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Detecting incomplete paravertebral block in real time during total mastectomy: when the ANI signals insufficient analgesia

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Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Between oceans and deserts: fluid balance and outcomes after liver transplantation

After liver transplantation, fluids can damage as much as they can save. In a recent fascicle of the *Brazilian Journal of Anesthesiology,* Lobo et al.[1] show that both too little and too much fluid are lethal. In a prospective cohort of OLT patients, mortality followed a striking U-shaped curve: those with negative or markedly positive balances fared far worse than those in between. Their message is unambiguous: in transplantation, as in critical care more broadly, both oceans and deserts of fluids are deadly.

The history of intravenous fluid therapy has always swung between extremes. The Swan-Ganz catheter, introduced in 1970,[2] promised precise hemodynamic guidance. It inspired attempts to achieve supranormal oxygen delivery, often by aggressive resuscitation, but these failed to improve outcomes[3] and later meta-analyses cast doubt on its benefit.[4] Decades later, Early Goal-Directed Therapy (EGDT) generated similar enthusiasm after Rivers et al. reported improved survival in septic shock.[5] Yet when rigorously tested in ProCESS, ARISE, and ProMISe, protocolized EGDT, when tested in multicenter RCTs proved no better than contemporary best practice.[6–8] Once again, rigid formulas collapsed under scrutiny.

Surgery has told the same story. Restrictive strategies were promoted to reduce pulmonary edema, but the RELIEF trial showed that excess restriction caused kidney injury, while liberal regimens increased pulmonary complications.[9] More recently, de Castro et al.[10] confirmed that cumulative perioperative balances independently predict pulmonary complications after abdominal surgery. The lesson is simple and consistent: rigid doctrines of fluid therapy — whether liberal or restrictive — carry harm.

Lobo et al.[1] extend this lesson into liver transplantation. Their prospective study of 73 patients stratified postoperative balances into negative, intermediate, and high. Mortality rates were 18.2%, 8.6%, and 40.5%, respectively. A positive balance on day one was independently associated with death from graft failure. This pattern is not incidental but pathophysiologically coherent. Excess fluids lead to interstitial edema, hepatic congestion, pulmonary dysfunction, renal venous hypertension, and intra-abdominal hypertension.[1,9–12,15] These mechanisms suffocate the graft and impair recovery. Conversely, inadequate resuscitation starves the graft of blood flow, risking ischemic dysfunction.[1,5,8,10] As Wise, Nasa, and Malbrain[12] have argued, "fluid accumulation syndrome" results not only from deliberate resuscitation but also from insidious "fluid creep." Together, these data explain why both extremes oceans and deserts of fluids harm. Balance is not nuance, it is survival.

These findings align with — rather than prove — broader evidence: in abdominal surgery, de Castro et al.[10] documented how positive balances drive pulmonary complications, echoing RELIEF.[9] In sepsis, large trials[5–8] and systematic reviews[11,15] have shown that excess fluids worsen outcomes. Malbrain and colleagues[15] emphasized the downstream consequences of edema and intra-abdominal hypertension. Across settings — OLT,[1] surgery,[9,10] sepsis,[5–8,11] and perioperative critical care[12,15] — the message converges: oceans and deserts of fluids are equally dangerous.

Likewise important is the identification of the SOFA-liver subscore as an independent predictor of mortality in OLT.[1] Each one-point increase nearly doubled the risk of death. This reinforces what prior transplant studies demonstrated:[13,14] global scores alone are insufficient. Organ-specific monitoring matters. In this population, SOFA-liver is not optional — it is indispensable. It offers a simple, bedside measure of graft function that should be integrated into every postoperative assessment, complementing biochemical markers and hemodynamic indices.[12–15]

The clinical implications are clear. First, fluids must be prescribed as diagnostic interventions, never as routine maintenance. Each bolus must be justified and reassessed. Second, multimodal monitoring should replace blind reliance on fluid balances. Bedside examination, capillary refill time, ultrasound-derived indices, lactate clearance, and organ scores provide a multidimensional view.[11–15] Third, timing is critical. Early resuscitation may require positive balances, but persistence of overload by 72 hours — as shown by Lobo et al.[1] — is

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a harbinger of death. At that point, clinicians must stop giving and start taking: diuretics and renal replacement therapy should be deployed to evacuate excess.

The four-phase ROSE framework — resuscitation, optimization, stabilization, evacuation — provides a useful model.[12,15] In OLT, these phases must progress rapidly. Too often, resuscitation bleeds into days of unnecessary accumulation. As Wise et al.[12] argue, failure to de-escalate is one of the main drivers of fluid-related harm. Malbrain et al.[15] remind us that unchecked edema and intra-abdominal hypertension compromise multiple organs. For transplant patients, the cost is even higher: edema and congestion may doom the graft itself.

Critics may point to the limitations of Lobo et al.'s study: single-center design, modest sample, and absolute rather than weight-adjusted balances.[1] These are valid. But the coherence of their findings with evidence from sepsis,[5–8,11] abdominal surgery,[9,10] and perioperative reviews[12,15] makes the message compelling. What we need now is not more observational studies but multicenter validation and randomized trials. These should test individualized, physiology-guided strategies, integrating multimodal monitoring, SOFA-liver, and structured de-escalation. The inclusion of bedside tools such as venous congestion ultrasound (VExUS)[12] could refine assessment of when to evacuate.

The broader story of fluid therapy is one of repeated corrections: from Swan-Ganz optimism[2–4] to EGDT collapse,[5–8] from surgical restriction[9] to recognition of balance.[10–12,15] Lobo et al.[1] remind us that in liver transplantation, this lesson is immediate and unforgiving. Their study shows that excess fluids kill, restriction kills, and only balance saves. For clinicians, the practical message is unavoidable: prescribe fluids as carefully as drugs, abandon rigid doctrines, and personalize therapy to phase, physiology, and organ function.

For the scientific community, the challenge is clear. Future trials must abandon the tired question of "restrictive versus liberal." That debate is obsolete. The real question is how to personalize fluid therapy — to integrate multimodal monitoring, SOFA-liver, and structured de-escalation into everyday practice.

For anesthesiologists and intensivists, this is not optional. The findings of Lobo et al.[1] demand change. Both oceans and deserts of fluids harm. Balance is not nuance — it is survival.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used CHATGPT in order to review language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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EDITORIAL

Therapeutic misconceptions: the protective role of the perioperative team

Informed research consent, by participants or their legal guardian, is a vital cornerstone of medical ethics, upholding patient autonomy and protecting research participants.[1] However, ethical conduct by researchers in obtaining signed consent, including interactions between researchers and their patients, and in case of minors or other vulnerable groups, also their families and/or guardians, is vital to ensure that the research participant is not only educated about the research, but also fully comprehends the information as it pertains to them including interventions, possible risks and benefits as well as handling of their personal data and if applicable, collection and storage of samples. Only then can the participants make a voluntary, truly informed decision to participate without coercion or undue influence from outside.

Patients, particularly minors, undergoing surgical procedures represent a vulnerable patient population who may experience a significant power imbalance with their treating clinical team, who are often also the research team, which could influence their decision to participate. The perioperative period has been highlighted by patients and their families as a stressful time with high levels of anxiety,[2,3] which can lead to a stress-induced decline in a patient's rational comprehension.[4] Emotional and cognitive distress, coupled with the hope for a cure or relief from their underlying illness, for which they are undergoing surgery, can increase the risk of a patient and/or, their families and/or guardians attributing a stronger personal benefit to the research than is really the case. The emotional desire for a positive outcome, a cure or simply symptom improvement can hinder full understanding of the research and make it even more difficult for patients to appreciate where standard clinical care ends and research begins. Patients and/or their families may also not comprehend that, in a randomized controlled trial, they may be assigned to a placebo and assume they will receive the active intervention if they participate.

Patients and/or their families may have an inappropriate belief, that their participation in research is primarily to provide an individual therapeutic benefit to them rather than to generate new knowledge for the benefit of future patients; this is called therapeutic misconception.[5,6] The incidence of therapeutic misconception is assumed to be 50%–75%[7] and it undermines the validity of any informed consent.

Causes of therapeutic misconceptions

Generally, the cognitive frames between researchers and patients/families differ fundamentally. The researcher's mindset is scientific and objective, focused on answering a research question and generating new knowledge. In contrast, the patient's cognitive frame is deeply personal, focusing on their individual health problems and outcomes, leading to a misinterpretation of study information. Simply adding more information to the informed consent documents is unlikely to mitigate this risk; it might exacerbate the overload.[8]

Therapeutic misconception is more likely when informed consent is performed by a person who holds dual roles, such as the treating physician and the study investigator.[1,9] This is particularly important for patients with chronic diseases who are reliant on a long-term good patient-physician relationship and, therefore, might be particularly disinclined to decline a suggestion by their treating physician but instead feel obliged to consent to research. What steps can researchers take to mitigate the risk of therapeutic misconceptions by potential study participants and their families?

Role of patient and public involvement

Patient and Public Involvement (PPI) also known as Consumer and Community Involvement (CCI) plays a vital role. It strengthens not only the acceptability of treatments, but it also improves trial design and the consenting process by taking patient/public preferences, values, as well as their concerns into consideration.[10] Careful study design and wording of information and consent forms in close collaboration with

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patients and community members will improve the readability of patient documents, thereby enabling a better understanding of the research as well as reducing the risk of therapeutic misconceptions. For pediatric patients, it is important that there is not only a parent/guardian information sheet but also an age-appropriate child and/or young adult information sheet, which has been developed in collaboration with consumers of all ages to ensure readability. When age-appropriate, assent should be sought from all children for the intervention in addition to parental consent.

Role of all perioperative team members

Anesthesiologists and other members of the perioperative team can play a critical role in minimizing the risks of therapeutic misconceptions and avoiding blurring of the lines between routine clinical care and research. As a vital foundation of good clinical research practice, there should be a focus on two-way communication around the research, rather than an over-reliance on the written informed consent process and the signing of the forms. Good communication may include plain language, visual aids or interactive media. The researcher should ensure, through conversation and questioning, that patients and if applicable their families/guardians understand what they are consenting to. Incorporating a teach back approach during the research consent process may help to reduce the risk of therapeutic misconception.

Dual roles as researchers and clinicians for the same patient should be avoided, if possible, to prevent subtle, even subconscious, coercion of patients into participation through the (direct or indirect) suggestion that participation is part of their personalized medical care. Not appreciating or failing to correct a perception that participation in the research is (in most cases) not part of a patient's personalized medical care is also problematic. An independent, well-trained consent provider may significantly reduce these risks. Dual roles can be even more problematic if there is no clear delineation between research and routine clinical care. Is the suggested treatment or intervention "cutting-edge" clinical care or research? In some cases, such as oncology, it may be difficult even for members of the Ethics Committee or clinical colleagues to determine where routine clinical care ends and research begins, let alone for the patient and their family. Clear delineation is crucial by highlighting both pathways, including deviations from any national and/or international standards, in ethics applications and to all patients and their families.

This is where the close working relationship between all perioperative disciplines is advantageous: perioperative clinicians usually have a very close working relationship with their multi-disciplinary colleagues. We share the care of our patients, we regularly discuss perioperative management plans, we learn from each other in theatre and often discuss treatment options or cases. We are one team caring for the patient. While we certainly do not have the same specialist understanding of other perioperative specialties, physicians of all perioperative craft groups often have a deep insight into what is standard of care for certain patient groups. It is important that we use this knowledge to question when we are unsure whether the lines between clinical routine care and research may have been blurred in our craft group or others.

At the time of sign-in to theatre, all surgical/interventional consents are checked by the anesthesiologist before inducing anesthesia. This check should be performed in an environment where the patient and/or their family/guardian feels comfortable asking questions without time pressure, fear of reprisal or jeopardizing their care. It is good clinical practice to not only check the signature is in the right place and the form in date but to also check the correct understanding of the patient and/or their carer/guardian about the procedure and to ensure all relevant questions have been answered. The same principle should apply to any consent to participate in perioperative research. Does the patient truly understand what they have consented to and what the research entails? Do they understand any differences from routine clinical care? In our institution, we have a huddle before the start of each operating list, where all patients and their management are discussed, including any participation in research within the current perioperative visit. To aid this, the research teams must provide a copy of the signed consent sheet plus the participant information form and an institutional document which is a brief description (one paragraph) of the study interventions/observations highlighting the duration of participation and potential implications on clinical care e.g., side effects, drug interactions. Such an approach provides opportunities for perioperative colleagues to be made aware of the research, to remind everyone of any study requirements and any potential therapeutic misconceptions. Peer-to-peer collaboration and feedback can help to improve perioperative communication and ensure that all research processes, including consent, are transparent and that all information is understood.

Furthermore, this is not only good clinical practice ensuring patient safety, and high-quality data collection in an ethical environment, but it is, in our experience, also a good starting point for further conversations (after the case in the break room), to discuss the research and to brainstorm further ideas to be explored. It spreads the word beyond just academic colleagues and supports an academic culture in everyday clinical practice.

Such an open and transparent system must include protections for any clinicians who speak up about potential therapeutic misconceptions. Speaking up for safety is not always easy and/or safe.[11,12] Chief investigators are often senior figures within the hospital who commonly have significant institutional support. Hierarchical structures may further complicate speaking up, particularly when institutions are fearful of a powerful perpetrator or wary of potential negative media. This may lead to institutional silence or inaction, leaving the problem unresolved. This can lead to the normalization of questionable or unethical behavior, leading to a decline in overall institutional culture and possibly to moral distress or moral injury of staff involved.[13] So how should we speak up? This very much depends on the situation, the players involved and the urgency to speak up (e.g., is there a risk for immediate patient harm?). In our experience, there is no one-size-fits-all approach. If oneself is not sure about the intervention, a good starting point would be to speak directly in a non-judgmental manner with a member of the research team in a quiet environment. A friendly request seeking further information about the

planned intervention and/or the rationale can start the conversation. This allows the colleague to give further background information and explain their reasoning, which most of the time will resolve the problem. Similarly, if there is any suspicion that the patient and their family may be at risk for a therapeutic misconception, simply highlighting the fact of a potential misunderstanding on the part of the patient/family to the colleagues involved, and asking them to clarify with the patient and/or their family is most often received with gratitude. The great majority of clinicians try their very best to give their patients a true picture of the planned research interventions. However, if this non-confrontational approach is not received in a positive way and/or there may be the potential for direct patient harm, reporting lines should be used to escalate the situation.

In conclusion, therapeutic misconceptions are unfortunately not uncommon in clinical research; however, in the perioperative environment, we can leverage a higher degree of peer feedback and control to optimize our communication and consent processes for clinical research. We must also ensure that any staff who speak up about potential therapeutic misconceptions are kept safe and protected.

Declaration of competing interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Analgesia nociception index as a tool to assess the effectiveness of paravertebral block in total mastectomy: a prospective cohort study

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Abstract

Background: Single-injection Paravertebral Block (PVB) is commonly used for analgesia in major breast surgery; however, its sensory effectiveness may be variable. This study investigated whether intraoperative changes in the Analgesia Nociception Index (ANI) are associated with PVB effectiveness.

Methods: This prospective observational study included 100 women scheduled for total mastectomy. A single-injection PVB was performed preoperatively under ultrasound guidance at the T3 level. Sensory testing was performed from T1 to T10, but block effectiveness was evaluated in the surgical field (T2–T6). PVBs were classified as effective (complete loss of cold sensation in all T2–T6 dermatomes) or incomplete (partial cold sensation in this range). ANI variations, intraoperative remifentanil consumption, postoperative pain scores, and morphine use were compared.

Results: Ninety-three patients were analyzed. PVB was effective in 75% and incomplete in 25%. The mean ANI variation was significantly greater in the effective group (+1.4 $\pm$ 10.3) compared to the incomplete group (-11.0 $\pm$ 7.1), with a mean difference of 12.4 (95% CI: 8.8 to 16.0; $p < 0.0001$). Remifentanil consumption was higher in the incomplete group (0.072 $\pm$ 0.018 $\mu g.kg^{-1}.min^{-1}$ vs. 0.054 $\pm$ 0.008 $\mu g.kg^{-1}.min^{-1}$), mean difference 0.018 (95% CI: 0.010 to 0.026; $p < 0.0001$). Pain score and morphine consumption were significantly higher for patients with incomplete PVB.

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Conclusion: In this observational study, a significant decrease in ANI values following skin dissection was associated with incomplete PVB. Early ANI monitoring may help identify insufficient regional block during total mastectomy, thus guiding intraoperative analgesic adjustment to improve patient comfort.

Introduction

Paravertebral Block (PVB) is a regional anesthesia technique in which a Local Anesthetic (LA) is injected into the thoracic paravertebral space between the costovertebral ligament and the pleura.[1,2] Ultrasound guidance has improved the safety and efficacy of this block, allowing a single injection with a larger volume, now commonly used for major breast surgery.[3] The breast is primarily innervated by thoracic dermatomes T2 to T6, and axillary dissection requires T2 coverage. However, the metameric spread of single-level PVB remains unpredictable, as demonstrated by an imaging study.[4]

PVB is usually performed just before induction or under General Anesthesia (GA), but its efficacy is difficult to assess intraoperatively. Traditional hemodynamic parameters such as blood pressure or heart rate are insufficiently sensitive to detect nociceptive responses reliably.[5-7] This makes real-time detection of incomplete blocks challenging. The Analgesia Nociception Index (ANI) (Metrodoloris Medical Systems, Lille, France) was developed to monitor the balance between nociception and antinociception during GA. It is based on heart rate variability analysis and reflects parasympathetic nervous system tone. ANI values tend to decrease in response to nociceptive stimuli and remain stable when analgesia is adequate.[8,9] Several studies have shown promising results for ANI as a nociceptive monitor during general anesthesia.

We hypothesized that variations in ANI following skin dissection could reflect the efficacy of preoperative PVB in patients undergoing total mastectomy under general anesthesia. The objective of this prospective observational study was to assess whether a decrease in ANI values shortly after skin incision is associated with insufficient regional analgesia.

Methods

Study setting

This prospective observational study was conducted at the Cancer Center (Institut de Cancérologie de Lorraine, Nancy, France) from May 2, 2019, to June 26, 2020. The objective was to determine whether a decrease in the mean ANI (ANIm) 1 minute after the end of the initial skin dissection could be associated with an incomplete or ineffective PVB. An incomplete or ineffective PVB was defined by the presence of cold sensation during an ice cube test between thoracic metameric levels T2 and T6. This study was approved by the French National Ethics Committee of the SUD-EST IV (Approval n° ID-RCB: 2019-A00121-56) and registered in ClinicalTrials.gov (NCT03832920). Informed consent was obtained from all participants.

The sample size was determined a priori using PASS software (version 08.0.15, NCSS, USA). Based on previous literature, we assumed a 10% incidence of incomplete or ineffective PVB.[4,10,11] Detecting this failure rate with a two-sided α risk of 5% and a statistical power of 80% (β = 0.20) required 100 patients. This calculation was based on a one-sample proportion test against the null hypothesis of a negligible failure rate (< 2%). The target sample size was also consistent with previous studies evaluating regional anesthesia efficacy in breast surgery.

Study participants

We enrolled 100 women aged 18 to 85 years with an American Society of Anesthesiologists (ASA) Physical Status of 1–3 and a body mass index between 17 and 30 kg.m^{-2}, scheduled for total mastectomy with or without sentinel lymph node dissection.

Exclusion criteria included: male sex, any interaction with physiological sinus rhythm (chronic arrhythmias, pacemaker, heart transplantation), any treatment affecting parasympathetic or sympathetic tone (e.g., beta blockers, intraoperative atropine administration), diabetes, neuromuscular disease, pregnancy, breastfeeding, bilateral surgery, chronic pain, LA allergy, infection at puncture site, immediate breast reconstruction, or protocol non-compliance.

Study protocol

No premedication was administered. An intravenous catheter was inserted into the forearm or hand for medication delivery. In the preoperative holding area of the Post-Anesthesia Care Unit (PACU), standard monitoring including electrocardiography, pulse oximetry, and non-invasive blood pressure monitoring was placed. Patients were positioned in the lateral decubitus position on the contralateral side of the surgery. The third thoracic paravertebral space (T3) was scanned using ultrasound (Model Sonosite SII, Fujifilm, Paris, France) with a 15–6 MHz linear probe. The T3 paravertebral level was identified using an ultrasound-guided anatomical counting method. The transducer was placed in a parasagittal orientation starting at the first rib, and ribs were counted caudally to locate the third rib. Then, the probe was placed in the transverse plane against the spinal process. Under aseptic conditions, a 22-gauge, 80 mm needle (SonoTAP, Pajunk, Germany) was advanced in an in-plane direction toward the paravertebral space, positioned immediately above the pleura and below the costotransverse ligament. The needle's position was confirmed by observing the descent of the pleura upon injecting 2–3 mL of saline for

hydrolocalization. Subsequently, 20 mL of 7.5 mg.mL^{-1} ropivacaine was injected, with intermittent negative aspiration tests conducted every 5 mL. All paravertebral blocks were performed by senior anesthesiologists with over five years of experience in regional anesthesia in breast surgery and proficiency in ultrasound-guided thoracic blocks (more than 100 PVB performed). This consistency in operator experience aimed to reduce variability in block performance and ensure a reproducible technique across all patients.

