table 1 (Continued)

Study	Country	Intervention	Patients, n (I/C)	Female, % (I/C)	Age ^a , Y (I/C)	Follow-up	ASA classification	Preanesthetic medication	Weight. Kg (I/C)
Lim 2000	Singapore	Esmolol (500 $\mu\text{g} \cdot \text{kg}^{-1}$, followed by esmolol infusions at 100 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or 200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	24/12	45.8/66.7	NA	5 min after extubation	I or II	NA	NA
Maharjan 2005	Nepal	Propranolol (1 mg or 0.5 mg)	42/21	19.0/14.3	44.9 (15.8) / 35.8 (11.0)	PO + 6 h	I or II	Diazepam (5 mg), ranitidine (150 mg), and metoclopramide (10 mg)	56.9 (8.9) / 60.9 (9.9)
Morais 2020	Brazil	Esmolol (0.5 $\text{mg} \cdot \text{kg}^{-1}$ bolus followed by an infusion at 15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	20/20	85/85	35.8 (10.9) / 33.2 (8.7)	PO + 24 h	II or III	Dipyron (2 mg) and parecoxib (40 mg)	105.6 (20.2) / 109.8 (11.2)
Radwan 2016	Egypt	Labetalol (infusion in a rate of 0.5 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$)	25/25	44/37	44 (6) / 40 (11)	PO + 4 h	I or II	Ranitidine (50 mg), metoclopramide (10 mg), and dexamethasone (0.15 $\text{mg} \cdot \text{kg}^{-1}$)	80 (10) / 79 (11)
Sohn 1995	South Korea	Esmolol (1 $\text{mg} \cdot \text{kg}^{-1}$)	30/30	43.3/40	36.3 (15.1) / 39.4 (16.4)	4 min after extubation	I or II	Midazolam (0.05 $\text{mg} \cdot \text{kg}^{-1}$)	58.6 (6.9) / 58.5 (8.3)
Felding 1994	Denmark	Metoprolol (0.07 $\text{mg} \cdot \text{kg}^{-1}$)	10/10	NA	56 (10) / 54 (12)	PO + 180 min after extubation	NA	Diazepam (0.2 $\text{mg} \cdot \text{kg}^{-1}$)	NA
Velayutham 2020	India	Atenolol (50 mg)	25/25	24/32	39 (11) / 38 (7)	PO + 12 h	I, II or III	Diazepam (10 mg)	61 (7) / 63 (5)
Vandenberg 1997	Saudi Arabia	Esmolol (4 $\text{mg} \cdot \text{kg}^{-1}$)	20/20	45/50	68/64	NA	I, II or III	Temazepam (10 mg) VO	64/63
Unal 2008	Turkey	Esmolol (0.1 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or 0.2 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	30/15	46.7/53.3	49.2 (16.4) / 50.3 (12.2)	30 min after extubation	I or II	NA	165.8(9.3) / 77.5(9.3)
Ersin 2005	Turkey	Esmolol (bolus dose at 1.5 $\text{mg} \cdot \text{kg}^{-1}$ for 30 seconds)	15/15	60/60	41.7 (12.8) / 38.5 (12.2)	10 min after extubation	I or II	NA	72.5(11) / 68.7(13.3)
Yoruglolu 1999	Turkey	Metoprolol (0.02 $\text{mg} \cdot \text{kg}^{-1}$)	15/15	NA	46 (6) / 41 (6)	5 min after extubation	I or II	Intramuscular atropine and pethidine	77(9) / 70(8)
Amar 1991	USA	Labetalol (infusion at 0.15 $\text{mg} \cdot \text{kg}^{-1}$ intravenous, followed by 0.25–0.3 $\text{mg} \cdot \text{kg}^{-1}$ every 3 min as needed)	8/8	100/100	43.9 (6.7) / 35.9 (10.3)	NA	I	Intravenous midazolam (0.5 mg)	70.0 (15.3) / 70.6 (10.2)

Table 1 (Continued)

Study	Country	Intervention	Patients, n (I/C)	Female, % (I/C)	Age ^a , Y (I/C)	Follow-up	ASA classification	Preanesthetic medication	Weight. Kg ^a (I/C)
Zhang 2017	China	Esmolol (continuous perfusion at a dose of 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during operation and infusion at a dose of 0.3 $\text{mg} \cdot \text{kg}^{-1}$ 3 min before tracheal intubation)	30/30	40/43.3	69.3 (5.4) / 66.1 (12.5)	30 min after extubation	I or II	NA	60.7(6.7) / 60.3(7.2)
Kurian 2008	United Kingdom	Esmolol (infusion of esmolol at 0-300 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	31/37	19.3/10.8	60.2 (6.7) / 61.1 (7.5)	180 min after extubation	NA	Lorazepam (2–3 mg)	82.5 (13.8) / 86.0 (14.1)
Nam 1996	South Korea	Esmolol (infusion at 1.5 $\text{mg} \cdot \text{kg}^{-1}$ 2 min before tracheal extubation)	20/20	NA	31.2 (9.6) / 33.2 (7.5)	5 min after extubation	I	Glycopyrrolate (0.2 mg) and intramuscular trifluoromazine HCL (15 mg)	69.1(9.4) / 64.8(8.5)
Zeng 2007	China	Esmolol (bolus at 0.5 $\text{mg} \cdot \text{kg}^{-1}$ for 5 min. followed by an infusion at 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until the end of surgery)	20/20	75/65	NA	5 min after extubation	I or II	NA	58(13)/57(10)
Lee 2010	South Korea	Esmolol (bolus at 1.0 $\text{mg} \cdot \text{kg}^{-1}$ followed by an infusion of 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	30/30	60/53.3	61.7 (6.3) / 58.6 (6.6)	PO + 24 h	I or II	Glycopyrrolate (0.2 mg)	161.8 (6.6) / 160.4 (6.3)

Study	Type of general anesthesia	Height ^a , cm (I/C)	SBP ^a , mmHg (I/C)	DBP ^a , mmHg (I/C)	MAP ^a , mmHg (I/C)	MHR ^a , beats/min (I/C)	Duration of surgery ^a , min (I/C)	Duration of anesthesia ^a , min (I/C)
Queiroz 2024	Balanced anesthesia or total intravenous anesthesia	NA	NA	NA	94.2/94.3	82.4/79.2	NA	NA
Mendonça 2023	Balanced anesthesia	165 (10) / 167 (10)	110.4 (15.1) / 108.0 (13.4)	NA	NA	77.8 (10.1) / 74.3 (10.2)	NA	NA
Alkaya 2014	Balanced anesthesia	NA	137/137	85/85	105/105	80/85	213.5 (78.2) / 220.9 (101.8)	203.7 (78.5) / 211.1 (102.4)
Arar 2007	Balanced anesthesia	NA	142.6 (15.5) / 140.7 (19.5)	76.4 (11.3) / 74.0 (10.7)	98.0 (10.2) / 96.6 (10.9)	98.8 (10.5) / 96.7 (13.0)	288 (43.6) / 298.2 (45.6)	314.1 (47.2) / 329.6 (50.9)
Hosseinzadeh 2013	Balanced anesthesia	NA	17.6 (109.7) / 14.9 (115.6)	13.5 (69.7) / 13.1 (72.0)	NA	NA	184.6 (42.7) / 186.6 (62.6)	NA

Table 1 (Continued)