Patients were transferred to the operating room no sooner than 15 minutes later. Just before GA induction, a thin ice block was used to conduct the cold sensation test on the anterior chest (results of the test blinded to the rest of the team). Patients were provided with a reference cold sensation on a thigh prior to measurement. The peak sensory cephalad and caudal block levels were assessed, and the number of blocked dermatomes was recorded. Routine monitoring was conducted in accordance with French guidelines. Intraoperative monitoring included the Bispectral Index (BIS) (Medtronic, Paris, France) and the Analgesia/Nociception Index (ANI, MDoloris Medical Systems, France). The ANI is a 0–100 index, with higher values (above 50) indicating a predominant parasympathetic tone (comfort, analgesia, adequate nociception/antinociception balance), while lower values (below 50) suggest a predominant sympathetic tone (stress, pain, inadequate nociception/antinociception balance). Dynamic variations in ANI provide better predictive performance for hemodynamic reactivity during GA than static values.[9] The ANI monitor continuously displays the instant ANI (ANIi), calculated every second, and the mean ANI (ANIm), which reflects the average ANI over the previous three minutes. In this study, ANIm was selected as the primary outcome measure because it provides a more stable and reliable indicator of autonomic balance during general anesthesia, by smoothing out transient fluctuations unrelated to nociceptive events. This makes it particularly suitable for assessing the nociceptive response to a defined surgical stimulus such as skin dissection. In the event of block failure (e.g., persistent cold sensation in all dermatomes T2–T6), intraoperative analgesia was managed using increased remifentanil infusion and, if necessary, rescue boluses of morphine in the PACU.

Anesthesia was induced and maintained with intravenous propofol targeting an effect concentration according to the BIS index (40–60) and intravenous remifentanil targeting an effect-site concentration based on the ANI index (over 60) and any nociceptive hemodynamic responses detected by the anesthesiologist. The choice of neuromuscular blocking agent, airway management, and lung ventilation strategies were left to the discretion of the anesthesiologist. Antiemetic prophylaxis and postoperative pain management included an intravenous injection of 8 mg dexamethasone at induction and paracetamol (1,000 mg) and ketoprofen (1 mg.kg^{-1}) administered at the end of the mastectomy before skin closure. The laryngeal mask or tracheal tube was removed in the operating room after reversal of neuromuscular blockade, when needed, and patients were then transferred to the PACU.

Postoperative pain intensity at rest was assessed upon arrival in the PACU and every 30 minutes using a Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain). If a VAS score exceeded 3/10 at rest in the PACU, intravenous morphine was titrated using 1 mg boluses every 5 minutes (with no limit in the dosage). Patients remained in the PACU until the Aldrete score was above 9/10 and the VAS score was less than or equal to 3. If nausea or vomiting occurred, 4 mg IV ondansetron was administered, followed by 1.25 mg IV droleptan if symptoms were insufficiently controlled.

Data collection

All study data were securely recorded and managed using CleanWeb (Telemedicine Technologies S.A.S.). For each patient meeting the inclusion criteria, the following parameters were measured: ANIm before surgical skin incision without stimulation, ANIm 1 minute after the end of the breast surgical skin dissection cephalad and caudal block level limits, any intraoperative administration of IV atropine or IV ephedrine, pain scores using a VAS at arrival and discharge from the PACU, and ultrasound visualization of the paravertebral space (good or bad).

The skin dissection included the upper and lower skin incisions (Fig. 1), hemostasis, and the separation of skin from the mammary gland before deep tissue dissections.

Sensor level of efficacy was assessed using an ice cube test, which allowed classifying blocks as effective, incomplete or ineffective. A standardized cold sensation test using an ice cube was performed by a blinded evaluator to assess the presence or absence of sensory block in the thoracic dermatomes corresponding to the surgical field. The test was applied bilaterally on the anterior and lateral chest wall,

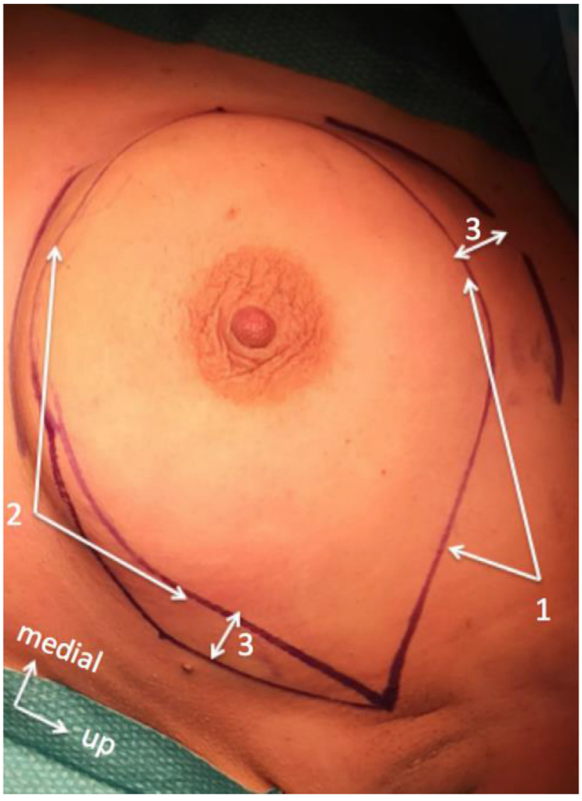


Fig 1 Surgical lines for breast skin dissection (1 = Line for upper total mastectomy incision, 2 = Line for lower total mastectomy incision, 3 = Minimal skin conservation for closure).

typically from T1 to T10, using a non-standardized craniocaudal sequence. The presence of cold sensation between T2 and T6 was used to define an incomplete or ineffective block. Although testing was extended from T1 to T10 for completeness, only the T2—T6 dermatomes, corresponding to the mastectomy surgical field, were considered for block efficacy assessment. Dermatomes of the upper limb were not assessed, as the focus was on regional anesthesia coverage of the breast and chest wall. The ice cube sensation test defined four groups: an effective group (no sensation between thoracic levels T2 and T6), an incomplete group (no sensation at 1, 2, 3, or 4 levels between T2 and T6), an ineffective group (no blocked levels), and a failure group (the sum of the incomplete and ineffective groups). The evaluation was systematically performed by the same trained anesthesiologist to ensure consistency and reduce inter-observer variability.

Outcomes

The primary outcome was the comparison of the variation in ANIm (before skin incision and 1 minute after the end of the surgical skin dissection) among the different groups (effective, incomplete, and ineffective). For the analyses, the ANI change (ΔANI) was calculated as the post-dissection ANIm value minus the pre-incision ANIm value.

The secondary outcomes included comparisons between PVB effectiveness groups for the following variables: intraoperative remifentanil consumption, PACU morphine consumption, and pain at rest in the PACU upon arrival and before discharge.

Statistical analysis

In univariate descriptive analysis, qualitative parameters were described by frequency and percentage, while quantitative parameters were described by mean ± standard deviation, median, minimum — maximum, and 1st and 3rd uartiles. In bivariate analysis, qualitative parameters were compared using a Chi-Squared test. Quantitative parameters were compared using the parametric Student's *t*-test if normality was met (Shapiro-Wilk test), or the non-parametric Wilcoxon-Mann-Whitney test, otherwise.

Effect sizes (mean differences) were calculated for continuous variables and corresponding 95% Confidence Intervals (95% CI) were reported to quantify the magnitude and precision of differences between groups. For categorical outcomes, Odds Ratios (OR) with 95% CIs were computed.

To evaluate the ability of ANIm values to predict effective PVB, a Receiver Operating Characteristic (ROC) curve analysis was performed. The area under the ROC Curve (AUC) was calculated to assess diagnostic performance, and the optimal threshold was defined using the Youden Index.

No multivariable regression analysis was performed because of the limited number of events (23 incomplete blocks) relative to the sample size, which would not allow for a robust model without risking overfitting. In addition, the study population was deliberately homogeneous (ASA I—III women, standardized oncologic breast surgery, and a uniform anesthesia protocol), which reduced the likelihood of major confounders. Nevertheless, we acknowledge this absence of multivariable adjustment as a limitation, as residual confounding cannot be fully excluded. However, this limitation is acknowledged in the discussion. No missing data were recorded for primary or secondary outcome variables (ANI values, pain scores, or opioid consumption) in the 93 analyzed patients.

The significance level was set at 5%. All analyses were conducted using RStudio software (version 2022.07.2+576; RStudio, Inc., Boston, USA).

Results

Demographics

One hundred women were screened and included in this study. Ninety-three patients were analyzed, as seven were excluded (four due to withdrawal of consent and three because PVB was not performed) (Fig. 2).

The demographic data of the patients are as follows: the mean age was 60.4 ± 12.8 years, and the mean Body Mass Index (BMI) was 24.3 ± 4.0 $kg.m^{-2}$. The distribution of the American Society of Anesthesiologists (ASA) Physical Status was as follows: 37% ASA I, 60% ASA II, and 3% ASA III. The proportion of patients undergoing sentinel lymph node dissection was 30% with no difference in outcomes compared to those underdoing total mastectomy without axillary surgery. Ultrasound visualization of the paravertebral space was deemed good in 96% of cases and poor in 4%. The mean duration of surgery was 67 ± 24 minutes, and the mean duration in the PACU was 77 ± 26 minutes. Demographic and baseline characteristics per group were reported in Table 1.

The distribution of results from the cold sensation test was as follows: effective group 75% (n = 70), incomplete group 25% (n = 23), and ineffective group 0%. Although sensory testing was systematically performed from T1 to T10 on the anterior chest wall, the classification of block efficacy was based on the presence or absence of cold sensation between T2 and T6, corresponding to the mastectomy surgical field. The upper metameric extensions were T1 15%, T2 62%, T3 16%, and T4 7%. The lower metameric extensions were T3 2%, T5 6%, T6 24%, T7 28%, T8 24%, T9 10%, and T10 6%. No intraoperative administration of IV atropine or IV ephedrine was reported. Since thoracic PVB does not affect the brachial plexus, no motor blockade of the upper limb is expected. Consequently, no formal motor assessment of the upper extremity was performed, and no motor symptoms were reported by patients.

Outcomes

The mean variation of ANIm, from before the surgical incision to one minute after the end of the skin dissection, decreased significantly in the incomplete PVB group -11.0 ± 7.1 compared to the effective PVB group 1.4 ± 10.3, with $p < 0.0001$ (Fig. 3). While the absolute difference in ANIm variation may seem modest, its clinical relevance is evident from consistent differences in intraoperative remifentanil consumption, postoperative pain scores, and PACU morphine use. Moreover, the ROC analysis demonstrated good predictive performance, indicating that even relatively small changes in ANIm values may reflect meaningful differences in analgesic efficacy.

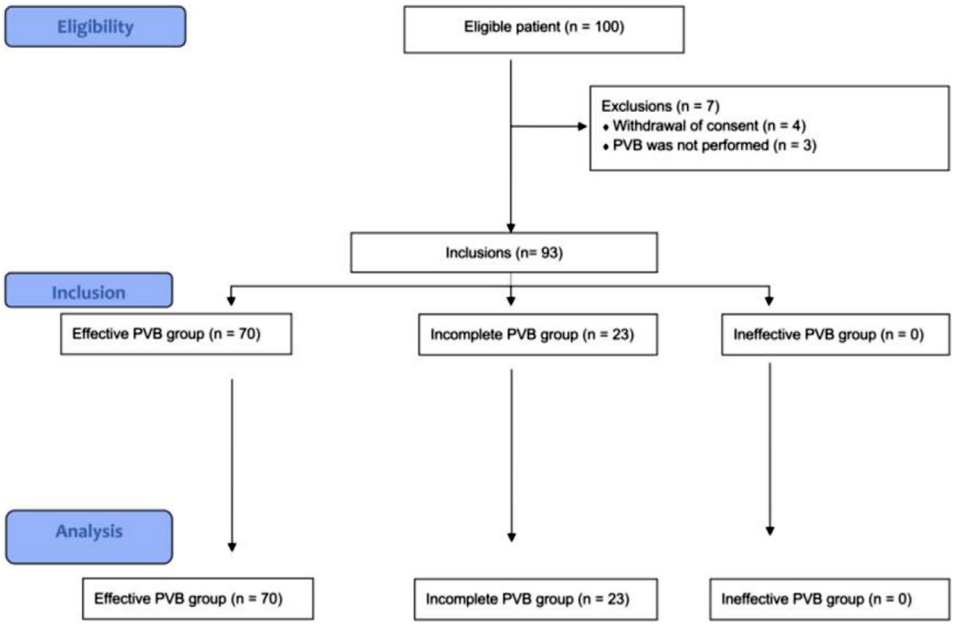


Fig 2 Flowchart (PVB, Paravertebral Block).

Table 1 Demographic and clinical data. Data are presented as mean ± SD or percent. In bivariate analysis, qualitative parameters were compared using a Chi-Squared test. Quantitative parameters were compared using the parametric Student's *t*-test if normality was met (Shapiro-Wilk test), or the non-parametric Wilcoxon-Mann-Whitney test otherwise.

	Incomplete PVB (n = 23)	Effective PVB (n = 70)	p-value
Age (years)	57.4 ± 12.7	61.3 ± 12.7	0.2
Body Mass Index	24.43 ± 4.95	24.28 ± 3.66	0.9
ASA I/II/III (%)	44/52/4	34/63/3	0.47
Type of surgery (%)			
Total mastectomy alone	65	71	0.76
Total mastectomy and sentinel lymph node dissection	35	29	
Good ultrasound visualization (%)	95	97	1
Duration of surgery (min)	64 ± 19	68 ± 25	0.46

PVB, Paravertebral Block.

The area under the ROC Curve (AUC) was 0.81, indicating good discriminative power for differentiating between effective and incomplete blocks (Fig. 4). The optimal threshold was identified using the Youden Index, corresponding to an ANIm.1 min (one minute after the end of skin dissection) score of 63.5. Patients with ANIm.1 min ≥ 63.5 were 17.4 times more likely to present with an effective block (OR = 17.4; 95% CI: 5.76–61.7; $p < 0.001$).

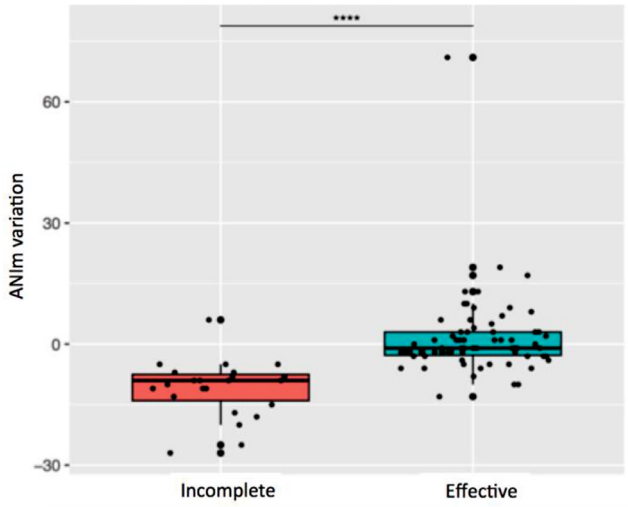
The mean intraoperative consumption of remifentanil was significantly higher in the incomplete group 0.072 ± 0.018 $\mu g.kg^{-1}.min^{-1}$ compared to the effective group 0.054 ± 0.008 $\mu g.kg^{-1}.min^{-1}$, $p < 0.0001$. The mean difference was 0.018 $\mu g.kg^{-1}.min^{-1}$ (95% CI: 0.010 to 0.026) (Fig. 5).

The mean pain scores in the PACU were significantly higher in the incomplete group: upon arrival, the incomplete group had a score of 3.7 ± 2.4 vs. 0.7 ± 1.1 in the effective group, mean difference 3.0 (95% CI: 1.94 to 4.07) $p < 0.0001$, and before discharge the PACU, the incomplete group scored 2.1 ± 0.9 vs. 1.0 ± 1.1 in the effective group, mean difference 1.1 (95% CI: 0.64 to 1.56) $p < 0.0001$. The mean morphine consumption during the PACU was significantly higher in the incomplete group 1.8 ± 1.5 mg compared to the effective group 0 ± 0.2 mg, the mean difference was 1.8 mg (95% CI: 1.15 to 2.45) $p < 0.0001$.

Discussion

This study highlights the relationship between ANI variations and the sensory effectiveness of PVB for total mastectomy. ANI measurements can also serve as a valuable tool directly at the beginning of surgery to assess the level of analgesia provided by the PVB. This study confirms the interindividual variability in sensory blockade achieved through single PVB injection.[4] Our data show a clear variation between effective and incomplete PVB distribution levels, also with a significant decrease in ANIm values reported after skin dissection.

Given the primary objective of evaluating the association between ANI variation and block efficacy, secondary



Group	n	min	median	q1	q3	iqr	mean	sd	max
Incomplete	23	-27	-9	-14.00	-7.5	6.50	-11.000	7.077	6
Effective	70	-13	-1	-2.75	3.0	5.75	1.386	10.306	71

Fig 3 ANIm variation from before surgical skin incision to one minute after the end of skin dissection (Wilcoxon test $p < 0.0001$) (min, Minimal; q1, 1st quartile; q3, 3rd quartile; iqr, Interquartile range; sd, Standard Deviation; max, Maximal).

outcomes (analgesic consumption, pain scores) were considered exploratory. Therefore, no correction for multiple comparisons was applied, as the analysis was not intended for definitive inferential testing but rather hypothesis generation. However, we acknowledge this as a limitation and interpret secondary findings with appropriate caution.

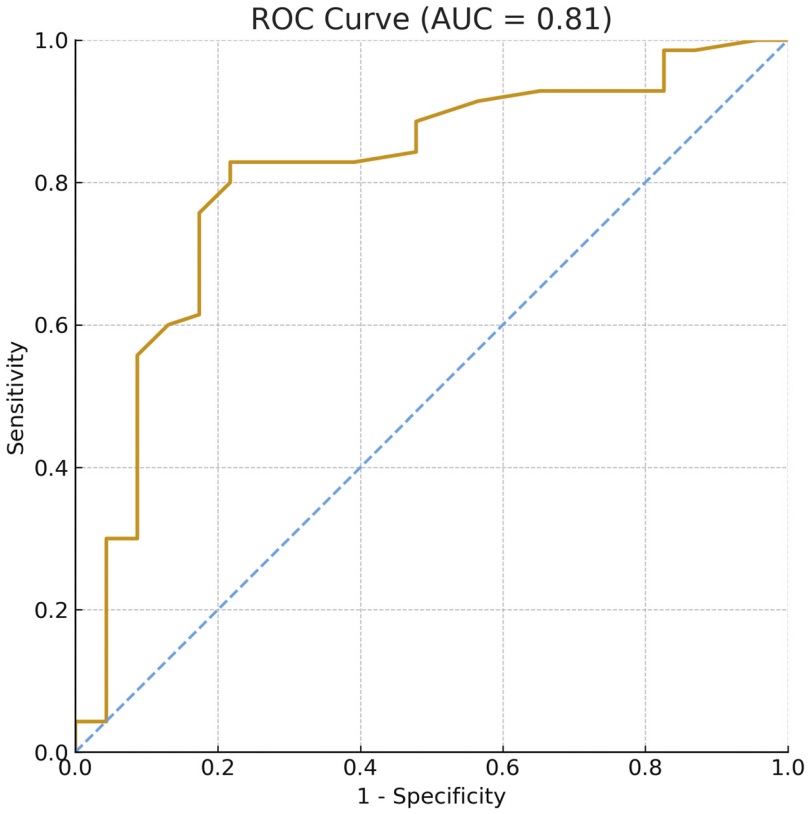
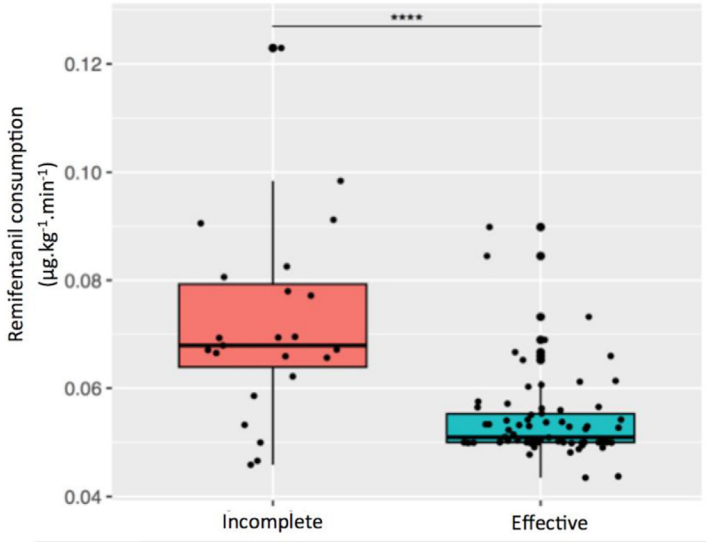


Fig 4 Receiver Operating Characteristic (ROC) curve assessing the predictive performance of ANIm.1 min for identifying effective Paravertebral Blocks. The Area Under the Curve (AUC) was 0.810, indicating good discriminative ability. A cutoff value of 63.5 for ANIm.1 min was identified using the Youden Index as the optimal threshold, providing the best balance between sensitivity and specificity in predicting effective block coverage from T2 to T6.



Group	n	min	median	q1	q3	iqr	mean	sd	max
Incomplete	23	0.046	0.068	0.064	0.079	0.015	0.072	0.018	0.123
Effective	70	0.043	0.051	0.050	0.055	0.005	0.054	0.008	0.090

Fig 5 Intraoperative consumption of remifentanil (Wilcoxon test $p < 0.0001$) (min, Minimal; q1, 1st quartile; q3, 3rd quartile; iqr, Interquartile range; sd, Standard deviation; max, Maximal).

This significant variation of ANI supports the notion that ANI can accurately represent patients' nociceptive state directly at the beginning of the surgery. Although no standardized threshold for ANI change has been defined, several studies have shown that dynamic variations, particularly sudden decreases in ANI in response to nociceptive stimuli, correlate with inadequate analgesia.[12,13] Our findings are consistent with this interpretation, as patients with incomplete blocks showed a significant decline in ANI following skin dissection. These changes may be more clinically meaningful than absolute values. ANI is effective not only in detecting but also in predicting an inadequate balance between nociception and antinociception during GA. However, variations in ANI may also be influenced by factors such as hemodynamic fluctuations, residual autonomic tone, or insufficiently stable anesthetic depth. Although propofol and remifentanil infusions were titrated using BIS and ANI targets, we acknowledge that intraoperative fluctuations could have introduced variability.

While the exact time between PVB completion and surgical incision was not recorded, all blocks were followed by a mandatory 15 minutes interval before sensory assessment, with general anesthesia and surgical preparation occurring thereafter. Given the pharmacodynamic profile of ropivacaine at 7.5 $mg.mL^{-1}$, typically achieving onset within 10 to 15 minutes, we believe that the LA had sufficient time to take effect prior to incision in all patients, even though the precise interval to incision was not recorded.[14,15] This delay, combined with block performed before general anesthesia, supports the reliability of sensory evaluation.

The lateral pectoral nerve is described as receiving nerve fibers from C5 to C7 nerve roots and the medial pectoral nerve from C8 and T1 with some variations.[16] They are primarily involved in motor innervation of the pectoral muscles, with only limited or indirect contribution to sensory perception in the anterior chest wall. These considerations could influence pain management during and after surgery. In our study, the maximal upper metameric extension was T1. PVB does not adequately cover the sensory distribution of these nerves, patients may experience pain during surgery, particularly during the dissection and manipulation of the pectoral muscles. Thus, early assessment during skin dissection may not fully capture incomplete regional analgesia across the entire breast. However, the lower mean intraoperative remifentanil consumption in the effective group of this study suggests that this influence is weak.

No adverse events or signs of Local Anesthetic Systemic Toxicity (LAST) were observed in this study. In this study, a fixed dose of 20 mL of 7.5 $mg.mL^{-1}$ ropivacaine (150 mg) was administered for all blocks, which remained well below the recommended maximum dose of 3 $mg.kg^{-1}$ or 200 mg.[17] Although the dose was not adjusted to body weight, no adverse effects were observed, and the fixed dosing protocol reflects standard practice in our institution. This is standard clinical practice for breast surgery. Ropivacaine is associated with a favorable safety profile due to its reduced cardiotoxicity and central nervous system toxicity compared to bupivacaine. Nevertheless, practitioners should remain vigilant for signs of LAST, particularly when using higher concentrations or in patients with low body mass or altered metabolism. Ultrasound guidance and aspiration before injection were systematically used to reduce the risk of intravascular administration. The absence of complications in our cohort further supports the safety of this approach when appropriately performed.

Strengths and limitations

The main strengths of this study include its prospective design, the homogeneous population of ASA I–III women undergoing standardized oncologic breast surgery, and the

use of a uniform anesthetic protocol. The absence of missing data for primary and secondary outcomes and the blinded sensory assessment before anesthesia induction further reinforce the internal validity of the findings.

Nevertheless, several limitations must be acknowledged. First, the study was observational and lacked randomization, which limits causal inference. Another limitation is the absence of multivariable adjustment. Although our study design and inclusion criteria aimed to minimize heterogeneity and potential confounding, residual confounders such as BMI, anxiety, or age-related autonomic variability may still have influenced ANI values. The relatively small number of incomplete blocks also precluded a meaningful multivariable analysis. Future larger studies should address this point with adequate adjustment. Furthermore, although BMI was recorded, no subgroup analysis was performed due to the limited sample size. Preoperative anxiety was not assessed, which may have influenced postoperative pain scores, representing an additional uncontrolled confounding factor.

Another limitation is the potential for incorporation (circularity) bias, as ANI values guided intraoperative remifentanil titration and were also used as a predictive variable. This dual role may have partially influenced the observed associations, although the consistency across analgesic outcomes (remifentanil consumption, PACU pain scores, and morphine use) supports the robustness of our findings.

Although the ice cube test is inherently subjective, its implementation in our study was designed to minimize potential bias. In particular, the assessment of the sensory block was conducted by a dedicated evaluator who was blinded to all intraoperative and postoperative outcomes. This evaluator performed the test just prior to the induction of general anesthesia and was not involved in the performance of the PVB or subsequent anesthesia management. Conversely, the anesthesiologists who managed intraoperative care and collected hemodynamic and analgesic data were not informed of the results of the sensory evaluation. This structure ensured a partial blinding model, in which the team performing the block and anesthesia did not influence nor were influenced by the sensory assessment outcome. Participants were not blinded to the sensory block assessment, which may have introduced bias in subjective pain reporting during the postoperative period. Although full double-blinding was not feasible in this observational setting, this separation of roles helped reduce potential observer and performance bias. However, interindividual variability in cold perception, the lack of inter-rater reliability assessment, and reliance on a single sensory modality (cold) may have introduced classification bias. The ice cube test does not assess other relevant sensory modalities (e.g., mechanical or nociceptive), which could affect the accuracy of block effectiveness classification.

Finally, this study did not include a stratified analysis of ANI responses or block effectiveness based on age. Moreover, the external validity of our findings may be limited due to the single-center nature of the study and the homogeneous population of ASA I—III women undergoing standardized oncologic breast surgery. These findings may not be generalizable to more diverse patient populations or clinical settings. Given the known physiological decline in autonomic responsiveness and heart rate variability in older adults, age may influence ANI measurements.[18] Further studies are needed to assess whether ANI thresholds should be adjusted according to patient age in the context of regional anesthesia.

Conclusion

In conclusion, this observational study suggests that intraoperative variations in ANI values may help identify ineffective paravertebral blocks during breast surgery. Patients with incomplete blocks demonstrated significant ANI decreases after skin dissection, alongside higher opioid requirements and postoperative pain scores. These findings support the potential role of ANI monitoring as an adjunctive tool for the early detection of inadequate regional analgesia. However, due to the non-randomized design of the study, no causal inference can be made. Future randomized controlled trials are needed to confirm whether ANI-guided intraoperative analgesia management improves clinical outcomes. Based on our ROC analysis, an ANIm threshold around 63.5 could help discriminate block effectiveness and guide intraoperative decisions, although this threshold requires further validation across different surgical contexts and regional techniques.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to institutional and ethical restrictions, but de-identified data can be made available from the corresponding author upon reasonable request and with permission from the Institut de Cancérologie de Lorraine.

Abbreviations

Paravertebral Block (PVB), Analgesia Nociception Index (ANI), Instant Analgesia Nociception Index(ANIi), Mean Analgesia Nociception Index (ANIm), Local Anesthetic (LA), Magnetic Resonance Imaging (MRI), Thoracic level (T) with the number of the level, General Anesthesia (GA), Electrocardiogram (EKG), Post-Anesthesia Care Unit (PACU), Bispectral Index (BIS), Visual Analog Scale (VAS), Intra Venous (IV), Local Anesthetic Systemic Toxicity (LAST), minimal (min), 1st quartile (q1), 3rd quartile q3, interquartile range (iqr), standard deviation (sd), maximal (max).

Approval

This study was approved by the French National Ethics Committee of the SUD-EST IV (Approval n° ID-RCB: 2019-A00121-56) and registered in ClinicalTrials.gov (NCT03832920). https://clinicaltrials.gov/study/NCT03832920?titles=Analgesia%20Nociception%20Index%20mastectomy&rank=2.

Previous presentation in conferences

Abstract presented at the French Society Congress (Société Française d'Anesthésie et de Réanimation), September 19th, 2024 in Paris, France.

Preprint

This trial is in a preprint process https://www.researchsquare.com/article/rs-5415736/v2?redirect=/article/rs-5415736.

Declaration of Generative AI in scientific writing

No AI was used.

Authors' contributions

All authors contributed to the study conception and design. Data collection were performed by JR and ASL. All authors contributed to material preparation and analysis. The first draft of the manuscript was written by JR and ASL. JR, ASL, CF and PR read and approved the final manuscript.

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Declaration of competing interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Mechanical needle guidance for ultrasound-guided parasagittal oblique in-plane paravertebral blocks: a cadaveric study

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Abstract
Background: Paravertebral blocks provide analgesia for a range of thoracoabdominal surgeries. However, visualizing the needle tip during the procedure can be challenging, especially for clinicians with limited experience, because the target is deep. We therefore tested the primary hypothesis that needle guidance by the Infiniti Plus system improves ultrasound visualization of the needle tip during thoracic paravertebral blocks performed by novice residents.
Methods: Nineteen clinical anesthesia residents each performed 20 bilateral ultrasound-guided thoracic paravertebral blocks (T2—T11) on 17 unembalmed cadavers, with and without the use of a fixed-angle mechanical needle guide in a randomized crossover design. The primary

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outcome, percent perfect needle visibility, was compared between guided and unguided methods using a paired *t*-test. Secondary outcomes, including time to needle visualization, number of needle insertion attempts, and subjective ease-of-use ratings, were analyzed using paired *t*-tests and Wilcoxon signed-rank tests, respectively. Inter-rater reliability for overall perception ratings was assessed using the Intraclass Correlation Coefficient (ICC).

Results: There were no significant differences in needle-target visualization (62% ± 17% with guidance vs. 64% ± 18% without, p = 0.15), time to target (HR = 1.00 [95% CI 0.86–1.16], p = 0.99), procedural difficulty scores, or number of insertion attempts between guided and unguided blocks.

Conclusion: The Infiniti Plus mechanical needle guide did not demonstrate improved ultrasound needle tip visualization during thoracic paravertebral blocks performed by novice clinicians in cadavers.

Introduction

Paravertebral blocks are an advanced regional anesthesia technique entailing unilateral block of spinal nerve roots as they exit intervertebral foramina.[1-4] Paravertebral blocks provide good analgesia for thoracic, breast,[5,6] abdominal,[7] and renal surgeries in adults and children.[8,9]

Ultrasound visualizes the anatomy of the paravertebral space and the real-time distribution of local anesthetics.[10,11] As expected, ultrasound guidance improves block success[12] and reduces complications.[13] However, ultrasound-guided paravertebral block requires excellent hand-eye three-dimensional coordination extrapolated from a two-dimensional ultrasound image. Even for experienced practitioners, the greatest challenge lies in visualizing the needle tip while advancing it towards the target.[11] Advancing the needle without needle tip visualization may lead to vascular, neural, or visceral injury.[13-15] Poor image quality in paravertebral blocks leads to higher failure rates.

Needle guidance techniques have been developed to improve the accuracy and safety of ultrasound-guided procedures by providing real-time visualization of the needle trajectory. Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) is a mechanical guidance system designed to improve ultrasound visualization (Fig. 1A–B). However, this system has not been tested for the paravertebral blocks by novice clinicians.

We thus evaluated whether mechanical needle guidance improves ultrasound visualization, procedural performance, and efficiency when used by novice anesthesia residents in a cadaver paravertebral block model. Specifically, we tested the primary hypothesis that mechanical needle guidance by Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) improves ultrasound visualization of the needle tip by novice clinicians. Secondarily, we tested the hypotheses that mechanical needle guidance reduces the time required to reach the target. Exploratory outcomes were procedural difficulty and the required number of needle insertion attempts.

Materials and methods

The Cleveland Clinic Institutional Review Board approved the participation of residents and use of fresh cadavers (n° 17-013, date 2016). All cadavers were legally donated to the Department of Anatomy at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University. There is no clinical trial registration since this study was a study in cadavers.

Cleveland Clinic Anesthesiology Institute Clinical Anesthesia year-1 (CA-1) and year-2 (CA-2) residents were recruited via e-mail. Written informed consent was obtained from all the residents who wanted to participate in the study. Results were coded to protect residents who performed poorly. Residents were *a priori* provided with educational materials about ultrasound-guided paravertebral blocks and were thereafter required to score at least 7 out of 10 questions correctly on an examination of anatomy and ultrasound imaging pertinent to paravertebral blocks.[16]

Bodies were donated to the Department of Anatomy at Cleveland Clinic for scientific research and educational purposes with relevant consent. We used a total of 17 unembalmed cadavers, male and female, and with a range of body habitus. We excluded cadavers with known thoracic spinal deformities, thoracic cavity disease, and those who had previous thoracic spinal surgery. One cadaver was used for each participating resident, each on a separate day. Cadavers were maintained at ambient temperature for at least 12 hours before being studied.

Protocol

The study was conducted in the anatomy laboratory at the Cleveland Clinic Main Campus. The cadavers were positioned prone with blankets under the abdomen to flex the thoracolumbar spine. The relevant skin landmarks, including thoracic spinous processes, were identified and marked. A point lateral to the tip of the spinous processes, a curvilinear ultrasound transducer (2–5 MHz) (M-Turbo USG system; Sonosite, Bothell, WA, USA) was used. The transducer was positioned parallel to the spinous process. The transverse process, the costo-transverse ligament and the parietal pleura were identified. Afterward, the probe tilted obliquely in the lateral direction to improve visualization of the parietal pleura. A 125 mm, 18-gauge echogenic Touhy needle (Pajunk Tuohy Sono, Geisingen, Germany) was used for all blocks. Needles were inserted at the caudal end of the ultrasound transducer. Using an in-plane technique, needles were directed towards the costo-transverse ligament. Passage of

Figure 1 (A) Infiniti Plus needle guidance system; blue circular segment fits in the top of the bracket; the red circular segment part fits in the bottom of the bracket. (B) Infiniti Plus needle guidance system with the needle fits in the bracket.

the needle through the costo-transverse ligament was associated with a tactile loss of resistance. When the resident believed the needle was properly positioned, 2–5 mL of normal saline was injected into the space. Appropriate spread was identified as anterior displacement of the parietal pleura. Ultrasound imaging and videos of the paravertebral block were recorded for later evaluations (Fig. 2).

In this randomized, paired design study, 19 novice anesthesia residents performed bilateral paravertebral blocks (T2—T11) on cadaver specimens, totaling 20 blocks per resident. Each side of the cadaver was randomly assigned to either the mechanical needle guidance system (Infiniti Plus in-plane, CIVCO Medical Solutions, Coralville, Iowa) or the free-hand technique, with the contralateral side serving as the paired control. Within-subject pairing effectively controlled for inter-individual variability, ensuring that observed differences in procedural outcomes were attributable to the guidance method rather than to anatomical or personal factors. Allocation was based on computer-generated randomization that was presented to the participating resident in a sealed envelope method on the day of the procedure. Allocation was thus concealed as long as it was practical.

Measurements

Demographic and morphometric characteristics of the cadavers were recorded. Relevant information about participating residents was similarly recorded.

Our primary outcome was the percentage of perfect visualization, defined as the percent of the time with perfect needle tip visibility. Four experienced assessors from our Regional Anesthesia group with experience in ultrasound-guided paravertebral blocks in at least 40 patients were

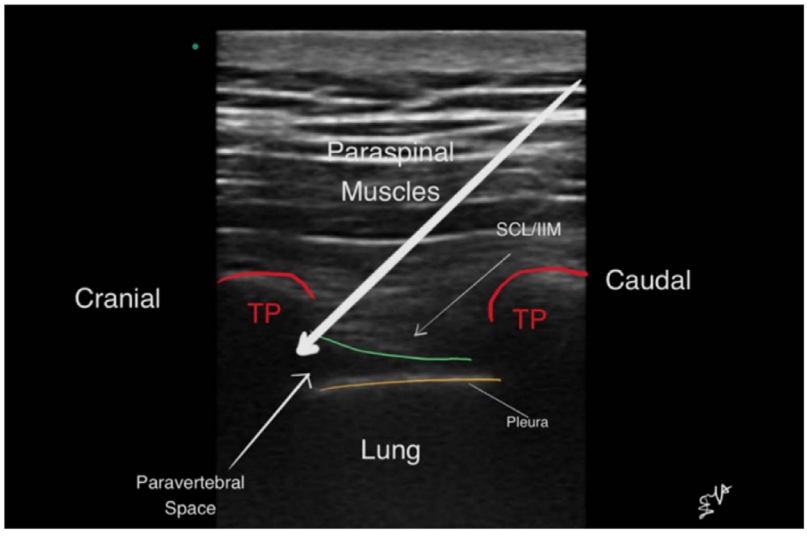

Figure 2 Ultrasound-guided paravertebral block using paramedian oblique sagittal scan without needle guidance at T4. The long white arrow represents the needle inserted parasagittal in-plane technique. TP, Transverse Process; SCL, Superior Costotransverse Ligament; IIM, Internal Intercostal Membrane.

asked to independently evaluate the percentage of the time that needle visualization was perfect. Assessors also gave their overall perception of needle visibility, which was evaluated on a five-point Likert scale. Assessors were blinded to the needle guidance system used for each paravertebral nerve block, but residents doing the injections were not.

Our secondary outcome, time to target, was defined as the time from the needle skin puncture to target site injection of saline in seconds as recorded by research assistants. Exploratory outcomes included the assessors' overall perception of needle visibility, the number of skin needle attempts, and procedural difficulty. The number of skin puncture attempts was defined as pulling block needle back to skin and reinserting it in the same or a different location. Overall procedural difficulty was rated by residents for needle-guided method and unguided method separately on each subject they performed blocks on after completing the blocks. Therefore, there were 2 procedural difficulty scores in total on each cadaver: one for the guided method and the other for the unguided method. The scale of procedural difficulty ranged from 1 (easy) to 10 (extremely difficult).

Statistical analysis

Prior to analysis, we assessed the normality of residuals and variables involved in the Generalized Estimating Equations (GEE) and Intraclass Correlation Coefficient (ICC) calculations using QQ-plots. No major deviations from normality were observed, supporting the assumptions of the applied statistical methods.

Exploratory analyses, including comparisons of procedural difficulty and the number of needle insertion attempts, were conducted descriptively. No p-values were calculated for these comparisons, as they were not prespecified in the statistical analysis plan. Instead, we report descriptive statistics and 95% Confidence Intervals to provide an overview of these outcomes.

Primary analysis

The primary outcome was the percentage of perfect needle visualization, defined as continuous, real-time identification of the entire needle shaft and tip throughout advancement. The needle appeared as a hyperechoic line within the ultrasound beam plane, without dropout or ambiguity. This definition aligns with established criteria for optimal needle visualization in ultrasound-guided procedures.

For each thoracic level (T2−T11) and side (left/right) in each cadaver, assessments from four independent observers were averaged to determine the final percentage of perfect visualization.

A generalized linear model with an identity link was fitted using the Generalized Estimating Equation (GEE) method, assuming an exchangeable covariance structure within subjects. The model included covariates for thoracic level, block side, and resident training level (CA-1 vs. CA-2) to adjust for potential confounding factors.

As a sensitivity analysis, comparisons were repeated using each assessor's evaluations separately. The distributions of the averaged and individual assessments were approximately normal, as evidenced by Q-Q plots.

"Target arrival" was operationally defined as the point at which the needle tip was visualized in-plane at the intended paravertebral target site under real-time ultrasound guidance, immediately followed by the observation of pleural displacement upon saline injection. This dynamic assessment ensured accurate needle placement and was consistently applied across all procedures.