Study	Type of general anesthesia	Height ^c , cm (I/C)	SBP ^c , mmHg (I/C)	DBP ^c , mmHg (I/C)	MAP ^c , mmHg (I/C)	MHR ^c , beats/ min (I/C)	Duration of surgery ^c , min (I/C)	Duration of anesthesia ^c , min (I/C)
Chia 2004	Balanced anesthesia	153.6 (5.4) / 155.6 (4.4)	NA	NA	87.6 (6.1) / 84.8 (6.1)	74.2 (7.8) / 71.6 (9.2)	122 (54) / 138 (50)	NA
Grillo 2003	Balanced anesthesia	165 (6) / 168 (6)	NA	NA	95 (12) / 88 (15)	76 (9) / 77 (7)	NA	NA
O'Dwyer 1993	Balanced anesthesia	NA	141 (10) / 135 (6.2)	77.8 (4.1) / 79.8 (3)	74.3 (5.2) / 89 (7.1)	70 (2) / 69 (3.7)	NA	NA
Elokda. 2015	Balanced anesthesia	165 (10) /166 (8)	130/131	73.0/71.5	62.1/30.0	81.2 / 81.2	60 (5) / 61.6 (8)	65.8 (7) / 63 (8)
Kshama 2022	Balanced anesthesia	158.55 (7.3) / 157.7 (6.6)	136.7 (14.7) / 130 (16.2)	86.0 (10.1) / 82.5 (12.9)	103.7 (12.2) / 98.8 (13.2)	96.3 (14) / 90.4 (10.1)	NA	NA
Vandenberg 1997	Balanced anesthesia	NA	NA	NA	NA	NA	34/24	NA
Song 2021	Balanced anesthesia	168.4 (7.4) / 170.0 (8.9)	NA	NA	104.9 (12.1) / 105.8 (11.3)	52.7 (21.4) / 57.3 (24.2)	216.3 (35.0) / 212.8 (26.1)	NA
Shetabi 2023	Balanced anesthesia	NA	121.2 (9.6) / 122 (8.8)	74.1 (6.2) / 77 (9.6)	104.9 (4.0) / 106.2 (8.6)	80.8 (9.2) / 85.6 (6.4)	NA	NA
Dash 2023	Balanced anesthesia	164.8 (9.9) / 163.8 (9.4)	119.9 (8.0) / 122.5 (11.0)	77.7 (6.0) / 75.7 (8.5)	91.7 (4.7) / 91.3 (6.4)	71.8 (4.5) / 75.2 (7.7)	NA	NA
Lim 2000	Balanced anesthesia	NA	131.5 (18.4) / 129 (15)	NA	NA	71.4 (7.4) / 70.8 (11.9)	NA	NA
Maharjan 2005	Balanced anesthesia	NA	NA	NA	102.5 (10.5) / 106.6 (12.7)	89.4 (23.4) / 95.6 (12.3)	72.7 (32.8) / 80.5 (19.2)	81.4 (30.3) / 91.4 (22.2)
Morais 2020	Balanced anesthesia	161.9 (8.0) / 164.4 (9.7)	NA	NA	NA	NA	104.3 (14.3) / 112.8 (12.5)	NA
Radwan 2016	Balanced anesthesia	170 (8) / 164 (6)	NA	NA	NA	NA	247 (74) / 243 (69)	NA
Sohn 1995	Balanced anesthesia	58.5 (8.3) / 58.6 (6.9)	125.2(15.76) / 130.25(19.2)	NA	NA	77.5 (9.1) / 82.7 (13.9)	175.5 (84.9) / 182.8 (73.1)	NA
Felding 1994	Balanced anesthesia	NA	NA	NA	91 (17) / 93 (15)	NA	NA	NA
Velayutham 2020	Balanced anesthesia	NA	NA	NA	92 (6) / 94 (5)	83 (9) / 81 (8)	NA	NA
Unal 2008	Balanced anesthesia	165.8 (9.3) / 168.3 (8.2)	NA	NA	124.2 (20.1) / 117.4 (9.4)	82.5 (9.9) / 89.4 (10.0)	134.1 (74.5) / 121.2 (62.8)	156.9 (74.4) / 145.5 (69.4)
Ersin 2005	Balanced anesthesia	NA	132.1 (9.2) / 133.1 (10.4)	78.3 (7.6) / 79 (6.1)	NA	87.2 (7.2) / 86.8 (8.2)	119.4 (5.7) / 117.4 (7.8)	137.7 (6.1) / 136.2 (8.1)

Table 1 (Continued)

Study	Type of general anesthesia	Height ^a , cm (I/C)	SBP ^a , mmHg (I/C)	DBP ^a , mmHg (I/C)	MAP ^a , mmHg (I/C)	MHR ^a , beats/ min (I/C)	Duration of surgery ^a , min (I/C)	Duration of anesthesia ^a , min (I/C)
Yoruglolu 1999	Balanced anesthesia	NA	126.96 (12.38) / 122.83 (12.38)	75.3 (10) / 85 (12.1)	89.7 (8.1) / 91.1 (8.4)	92.2 (7.4) / 88.7 (10.5)	88 (12) / 92 (6)	NA
Lee 2010	Total intravenous anesthesia	161.8 (6.6) / 160.4 (6.3)	NA	NA	89.8 (13.3) / 90.2 (12.2)	71.6 (9.5) / 72.3 (11.2)	42.5 (4.8) / 41.3 (7.2)	57.5 (2.8) / 56.3 (5.2)
Amar 1991	Balanced anesthesia	NA	130.23/124.20	70.5/68.9	93.9 / 91.6	82.4 / 81.3	120.0 (29.7) / 125.6 (50.0)	160.6 (34.0) / 159.4 (51.8)
Zhang 2017	Total intravenous anesthesia	NA	NA	NA	92.7 (7.7) / 95.9 (6.4)	76.8 (6.5) / 73.7 (8.2)	180.5 (16.5) / 180.3 (18.2)	NA
Kurian 2008	Balanced or Total Intrave- nous anesthesia	170.7 (8.0) / 173.1 (7.8)	119.56 (4.15) / 122.57 (3.53)	NA	NA	86.1 (2.2) / 95.3 (2.2)	NA	NA
Nam 1996	Balanced anesthesia	NA	121 (7.1) / 118 (6.2)	77 (5.3) / 78 (4.3)	NA	79 (7.3) / 80 (5.9)	45 (15.6) / 38 (20.4)	NA
Zeng 2007	Total intravenous anesthesia	159 (8) / 160 (9)	112.9 (9) / 117.8 (9.6)	77.5 (7.1) / 78.4 (8)	NA	85 (6.6) / 88.8 (10.3)	88 (3) / 74 (28)	102 (31) / 92 (3)
Kawaguchi 2010	Balanced anesthesia	159 (7)/ 162 (7)	148 (19) / 150 (19)	85 (11) / 85 (10)	63.6 (6.3) / 64.1 (9.1)	72 (11) / 70 (14)	228 (82) / 251 (108)	309 (83) / 331 (126)

^a Mean (standard deviation).^b Mean (range); n, Number; y, Years; kg, Kilogram; mg, Miligram; n, Nanogram; μ , Microgram; mL, Militer; min: minutes; h, Hours; s, Seconds; ASA, American Society of Anesthesiologists classification; I/C, Intervention group/Control group; PO, Post-Operatory; NA, Not Available.^c Mean (standard deviation); cm, Centimeter; mmHg, Millimeter of mercury; min, Minutes; I/C, Intervention group/Control group; NA, Not Available; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; HR, Heart Rate.

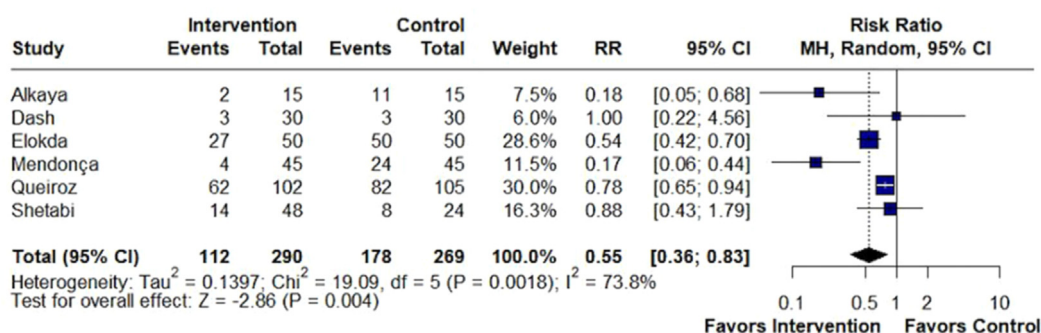


Figure 2 Beta-blockers significantly reduced the incidence of cough in patients undergoing tracheal extubation compared with placebo. MH, Mantel-Haenszel; CI, Confidence Interval.