Assessing inter-rater reliability

We assessed Inter-Rater Reliability (IRR) for the primary outcome-percent perfect visualization-using two forms of the Intraclass Correlation Coefficient (ICC), each capturing different aspects of rater agreement:

ICC(C,k): This metric evaluates the consistency of ratings when averaged across all assessors. It is appropriate when the focus is on the reliability of the mean rating, assuming that systematic differences between assessors (e.g., one assessor consistently rating higher or lower) are not of primary concern.

ICC(2,1): This metric assesses the absolute agreement between individual assessors, considering both random and systematic differences. It is suitable when each assessor's rating is of interest, and when assessors are considered representative of a larger population.

By utilizing both ICC(C,k) and ICC(2,1), we provide a comprehensive assessment of inter-rater reliability, capturing both the consistency of average ratings and the agreement among individual assessors.

Secondary analysis

In our secondary analysis, we compared the time from needle skin puncture to successful needle-target site saline injection between the two needle insertion techniques. Given that some procedures were censored due to incomplete injections, we employed a Cox proportional hazards model with robust sandwich estimates for the covariance matrix to account for potential intra-subject correlation and model misspecification. This approach allowed us to estimate hazard ratios with corresponding 95% Confidence Intervals, providing a measure of the relative efficiency of each technique in achieving the target site. It is important to note that the procedural time did not include the setup of the Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa), which may have influenced overall efficiency, particularly in time-sensitive clinical settings.

Given the limited number of pre-specified secondary outcomes and the exploratory nature of these analyses, we did not apply formal corrections for multiple comparisons. We recognize the potential for increased Type I error and have interpreted these findings with appropriate caution.

Exploratory analysis

The number of attempts to complete a paravertebral block was summarized by means ± SDs and counts (%). Procedural difficulty was summarized as means ± SDs. The adjudicators' overall perceptions of needle visibility were also summarized and reported. The inter-rater reliability of overall perception consistency was reported using the same method of calculating inter-rater reliability of percent perfect

visualization. All needle insertions were performed under dynamic ultrasound guidance, with real-time visualization throughout needle advancement.

Sample size

Our study was designed to have 80% power at the 0.05 significance level to detect an absolute 20% difference in perfect needle visibility between needle insertion technique groups. In a previous study, perfect needle visibility with ultrasound was achieved 55% (SD 26%) without mechanical guidance.[17] Assuming that each resident performed 20 paravertebral blocks and a moderate intra-class correlation coefficient of 0.3, at least 20 residents needed to perform 20 blocks each to detect a 20% absolute difference in needle visibility.

Given the observed SD of 17% and ICC of 0.25, the study had 76% power to detect a 20% absolute difference with the existing sample size. This marginal underpowering may diminish sensitivity to small effect sizes and increase Type II error risk.

Primary and secondary hypotheses were evaluated under a significance criterion of 0.05. All analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and *R* statistical software version 3.3.2 (The *R* Foundation for Statistical Computing, Vienna, Austria). The inter-rater reliability test was conducted using the "icc" function in "irr" package in *R*.

Power analysis

Prior to the study, we conducted an a priori power analysis to determine the necessary sample size to detect a clinically meaningful difference in perfect needle visibility between the needle guidance methods. Assuming a baseline visibility rate of 55% (SD 26%) without mechanical guidance, an anticipated absolute improvement of 20%, an intra-class correlation coefficient of 0.3, and a significance level of 0.05, we calculated that enrolling at least 20 residents, each performing 20 blocks, would provide 80% power to detect the specified difference.

After data collection, we performed a post hoc power analysis to assess the actual power achieved based on observed data. With 19 residents completing the study, an observed standard deviation of 17%, and an intra-class correlation coefficient of 0.25, the post hoc analysis indicated a power of 76% to detect a 20% absolute difference in needle visibility. While slightly below the initial target, this level of power is considered acceptable for exploratory research.

It's important to note that while a priori power analysis is essential for study planning and is widely endorsed, post hoc power analysis is more controversial and should be interpreted with caution.

Results

We recruited 21 residents, but two were excluded because of a video recording failure. Therefore, 19 residents' blocks on 17 cadavers were analyzed. The number of cadavers was less than the number of residents since two cadavers were used by two residents each at separate times.

A total of 19 residents successfully completed the study, with 10 (53%) being CA-1 and 9 being CA-2. The cadavers had a mean ± SD BMI of 24 ± 4 $kg.m^{-2}$, with 9 (53%) males and 8 females. Assessments were available for 186 blocks completed with combined mechanical and ultrasound needle guidance, and 188 completed with only ultrasound guidance.

Primary analysis results

The mean percentage of perfect visualization was 62% (SD 17%) for blocks performed with mechanical guidance and 64% (SD 18%) for blocks performed with ultrasound alone (Fig. 3). There was no statistically significant difference in the percent perfect visualization between the two techniques, with the difference (mechanical guidance vs. without) estimated as -1.8% (95% CI [-4.2%, 0.6%], p = 0.15).

Overall consistency on perfect visualization among the 4 assessors was good at 0.85 (95% CI: 0.82, 0.87). This means using the average of 4 assessors' results as the final percentage perfect visualization was reliable.

The sensitivity analysis using each evaluator's assessments of percent perfect visualization separately for the

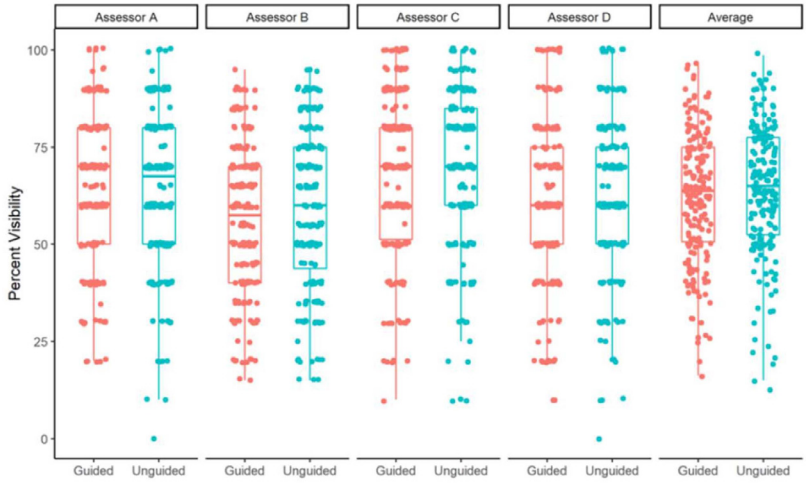

Figure 3 Percent variability for blocks with and without mechanical needle guidance. Assessor A, B, C, D represents four assessors.

Table 1 Summary of results (subject n = 19).

Outcomes	Needle Guided[d] (n = 190)	Unguided[d] (n = 190)	Missing	Difference (95% CI)	p-value
Primary Analysis[a]					
Percent perfect visualization, averaged	62 ± 17	64 ± 17	10	-1.8 [-4.2, 0.6][a]	0.15
Sensitivity Analysis					
Percent perfect visualization, separately					
Assessor A	64 ± 19	64 ± 19	6	0.6 [-1.9, 3.0][a]	0.65
Assessor B	56 ± 19	59 ± 21	6	-3.7 [-6.6, -0.7][a]	0.01
Assessor C	68 ± 21	70 ± 20	6	-1.7 [-4.8, 1.4][a]	0.29
Assessor D	61 ± 21	63 ± 20	10	-2.4 [-6.1, 1.3][a]	0.21
Secondary Analysis[b]					
				Hazard ratio	
Time to target (seconds)	34 [30, 39]	35 [31, 40]	2	1.00 [0.86, 1.16]	0.99
Exploratory Analysis					
Overall perception of needle visualization, averaged	3 ± 1	3 ± 1	11		
Sensitivity Analysis					
Overall perception of needle visualization, separately					
Assessor A	3 ± 1	3 ± 1	6		
Assessor B	3 ± 1	3 ± 1	6		
Assessor C	3 ± 1	3 ± 1	6		
Assessor D	3 ± 1	3 ± 1	11		
Number of Attempts	1.2 ± 0.6	1.3 ± 1.1	2		
1	162 (85)	160 (84)			
2	18 (9)	19 (10)			
> 3	10 (5)	11 (6)			
Procedural difficulty[c]	6.5 ± 1.9	6.6 ± 1.5			

[a] Difference is assessed as mean difference through the generalized linear model using GEE (Generalized Estimation Equation) method assuming exchangeable correlation within subjects.
[b] Guide system effect was assessed as hazard ratio through Cox-proportional survival model using sandwich estimator for covariance matrix to account for within-subject correlation. The summary statistics of each group was median time to target with 95% CI.
[c] Procedural difficulty of needle-guided systems/without needle-guided systems were rated at subject level, which ranged from 1 to 10, with 1 = easy and 10 = extremely difficult.
[d] Summary statistics were calculated by simply treating each target as independent and represented as mean ± SD, median [Q1, Q3], or n (%). The total N at each column represent the number of blocks.

comparison between guided method and unguided method showed a similar result to our primary analysis for three evaluators, that no statistically significant difference was detected between the two methods (Table 1). Except for one evaluator, we found the guided method had a lower percentage of perfect visualization with an estimated mean difference of -3.7% (95% CI: [-6.6, -0.7], p = 0.01) comparing guided to unguided insertion.

Secondary analysis results

The median time to finish the block was 34 (IQR: 18, 69) seconds for blocks performed under the needle guidance system and 35 (19, 65) seconds for blocks performed without the needle guidance (Fig. 4). Time to reach the target also did not differ significantly with an estimated hazard ratio of 1.00 (95% CI: [0.86, 1.16], p = 0.99). Finally, time to reach the target site did not differ significantly between groups (95% CI: 14% slower to 16% faster), indicating no clear difference compared to the unguided group.

Exploratory analysis results

Averaged assessors' overall perception was estimated as 3 ± 1 in both groups (Table 1). Estimated inter-rater reliability of consistency of 0.84 (95% CI: 0.81, 0.86) on overall perception rating, indicates good consistency among assessors. The evaluator's overall perception was also summarized separately by treatment groups in Table 1. The residents' procedural difficulty was rated 6.5 ± 1.9 under needle guidance and 6.6 ± 1.5 without needle guidance. The average number of attempts needed to perform each block was 1.2 ± 0.6 with mechanical guidance, and 1.3 ± 1.1 without (Table 1).

Data from all assessors were analyzed; missing values were excluded from the analysis. No imputation methods were applied.

Discussion

Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) mechanical needle guidance did not improve

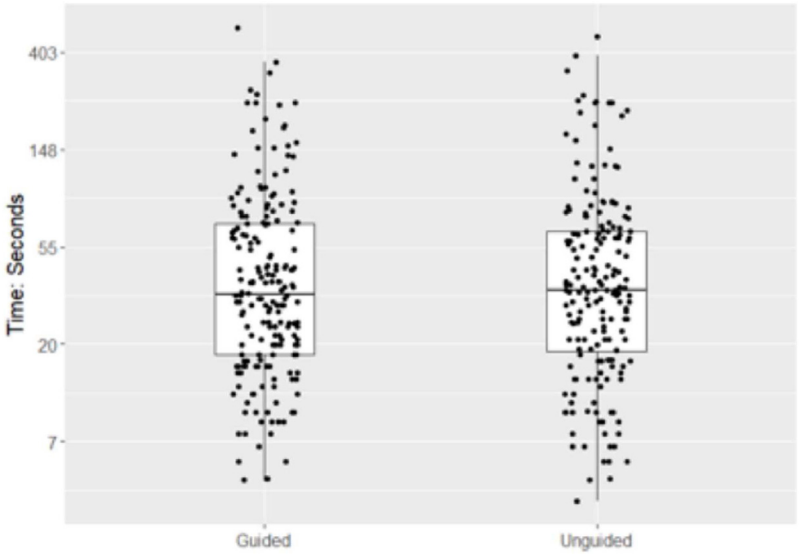

Figure 4 Time to reach target in blocks using needle guidance system vs. without needle guidance.

ultrasound needle visibility during thoracic paravertebral block by novice residents. Additionally, time to reach the target, and assessors' overall perception, residents' evaluation, and the average number of attempts were similar with or without the needle guidance.

In a previous study, Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) needle guidance did not improve the percentage of perfect needle visibility during ultrasound-guided femoral nerve catheter placement.[17] Additionally, Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) guidance did not improve the fraction of successful femoral nerve catheter insertions or the number of attempts. However, the median time to properly position femoral nerve catheters was about a minute shorter with guidance, apparently because the device kept the needle tracking towards the target even when ultrasound visibility was imperfect.

Mansour et al.[18] evaluated a different CIVCO's needle guide called the Ultra-Pro II. The Ultra-Pro II is a two-part system consisting of custom reusable bracket and a disposable snap-on needle guide. Multi-angle brackets provide different angles appropriate for various blocks. This system improves needle visibility score, and reduces time needed to perform a parasagittal in-plane thoracic paravertebral block. The number of needle passes was lower with guidance than without. Physician and patient satisfaction were better when using the needle guide.

The Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) needle guide that we used in our study has a fixed angle which sometimes made needle manipulation difficult. The fixed angle may explain why the Infiniti Plus (In-plane, CIVCO Medical Solutions, Coralville, Iowa) guide did not improve the evaluator's overall perception of needle visibility, time to reach the target site, the number of attempts, and procedural difficulty evaluated by novice residents. Additionally, previous trials of the Infiniti Plus and Ultra-Pro[17,18] involved experienced anesthesiologists, whereas our procedures were conducted by novice residents.

Gupta et al.[16] reported also that Ultra-Pro II multi-angle in-plane needle guidance reduces median time to complete a simulated nerve targeting task in a phantom gel simulation of the regional block by novice sonographers by 27%, and the needle guide system provided improved needle view at the completion of the task by a factor of three. Both that study and ours used novice sonographers, but their phantom gel simulation may not entirely reflect needle insertion in human tissue planes.

The Infiniti Plus system is shown to offer an open-channel design with infinite angle adjustability and broad-gauge compatibility via a snap-on disposable guide and reusable bracket, optimized for in-plane procedures such as biopsies, fluid aspiration, and catheter placement. By contrast, the Ultra-Pro II employs a multi-angle bracket with discrete insertion angles and a larger quick-release tab, accepting a slightly different gauge range and offering alternative cover formats tailored for regional blocks and line placements.

The comparison clarifies that Infiniti Plus prioritizes continuous angle flexibility and broad-gauge acceptance, whereas Ultra-Pro II emphasizes preset entry angles and an enhanced quick-release feature, each addressing different clinical workflow preferences.

While mechanical guides simplify in-plane alignment, fixed-angle systems can impede ergonomic probe handling and real-time needle redirection, particularly in obliquely angled or deep thoracic paravertebral blocks where minor trajectory adjustments are crucial.[19,20] The rigid sleeve may force suboptimal wrist postures and limit probe tilt, increasing musculoskeletal strain and reducing beam-needle alignment efficiency.[21] In parasagittal approaches to the paravertebral space, where navigation around ribs and variable tissue depths demands frequent small angulation changes, fixed guides may hinder nuanced needle advancement, potentially prolonging procedure time or risking misplacement.[22]. We suggest that variable-angle or multi-angle guides could offer superior adaptability and ergonomics for thoracic blocks.

Several complementary technologies beyond the Infiniti Plus mechanical guide have been developed to enhance

ultrasound needle visualization: echogenic needles, which feature surface coatings or textured grooves to increase backscatter and markedly improve needle tip conspicuity in vivo, especially at steep insertion angles,[23,24] electronic beam steering, wherein the ultrasound beam is dynamically tilted to maintain near-perpendicular incidence on the needle shaft, has been shown to significantly enhance needle and tip visibility by subjective inspection;[25] active needle-tracking systems like Onvision employ a piezoelectric sensor near the needle tip and provide real-time visual overlays (e.g., colored circles) on the ultrasound screen, improving tip localization in infraclavicular and other regional blocks.[26]

Mechanical needle guides may be a valuable bridging tools for novices by providing consistent entry angles and reducing cognitive load during the earliest stages of ultrasound-guided block training. However, reliance on structured guides risks delaying the acquisition of proprioceptive skills and intuitive probe-needle coordination that are essential for independent free-hand practice. To ensure balanced skill development, we recommend integrating mechanical guidance into a graduated curriculum, with early use under expert supervision, followed by systematic weaning toward unguided techniques, to reinforce both anatomical understanding and hand-eye alignment proficiency.

While our cadaver study showed no benefit of the Infiniti Plus mechanical guide in novice resident-performed thoracic paravertebral blocks, mechanical guidance has been shown to improve first-pass success and reduce needle passes in peripheral nerve blocks such as femoral and sciatic blocks, enhancing procedural efficiency and safety.[27,28] It can also stabilize needle trajectory during central venous catheterization, reducing inadvertent vessel punctures and improving placement accuracy in both emergency and routine vascular access.[29,30] Mechanical guides further aid deep or technically demanding blocks, like lumbar plexus and quadratus lumborum, by maintaining consistent in-plane alignment at steep insertion angles, thereby enhancing needle tip visibility.[31,32] Experienced anesthesiologists may benefit from reduced ergonomic fatigue and improved precision during prolonged procedures or challenging anatomies, as mechanical guidance mitigates inadvertent beam-angle deviations caused by operator fatigue or transducer movement.[33,34]

A limitation of our study was that some information regarding the cadavers was incomplete. For example, 5 were missing BMI and the sex of two was unknown. A limitation of any study in cadavers is the physiological differences between living and deceased tissues. We mitigated this shortcoming by using unembalmed human cadavers at room temperature to simulate the tissue elasticity of live humans. Cadaver studies allowed many procedures to be tested by novice residents which is not possible in patients. Evidence from cadavers may not directly predict clinical outcomes, thus cautious interpretation of the results in cadavers is warranted, and future study in patients in a randomized trial is necessary. Additionally, we did not record needle guidance system set-up time, although set-up time contributes to overall procedure duration. Our aim was to evaluate the usability of mechanical needle guidance among novice residents; participants were intentionally selected as inexperienced in ultrasound-guided techniques. We assume that procedural skills improved over the course of the study, potentially influencing needle visualization outcomes. Anatomical differences across the various cadavers and spinal levels were considered to ensure that our results reflect real-world applicability rather than being limited to findings in cadavers.

The lack of significant difference between guided and unguided methods may reflect ceiling effects, given that both approaches were already relatively successful in reaching the target site.

Although cadaver models offer high−fidelity anatomy and safe practice conditions, they lack several critical in vivo characteristics, namely real−time bleeding, respiratory excursion, and native tissue turgor, which can substantially affect needle handling and visualization during regional anesthesia.[35,36] The absence of bleeding removes the challenge of managing artifact and hemodynamic changes seen during live procedures, while static lungs preclude practicing needle redirection under respiratory motion. Moreover, postmortem tissue dehydration and fluid shifts alter normal turgor, potentially overestimating needle tip conspicuity and underrepresenting the force required for ligament penetration. Consequently, our negative findings in a cadaver setting may not fully translate to clinical practice, and future work should validate mechanical guidance systems under live conditions or with dynamic cadaver preparations (e.g., perfused, ventilated, or Thiel−embalmed models) to better simulate real−world challenges.[37]

Our study's achieved power of 0.76, just below the 0.80 convention, reflects a slight underpowering due to exclusion of two residents. Borderline underpowered trials are prone to Type II errors, whereby true effects may go undetected, and thus our non-significant results should be interpreted with appropriate caution. We recommend that subsequent investigations aim for larger sample sizes or multicenter designs to ensure adequate power for detecting clinically relevant differences.

We did not evaluate within-participant performance over the sequential blocks, so it remains possible that residents improved with practice in a way that could mask or modify any early advantage of the mechanical guide. Future studies should incorporate formal learning-curve analyses, such as comparing early versus late block performance, to clarify whether guidance systems confer the greatest benefit during initial skill acquisition.

Some outcomes in our study, such as procedural difficulty and needle visualization scores, relied on subjective assessment. While blinding of assessors was implemented to reduce bias, subjective scoring inherently introduces variability and potential bias. This limitation should be considered when interpreting our findings.

Conclusion

In this cadaveric model of thoracic paravertebral blocks performed by novice residents, the Infiniti Plus mechanical guide did not confer measurable improvements in needle visualization, procedural efficiency, or ease of block insertion compared to freehand technique. These findings contrast with prior evidence suggesting that certain mechanical guides, particularly variable- or multi-angle systems, may enhance first-pass success and reduce procedure time in

other block settings. The fixed-angle design of the Infiniti Plus may limit ergonomic flexibility and hinder nuanced adjustments required for complex thoracic approaches.

Although our results did not demonstrate clear benefits, mechanical guidance devices may still serve a role in early training by providing consistent entry angles and reducing cognitive load for beginners. However, their utility should be balanced against the risk of slowing the development of freehand skills critical for independent practice. Future research should validate these findings in live patient models, with larger multicenter samples and formal learning-curve analyses, to determine whether mechanical guidance systems hold value in clinical training or specific block types. Ultimately, careful integration of such tools into structured educational curricula may help optimize both novice learning and procedural safety.

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 listed authors have made significant contributions to this work, including study design, data collection, analysis, interpretation, and manuscript preparation. Their collective efforts justify their recognition as authors.

Declaration of competing interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844716.

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ORIGINAL INVESTIGATION

Comparative effectiveness of TAP block, EOIP block, and standard care for postoperative analgesia in renal transplantation: a retrospective study

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Abstract

Background: Effective pain management following renal transplantation is crucial. While various regional analgesic techniques have been studied, the optimal approach remains unclear. We compared the additive value of Transversus Abdominis Plane (TAP) and External Oblique Intercostal Plane (EOIP) blocks to Standard Care (SC) on postoperative pain and opioid consumption.

Methods: This retrospective study included 237 renal transplant recipients (127 SC, 75 TAP, 35 EOIP) between January 2023 and December 2024. Multivariable regression analysis assessed the association of block type on postoperative pain and opioid consumption.

Results: TAP block was associated with significantly lower pain scores than SC during the first eight postoperative hours (5.0 vs. 7.0, $p < 0.001$). Pre-incision TAP block demonstrated the most significant reduction in both pain scores (β = -2.21, 95% CI -3.38 to -1.05, $p < 0.001$) and opioid consumption (β = -13.56, 95% CI: -21.59 to -5.52, p = 0.001). EOIP block showed no significant advantages over SC and was associated with higher opioid consumption compared to TAP block.

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Conclusion: Pain predominantly manifested in the first eight postoperative hours. TAP block, particularly when administered pre-incision, was associated with superior pain control compared to SC or EOIP block. Living donor recipients experienced significantly higher pain scores regardless of technique, warranting further investigation.

Introduction

Though Renal Transplantation (RT) is the definitive treatment for end-stage renal disease, offering significant improvements in quality of life and survival compared to dialysis,[1] it is frequently associated with moderate to severe postoperative pain.[2] Pain management in this specific patient population is particularly challenging due to impaired renal function, which restricts the use of many analgesics.[3]

Enhanced Recovery After Surgery (ERAS) protocols have emerged as a promising approach for RT, reducing both pain scores and opioid consumption while leading to shorter hospital stays, decreased morbidity, and improved patient satisfaction.[4–6]

As part of the ERAS pathway for RT, various regional analgesic techniques have been investigated.[7–12] The Transversus Abdominis Plane (TAP) block has emerged as one of the most widely studied regional techniques in this context. However, despite promising results, there is still no consensus on the optimal regional analgesia approach for this surgery.

The External Oblique Intercostal Plane (EOIP) block has recently emerged as a promising novel technique, gaining attention for both its simplicity and effectiveness.[13] By blocking the intercostal nerves from T6 to T11, it provides effective analgesia for the anterolateral upper abdominal wall.[13] However, the Gibson incision used for renal transplantation typically involves dermatomes from T10/11 to L1/2, which extends beyond the EOIP block coverage. Although the EOIP block only partially covers the dermatomal distribution of the Gibson incision, its potential utility in RT has been suggested in the literature. Notably, in the original case series by Elsharkawy et al. that introduced this block, one of the 22 reported patients had received the EOIP block for RT.[13] The block's practical advantages – including technical simplicity, distance from the surgical site, and elimination of dressing manipulation – make it an attractive option for investigation in this setting.

Given the absence of consensus guidelines for optimal analgesic protocol in RT and the theoretical potential of EOIP block despite partial dermatomal coverage, we conducted this retrospective study to compare the efficacy of commonly used analgesic techniques and identify factors associated with improved pain control and reduced opioid consumption.

Methods

Ethics, design, and settings

This retrospective exploratory study was conducted at Rabin Medical Center, Beilinson Hospital, Israel (the Israeli National Transplantation Center). Ethical approval (0649–24-RMC) was provided by the Institutional Review Board (Chairperson Prof. Ran Tur-Kaspa) in January 2025. Written informed consent was waived due to the retrospective, non-interventional nature of the study. This manuscript adheres to the STROBE statement.

Study population

We included patients aged 18 years, and above who underwent RT and had complete medical records available. Patients were excluded if they had undergone dual organ transplantation (such as liver, and RT or pancreas and RT), experienced intraoperative bleeding requiring transfusion of more than three blood products, had surgeries lasting longer than six hours, received additional regional analgesic techniques beyond the study focus (such as quadratus lumborum, erector spinae plane, intercostal, ilioinguinal-iliohypogastric blocks, or combination of more than one block), required rescue blocks in the Post Anesthesia Care Unit (PACU), were transferred to PACU while on mechanical ventilation, had a PACU stay exceeding eight hours, or were directly transferred to the Intensive Care Unit (ICU) immediately after surgery.

Anesthetic and analgesic care

At the study institution, RT recipients typically receive the following Standard Care (SC), although minor variations in drug selection and dosing may occur based on the anesthesiologist's clinical judgment and patient-specific conditions.

Intraoperative care

Anesthesia was induced intravenously using fentanyl (1–3 $mg.kg^{-1}$), propofol (1–2 $mg.kg^{-1}$), and either rocuronium (0.6–1.2 $mg.kg^{-1}$) or atracurium (0.3–0.5 $mg.kg^{-1}$). Dosing was individualized based on patient characteristics and comorbidities. Anesthesia was maintained using volatile anesthetic agents. Unless contraindicated, patients received intraoperative multimodal analgesia consisting of intravenous paracetamol (1 g), tramadol (100 mg), and dipyrone (1 g).

Regional analgesic techniques

Based on anesthesiologist discretion, in addition to the SC, some patients received ultrasound-guided (GE Healthcare, Venue GO, Chicago, IL, USA) TAP or EOIP block, either pre- or post-incision (at the end of surgery). For the TAP block, a high-frequency linear probe (6–12 MHz) was used for imaging, and a 22 $G \times 50$ mm or 22 $G \times 80$ mm needle (SonoTAP®; PAJUNK® GmbH, Medizintechnologie, Geisingen, Germany)

was used to inject local anesthetic into the plane between the internal oblique and transversus abdominis muscles at the triangle of Petit.[14] For the EOIP block, a high-frequency linear probe (6–12 MHz) was used for imaging, and a 22 $G \times 50$ mm needle (SonoTAP®; PAJUNK® GmbH) was used to inject a local anesthetic into the fascial plane between the external and internal oblique muscles at the level of the 6th to 7th ribs along the anterior axillary line.[13] The volume of the local anesthetic was adjusted according to the patient's weight while maintaining local anesthetic safety limits. Typically, bupivacaine 0.25 % with epinephrine (Bupicain® with epinephrine, Monico spa, Venezia, Italy) was injected at a dose of 0.3–0.6 $mL.kg^{-1}$.

Postoperative care

In the PACU, breakthrough pain was managed with intravenous tramadol 100 mg, followed by titrated doses of intravenous morphine (3–5 mg) as needed. All patients received scheduled intravenous paracetamol (1 g) and dipyrone (1 g) every eight hours. After transferring to the surgical ward, patients continued with scheduled paracetamol and dipyrone. For breakthrough pain (NRS > 5), patients received either tramadol (100 mg), oxycodone (5–10 mg), or combination analgesics such as paracetamol 325 mg/oxycodone 7.5 mg or paracetamol 500 mg/caffeine 30 mg/codeine phosphate 10–15 mg.

Study groups

Patients were categorized into three groups based on the analgesic technique received: SC group, which received SC alone; TAP group, which received SC and TAP block; EOIP group, which received SC and EOIP block.

Study objectives

The objectives of this retrospective study were to:

1. Compare pain scores and opioid consumption during the first 72 hours postoperatively among the study groups and identify factors associated with these outcomes;
2. Compare the incidence of postoperative complications, PACU length of stay, and hospital length of stay among the study groups;
3. Assess the impact of regional block timing (pre-incision vs. post-incision) on analgesic efficacy in the TAP and EOIP groups.

Measurements and data collection

Data were extracted from the electronic medical record systems (Metavision, iMDSoft, Israel; and Chameleon™, Elad Health, Israel). Pain scores were assessed using the numeric rating scale (NRS), recorded at least twice per 8-hour shift per institutional protocol, with additional measurements for patients reporting pain. The first 24 hours were divided into 8-hour intervals (0–8, 8–16, 16–24 hours) to provide higher temporal resolution during the period of expected peak postoperative pain, followed by 24–48 and 48–72 hour periods. The maximum NRS value from all recordings within each time period was used to capture clinically significant pain episodes and prevent underestimation in patients with intermittent severe pain. Opioid consumption was quantified as the oral Morphine Milligram Equivalents (MME) and calculated both for intraoperative and each postoperative period. Oral MME was calculated using standardized conversion factors (e.g., 0.2 for 1 mg of intravenous tramadol, 3 for 1 mg of intravenous morphine, 1.5 for 1 mg of oral oxycodone, 0.15 for 1 mg of oral codeine, and 300 for 1 mg of intravenous fentanyl).[15]

In addition, sociodemographic and medical history data were collected, including age, gender, Body Mass Index (BMI), the American Society of Anesthesiologists (ASA) physical status, comorbidities, and concurrent medications. Intraoperative data included surgery duration and type (living or deceased donor), analgesic technique (SC, TAP block, or EOIP block), and block timing. Postoperative data included analgesic and anesthetic drug administration up to 72 hours postoperatively, complications (such as reoperation, surgical site infection, and unplanned ICU admission) within 72 hours, PACU and hospital length of stay, in-hospital mortality, and 30-day mortality.

Statistical methods

Descriptive statistics were used to summarize the data. The distribution of continuous variables was assessed visually using histograms and Q-Q plots. As none of the continuous variables were normally distributed, continuous variables were reported as medians with interquartile ranges [25th, 75th percentiles] and compared using the Kruskal-Wallis test, followed by Dunn's post hoc test with Bonferroni correction for pairwise comparisons. Categorical variables were presented as counts and percentages (%) and compared using the Chi-Square test or Fisher's exact test, as appropriate.

Multivariable regression models were employed to evaluate the association between analgesic techniques and pain scores and opioid consumption, adjusted for potential confounders, including age, gender, BMI, diabetes mellitus, analgesic modality, and intraoperative MME. Regression results were reported as beta coefficients with corresponding 95 % Confidence Intervals (95 % CIs) and p-values. Subgroup analyses were performed to investigate the impact of TAP block timing (pre- vs. post-incision) on pain scores and opioid consumption. All statistical tests were two-sided; a p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using *R* statistical software (version 4.4.1).

Results

Between January 1, 2023, and December 31, 2024, a total of 237 patients met the study inclusion criteria and were included in the analysis. Of these, 127 were in the SC group, 75 in the TAP group, and 35 in the EOIP group. The participant inclusion flow diagram is illustrated in Figure 1.

Table 1 presents detailed baseline characteristics and intraoperative data stratified by analgesic technique. Baseline characteristics were comparable across the groups, with a median age of 55.0 (43.0, 64.0) years and a male

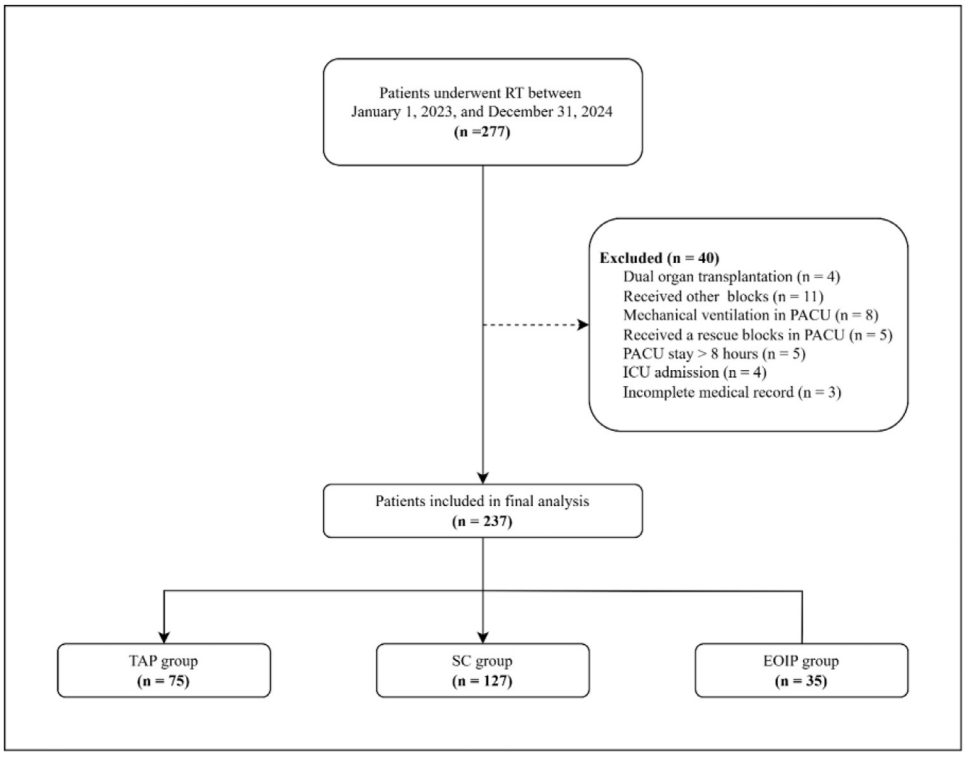

Figure 1 Patient inclusion flow diagram. EOIP, External Oblique Intercostal Plane; ICU, Intensive Care Unit; PACU, Post Anesthesia Care Unit; RT, Renal Transplantation; SC, Standard Care; TAP, Transversus Abdominis Plane.

predominance of 168 (71 %). There were no significant differences in BMI, ASA physical status, or key comorbidities. Most kidney grafts, 165 (70 %), were from living-related donors. Of the regional blocks performed, 81 (74 %) were administered post-incision. The median duration of surgery was 3.4 (3.0, 3.9) hours. Intraoperative opioid consumption, measured in MME, differed significantly among groups, with the SC group requiring higher doses compared to the TAP group (95.0 [80.0, 110.0] vs. 80.0 [80.0, 95.0], $p = 0.011$).

Postoperative outcomes are detailed in Table 2. Maximum pain scores in the first 24 hours were significantly different across groups ($p < 0.001$), with the TAP block group showing lower scores compared to the SC group (5.0 [2.0, 7.0] vs. 7.0 [5.0, 7.5], $p < 0.001$). This difference was primarily driven by pain scores in the first eight hours postoperatively (5.0 [1.5, 7.0] vs. 7.0 [5.0, 7.5], $p < 0.001$). Beyond eight hours, pain scores were comparable across all groups, with median NRS scores remaining below two from eight to 72 hours postoperatively. Total opioid consumption in the first 24 hours differed significantly between groups ($p = 0.009$), with higher consumption in the EOIP group compared to the TAP group (50.0 [35.0—58.8] vs. 30.0 [18.6, 50.0] MME, $p = 0.010$). This difference was most pronounced in the first eight hours after surgery (50.0 [30.0, 50.0] vs. 30.0 [15.0, 50.0] MME, $p = 0.015$). Beyond 24 hours, opioid requirements were minimal across all groups, with a median consumption of 0 MME and no significant differences between groups. Figure 2 illustrates the temporal changes in pain scores and opioid consumption across the three groups during the first 72 postoperative hours.

Multivariable regression analysis adjusting for age, sex, BMI, diabetes mellitus, living donor status, and intraoperative MME confirmed the independent association between TAP block and early postoperative pain control (Table 3). Compared to SC, TAP block was associated with significantly lower pain scores ($\beta = -1.60$, 95 % CI: -2.36 to -0.84, $p < 0.001$) and reduced opioid consumption ($\beta = -7.32$, 95 % CI: -12.56 to -2.08, $p = 0.006$) in the first eight hours after surgery. EOIP block showed no significant difference from SC in either pain scores ($\beta = -0.55$, 95 % CI: -1.55 to 0.45, $p = 0.282$) or opioid consumption ($\beta = 1.22$, 95 % CI: -5.69 to 8.13, $p = 0.728$). Living donor transplantation was independently associated with higher pain scores ($\beta = 0.91$, 95 % CI: 0.13 to 1.68, $p = 0.022$).

Further subgroup analysis accounting for block timing revealed that the analgesic benefit of TAP block was most pronounced when administered before surgical incision (Table 4). Pre-incision TAP block was associated with the largest reduction in both pain scores ($\beta = -2.21$, 95 % CI: -3.38 to -1.05, $p < 0.001$) and opioid consumption ($\beta = -13.56$, 95 % CI: -21.59 to -5.52, $p = 0.001$) compared to SC. While post-incision TAP block also reduced pain scores significantly ($\beta = -1.32$, 95 % CI: -2.18 to -0.47, $p = 0.003$), its effect on opioid consumption was not statistically significant ($\beta = -4.55$, 95 % CI: -10.44 to 1.35, $p = 0.130$). Neither pre- nor post-incision EOIP block showed significant differences from SC in pain scores or opioid requirements.

Postoperative complications were rare and occurred at similar rates across groups (Table 2). Overall, only 6 (2.5 %) patients were admitted to the ICU, 7 (3.0 %) patients developed a surgical site infection, and 5 (2.1 %) patients required reoperation. Median length of stay in PACU (3.3 [2.7, 4.1] hours) and hospital (6.5 [6.3, 8.5] days) were also comparable across groups.

Table 1 Baseline patient characteristics and intraoperative data by analgesic technique.

	Overall (*n* = 237)	SC (*n* = 127)	TAP block (*n* = 75)	EOIP block (*n* = 35)	Overall *p*-value	Post hoc *p*-value
Baseline patient characteristics						
Median age [IQR], years	55.0 [43.0, 64.0]	58.0 [44.5, 64.5]	55.0 [42.5, 64.0]	49.0 [36.0, 60.5]	0.107	
Sex, n (%)					0.507	
Male	168 (71 %)	94 (74 %)	51 (68 %)	23 (66 %)		
Female	69 (29 %)	33 (26 %)	24 (32 %)	12 (34 %)		
Median BMI [IQR], $kg.m^{-2}$	26.0 [22.9, 29.4]	26.2 [23.3, 30.0]	25.4 [21.9, 28.7]	25.9 [23.1, 29.0]	0.3	
ASA physical status					0.118	
Class III	154 (65 %)	80 (63 %)	55 (73 %)	19 (54 %)		
Class IV	83 (35 %)	47 (37 %)	20 (27 %)	16 (46 %)		
Background disease, n (%)						
Hypertension	146 (62 %)	83 (65 %)	44 (59 %)	19 (54 %)	0.402	
Ischemic heart disease	50 (21 %)	32 (25 %)	14 (19 %)	4 (11 %)	0.173	
Congestive heart failure	15 (6.3 %)	10 (7.9 %)	3 (4.0 %)	2 (5.7 %)	0.572	
Peripheral vascular disease	14 (5.9 %)	6 (4.7 %)	6 (8.0 %)	2 (5.7 %)	0.598	
Atrial fibrillation	7 (3.0 %)	2 (1.6 %)	4 (5.3 %)	1 (2.9 %)	0.256	
OSA	8 (3.4 %)	3 (2.4 %)	3 (4.0 %)	2 (5.7 %)	0.427	
Obesity	54 (23 %)	32 (25 %)	14 (19 %)	8 (23 %)	0.565	
COPD/Asthma	12 (5.1 %)	9 (7.1 %)	1 (1.3 %)	2 (5.7 %)	0.182	
Active smoking	48 (20 %)	24 (19 %)	17 (23 %)	7 (20 %)	0.812	
CVA/TIA	14 (5.9 %)	7 (5.5 %)	4 (5.3 %)	3 (8.6 %)	0.696	
Diabetes mellitus	61 (26 %)	33 (26 %)	18 (24 %)	10 (29 %)	0.874	
Intraoperative data						
Donation type, n (%)					0.180	
Deceased donor	72 (30 %)	42 (33 %)	24 (32 %)	6 (17 %)		
Living donor	165 (70 %)	85 (67 %)	51 (68 %)	29 (83 %)		
Block timing					0.167	
Before incision	29 (26 %)		23 (31 %)	6 (17 %)		
After incision	81 (74 %)		52 (69 %)	29 (83 %)		
Intraoperative MME, median [IQR]	80.0 [80.0—110.0]	95.0 [80.0—110.0]	80.0 [80.0—95.0]	80.0 [80.0—92.5]	**0.004**	**0.011**[a]
Surgery duration, median [IQR], hours	3.4 [3.0, 3.9]	3.3 [2.9, 3.8]	3.5 [3.0, 3.9]	3.5 [3.1, 3.9]	0.314	

Continuous variables were reported as medians with interquartile ranges (25th and 75th percentiles). Categorical variables were presented as counts and percentages (%). Statistical comparisons across groups were performed using the Kruskal-Wallis test for continuous variables and Chi-Square or Fisher's exact test for categorical variables. Adjusted pairwise comparisons were conducted using Dunn's test with Bonferroni correction for significant KW tests.