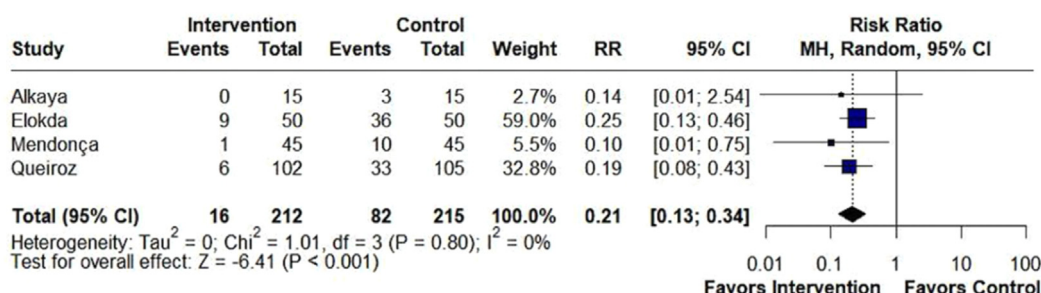


Figure 3 Beta-blockers significantly reduced the incidence of moderate/severe cough in patients undergoing tracheal extubation compared with placebo. MH, Mantel-Haenszel; CI, Confidence Interval.

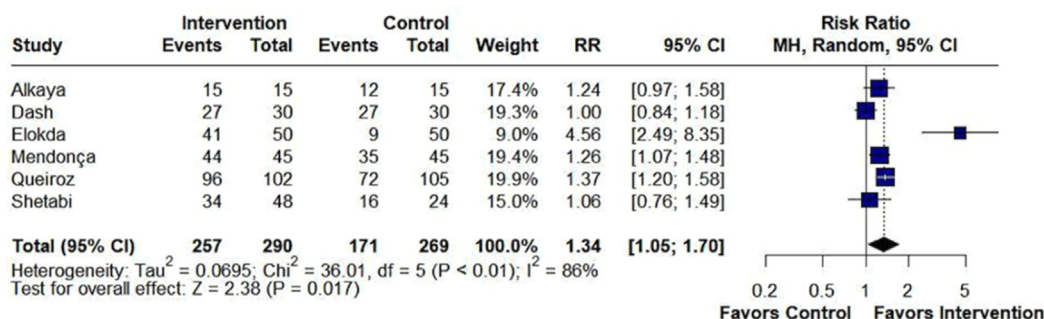


Figure 4 Beta-blockers significantly increased the incidence of no/mild cough in patients undergoing tracheal extubation. MH, Mantel-Haenszel; CI, Confidence Interval.

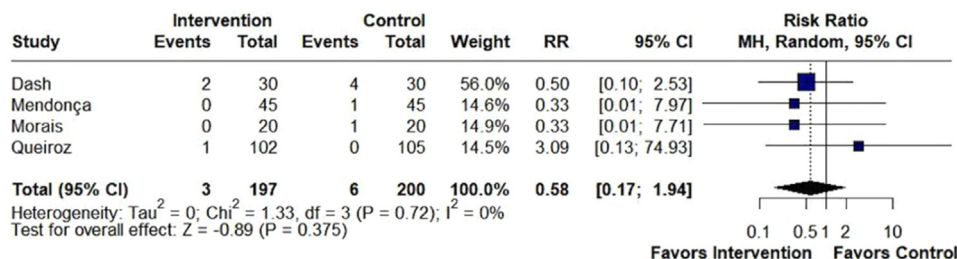


Figure 5 There was no difference between groups in the incidence of bronchospasm in patients undergoing tracheal extubation. MH, Mantel-Haenszel; CI, Confidence Interval.

considered at moderate risk of bias. Twelve studies presented moderate bias in bias from randomization process, nine in bias due to deviations from intended interventions, three in bias in measurement of the outcomes and twenty-two in the selection of the reported result. Nine RCTs were

considered at high risk of bias and the others were classified as low risk of bias.

Publication bias was investigated for the outcomes of SBP, DBP, MAP, and MHR for every subgroup that had at least 10 studies (Supplementary Fig. 11). The visual inspection of

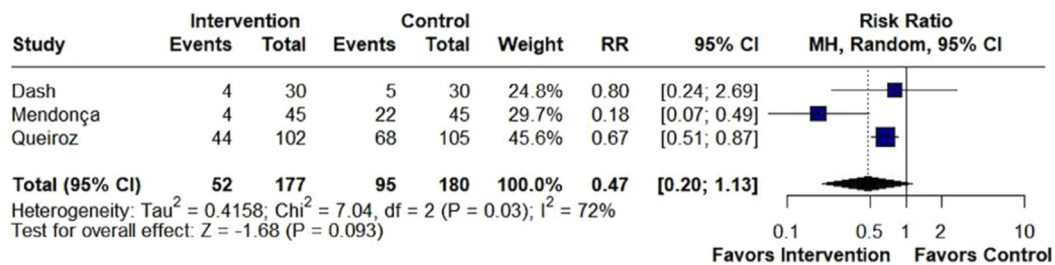


Figure 6 There was no difference between groups in the incidence of bucking in patients undergoing tracheal extubation. MH, Mantel-Haenszel; CI, Confidence Interval.

the funnel plots with enhanced contour showed no visible signs of the “small study effect” with symmetrical funnel plots for most of the subgroups. This finding is corroborated by the results of the Egger’s Test (Supplementary Table 6).

Discussion

In this systematic review and meta-analysis of 31 RCTs, including 1,803 patients, we compared the use of beta-blockers with placebo in preventing complications in patients undergoing tracheal extubation. The main findings from the pooled analysis were: (1) The use of beta-blockers was associated with a reduced risk and intensity of cough; (2) The risk of hypertension, tachycardia and nausea or vomiting was significantly reduced in the beta-blocker group compared with the placebo group.

About 70% of patients undergoing procedures requiring general anesthesia and tracheal intubation may experience coughing.⁵¹ Coughing during tracheal extubation can lead to significant complications for patients, such as hypertension, tachycardia, myocardial ischemia, surgical bleeding, laryngospasm, bronchospasm, and increased intracranial and intraocular pressure.⁵ There is evidence that beta-blocker reduce the incidence of coughing in these patients by blocking ion channels, particularly voltage-dependent sodium channels and L-type calcium channels, in unmyelinated C fibers of vagal afferent nerves that innervate the upper airway and proximal bronchioles, thereby reducing excitability during procedures such as orotracheal intubation and extubation.^{52–55}

This meta-analysis showed that approximately 11% of patients receiving beta-blocker experienced significant coughing (moderate/severe intensity) during the peri-extubation period, compared to an incidence of 36% among those who received placebo. These findings are consistent with individual data from RCTs that investigated the incidence of this outcome in the population in question.^{12,18,33} Thus, it is evident that beta-blockers may be a promising alternative to prevent cough and reduce complications during tracheal extubation.

Moreover, the effectiveness of beta-blockers in reducing bucking can be attributed to their ability to block the effects of the sympathetic nervous system, specifically by antagonizing beta-adrenergic receptors.⁵⁶ This inhibition leads to a decrease in heart rate, blood pressure, and overall sympathetic output, which can calm reflexive responses, such as coughing or bucking, particularly during anesthesia or intubation.⁵⁷ By reducing the surge of adrenaline, beta-blockers helps stabilize cardiovascular and respiratory functions, minimizing involuntary

movements that could disrupt medical procedures.⁵⁸ Queiroz (2024)³³ and Mendonça (2023)¹² showed significantly lower risk in the beta-blocker group, and Dash (2023)¹⁷ indicated lower risk but with no statistical difference, suggesting that the intervention may be effective in reducing bucking. However, the limited number of patients led to Queiroz’s (2024)³³ results dominating the analysis. Thus, more RCTs evaluating bucking are needed to reach a more robust conclusion.

Furthermore, cardioselective beta-blockers, such as metoprolol, block the β_1 -adrenoceptor, leaving the β_2 -adrenoceptor free in the adrenergic response during extubation, which may help to prevent bronchospasm in this group of patients.⁵⁹ Our data indicated a slight trend toward a reduction in the incidence of bronchospasm in the beta-blocker group, with a 48% lower relative risk of this complication in patients who received beta-blocker compared to those who received placebo. However, neither the individual studies^{12,17,30,33} nor the pooled analysis results were statistically significant. Therefore, it is crucial to re-emphasize the need for more RCTs evaluating the impact of these medications on the incidence and severity of bronchospasm.

Additionally, the manipulation of the larynx and pharynx during the transition from “asleep” to “awake” at tracheal extubation triggers exaggerated neural responses, leading to hemodynamic instability (hypertension and tachycardia) in 10%–50% of cases.^{60,61} In this meta-analysis, beta-blockers reduced the incidence of tachycardia and hypertension by 80% and 72%, respectively compared with placebo. This effect may be expected due to the inhibitory action of beta-blockers on adrenergic receptors, which counteracts the effects of sympathetic activation during acute stress, mitigating cardiovascular alterations and nocive events in tracheal extubation.^{11,12}

Patients undergoing tracheal extubation experience a 10%–30% increase in blood pressure and MHR lasting approximately 5–15 minutes, which can precipitate various cardiovascular events such as myocardial infarction, arrhythmias, cerebral edema, hemorrhage, and other complications.^{17,61} Therefore, the use of beta-blockers emerges as a potential intervention to stabilize these hemodynamic parameters, given their ability to mitigate exaggerated sympathetic responses.^{11,12} This meta-analysis revealed a statistically significant reduction in SBP, DBP, MHR, and MAP with the use of beta-blocker compared to placebo, with the most pronounced mean differences observed within the first 5 minutes post-extubation. Recent RCTs have also demonstrated significant reductions in these hemodynamic outcomes in the intervention group compared to placebo, further supporting the findings of this analysis.^{12,62} Future studies should focus on optimizing beta-blocker dosing

protocols to maximize efficacy while minimizing adverse effects, particularly in patients with preexisting cardiovascular conditions.

The mechanism underlying nausea or vomiting potentially involves the blockade of adrenergic receptors, which can disrupt the cascade of events leading to these adverse events. In some cases, the use of short-acting beta-blockers, such as esmolol, has been shown to effectively manage the hemodynamic fluctuations that can occur during extubation, thereby potentially reducing the incidence of nausea or vomiting.⁵⁶ Our results revealed a 40% reduction in the incidence of nausea and vomiting in patients undergoing tracheal extubation who received beta-blocker compared to those given a placebo. These findings are consistent with previous research, which suggests that beta-blockers can positively impact in incidence of nausea or vomiting.⁵⁷

Our study has some important limitations. Despite our findings showing that beta-blockers effectively reduce hemodynamic complications during extubation, previous studies have reported conflicting results. These discrepancies can be attributed to variations in study design, such as differences in drug dosage, timing of administration (pre-anesthesia vs. intraoperative), and the type of beta-blockers used (e.g., cardioselective vs. non-cardioselective). Additionally, the type of surgery and patient characteristics, such as comorbidities, may affect responses to beta-blockers, with more complex surgeries or patients with cardiovascular issues showing different results. The diversity in anesthetic protocols, particularly the use of pre-anesthetic medications, may also influence outcomes, either masking or enhancing the effects of beta-blockers. Furthermore, discrepancies in outcome measurement, particularly the distinction between “cough” and “bucking” could lead to inconsistent findings. Furthermore, it is important to emphasize that post-extubation cough may also be a consequence of airway manipulation during intubation, which, therefore, represents a limitation in establishing a definitive causal relationship between the observed events. Finally, the primary outcomes were under reported with a greater focus on secondary outcomes. Additionally, the use of univariate meta-regression may have limited the assessment of heterogeneity, as it does not account for potential interactions between covariates. Unfortunately, this limitation exceeds the capacity of the present study to resolve or accurately address. To resolve these inconsistencies, future studies should standardize beta-blocker protocols, patient inclusion criteria, and outcome definitions to provide clearer insights into their hemodynamic benefits during extubation.

Conclusion

This meta-analysis compared beta-blockers with placebo in 1,803 patients who underwent tracheal extubation. Beta-blockers were associated with lower cough intensity, nausea or vomiting, hypertension, and tachycardia compared with placebo, without significant side effects. These results suggest the potential protective use of these drugs during the peri-extubation period. In this context, their use may be considered to prevent cardiorespiratory responses upon emergence from anesthesia.

This meta-analysis supports the use of beta-blockers to mitigate peri-extubation hemodynamic and airway

complications. Further research should focus on defining optimal dosing regimens and identifying patient subgroups who would benefit most from this intervention.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest and Funding

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. There was no financial support for this research.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.bjane.2025.844659](https://doi.org/10.1016/j.bjane.2025.844659).

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SHORT COMMUNICATION

Variable ventilation with two PEEP levels (BiPEEP) in patients with acute respiratory distress syndrome: a pilot study[☆]

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Patients with Acute Respiratory Distress Syndrome (ARDS) commonly require Mechanical Ventilation (MV) to restore or maintain adequate oxygenation when critically ill. Previous studies suggest that Variable Ventilation (VV) is able to induce pulmonary recruitment,¹ and especially to prevent alveolar derecruitment.^{2,3} This mechanism is of paramount importance in ARDS, when the major challenge is not just recruiting the injured lung, but maintaining recruitment when protective mechanical ventilation is advocated. No previous study has used PEEP as a variability variable. Based on experimental studies,²⁻⁴ our hypothesis is that in the short term, VV with two PEEP levels (BiPEEP) would result in comparable gas exchange, better respiratory mechanics without changing hemodynamics.

We performed a crossover randomized clinical trial with return. This study was reviewed and approved by the Research Ethics Committee of the Santa Casa Hospital Complex of Porto Alegre (registry 928.,427) and is registered in the Brazilian Registry of Clinical Trials (RBR-5bb65v).

The study population included 8 patients admitted to the intensive care unit who met the following inclusion criteria:

age > 18 years, mechanical ventilation > 24 hours, diffuse infiltrate on chest X-Ray, arterial partial Pressure of Oxygen/Fraction of Inspired Oxygen (PaO₂/FiO₂) ratio 100–300 mmHg. Patients were excluded if they presented lung emphysema, pneumothorax or lung barotrauma of any kind, and chest drain. Informed consent was obtained from family members or caregivers as soon as they were eligible for the study. Clinical data, current therapy and diagnosis were reviewed and obtained through the ICU electronic data system.

During the three-hour study period, all patients were ventilated with Conventional Ventilation (CV) and variable ventilation with two levels of PEEP (BiPEEP) for one hour each, alternating them randomly. Randomization was performed on the website www.randomization.com, with a 1:1 allocation frequency using blocks of 4 patients to determine the sequence of MV modes (BiPEEP - CV - BiPEEP or CV - BiPEEP - CV). The assessor was not blinded to the randomization of the ventilation mode. Data analysis was performed by a blinded assessor. This methodology was used to assess whether the effects of ventilatory modes return to their baseline patterns.