[a] Significant difference between SC and TAP.

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebrovascular Accident; EOIP, External Oblique Intercostal Plane; ICU, Intensive Care Unit; IQR, Interquartile Range; KW, Kruskal-Wallis; MME, Morphine Milligram Equivalent; OSA, Obstructive Sleep Apnea; PACU, Post Anesthesia Care Unit; SC, Standard Care; TIA, Transient Ischemic Attack; TAP, Transversus Abdominis Plane.

Table 2 Postoperative outcomes by analgesic technique.

	Overall ($n = 237$)	SC ($n = 127$)	TAP block ($n = 75$)	EOIP block ($n = 35$)	Overall *p*-value	Post hoc *p*-value
Pain scores, median [IQR]						
Maximum NRS for 0–24 hours	6.0 [4.0–7.0]	7.0 [5.0–7.5]	5.0 [2.0–7.0]	6.0 [5.0–7.0]	**< 0.001**	**< 0.001**[a]
0–8 hours	6.0 [4.0–7.0]	7.0 [5.0–7.5]	5.0 [1.5–7.0]	6.0 [5.0–7.0]	**< 0.001**	**< 0.001**[a]
8–16 hours	1.0 [0.0–1.0]	1.0 [0.0–1.0]	1.0 [0.0–1.5]	1.0 [0.0–1.0]	0.426	
16–24 hours	1.0 [0.0–2.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.987	
Maximum NRS for 24–48 hours	2.0 [1.0–2.0]	2.0 [1.0–2.0]	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.692	
Maximum NRS for 48–72 hours	1.0 [0.0–2.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	2.0 [1.0–2.0]	0.077	
Opioid consumption, median [IQR]						
Total MME for 0–24 hours	35.0 [20.0 –50.0]	37.5 [27.5 –50.0]	30.0 [18.6 –50.0]	50.0 [35.0 –58.8]	**0.009**	**0.010**[b]
0–8 hours	30.0 [20.0 –50.0]	30.0 [20.0, 50.0]	30.0 [15.0, 50.0]	50.0 [30.0, 50.0]	**0.012**	**0.015**[b]
8–16 hours	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.408	
16–24 hours	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–1.1]	0.882	
Total MME for 24–48 hours	0.0 [0.0–9.8]	0.0 [0.0–3.8]	0.0 [0.0–12.3]	0.0 [0.0–20.0]	0.316	
Total MME for 48–72 hours	0.0 [0.0–2.3]	0.0 [0.0–0.0]	0.0 [0.0–2.3]	0.0 [0.0–2.3]	0.394	
Postoperative complications, n (%)						
ICU admission	6 (2.5 %)	4 (3.1 %)	1 (1.3 %)	1 (2.9 %)	0.736	
Surgical site infection	7 (3.0 %)	6 (4.7 %)	0 (0 %)	1 (2.9 %)	0.169	
Reoperation	5 (2.1 %)	2 (1.6 %)	2 (2.7 %)	1 (2.9 %)	0.699	
PACU stay, median [IQR], hours	3.3 [2.7, 4.1]	3.3 [2.8, 4.1]	3.2 [2.5, 3.8]	3.0 [2.6, 4.3]	0.282	
Hospital stay, median [IQR], days	6.5 [6.3, 8.5]	6.7 [6.3, 9.4]	6.7 [6.3, 8.3]	6.3 [6.0, 7.3]	0.108	

Continuous variables were reported as medians with interquartile ranges (25th and 75th percentiles). Statistical comparisons across groups were performed using the Kruskal-Wallis test for continuous variables and Chi-Square or Fisher's exact test for categorical variables. Adjusted pairwise comparisons were conducted using Dunn's test with Bonferroni correction for significant KW tests:

[a] Significant difference between SC and TAP.

[b] Significant difference between TAP and EOIP.

EOIP, External Oblique Pentercostal Plane; ICU, Intensive Care Unit; IQR, Interquartile Range; KW, Kruskal-Wallis; MME, Morphine Milligram Equivalent; NRS, Numerical Rating Scale; PACU, Post Anesthesia Care Unit; SC, Standard Care; TAP, Transversus Abdominis Plane.

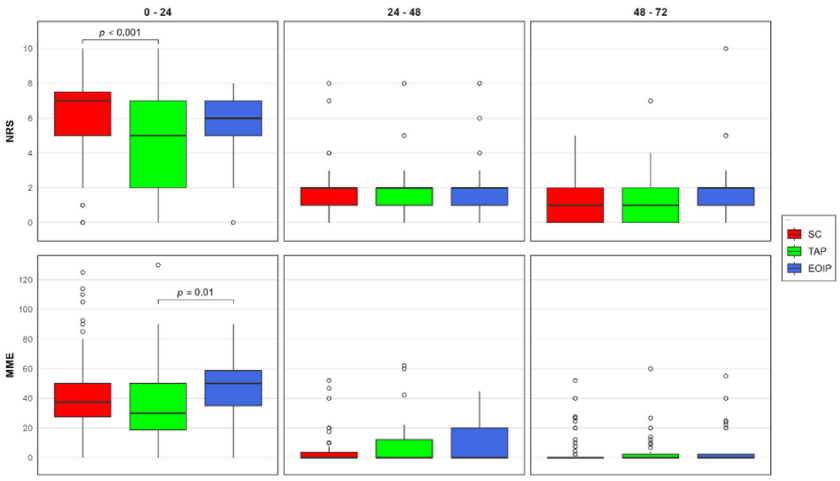

Figure 2 Pain scores and opioid consumption by analgesic technique during the first 72 postoperative hours. The upper panel represents pain (maximum NRS pain score) measured over time. The lower panel represents opioid consumption (MME) over time. In the box plots, medians are indicated by the central lines inside the boxes, IQRs are represented by the boxes, and the whiskers extend to 1.5 times the IQRs. Outliers, denoted by circles, are also displayed to highlight extreme data points. Significant differences between groups are shown with brackets and *p*-values from post-hoc Dunn's test with Bonferroni correction. EOIP, External Oblique Intercostal Plane; IQR, Interquartile Range; MME, Morphine Milligram Equivalent; NRS, Numeric Rating Scale; SC, Standard Care; TAP, Transversus Abdominis Plane.

Discussion

In this retrospective study comparing different analgesic approaches for RT recipients, we found that TAP block, particularly when administered pre-incision, was associated with superior early postoperative pain control compared to SC. This benefit was evident in both reduced pain scores and decreased opioid consumption during the first eight postoperative hours. EOIP block did not demonstrate significant advantages over SC and was associated with higher opioid consumption compared to TAP block. However, these findings should be interpreted cautiously given the small EOIP sample size (n = 35). Notably, beyond eight hours, pain scores and opioid requirements were minimal across all groups. An unexpected finding was that living donor recipients experienced significantly higher pain scores regardless of the analgesic technique employed.

Our findings regarding TAP block efficacy align with previous evidence in RT literature. While the observed reduction in pain score with the TAP block was statistically significant, its clinical relevance warrants further consideration. With our institutional threshold for breakthrough pain defined as NRS > 5, the reduction from median NRS 7.0 (SC) to 5.0 (TAP) represents a clinically meaningful change that reduces the need for rescue analgesia. This clinical significance is further supported by the corresponding reduction in opioid consumption observed in the TAP group. A meta-analysis by Singh et al., which evaluated TAP blocks across ten trials (258 control patients and 237 receiving TAP blocks), demonstrated that TAP blocks reduced 24 hour postoperative

Table 3 Multivariable linear regression analysis of factors associated with pain scores and opioid consumption during the first eight postoperative hours.

	NRS 0h – 8h		MME 0h – 8h	
	β coefficient (95 % CI)	*p*-value	β coefficient (95 % CI)	*p*-value
Age, years	0.00 (−0.03, 0.02)	0.926	−0.12 (−0.30, 0.06)	0.176
Male sex	−0.13 (−0.87, 0.60)	0.720	−0.90 (−6.00, 4.19)	0.727
BMI, kg.m^{-2}	−0.05 (−0.12, 0.02)	0.140	−0.36 (−0.85, 0.13)	0.146
Diabetes mellitus	−0.39 (−1.23, 0.44)	0.354	−1.69 (−7.44, 4.07)	0.564
Living donor	0.91 (0.13, 1.68)	**0.022**	4.97 (−0.38, 10.32)	0.068
Analgesic modality[a]				
TAP	−1.60 (−2.36, −0.84)	**< 0.001**	−7.32 (−12.56, −2.08)	**0.006**
EOIP	−0.55 (−1.55, 0.45)	0.282	1.22 (−5.69, 8.13)	0.728
Intraoperative MME	0.00 (−0.01, 0.02)	0.827	−0.01 (−0.11, 0.08)	0.782

Data presented as β coefficients with 95 % CI from multiple regression analysis.
[a] Analgesic modality comparisons are made with SC as the reference group.
BMI, Body Mass Index; CI, Confidence Interval; EOIP, External Oblique Intercostal Plane; MME, Morphine Milligram Equivalent; NRS, Numerical Rating Scale; SC, Standard Care; TAP, Transversus Abdominis Plane.

Table 4 Multivariable linear regression analysis of factors associated with pain scores and opioid consumption during the first eight postoperative hours, accounting for block timing.

	NRS 0h – 8h		MME 0h – 8h	
	β coefficient (95 % CI)	*p*-value	β coefficient (95 % CI)	*p*-value
Age, years	0.00 (−0.03, 0.03)	0.948	−0.12 (−0.30, 0.06)	0.186
Male sex	−0.06 (−0.81, 0.69)	0.875	−0.17 (−5.29, 4.95)	0.948
BMI, kg.m^{-2}	−0.05 (−0.13, 0.02)	0.130	−0.38 (−0.87, 0.11)	0.131
Diabetes mellitus	−0.41 (−1.25, 0.42)	0.332	−1.86 (−7.60, 3.87)	0.522
Living donor	0.90 (0.12, 1.67)	**0.023**	4.91 (−0.42, 10.23)	0.071
Block timing[a]				
TAP pre-incision	−2.21 (−3.38, −1.05)	**< 0.001**	−13.56 (−21.59, −5.52)	**0.001**
TAP post-incision	−1.32 (−2.18, −0.47)	**0.003**	−4.55 (−10.44, 1.35)	0.130
EOIP pre-incision	−0.96 (−3.11, 1.20)	0.382	−2.14 (−16.95, 12.68)	0.777
EOIP post-incision	−0.45 (−1.54, 0.63)	0.409	1.99 (−5.45, 9.44)	0.598
Intraoperative MME	0.00 (−0.01, 0.02)	0.856	−0.02 (−0.11, 0.08)	0.748

Data presented as β coefficients with 95 % CI from multiple regression analysis.

[a] Block timing comparisons are made with SC as the reference group.

BMI, Body Mass Index; CI, Confidence Interval; EOIP, External Oblique Intercostal Plane; MME, Morphine Milligram Equivalent; NRS, Numerical Rating Scale; SC, Standard Care; TAP, Transversus Abdominis Plane.

opioid consumption by approximately 42.7 % in RT recipients and decreased intraoperative opioid requirements and pain scores in both early and delayed postoperative phases.[16] However, the optimal timing of TAP block administration, whether pre- or post-incision, remains a topic of debate. While some studies suggest that pre-incision administration may offer superior analgesia,[17,18] a recent meta-analysis reported that post-incision TAP blocks may be slightly more effective in reducing 24-hour postoperative opioid consumption and postoperative nausea and vomiting compared to pre-incision blocks.[19] In our cohort, pre-incision TAP block was associated with the largest reductions in both pain scores and opioid consumption compared to SC, while post-incision administration was associated with more modest benefits for pain scores, without significantly affecting opioid consumption. These findings suggest a potential association between pre-incision TAP blocks and improved analgesic outcomes, possibly related to pre-emptive analgesia and preservation of anatomical plane integrity before surgical manipulation.

This is the first study to evaluate the efficacy of the EOIP block in RT recipients. We investigated the EOIP block based on literature precedent and its practical advantages (technical simplicity, distance from the surgical site), despite acknowledging its partial dermatomal coverage. Given the absence of consensus guidelines for RT analgesia, this prompted our systematic comparison. The EOIP block has demonstrated effectiveness in reducing pain scores and opioid requirements across various upper abdominal surgeries, including subxiphoid video-assisted thoracoscopic surgery,[20] laparoscopic cholecystectomy,[21–23] laparoscopic sleeve gastrectomy,[24,25] living kidney donor open nephrectomy,[26] and management of chronic post-surgical neuropathic pain.[27] Despite its proven efficacy in these procedures, limited data exists regarding its application in RT.[13] In our study, the EOIP block did not show a significant advantage over SC in RT recipients and was associated with higher opioid consumption compared to the TAP block. However, with only 35 patients in the EOIP group (including only six pre-incision blocks), our study was underpowered to detect potential benefits of this technique. Several factors may explain these findings. First, the dermatomal coverage of the EOIP block (T6–T11)[13] only partially overlaps with the Gibson incision (T10/11–L1/2), which is the standard surgical approach for RT at the study institution. This partial overlap may leave the lower segments of the surgical field inadequately covered. Second, as evidenced by our TAP block findings, the timing of block administration appears to be associated with different outcomes, with pre-incision blocks showing associations with superior efficacy.

Our study demonstrated minimal pain and opioid consumption beyond eight hours postoperatively, reinforcing the utility of multimodal analgesia and corroborating findings from other studies on this topic.[28–30]

Another interesting finding was that living donor transplantation was independently associated with significantly higher pain scores. This finding appears counterintuitive, given that living donor transplantation typically allows for more controlled operative conditions and shorter cold ischemia times than deceased donor procedures. Living donor recipients are generally healthier and younger, which might contribute to differences in pain perception compared to deceased donor recipients, who often have longer histories of dialysis and more comorbidities. However, this finding requires further investigation to understand the underlying mechanisms.

Limitations and future direction

There are several limitations to our study. The retrospective nature of our study introduces potential selection bias, as the choice of analgesic technique was not randomized but based on individual anesthesiologist preference and expertise. The study was also limited by sample size disparities between groups, particularly in the EOIP group (n = 35), with notably few pre-incision blocks (n = 6). This imbalance might have affected our ability to detect the potential benefits of EOIP block, especially regarding the timing-dependent

effects we observed with TAP blocks. The single-center design may affect the generalizability of our findings, as our institutional protocols and surgical approaches might differ from other transplant centers. Furthermore, due to the retrospective design, we could not assess several relevant outcomes, such as patient satisfaction, chronic pain development, or long-term functional recovery. Future prospective randomized trials should focus on comparing different regional analgesic techniques, particularly block timing. The EOIP block findings warrant further investigation with larger sample sizes. The observed association between donor type and postoperative pain also merits a dedicated study to understand the underlying mechanisms better and optimize pain management strategies.

Conclusion

This retrospective study demonstrates that the TAP block, particularly when administered pre-incision, was associated with superior early postoperative pain control in RT recipients compared to SC. EOIP block showed no significant benefit, though the small sample size limits definitive conclusions. The critical period for pain management was the first eight postoperative hours.

Data availability

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.

Clinical trial registration

N/A.

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

During the preparation of this work, the authors used "Claude AI" for text and grammar correction. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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ORIGINAL INVESTIGATION

Effect of lidocaine and magnesium sulfate on rocuronium onset time: a randomized controlled experimental study

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Abstract

Background: Neuromuscular blockers such as succinylcholine are widely used for airway management in critically ill patients; but their use may be contraindicated due to adverse effects. In rapid sequence intubation, the onset time of the neuromuscular blocker is critical and should be as short as possible. This study investigates whether lidocaine and magnesium sulfate could reduce the onset time of rocuronium bromide in an experimental model.

Method: Eighteen animals were randomly assigned to three groups and treated with lidocaine, magnesium sulfate, or saline before receiving rocuronium bromide (3 $mg.kg^{-1}$). After 10 minutes of neuromuscular blockade, reversal was performed with sugammadex (9 $mg.kg^{-1}$). Onset and reversal times were measured by acceleromyography. Doses were standardized in a pilot study with four animals. Data were tested for normality using the Shapiro-Wilk and Anderson-Darling tests. Onset times are tested with a one-way ANOVA, followed by Fisher's (LSD) post hoc test, and mean arterial pressure and heart rate with a two-way ANOVA, followed by Tukey's post hoc test. Statistical significance was set at $p \leq 0.05$.

Results: The results showed that lidocaine and magnesium sulfate significantly reduced the onset time of rocuronium bromide compared to the saline solution ($p < 0.05$) and did not affect the onset time of reversal with sugammadex ($p > 0.05$). Both adjuvants caused hypotension, with a more significant effect observed with magnesium sulfate; however, blood pressure returned to baseline values.

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Conclusion: In conclusion, lidocaine and magnesium sulfate facilitate airway access by reducing the onset time of rocuronium bromide.

Animal Ethics Committee approved 1749/2022.

Introduction

Endotracheal intubation for airway protection plays a crucial role in various settings, including pre-hospital care, emergency rooms, operating rooms, and intensive care units.[1] Neuromuscular blockers are essential for tracheal intubation in situations involving the risk of gastric content aspiration or respiratory failure with severe hypoxemia.[2] Their selection must be based on a thorough understanding of the drug's pharmacological properties, as well as the specific characteristics of each patient and clinical scenario.[3]

Although widely used, succinylcholine has several adverse effects, leading to the search for new non-depolarizing agents. Rocuronium bromide provides optimal intubation conditions within 60 seconds when administered at a dose of 1.0 mg.kg^{-1}.[3,4] It acts by competing for nicotinic cholinergic receptors at the motor endplate and can have its effect reversed by a specific agent or anticholinesterase drugs. Rocuronium is the preferred alternative when succinylcholine is contraindicated.[3]

To further shorten the onset time of rocuronium, the investigation of adjuvant drugs is warranted. Clinically established agents such as lidocaine and magnesium sulfate have been suggested to enhance neuromuscular blockade. Magnesium exerts presynaptic effects mainly through calcium interaction, inhibiting acetylcholine release, whereas lidocaine can bind to specific sites on acetylcholine receptors, leading to receptor desensitization and post-synaptic blockade. Therefore, this study aimed to evaluate the influence of lidocaine and magnesium sulfate on the onset time of rocuronium bromide, as well as its reversal with sugammadex, using Train-Of-Four (TOF) monitoring with acceleromyography in an experimental model.

Materials and methods

The study was approved by the Animal Ethics Committee of the Faculty of Medicine of the University of São Paulo (FMUSP) under protocol number 1749/2022. It was conducted at the Medical Investigation Laboratory 08 (LIM-08) of the same institution. All procedures were performed in accordance with the Brazilian guidelines for the care and use of laboratory animals and were reported according to the ARRIVE guidelines. Animal Ethics Committee approved 1749/202.

Animals

A total of 22 pigs, weighing between 25—30 kg, were used. They were sourced from commercial farms previously selected for their high sanitary standards. Physical and laboratory examinations were performed beforehand, and exclusion criteria included plasma hemoglobin levels below 9 mg.dL^{-1}, abnormal baseline blood gas values, and clinical signs of infection. After selection, the animals underwent a 12-hour fasting period with free access to water prior to the procedure.

Anesthetic procedure

The animals were sedated with intramuscular ketamine (5 mg.kg^{-1}) combined with midazolam (0.25 mg.kg^{-1}). After 15 minutes, the marginal ear vein was catheterized. An intravenous dose of 5 mg.kg^{-1} propofol was then administered for anesthesia induction. Following orotracheal intubation, the animals were placed in the supine position and mechanically ventilated (Servo-i — Maquet, Sweden) in volume-controlled mode with a tidal volume of 8 mL.kg^{-1}, a respiratory rate adjusted to maintain normocapnia, an inspired oxygen fraction of 0.40, and zero Positive End-Expiratory Pressure (PEEP). The anesthetic plane was maintained with continuous infusion of propofol (200 mcg.kg^{-1}.min^{-1}), fentanyl (10 mcg.kg^{-1}.h^{-1}), and midazolam (0.5 mg.kg^{-1}.h^{-1}) and was assessed using the Bispectral Index (BIS). Once an adequate anesthetic plane was achieved, with BIS values between 40 and 60 [5], cardiovascular monitoring was initiated, including invasive blood pressure measurement and electrocardiography using a multiparameter monitor (NIHON KOHDEN — Japan). The study did not have humane endpoints, and no animals were excluded from the statistical analysis. At the end of experimental procedure, the animals were euthanized by deepening anesthesia (isoflurane 5%) and potassium chloride administration (19.1%, 1 mL.kg^{-1}).