All patients were monitored with continuous electrocardiogram, pulse oximetry, and invasive blood pressure. Once the intensivist in charge and the investigators considered it safe, each patient was transferred to the study ventilator

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and a 10-minute period was given prior to baseline measurements. After baseline measurements, the MV sequence was randomized and patients were ventilated for three consecutive hours, with a 10-minute wash-out period, alternating CV with BiPEEP, one hour in each ventilatory mode. The study was discontinued if any of the following criteria were present: increased Heart Rate (HR) > 20% compared to baseline, or < 50 bpm, or > 130 bpm; increase in MAP > 20% from

baseline, or < 60 mmHg, or > 110 mmHg. After the study protocol was completed, patients were returned to the previous mechanical ventilator. Ventilatory mechanics and arterial blood gas were obtained at the beginning and end of each of the three ventilation periods. The Intermed 7 Plus[®] ventilator (CareFusion, São Paulo, Brazil) was used for both CV and BiPEEP modes. Both MV modes were performed in Pressure-Controlled Ventilation (PCV). The mechanical

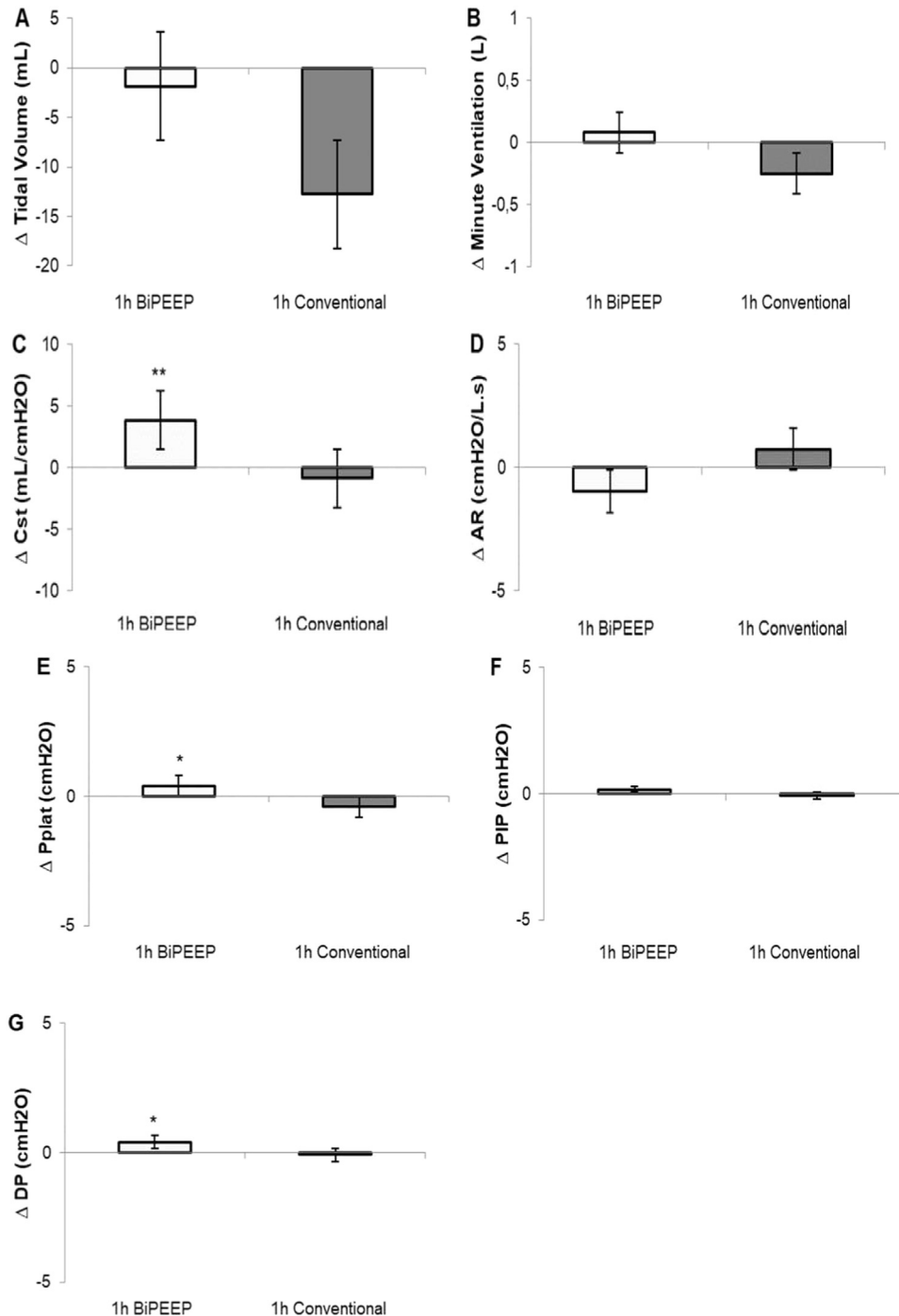


Figure 1 Respiratory mechanics. Respiratory mechanics after one hour of conventional and variable ventilation with BiPEEP. (A) Tidal Volume (VT); (B) Minute Ventilation (VMin.); (C) Static Compliance (Cst); (D) Airway Resistance (AR); (E) Plateau Pressure (Pplat); (F) Peak Pressure (PIP); (G) Driving Pressure (DP). Data are presented as baseline delta (Δ) difference between initial and final measurements. Values are showed as mean and standard error (* $p < 0.05$; ** $p < 0.001$).

ventilation was set to a VT of 6 mL.kg⁻¹ of predicted weight and a peak airway pressure $\leq$ 35 cm H₂O, respiratory rate of 20 breaths/min, inspiratory Time (Ti) of 1.0 second and 100% Inspired Oxygen Fraction (FiO₂). To perform ventilation with BiPEEP, the mechanical ventilator has an adjustment that allows the automatic elevation of PEEP: the baseline PEEP used in BiPEEP was 5 cm H₂O and it was automatically increased to 10 cm H₂O every four ventilatory cycles. PEEP switching was fully automated.

Data are presented as mean and standard error. The comparison between VC and BiPEEP was performed using ANOVA – Latin Square 2×3 to counteract the effects of patient variability over time, each ventilation in each patient was tested once each time. Thus, the baseline of the two types of ventilation (treatment) was analyzed in three periods of one hour (sequence). Therefore, baseline, treatment and sequence analyses are presented, in which the difference in the variables was verified according to the randomization of the treatment sequence. A Latin square is a design used in experiments in which each subject is measured in each treatment and changes in conditions need to be controlled. It is a design in which each treatment is assigned to each time period and to each subject an equal number of times. All tests were performed using the Statistical Package for the Social Sciences (version 19.0). Statistical significance was accepted with a $p < 0.05$. The data showed normal distribution.

All patients (4 men/4 women) were between 34 and 78 years of age, and PaO₂/FiO₂ on inclusion ranged from 119 to 204. All patients completed all phases and even if any data points were excluded, and all patients tolerated the intervention without protocol violations or adverse events.

Gas exchange and acid-base parameters did not differ between CV and BiPEEP. HR significantly decreased during BiPEEP. Initiating MV with CV significantly reduced MAP compared to BiPEEP. However, this change was not clinically significant and there was no need to interrupt the protocol.

Among the gas exchange, hemodynamic and acid-base balance variables, only SpO₂ showed carryover ($p = 0.025$).

Pressure level (Δ pressure) and Peak airway Pressure (PIP), as well as expiratory resistance, VT and minute ventilation did not differ between CV and BiPEEP. Static pulmonary compliance was significantly higher with BiPEEP, while Pplat and Driving Pressure (DP) increased compared to CV (Fig. 1A–G). Starting the MV sequence with BiPEEP significantly increased minute ventilation, Pplat, PIP, and DP compared to CV, possibly by the difference in PEEP values between ventilatory modes (Table 1). Among the respiratory mechanic parameters, minute ventilation showed carryover ($p = 0.020$).

This is the first pilot study with a clinical trial design with BiPEEP, to our knowledge. The main finding of the present study was that VV with BiPEEP appears to be safe and viable in patients with mild to moderate ARDS.

The use of VV in experimental ARDS models has shown a consistent improvement in arterial oxygenation, as well as respiratory mechanics.² In this study, gas exchange did not differ significantly between CV and BiPEEP. Our findings are similar to the study using variable support Pressure Ventilation (PSV) in 13 patients with mild to moderate acute hypoxemic respiratory failure,⁴ in which variable PSV was associated with better patient-ventilator synchrony and comparable levels of gas exchange. One possible explanation for the absence of significant gas exchange improvement may have been the relatively short time period in which BiPEEP was employed and thus improvement in lung compliance was not accompanied by a change in gas exchange. In fact, most studies that had positive results on arterial oxygenation applied VV over a period of 3–6 hours.^{2,5-7}

A preclinical study of VV with BiPEEP showed that PEEP variability did not cause new pulmonary and inflammatory structural changes.⁸ In the present study, BiPEEP triggered a significant improvement in static lung compliance, while increasing Pplat and DP. The increase in Pplat secondary to

Table 1 Respiratory mechanics.

	Basal		Sequence		p
	BiPEEP	Conventional	BiPEEP - Conventional - BiPEEP	Conventional - BiPEEP - Conventional	
VT (mL)	382.2±37.8	361.5±37.3	-7.50 (4.30)	-7.08 (3.93)	0.943
VMin (L)	8.2±1.8	8.4±1.8	0.13 (0.12)	-0.30 (0.30)	0.001 ^a
Cst (mL.cm ⁻¹ H ₂ O)	29.4±6.5	28.5±8.2	0.88 (1.2)	2.15 (1.32)	0.479
Rva (cm H ₂ O/L.s)	26.0±7.9	25.4±8.3	-0.37 (0.43)	0.15 (0.39)	0.364
Pplat (cm H ₂ O)	18.1±3.6	18.2±4.0	0.41 (0.29)	-0.41 (0.27)	0.039 ^a
PIP (cm H ₂ O)	19.7±3.3	20.2±4.2	0.33 (0.20)	-0.25 (0.21)	0.050 ^a
DP (cm H ₂ O)	13.1±3.6	13.2±4.0	0.41 (0.29)	-0.41 (0.27)	0.039 ^a

Sequence data is expressed as delta: the difference between the initial and final measurement.

Baseline Conventional Ventilation – Pressure Controlled Ventilation (PCV) with PEEP 5 cm H₂O, tidal volume of 6 mL.kg⁻¹ of predicted weight and a peak airway pressure $\leq$ 35 cm H₂O, respiratory rate of 20 breaths/min, inspiratory time (Ti) of 1.0 second and 100% inspired oxygen fraction (FiO₂).

Baseline BiPEEP – Pressure Controlled Ventilation (PCV) with PEEP 5 cm H₂O and every four ventilatory cycles it was automatically increased to 10 cm H₂O, tidal volume of 6 mL.kg⁻¹ of predicted weight and a peak airway pressure $\leq$ 35 cm H₂O, respiratory rate of 20 breaths/min, inspiratory Time (Ti) of 1.0 second and 100% inspired oxygen fraction (FiO₂).

VT, Tidal Volume; VMin, Minute Ventilation; Cst, Static Compliance; Rva, Airway Resistance; Pplat, Plateau Pressure; PIP, Peak Pressure; DP, Driving Pressure. Values are presented as mean and standard deviation.

The comparison between conventional ventilation and BiPEEP was performed using ANOVA of repeated measures (Latin Square 2×3).

^a p-value based on the sequence.

PEEP elevation during VV, although statistically significant, remained below the safety limit for protective ventilation in ARDS. In addition, we found no significant difference in VT during ventilation with CV and BiPEEP. The increase in Pplat and DP above safe values are related to increased lung injury caused by mechanical ventilation, and DP is also related to increased risk of mortality.⁵

Interestingly, one group of investigators showed that the type of variability, natural (recorded from subjects) or random (randomly generated by a computer), seems not to play a major role in the effects of VV.⁹

They concluded that the percentage, but not the type of respiratory variability is crucial to VV success. In the present study, PEEP was varied every four respiratory cycles, yielding a variability of approximately 25%. The variability employed in this study is closely related to the physiological variability of the respiratory system.¹⁰ A possible limitation of the study is related to the ventilation time at each mode (1-hour) that may not have been sufficient to capture significant changes in gas exchange. Furthermore, it was not possible to evaluate outcomes such as recruitment or long-term oxygenation, lack of imaging (e.g., lung ultrasound or computed tomography) or biomarkers to assess derecruitment. No correction for multiple comparisons was performed, which may be considered a limitation of the study. The small sample size limits the generalizability of the results as well as the assessment of feasibility and safety. No power calculations were performed due to the pilot nature of the study. Therefore, larger studies with longer observation periods are needed to validate the present results.

Compared to CV, VV with BiPEEP in a clinical setting, improved static pulmonary compliance with comparable levels of gas exchange. In the short term, BiPEEP appears to be safe and feasible in patients with mild to moderate ARDS.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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SHORT COMMUNICATION

Perioperative microcirculatory monitoring using handheld video microscopy: a proof-of-concept observation

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Microcirculation exhibits a remarkable capacity for adaptation to its cellular surroundings and can autoregulate, thus preserving a constant blood flow that remains unaffected by alterations in systemic blood pressure under physiological conditions.¹ In this context, hemodynamic coherence plays a crucial role in maintaining homeostasis and supporting proper organ function.² Nevertheless, various factors may lead to disconnection between macro- and microcirculation and subsequent tissue damage.³ Notably, microcirculatory alterations can occur even when global systemic hemodynamics are preserved, resulting in the functional decoupling of macrocirculation and microcirculation, a phenomenon also known as “hemodynamic incoherence”.² These factors include sepsis or shock, alterations in blood viscosity and shear stress, and iatrogenic injury.⁴

The perioperative setting is complex, involving diverse patient populations, varying illness severity, and differences in surgical and anesthetic approaches. In the intraoperative phase, various factors, such as surgical procedures, bleeding, low body temperature, and the administration of anesthetics and vasopressors, can lead to changes in the microcirculation and reduced blood flow to tissues. However, improvements in systemic hemodynamic parameters may not always lead to a corresponding improvement in microcirculatory flow.² The apparent effects of anesthesia on the vascular system may cause changes in microcirculation

and, consequently, in tissue parameters and oxygenation. The induction of anesthesia, for example, diminishes capillary red blood cell flow, as evidenced by reduced red blood cell velocity and a smaller proportion of perfused vessels, while simultaneously increasing capillary vessel density.⁵ In this context, the key objective of perioperative microcirculation monitoring is to guide therapeutic interventions that specifically target the microcirculation. Nevertheless, there is a lack of specific studies on point-of-care (bedside) testing with minimally invasive devices, such as handheld cameras, in patients under general anesthesia.

The objective of this preliminary study was to establish the feasibility of the sublingual microcirculation monitoring method in a clinical surgical scenario under general anesthesia. Accordingly, we report the case of a patient who underwent laparoscopic cholecystectomy surgery. In this study, we evaluated the microcirculation status using a real-time, noninvasive, point-of-care microcirculatory imaging technique. More precisely, we utilized an incident dark field camera (Fig. 1) to examine sublingual microcirculation. The Cytocam-IDF is a third-generation handheld microscope that features a high-density pixel-based imaging chip and a short-pulsed illumination source controlled by a computerized system. This system allows serial measurements to be made without the need to refocus, an important feature compared with previous generation devices that require time-consuming manual adjustment of focus controls. The IDF-Cytocam imaging system allows a direct and noninvasive view of microvessels up to a diameter of 50 μm , including

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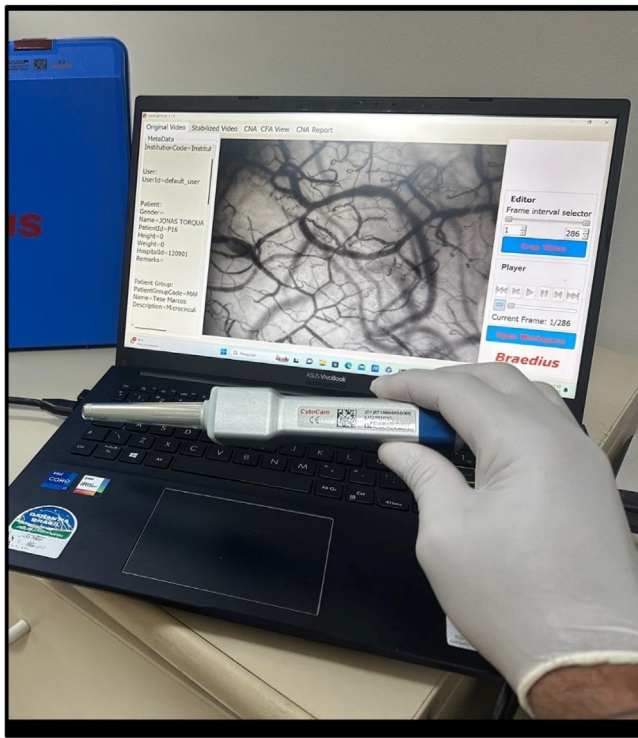