Pilot study (dose determination)

To determine the appropriate dose of rocuronium bromide, aiming for a 90% reduction in T1 in the TOF monitoring using Acceleromyography (AMG), a pilot study was conducted with four animals. The rocuronium bromide dose required in pigs has been reported to be approximately 7-fold higher than in humans.[6] Therefore, in the pilot study, different doses were tested to establish the onset time of rocuronium bromide in pigs. The onset times obtained were: 9'10" at 0.6 mg.kg^{-1}, 2'40" at 1.2 mg.kg^{-1}, 4'23" at 2.4 mg.kg^{-1} and 1'40" at 3 mg.kg^{-1}.

In the same four animals, after 5 minutes of neuromuscular blockade, sugammadex was administered in varying doses (2 mg, 5 mg, 7 mg, and 9 mg) to achieve blockade reversal, targeting a T4/T1 ratio of $\geq$ 0.9 within 5 minutes using AMG. Only the 9 mg.kg^{-1} dose of sugammadex successfully reversed the effects of 3 mg.kg^{-1} of rocuronium bromide, maintaining a TOF ratio of 0.9 with a 5% variation in response over 2 minutes.

With respect to lidocaine and magnesium sulphate dosing, no studies employing these agents in pigs were identified in the literature. Therefore, the upper limits of the commonly reported dosage ranges were selected: 1.5—2 mg.kg^{-1} for lidocaine and 30—50 mg.kg^{-1} for magnesium sulphate.

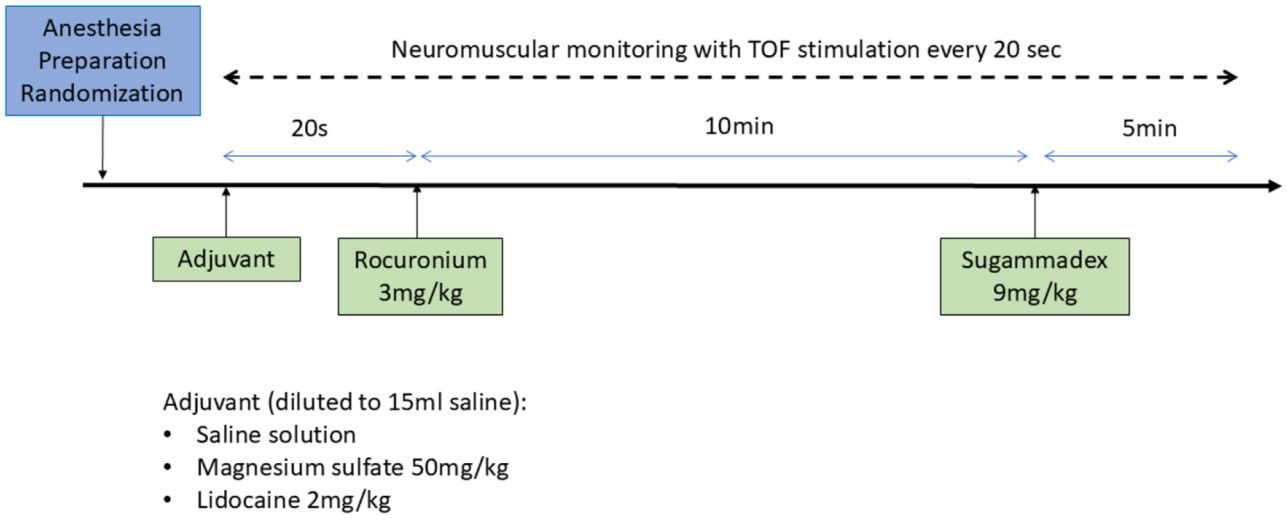

Figure 1 Study design.

Neuromuscular blockade monitoring

Neuromuscular blockade monitoring was performed using the TOF module of Nihon Kohden (model AF-101P). The acceleration transducer was positioned on the facial nerve (orbicularis oculi muscle) to quantitatively assess muscle response to electrical stimulation from the transducer.

The TOF module was calibrated before each administration of rocuronium bromide, with a sensitivity range of 0—812 and an electrical current range of 0—60 mA, allowing automatic calculation of the supramaximal stimulation current. Recalibration was performed whenever the contraction height exceeded 5%. In TOF mode, three stimuli were delivered at 20 ms intervals, followed by a fourth stimulus at 0.75s.

Three baseline measurements were taken for each animal. The TOF ratio (TOFratio), TOF count (TOFcount), T1, T2, T3, and T4 values were recorded every 20 seconds for 15 minutes following calibration and baseline measurements (Fig. 1) and subsequently analyzed.

The onset time of the neuromuscular blocker was defined as the point when T1 decreased by 90% after administration, while the reversal time was recorded when T4/T1 reached 0.9 or higher after sugammadex administration. Drug onset and reversal times were precisely recorded and video-documented for further verification.

Experimental design

This was a randomized study in which eighteen animals were allocated into three experimental groups, each consisting of six animals. Randomization was performed on the site (www.randomization.org) and the allocation list was placed in envelopes numbered 1 to 18, which were opened consecutively on the day of the experiment of each animal after preparation. Treatments were diluted to the same final volume (15 mL) by a staff member not involved in the evaluations and administered at the same speed (20 seconds) in a blinded manner.

- Saline (n = 6): Administration of 0.9% saline solution (15 mL) over 20 seconds, followed immediately by rocuronium bromide (3 $mg.kg^{-1}$) over 5 seconds.
- Magnesium sulfate (n = 6): Administration of 10% magnesium sulfate (50 $mg.kg^{-1}$) over 20 seconds, followed immediately by rocuronium bromide (3 $mg.kg^{-1}$) over 5 seconds.
- Lidocaine (n = 6): Administration of 2% lidocaine (2 $mg.kg^{-1}$) over 20 seconds, followed immediately by rocuronium bromide (3 $mg.kg^{-1}$) over 5 seconds.

After 10 minutes of neuromuscular blockade, reversal was performed with sugammadex (9 $mg.kg^{-1}$).

Table 1 Onset time of rocuronium (3 $mg.kg^{-1}$) and the antagonist sugammadex (9 $mg.kg^{-1}$), in seconds, with and without adjuvants, lidocaine (2 $mg.kg^{-1}$), and magnesium sulfate (50 $mg.kg^{-1}$), in an experimental model.

	Group (n = 6/group)	Onset time (sec)		ANOVA p
		Mean (SD)	95% CI	
Rocuronium	Lidocaine	81 (19)[a]	[60.8; 100.9]	p = 0.0317
	Magnesium	69 (19)[b]	[49.1; 88.7]	
	Saline	143 (77)	[63.2; 223.4]	
Sugammadex	Lidocaine	206 (35)	[170; 243]	p = 0.5976
	Magnesium	160 (87)	[69; 251]	
	Saline	207 (127)	[74; 341]	

SD, Standard Deviation; One-way ANOVA and Fisher LSD post hoc test.
[a] Difference between Lidocaine and Saline (p = 0.037).
[b] Difference between Magnesium and Saline (p = 0.016).

Statistical analysis

This was an exploratory study, and no a priori sample size calculation was performed. A post hoc sample size calculation was performed based on the rocuronium onset time results obtained from groups of 6 animals each. The estimated required sample size ranged from 10 to 14 animals per group, assuming an alpha level of 0.05 and a statistical power of 0.80. With the current sample size of 6 animals per group, the calculated power was 0.41 for the comparison between saline and lidocaine and 0.55 for the comparison between saline and magnesium. We decided to keep the sample size at 6 per group, considering ethical concerns regarding animal use and the associated costs.

Normality was assessed using the Shapiro-Wilk and Anderson-Darling tests. Onset times of the neuromuscular blocker and the reversal agent were analyzed with a one-way ANOVA, followed by Fisher's Least Significant Difference (LSD) post hoc test. Mean arterial pressure and heart rate were analyzed with a two-way ANOVA, followed by Tukey's post hoc test. Statistical significance was set at $p \leq 0.05$

Results

The onset time for rocuronium bromide and sugammadex are presented in Table 1. Both adjuvants, lidocaine and magnesium sulfate, significantly reduced the mean onset time compared with saline [$F(2,15) = 4.385$, $p = 0.0317$]. However, no difference was observed in the reversal with sugammadex.

The Mean Arterial Pressure (MAP) and Heart Rate (HR) values are summarized in Tables 2 and 3. Differences in MAP were observed across time points in the groups that received magnesium sulfate and lidocaine. In both adjuvant groups, MAP was lower than in the saline group after rocuronium administration. No difference was observed between groups in HR.

Discussion

A significant reduction in the onset time of rocuronium was observed with lidocaine and magnesium sulfate compared to saline. Regarding the reversal of the blockade, adjuvants did not significantly interfere with reversal after sugammadex administration. This approach may be valuable in situations that require rapid sequence intubation, offering an alternative to succinylcholine in scenarios where this agent is contraindicated.

The need to shorten the onset time of non-depolarizing neuromuscular blockers is crucial in urgent intubation scenarios.[7] Translational studies are particularly valuable in this context, as they allow the evaluation of pharmacological strategies for emergency situations without exposing critically ill patients to additional risks. Although experimental doses require adjustment for clinical practice and metabolic differences exist between pigs and humans, animal models remain an essential first step for validating new treatments and interventions.

The TOF monitoring was employed to assess both onset and reversal of the blockade, in accordance with the recommendations of the American Society of Anesthesiologists

Table 2 Mean arterial pressure and heart rate with the use of rocuronium (3 mg.kg^{-1}) and the antagonist sugammadex (9 mg.kg^{-1}), with and without adjuvants, lidocaine (2 mg.kg^{-1}), and magnesium sulfate (50 mg.kg^{-1}), in an experimental model.

	Group (n = 6/group)	Baseline		After adjuvant		After rocuronium		Muscular blockade		After reversion	
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
HR	Lidocaine	92 (20)	71; 114	98 (22)	75; 122	101 (21)	78/123	105 (21)	83; 127	103 (19)	83; 123
	Magnesium	95 (12)	82; 107	93 (16)	76; 110	93 (17)	75; 111	102 (17)	85; 119	96 (16)	79; 114
	Saline	88 (14)	73; 102	87 (16)	70; 104	96 (18)	77; 115	101 (25)	75; 127	92 (30)	71; 114
MAP	Lidocaine	71 (11)	59; 83	69 (11)	57; 80	63 (12)[c]	50; 76	72 (22)	49; 95	74 (11)	62; 86
	Magnesium	73 (7)	65; 80	65 (7)[c]	58; 72	58 (7)[a,c]	51; 66	68 (7)	60; 75	72 (7)[b]	65; 80
	Saline	79 (7)	70; 91	81 (10)	71; 91	86 (12)	74; 99	82 (14)	67; 96	84 (14)	70; 99

MAP, Mean Arterial Pressure; HR, Heart Rate; SD, Standard Deviation; Two-way ANOVA with Tukey post hoc test for difference between groups and time points.
[a] $p < 0.05$ vs. Basal;
[b] $p < 0.05$ vs. After rocuronium;
[c] $p < 0.05$ vs. Saline group.

Table 3 Two-way ANOVA summary.

	SS	DF	MS	F (DFn, DFd)	p-value
HR					
Interaction	365.5	8	45.69	F (8. 60) = 0.3752	p = 0.9297
Time	1442	4	360.6	F (1.826. 27.39) = 2.961	p = 0.0727
Grupo	760.8	2	380.4	F (2. 15) = 0.3038	p = 0.7425
Subject	18786	15	1252	F (15. 60) = 10.29	p < 0.0001
Residual	7305	60	121.8		
MAP					
Interaction	895.7	8	112.0	F (8. 60) = 2.561	p = 0.0179
Time	608.4	4	152.1	F (2.071. 31.06) = 3.479	p = 0.0419
Grupo	4058	2	2029	F (2. 15) = 4.204	p = 0.0355
Subject	7239	15	482.6	F (15. 60) = 11.04	p < 0.0001
Residual	2623	60	43.71		

MAP, Mean Arterial Pressure; HR, Heart Rate; SS, Sum of Squares; DF, Degrees of Freedom; MS, Mean Square; F, F-statistic.

(ASA), which emphasize the importance of adequate monitoring, particularly during reversal, to avoid residual blockage and mitigate individual variability.[8]

Rocuronium provides excellent conditions for intubation in an estimated time of 90 seconds, considered satisfactory for this purpose.[9] When administered after saline solution, a more prolonged blockade onset was observed compared to magnesium and lidocaine, with a duration ranging between 80 and 240 seconds.

The main results of this study indicate that both lidocaine and magnesium sulfate were effective in reducing the onset time of the non-depolarizing neuromuscular blockade caused by rocuronium bromide. However, some limitations must be acknowledged. The small sample size may increase the risk of type II error and bias, while the homogeneity of the experimental animals could compromise the generalizability of our findings. Additionally, adverse systemic effects, such as electrolyte alterations related to magnesium, were not assessed.

In the magnesium group, the maximum blockade time was 90 seconds, which is close to the minimum time in the lidocaine group, at 80 seconds. One limitation of the study was the absence of a group combining both adjuvants; however, such a combination is not commonly used in practice.

Magnesium sulfate demonstrated a significant reduction in the onset time of rocuronium bromide, and this efficacy is attributed to possible pre- and post-synaptic mechanisms of action. By competing with calcium, magnesium reduces acetylcholine release at the neuromuscular junction, thereby facilitating the effect of neuromuscular blockers.[10] This interaction may explain the reduced onset time observed in our study.

For lidocaine, the reduction in onset time of rocuronium bromide may be attributed to a likely post-synaptic mechanism, through binding to acetylcholine receptors, leading to receptor desensitization and transient channel blockade. Lidocaine may also impair both pre- and post-junctional nerve conduction, further enhancing neuromuscular blockade.[11]

Among the various neuromuscular monitoring modalities available in acceleromyography, TOF is highlighted for its reliability and was selected in this study, consistent with the most recent ASA guidelines.[11]

Regarding reversal with sugammadex, lidocaine and magnesium sulfate did not produce clinically relevant interference with reversal of muscle function. In a previous study,[12] involving 125 adult patients with ASA I or II physical status, they concluded that the combination of lidocaine (1.5 mg. kg^{-1}) and rocuronium at low doses (0.6 mg.kg^{-1}) was equivalent to succinylcholine. The doses used in our experimental model were higher than those commonly applied in clinical practice, which limits direct extrapolation to humans. In addition, we observed a wide variability in reversal times, which may be more related to the experimental porcine model than to a true pharmacological effect. This variability, together with the limited statistical power of our study, may also have hindered the detection of potential secondary effects.

Previous studies[13] also demonstrated that magnesium pre-treatment enhances the neuromuscular blockade effect of rocuronium, reducing its onset time without clinically significant prolongation of blockade duration, in agreement with our findings.

Regarding the reversal of neuromuscular blockade, the magnesium-treated group showed a prolonged reversal time, reaching 320 seconds. This difference may be attributed to several causes, as discussed previously.[14] The presence of magnesium appears to enhance the effects resulting from partial occupation of post-junctional nicotinic receptors by free rocuronium molecules, leading to a longer reversal time in this specific group.

Finally, a significant reduction in blood pressure was observed in groups treated with lidocaine and magnesium, compared to saline. Lidocaine may reduce vascular resistance, while magnesium sulfate decreases intracellular calcium by acting as a calcium channel blocker, promoting vasodilation.[15] Both mechanisms resulted in a more pronounced reduction in blood pressure in the magnesium group compared to lidocaine. Despite this, blood pressure was restored without intervention, suggesting that the hypotensive effect may have limited clinical relevance. Nonetheless, further studies are warranted to better define these hemodynamic effects and their implications.

Conclusion

Lidocaine and magnesium sulfate were effective in reducing the onset time of the non-depolarizing blocker rocuronium bromide. This research demonstrates that both lidocaine and magnesium sulfate did not interfere with the reversal of neuromuscular blockade and reduced its onset time, presenting themselves as good alternatives for rapid access to the airways.

Data availability

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.

Associate Editor

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ORIGINAL INVESTIGATION

Evolution of patients with chronic pain undergoing standard treatment: a prospective longitudinal follow-up study

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ABSTRACT

Introduction: Chronic pain greatly affects quality of life and, consequently, impacts the psychological state, a condition that needs to be addressed. A 30% reduction in pain intensity is clinically significant. The objective of this study was to describe the clinical and psychological aspects of individuals with chronic pain undergoing standard treatment.

Methods: Descriptive longitudinal study involving individuals with chronic pain undergoing treatment at the Pain Outpatient Clinic of the Federal University of Bahia, in Salvador, Bahia, between June 2016 and December 2017. The variables studied were pain intensity, quality of life, sleep disorders, stress level, and the presence of anxiety and depression symptoms. Descriptive statistics were performed, and Student's t-test, and Fisher's Chi-Square test were used to compare the groups.

Results: We studied 134 individuals with a mean (standard deviation) age of 50 (10) years, 89.6% of whom were female. There was an improvement in quality of life and sleep, anxiety and depressive symptoms, and 58.2% of patients showed a 30% reduction in pain intensity. Among the factors associated with pain reduction, having a partner was a significant factor (73.7% vs. 52.1%; p = 0.030). However, symptoms of anxiety (81.6% vs. 75.0%; p = 0.436), symptoms of depression (63.2% vs. 58.3%; p = 0.718), and stress (92.1% vs. 87.5%; p = 0.846) were not associated with pain reduction.

Conclusion: This study suggests that multidisciplinary treatment can reduce pain intensity in chronically affected patients, as most patients exhibited a clinically significant response, accompanied by global improvement.

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Introduction

In 2020, a task force comprised of members of the International Association for the Study of Pain (IASP), and the World Health Organization (WHO) reviewed the pathophysiological and research concepts of pain. They added that pain is an individual perception, the report of which must be respected and is directly associated to each person's life experiences.[1] It is estimated that, worldwide, around 60 million people suffer from chronic pain, corresponding to 10% of the global population, with lower back pain being the most prevalent location, followed by headaches. In contrast, a systematic review revealed that approximately 45.6% of the Brazilian population suffers from the same condition, representing around 95 million people, and this condition is more prevalent in the Central-West region.[2] Pain is the primary complaint that explains the frequency with which these individuals seek health services.[3]

Pain influences several aspects of a person's life and contributes to a decline in quality of life.[4] A systematic review analyzed 10 double-blind studies with a total of 2,724 individuals with chronic pain. It concluded that a reduction of approximately two points on the numerical pain scale, or a 30% decrease, represents a clinically significant improvement.[5] This reduction is more effective when a planned multidisciplinary approach is adopted.

Considering the impact of chronic pain on a person's life and the improvement in pain intensity with multidisciplinary treatment, this study aimed to describe the clinical and psychological evolution of subjects with chronic pain treated by a multidisciplinary team at a specialized referral center in the Unified Health System (SUS). The central hypothesis is that treatment in a specialized center leads to improvement in pain intensity. Quantitative analysis of data obtained in a survey with a representative sample was used to test this hypothesis.

Methods

Type of research

This descriptive longitudinal study was conducted at the Pain Outpatient Clinic of the University Hospital of the Federal University of Bahia, Salvador, Bahia, Brazil. It included individuals with chronic pain who were undergoing standard treatment according to the WHO analgesic ladder.[6]

Participants and procedures

The subjects were interviewed three times between June 2016 and December 2017: at the initial consultation, and then 3 and 6 months later. At the initial consultation, each subject completed both the sociodemographic questionnaire and the evaluation scales. At the two subsequent consultations, each subject only completed the evaluation scales. Subjects of both sexes aged 18—80 years and regularly enrolled in the outpatient care service, and who were present at all three appointments were included. Those diagnosed with pain of oncological origin and who had difficulty understanding the study were excluded.

Research development

Once a subject was enrolled in the service, during the initial consultation, the unit's attending physician confirmed a previous diagnosis of chronic pain in the subject's medical report. The same researcher, a psychologist with a PhD and 25 years of experience in chronic pain care, applied all scales. The research was conducted over 18 months; however, the subjects were included at different times, as shown in Figure 1.

Instruments

A sociodemographic questionnaire was used to collect the age, sex, marital status, religion, educational background, and employment status of each subject.