Figure 1 The CytoCam-IDF handheld video microscope used for the visualization of microcirculatory parameters in our work, which is based on Incident Dark Field (IDF) technology. The CytoCam is a pen-like device and is held as such. The low weight of the device (120 g) minimizes pressure artifact problems that were present in earlier heavy devices. The camera is connected to a device controller based on a medical-grade computer or a suitable portable device, such as a laptop or tablet, which is used for image storage (from <https://braedius-medical.com/products/>).

arterioles, capillaries, and venules.⁶ Importantly, the validity of this imaging technique has been previously established and documented.^{7,8} Moreover, previous research has shown that the sublingual region has a uniform spatial distribution, allowing the assessment of several microvascular parameters, such as total and functional vascular density.⁹ The video microscopic assessment of mucosal sublingual microcirculation has been considered a sensitive indicator of systemic microvascular alterations, including circulatory failure.¹⁰

Given that the handheld device is still in experimental use and could be established as a perioperative monitoring device, the recommendation is to test it only in patients with steady cardiovascular systems. This specific case seeks to demonstrate the viability of the approach for monitoring perioperative microcirculation without assuming a positive postoperative result. The subject read and signed a specific informed consent form concerning the present publication.

It is important to note that our study is a proof-of-concept investigation. As a small-scale, preliminary study, its primary goal is to assess the feasibility and viability of a new methodology for evaluating tissue perfusion by examining systemic microcirculation using handheld camera-based technology. Additionally, this study could help identify

potential challenges or limitations associated with this methodology.

A 74-year-old female (BMI 32.0 kg.m⁻²) with hypertension and hypothyroidism (ASAI) was diagnosed with cholelithiasis and underwent uneventful laparoscopic cholecystectomy. The patient did not present any pre-existing vascular condition that could alter microcirculatory responses. Moreover, the patient did not present any sign of dehydration and received IV infusion of 5 mL.kg⁻¹.h⁻¹ ringer lactate during surgery (total 1,200 mL). The anesthetic technique utilized was balanced veno-inhalation. Induction was performed with 240 µg fentanyl (3 µg.kg⁻¹), 160 mg propofol (2 mg.kg⁻¹), 50 mg rocuronium (0.6 mg.kg⁻¹) and 120 mg lidocaine (1.5 mg.kg⁻¹). After orotracheal intubation with a videolaryngoscope (King Vision, King Systems, Noblesville, USA), anesthesia was maintained by sevoflurane (0.5 MAC), an inhalational anesthetic agent, plus dexmedetomidine infusion (0.5 µg.kg⁻¹.h⁻¹) initiated at the beginning of induction.

Anesthetic depth was considered as maintained when the Bispectral Index™ (BISTM) monitoring system values (Medtronic, Watford, United Kingdom) remained between 40 and 60 and when the mean arterial pressure and heart rate remained within 10%–20% of their preoperative values; the use of vasopressors was not necessary during surgery. The total anesthesia and surgical times were 180 and 135 minutes, respectively. Neuromuscular blockade was reversed at the end of the surgical procedure through intravenous administration of sugammadex (2 mg.kg⁻¹).

A microcirculatory evaluation was performed four times: before anesthesia induction (time 1), 45 min (time 2), and 60 min (time 3) after starting dexmedetomidine infusion, and after anesthetic recovery (time 4). The peak effect of the continuous infusion of dexmedetomidine is known to occur between 45 and 60 minutes. At each time evaluation, we took five videos (5-sec duration) for further analysis. In the laboratory, we selected the top three video quality scores and extracted some microcirculation data using CytoCam Tools 3.1.4 software (Braedius Medical, Huizen, The Netherlands). We consider that the most clinically relevant microvascular parameters are total number of capillary vessels and capillary vessel density, because they reflect tissue perfusion and oxygenation. The key microcirculatory parameters obtained are summarized in Table 1.

We found a marked increase in the total capillary number, capillary vessel density and total number of microvessels at times 2 and 3, and a slighter increase in the number and density of noncapillary vessels. Some prospective randomized studies with the same microcirculation evaluation methods reported similar results under dexmedetomidine infusion.^{11,12} In these studies, researchers included patients undergoing on-pump coronary artery bypass graft and compared the single use of dexmedetomidine, or in association with propofol infusion, and found improved sublingual microcirculation indices. An interesting point is that cardiopulmonary bypass is known to impair sublingual microcirculation.¹¹

The primary focus of hemodynamic monitoring in conventional practice is directed toward the assessment of macrocirculatory parameters. This paper indicates the potential for a new procedure better suited for intraoperative situations. However, it is important to note that the macrocirculatory profile may not accurately represent tissue perfusion. Even with adequate blood pressure and cardiac output,

Table 1 Analysis of key microvascular parameters in the sublingual region, assessed using a handheld Incident Dark-Field (IDF) imaging camera at baseline, 45 and 60 minutes after the initiation of dexmedetomidine infusion, and following anesthetic recovery. The evaluation included capillary vessels (diameter: 6–16 μm), non-capillary vessels (diameter: 16–50 μm), and the total vessel count, encompassing all microvessels with a diameter of less than 50 μm .

	Baseline	45 min	60 min	Recovery
Total number of capillary vessels (n)	686	888	1058	563
Capillary vessel density ($\text{mm} \cdot \text{mm}^{-2}$)	11.42	13.74	17.28	10.77
Total number of noncapillary vessels (n)	89	97	112	73
Noncapillary vessel density ($\text{mm} \cdot \text{mm}^{-2}$)	1.09	1.08	1.47	1.16
Total vessel number (n)	764	972	1170	636

peripheral tissues may experience insufficient perfusion, leading to ischemia and organ dysfunction.²

Conversely, confirming the condition of the microcirculatory environment may help prevent unwarranted increases in the use of vasopressor medications and other measures that could cause injury in individuals with low blood pressure. A better understanding of perioperative microcirculatory dynamics could improve individualized hemodynamic management and optimize patient outcomes.

Although handheld vital microscopes remain experimental for systemic microcirculatory assessment, they hold potential for future integration into routine perioperative monitoring by physicians and nurse specialists. Cytocam, the handheld microcamera used in the present study, enables the visualization of microcirculation at the tissue level, which is crucial during anesthesia. By providing clear, real-time imaging of capillaries, arterioles, and venules, it could help anesthesiologists closely monitor the effects of anesthesia on circulation and oxygenation with great precision. Additionally, it aids in assessing tissue perfusion and detecting early signs of ischemia or hypoxia, both of which are critical to monitor during anesthesia, particularly in high-risk surgeries or for patients with complex medical conditions.

In terms of research applications, Cytocam can be employed in clinical studies to examine how anesthesia impacts vascular function, especially in relation to specific anesthetic agents or techniques. It can also be used to explore how various confounding factors (e.g., age, comorbidities) influence the response to anesthesia, paving the way for the development of more personalized, patient-specific anesthetic protocols. Furthermore, in drug testing and evaluation for pharmaceutical studies, Cytocam offers a valuable tool for assessing the effects of new anesthetic or vasodilatory drugs on microvascular function, thus supporting the creation of safer and more effective anesthetic agents.

Limitations of the study

This study is a proof-of-concept report, with the primary goal of presenting a novel and useful device for use in the perioperative period. As this is a single case, it does not include a control group. These data will be presented in a clinical trial when available. This case involves a routine cholecystectomy, a procedure that typically has favorable postoperative outcomes. The key value of this report lies in demonstrating the effectiveness of the method in evaluating systemic microcirculation in a patient with a stable cardiovascular status.

While Cytocam offers significant advantages in monitoring microcirculation during anesthesia, its use is also associated with several limitations and challenges, including technical issues, reproducibility concerns, and constraints in broader clinical applicability. Image quality can be affected by factors such as camera positioning and patient movement, potentially leading to blurry or distorted visuals, especially if the device is not held correctly or if the patient moves during the procedure.

Effective use of Cytocam requires technical proficiency, as anesthesiologists and medical staff must be trained to operate the device properly and accurately interpret the images. Additionally, the cost of acquiring and maintaining Cytocam can be expensive, particularly for smaller hospitals or health-care facilities with limited budgets, potentially restricting its use to well-funded academic or research institutions.

In conclusion, further clinical validation and improvements in availability will be crucial for the widespread adoption of Cytocam in anesthesia and other medical fields. In this regard, a clinical study is currently underway within our research team to evaluate the systemic microvascular effects of continuous dexmedetomidine infusion, using Cytocam in the sublingual region, in low-risk patients undergoing laparoscopic cholecystectomy. The present proof-of-concept report demonstrates that monitoring systemic microcirculation using a handheld, microcamera-based technology in the sublingual region is feasible during surgery under general anesthesia. The observed increases in the number and density of microvessels during anesthesia maintenance, followed by a return to baseline values during recovery, suggest that this technology is reliable for evaluating microvascular perfusion during anesthetic procedures.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

RML and ET contributed to the conception and design of the study and to the analysis and interpretation of the data; and RML and ET were involved in the drafting of the manuscript and the literature review. Both authors have approved the final version to be published and are publicly responsible for its content.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

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LETTER TO THE EDITOR

Sex-specific considerations in chronic osteoarthritis pain research: commentary on Pacheco-Barrios et al. (2025)



KEYWORDS

Sex-specific;
Osteoarthritis;
Pain

Dear Editor,

We read with great interest the article titled “*The role of biological sex in neurophysiological associations of patients with chronic osteoarthritis pain: a prospective cross-sectional study*” by Pacheco-Barrios et al. (2025),¹ recently published in *The Brazilian Journal of Anesthesiology*. This study addressed a crucial gap by examining whether biological sex influences the associations between clinical, pain-related, and neurophysiological outcomes in patients with chronic knee Osteoarthritis (OA) pain. While the research makes a significant contribution to the field, several methodological and interpretive issues merit further discussion.

Despite aiming to explore the role of biological sex, the sample was notably unbalanced, with a predominance of female participants ($n = 94$) compared to males ($n = 19$) out of a total of 113. As noted by Bartley and Fillingim,² uneven sex distribution in pain research may obscure actual sex-based differences, possibly leading to overgeneralizations or misinterpretations. Future research should aim for more representative sampling to enable robust sex-based comparisons.

The study was conducted at a single rehabilitation hospital in Brazil with a relatively small sample size. This constrains the generalizability of findings to broader populations with diverse demographic and clinical characteristics. As Witowich et al.³ have emphasized, sex-disaggregated analyses require adequately powered and representative samples to yield valid conclusions about sex differences in biomedical research.

The authors suggest that the predominance of postmenopausal women may have mitigated hormonal variability.

However, the absence of specific data on menopausal status, hormone replacement therapy, or gonadal hormone levels is a critical limitation. Without controlling for these variables, it becomes difficult to distinguish between biological sex effects and hormonal influences. This is particularly relevant when analyzing neurophysiological metrics such as EEG or TMS, which are sensitive to fluctuations in estrogen and testosterone. Prior work has shown that the menstrual cycle significantly impacts stress response circuitry and neural activation in women.⁴

The recent study by McCabe et al. (2025)⁵ highlights sex-specific diagnostic models for knee osteoarthritis and the importance of incorporating individualized variables, including hormonal history. Their findings support a broader framework that integrates not just demographics and clinical variables but also neurophysiological biomarkers such as quantitative EEG and functional MRI to better understand the central mechanisms underlying pain. Furthermore, expanding such models to diverse global cohorts and targeting early interventions may enhance diagnostic accuracy, clinical equity, and prevention strategies.

In conclusion, while Pacheco-Barrios et al. make a commendable effort to address sex-related differences in chronic osteoarthritis pain, we urge future studies to prioritize balanced sampling, consider hormonal status variables, and explore integrative models that reflect both peripheral and central contributors to pain. Such efforts will advance the path toward truly personalized pain management.

After a few attempts to contact the original authors of the study, we did not receive a response.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Isra Panhwer: Contributed to critique on lack of hormonal and menopausal data.

Anzalna Bashir: Contributed to critique on uneven sex distribution and limited sample size, and she is also our corresponding author.

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Safia Panhwer: Contributed to emphasize the importance of incorporating sex-specific diagnostic models in chronic pain research to improve clinical relevance.

Kalpana Singh: Revised the entire article and modified it.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

The venous sympathetic block in chronic pain practice: absence of evidence, presence of use?



Dear Editor,

In Brazil, the practice commonly referred to as “Venous Sympathetic Block” (BSV in Portuguese) has gained recognition among anesthesiologists, pain specialists, and patients with chronic pain. This technique involves the slow systemic intravenous infusion of a pharmacological mixture and is entirely distinct from the regional venous sympathetic block described in existing literature. The typical combination administered includes variable doses of ketamine (0.2–1 mg.kg⁻¹), dexmedetomidine (0.5–1 mcg.kg⁻¹) or clonidine, lidocaine (1–3 mg.kg⁻¹), and magnesium sulfate (1–3 g). Importantly, this systemic intravenous method and its precise pharmacological composition lack a standardized definition in indexed scientific literature, leading to significant variability based on practitioner preferences.

Although the relationship between ketamine and the autonomic nervous system has been the focus of studies with counterintuitive findings, it is appropriate to begin with a note of perplexity: the notion of suppressing sympathetic activity using a pharmacological agent classically classified as sympathomimetic.¹⁻³ Perhaps this is merely a semantic diversion – a lateral digression that, while intellectually valid, lies outside the central scope of this text: how is the routinely employed BSV described and supported in the scientific literature?

On May 23, 2025, a search on PubMed for the term “*bloqueio simpático venoso*” (Portuguese) yielded no results.

On the same date, a search for the English term “venous sympathetic block” returned 275 publications. However, a title-by-title review revealed that none of them pertained to the clinical practice in question. The alternative term “sympathetic venous block” produced 438 results, which were likewise irrelevant to the subject of this analysis.

A Google search in Portuguese finally led to a case report published in the Annals of the Scientific Week of the *Faculdade de Medicina de Campos* (2024), titled “Venous sympathetic block in the treatment of chronic pain in a patient with fibromyalgia: a case report”. The brief text defines venous sympathetic block as “slow infusion of drugs such as lidocaine, ketamine, and clonidine via the venous route. This procedure

promotes, in addition to sympathetic blockade, anesthesia of vascular endothelial nerve endings, analgesia, and vasodilation, leading to pain reduction or elimination” (free translation from Portuguese into English). Unfortunately, the document does not include any references.⁴

Considering that the above case report dates from 2024 and that BSV has been performed for several years, it is not possible to infer that current clinical practice originates from or is based on this document.

In keeping with our zeitgeist, a search was conducted using the Investigate feature of ChatGPT Pro and identified publications relevant to regional venous sympathetic block, as well as the same case report previously mentioned.⁴

In the widely used Unified Supplementary Health Terminology Table (TUSS), we find the entry “Sympathetic block via venous route” (code 31602177).⁵ However, this item is listed under a subgroup of surgical and invasive procedures, which suggests it refers to regional venous sympathetic block. Yet once again, there is no bibliography that clearly defines the concept underlying the code, nor is there any explanatory text indicating to which therapies the code does or does not apply.

In light of the absence of relevant entries in indexed databases and the limitations of this brief exploratory investigation, we encourage academic centers to investigate the physiological rationale, safety profile, and effectiveness of this practice through clinical trials and pharmacological analyses.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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