A Visual Numeric Scale (VNS) was used to assess pain intensity, ranging from 0 (no pain) to 10 (unbearable pain). A 30% reduction in pain intensity was considered to indicate a clinically significant improvement.[7]

The Short Form-36 (SF-36) was used to assess quality of life. It contains eight domains: functional capacity assesses physical capacity; physical aspect assesses physical limitations; pain assesses the presence of pain and interference in activities of daily living; general health assesses overall health; vitality assesses energy level and fatigue; social aspect assesses integration in social activities; emotional aspect analyzes the impact of psychological aspects on the patient's well-being; and mental health assesses symptoms and psychological well-being. The scale ranges from 0 to 100, with 0 indicating the worst health status and 100 indicating the best health status. Given that it is a subjective assessment, it has no cut-off point.[8]

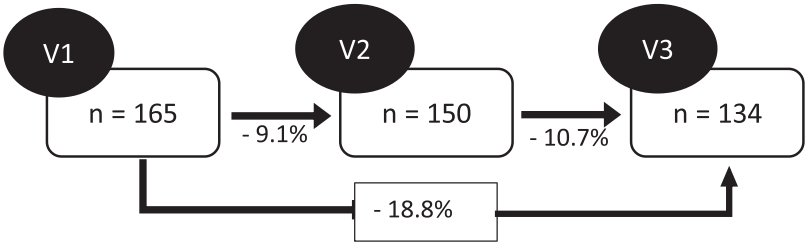

Figure 1 The number of participants at each time point of the study – V1 (initial), V2 (after 3 months), and V3 (after 6 months) – and the percentage loss at each time. At each time, all instruments were applied to subjects with pain treated at Pain Outpatient Clinic of the University Hospital of the Federal University of Bahia. Note: Only the 134 patients who had data from all three visits were included in the sample.

The Mini-Sleep Questionnaire (MSQ) assesses the presence of sleep disorders. The score is categorized as follows: 10–24 points indicate "good sleep"; 25–27 points indicate "mild disorder"; 28–30 points indicate "moderate disorder"; and > 30 points indicate "severe disorder".[9]

The Pittsburgh Sleep Quality Index (PSQI) is a scale that measures sleep quality. The maximum total score is 21 points. The higher the score, the worse the sleep quality.[10]

The Hospital Anxiety and Depression Scale (HAD) assess the presence of anxiety and depression symptoms. It has a cut-off point of 8 for anxiety and 9 for depression.[11]

Lipp's Stress Symptom Inventory for Adults (LSSI) is an instrument comprising 37 items, divided into three tables that refer to the phases of stress. The first table pertains to physical or psychological symptoms experienced in the last 24 hours, the second to those experienced in the previous week, and the third to those experienced in the previous month.[12]

Statistical analysis

SPSS Statistics version 17.0 was used for data analysis. Quantitative variables are expressed as mean and Standard Deviation (SD), and categorical variables are expressed as absolute and relative frequency. Descriptive statistics, normality graphs (histogram, boxplot, and Q–Q plots), and the Shapiro-Wilk test were used to assess the normality of the variables. The variables, expressed as scores and evaluated by the scales, were considered ordinal and are presented as medians and interquartile ranges.

Patients were initially divided into two groups: those who showed any improvement in pain intensity (one or more VNS scores) and those who showed no improvement or worsened. The scales related to quality of life, sleep, stress, and anxiety and depression symptoms were then compared at the initial (V1) and final (V3) visits. The McNemar and Wilcoxon tests were used to compare categorical and ordinal variables, respectively.

Considering that a 30% reduction in pain intensity is a good clinical response to treatment for this condition, and to investigate the factors associated with this improvement, patients were again divided into two groups based on this characteristic: those who achieved less than 30% improvement or no improvement, and the other group with an improvement in the VNS score greater than or equal to 30% compared to baseline (V1). Student's *t*-test, Pearson's Chi-Square test, and Fisher's exact test were used to compare these groups. Binary logistic regression was performed to investigate the effect of confounding variables associated with pain intensity improvement. The following variables were included in the model: gender, marital status, anxiety symptoms, depression and stress symptoms (independent variables), and pain intensity reduction (dependent variable). The reasons for including variables in the model were: plausibility of interference in the association and p-value < 0.05 in the bivariate analysis. A p-value < 0.05 was considered to be statistically significant.

Results

A total of 165 individuals were selected, but only those who attended all three moments comprised the sample. Thus, 134 were included in the sample, representing a loss of 18.8% due to difficulty in contacting, treatment abandonment, change of address, or other reasons. The sociodemographic characteristics observed in the group lost to follow-up are similar to the study sample, with a mean age of 49.4 (10.6), all female, the majority had (60%) and religion (85%), and pain intensity had a median of 7 (6–8). The mean (SD) age was 50 (10) years. Most of the subjects were female (89.6%), had a partner (58.2%), were of mixed race (51.5%), were unemployed (63.4%), and declared a religion (94.8%) (Table 1). In addition, 59.7% reported that they did not perform physical activity regularly, 7.5% consumed alcohol, and 18.7% smoked. Regarding the pain pattern, 51.5% reported that there was no specific time for the pain to become more intense; however, 25.4% reported that the pain worsened at night.

Table 1 Sociodemographic characteristics of 134 patients with chronic pain treated at the Pain Outpatient Clinic of C-HUPES/UFBA, Salvador–Bahia.

Variables	Results
Age in complete years[a]	50 (10)
Female Sex	120 (89.6%)
Marital Status	
With partner	78 (58.2%)
Without partner	56 (41.8%)
Religion	127 (94.8%)
Education	
No education	2 (1.5%)
Elementary school complete and incomplete	50 (37.3%)
High school complete and incomplete	71 (53%)
High school complete and incomplete	11 (8.2%)
Ethnicity	
Mulatto/Mixed race	69 (51.5%)
Black	38 (28.4%)
White	27 (20.1%)
Employment Status	
Employed	35 (26.1%)
Unemployed	85 (63.4%)
Retired	14 (10.4%)
Pain Intensity[a]	7 (6 - 8)

[a] Values expressed as mean and standard deviation.

For comparison purposes, the subjects were divided into two groups based on the evolution of pain: those who showed improvement in pain, representing 58.2% of the subjects, and those who remained with an unchanged or worsening pain level, representing 41.8% of the subjects. The group that showed an improvement in pain also showed improvement in all domains of the SF-36, depressive and anxiety symptoms, stress level, and sleep pattern. However, the group that showed no change or worse pain improved in only one domain of the SF-36 and the sleep pattern (Table 2).

Regarding the factors associated with clinically significant pain improvement (i.e., ≥ 30% improvement during treatment at the specialized center), only having a partner was associated with a reduction in pain intensity (Table 3).

Table 2 Evolution of 134 patients with chronic pain before and after six months of follow-up divided into groups in which the pain improved or worsened/remained unchanged at the Pain Outpatient Clinic of C-HUPES/UFBA, Salvador–Bahia, 2016–2017.

Variables	Worsened/Unchanged 56 (41.8%)		p	Improved 78 (58.2%)		p
	V1	V3		V1	V3	
Anxiety Symptoms	39 (70%)	45 (80%)	0.180	64 (82%)	52 (67%)	0.038
Depressive Symptoms	28 (50%)	30 (54%)	0.508	52 (67%)	30 (39%)	0.001
Stress	46 (82%)	45 (80%)	1.000	73 (94%)	58 (74%)	0.001
Quality of Life						
Functional Capacity	30 (15–45)	30 (20–45)	0.331	25 (15–35)	42 (32–52)	< 0.001
Physical Limitations	0 (0–25)	23 (0 – 35)	0.021	0 (0–0)	42 (0–54)	< 0.001
Pain	22 (12–35)	24 (22–41)	0.460	22 (12–31)	42 (34–53)	< 0.001
General Health	34 (23–51)	37 (25–52)	0.929	35 (23–50)	48 (36–58)	< 0.001
Vitality	27 (15–59)	35 (25–56)	0.252	26 (15–35)	55 (40–67)	< 0.001
Social Aspects	42 (13–57)	38 (25–58)	0.929	38 (25–50)	50 (39–63)	< 0.001
Emotional Limitations	33 (0–68)	33 (0–51)	0.320	0 (0–89)	50 (26–69)	0.008
Mental Health	42 (24–68)	37 (20–52)	0.223	38 (28–65)	46 (37–66)	0.029
Sleep						
Quality	13 (10–17)	12 (6–14)	0.001	14 (10–17)	8 (5–11)	< 0.001
Disorders	44 (32–49)	38 (30–48)	0.016	46 (41–53)	31 (28–34)	< 0.001
Pain Intensity	6 (5–7)	6 (5–8)	< 0.001	8 (7–9)	5 (5–6)	< 0.001

Note: McNemar and Wilcoxon tests were used.

Discussion

In this study, most subjects treated for chronic pain who experienced an improvement in their pain intensity also showed an improvement in their sleep patterns, stress, anxiety, and depression symptoms, and all domains of quality of life. The group that showed unchanged or worsened pain only improved in terms of sleep and in only one domain of the quality-of-life scale. In addition, having a partner was associated with a greater reduction in pain intensity, perhaps due to better therapeutic adherence (i.e., having another person to dispense medications) as well as financial and emotional support.[13] This, however, is a hypothesis generated in this study that should be interpreted with caution.

The negative impact of chronic pain on quality of life is well known. Our findings support the association between reduced pain intensity and an overall improvement in quality of life. The specific improvement in the physical aspect's domain in subjects with no change in pain or worsened pain intensity may be due to the subject's ability to reframe pain by adapting to these limitations, in addition to the multidisciplinary treatment that improves mobility.[14] A 2022 study involving 379 participants demonstrated that the perception of quality of life varies according to the intensity of pain.[15]

Pain is one of the triggers of stress, generating physiological responses that release catecholamines and increase cortisol production. If prolonged, this situation impairs daily activities and physiological cycles.[16] These changes may be associated with genetic factors that make susceptible subjects more sensitive to the effects of catecholamines and, consequently, increase pain. The OPPERA study evaluated the factors associated with the development of orofacial pain. It concluded that stress only acts as an additive risk

Table 3 Factors associated with pain reduction in 134 patients with pain being treated at the Pain Outpatient Clinic of C-HUPES/UFBA, Salvador–Bahia.

Variables	Pain Reduction		p	OR (95% CI)
	≥ 30%	< 30%		
	38 (28.4%)	96 (71.6%)		
Age	51 (10)	50 (10)	0.757	–
Sex			0.220	1.807 (0.545 – 5.990)
Female	32 (84.2%)	88 (91.7%)		
Male	6 (15.8%)	8 (8.3%)		
With partner	28 (73.7%)	50 (52.1%)	**0.022**	**2.533 (1.094 – 5.869)**
Anxiety Symptoms	31 (81.6%)	72 (75%)	0.416	0.602 (0.168 – 2.157)
Depressive Symptoms	24 (63.2%)	56 (58.3%)	0.608	1.216 (0.422 – 3.505)
Stress (ISSL)	35 (92.1%)	84 (87.5%)	0.555	0.869 (0.211 – 3.586)

Note 1: The *t*-test, Pearson's Chi-Square test and Fisher's exact test were used.
Note 2: Variables were included in the model: gender, marital status, anxiety symptoms, depression and stress symptoms (independent variables), and pain intensity reduction (dependent variable).

factor for increased pain in individuals without preexisting psychological symptoms.[17]

Chronic pain leads to a pattern of depressive and anxious responses with symptoms such as low mood and changes in sleep patterns.[18] The greater the intensity of pain and the number of painful points, the greater the magnitude of these symptoms tends to be.[19] In our study, the group that showed an improvement in pain intensity also showed a reduction in the number of subjects with anxious and depressive symptoms, corroborating the aforementioned association.

Chronic pain treatment guidelines from around the world agree that interdisciplinary intervention is necessary, with pharmacological treatment being one of the pillars.[20] During this study, the subjects underwent psychological evaluation with a cognitive-behavioral approach. This intervention has been shown to improve pain and might explain the improvement in the pattern of depressive and anxious responses presented by these subjects.[21]

Changes in sleep patterns are risk factors for the exacerbation and chronicity of pain. On the other hand, impaired sleep quality exacerbates pain, highlighting a bidirectional connection between sleep and pain, which is due to modifications in the circadian cycle and modulation of neurotransmitters associated with this process.[22] The improved sleep patterns of the subjects may have been due to the use of adjuvant drugs such as antidepressants. Although antidepressants are not commonly used at therapeutic doses to treat sleep disorders, their most common adverse effect is drowsiness. Moreover, according to the WHO analgesic ladder, regardless of the level of pain, the use of antidepressants is recommended.[23]

The intensity of pain and its interference with the life of a subject with chronic pain are determinants of the severity of the disease.[24] Improvement in this parameter reflects a clinical improvement for these subjects. When treating patients with chronic pain, any clinical improvement is important; hence, according to the literature, a 30% reduction in pain score relative to the initial score is considered clinically significant.[25] This may be attributed to the multidisciplinary treatment of the subject.

Although there was no control over medication use in this study, the improvement observed in pain intensity, regardless of the pathophysiological mechanism and etiological diagnosis, may be attributed to the fact that the subjects were part of an outpatient clinic specializing in chronic pain and had access to a multidisciplinary team.

Other authors have also observed the link between clinical improvement in the underlying condition and marital status. Vance et al.[25] conducted a randomized clinical trial in 2021 with 301 patients in the United States to evaluate the response to Transcutaneous Electrical Nerve Stimulation (TENS) in women with fibromyalgia. They found that married women responded better to the treatment. The authors attributed this to better adherence to the therapeutic protocol; we also speculate that this group had greater social support, which contributed to the positive outcome.

This study had some limitations. First, we were unable to confirm the etiology of the pain, as the subjects entered the service with a diagnosis provided by the attending physician. Second, although the subjects received standard treatment, it was not possible to determine the frequency of consultations, the interventions performed, or adherence to medication therapy, as these were individualized. Another aspect is the possibility of unmeasured confounding factors, as well as losses during the longitudinal study (18.8%). Finally, the convenience sample may compromise the sample size and, consequently, the power of the study.

On the other hand, we consider possible biases, such as selection and confounding, to be unlikely. First, all patients were invited and accepted participation, which made selection bias possible; second, the second bias was minimized by controlling for potential confounding variables using binary logistic regression.

Generalization of data should be done with caution. Given that the patients studied were followed up at an outpatient clinic of the Unified Health System, data/results should only be generalized to similar services.

In future studies, the specific drug therapy should be determined, and there should be greater control of therapeutic adherence to establish assertive longitudinal study criteria that will improve the quality of the service provided.

Conclusion

In this observational study, approximately half of the subjects with chronic pain reported a clinically significant reduction in pain after standard treatment. The subjects also showed improvements in sleep quality and emotional well-being. However, given the absence of a control group and the observational design, these findings should be interpreted with caution.

The evolution of pain intensity is associated with the presence of anxiety and depression symptoms, stress, sleep patterns, and quality of life. Although the subjects who reported improvement in pain intensity also showed improvement in the other parameters studied, it is not possible to establish whether improvements in the psychological status and sleep improve pain or vice versa.

Ethical aspects

This study was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by the Research Ethics Committee of Professor Edgard Santos University Hospital (opinion n° 1.446.343 and CAAE n° 4990615.8.0000.0049).

Data availability statement

The data supporting the findings of this study are available upon reasonable request to the corresponding author [CC]. The data are not publicly available due to ethical constraints, such as containing information that could compromise the privacy of research participants.

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.2025.844700.

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REVIEW ARTICLE

Efficacy of magnesium sulfate as an adjuvant to local anesthetics in supraclavicular brachial plexus block: a meta-analysis of randomized trials

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Abstract

Background: Magnesium Sulfate (MS) maintains physiological functions in the body. Studies suggest its safety in regional anesthesia, despite off-label perineural use. We conducted a systematic review and meta-analysis to evaluate MS efficacy as an adjuvant in supraclavicular brachial plexus block.

Methods: The study was registered in PROSPERO (CRD42025641627) on 01/21/2025. We searched PubMed, Embase, Cochrane, clinicaltrials.gov and gray literature for eligible studies. We included RCTs that: enrolled adult patients; involved orthopedic surgery with supraclavicular block; compared LA alone versus LA with MS; and reported primary outcomes. Primary outcomes were duration of sensory and motor block, while secondary outcomes included onset of sensory and motor block, PONV and rescue analgesia needs postoperatively. RoB2 tool and GRADE assessed bias risk and evidence certainty. Variables were examined using DerSimonian-Laird random-effects model.

Results: Analysis included 10 studies and 734 patients. The intervention group showed longer sensory and motor block than controls. The Mean Difference (MD) was 180.84 minutes (95% CI [154.09, 207.59], 95% PI [71.67, 289.77], $p < 0.00001$, $I^2 = 97\%$) and 151.26 minutes (95% CI [99.78, 202.74], 95% PI [-23.12, 325.63], $p < 0.00001$, $I^2 = 99\%$). The magnesium group showed statistical difference in onset of sensory and motor blockade and rescue analgesia needs, with no difference in PONV. Evidence certainty was rated low to moderate. Risk of bias "high" in three studies, "some concerns" in four studies and "low" in three studies.

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Conclusion: Our meta-analysis supports MS as adjuvant in supraclavicular block. Further research is needed due to high heterogeneity.
PROSPERO registration: CRD42025641627.

Introduction

The supraclavicular block is a regional anesthetic technique for primary regional anesthesia during surgeries and/or postoperative pain control to the distal two-thirds of the upper extremity, or from the mid-humerus to the fingertips.[1]

Although Local Anesthetic (LA) agents provide superior analgesia compared to opioid-based regimens, their effect is time-limited and may not adequately cover the postoperative pain period.[2] As a result, strategies to prolong the duration of single-shot nerve blocks have become a clinical priority. One such strategy is the use of perineural adjuvants – pharmacologic agents co-administered with Las – to extend block duration and improve analgesic quality. This approach is especially valuable in outpatient and daycare surgeries, where prolonged anesthesia may reduce the need for continuous catheter placement and lower the risk of catheter-related infections.[3]

Several agents have been studied as adjuvants to LAs, including alpha-2 adrenergic agonists and glucocorticoids. Magnesium Sulfate (MS) is an N-Methyl-D-Aspartate (NMDA) receptor antagonist that modulates pain transmission and plays an essential role in maintaining physiological homeostasis. While its perineural use remains off-label, multiple studies have suggested its safety in regional anesthesia.[4-6]

Despite promising findings, high-quality evidence remains limited regarding magnesium sulfate's efficacy and safety as an adjuvant in Peripheral Nerve Blocks (PNBs). Existing studies[6-8] vary in block technique and outcome reporting, contributing to heterogeneity and limiting generalizability. We conducted a systematic review and meta-analysis of randomized controlled trials to evaluate magnesium sulfate as a perineural adjuvante, focusing on a widely used upper limb block[9] — the supraclavicular block. We hypothesized that MS would prolong sensory and motor block duration, reduce block onset time, and not increase adverse effects compared to local anesthetic alone.

Methods

The study was registered in PROSPERO (identifier CRD42025641627) on 01/21/2025 and was conducted using PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Gray literature (opengrey.eu) and trial registries (clinicaltrials.gov) databases to identify eligible studies. During the review process, a small deviation from PROSPERO occurred: (1) The search strategy was updated to include additional descriptors, which resulted in the inclusion of more studies. Two researchers (W.B.S. and I.E.C.) independently conducted the database searches, which was completed in January 31, 2025, without imposing any limitations. Any discrepancies between the two researchers were resolved through discussions with a third author (R.R. B.C.). Supplemental Table 1 presents the detailed search strategy: ('magnesium sulfate'/exp OR 'magnesium sulfate':ti,ab) AND ('brachial plexus block'/exp OR 'brachial plexus block':ti,ab OR 'block, brachial plexus':ti,ab OR 'blocks, brachial plexus':ti,ab OR 'brachial plexus blocks':ti,ab OR 'brachial plexus anesthesia':ti,ab OR 'anesthesia, brachial plexus':ti,ab OR 'brachial plexus blockade':ti,ab OR 'blockade, brachial plexus':ti,ab OR 'blockades, brachial plexus':ti,ab OR 'brachial plexus blockades':ti,ab OR 'plexus blockade, brachial':ti,ab OR 'plexus blockades, brachial':ti,ab OR 'brachial plexus'/exp). Our study adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[10] Cochrane Handbook for Systematic Reviews of Intervention[11] and when applicable, other generated guidelines.[12,13]

Selection of the papers

The primary outcomes assessed were the duration of sensory and motor block. Secondary outcomes included the onset of sensory and motor block, Postoperative Nausea and Vomiting (PONV), and the need for rescue analgesia within 24 h postoperatively. Rescue analgesia was defined as the total amount of analgesic drug administered during the first 24 hours after surgery, recorded in milligrams of the specific medication used in each trial. The systematic review and meta-analysis included Randomized Controlled Trials (RCTs) that met the following criteria: 1) Enrolled adult patients; 2) Involved orthopedic surgery with a supraclavicular block; 3) Compared LA alone versus LA with MS; and 4) Reported both primary outcomes defined in this review. Studies were excluded if they 1) Included urgent or emergency surgery, or 2) Had an ASA status equal to or greater than III. The rationale for the inclusion and exclusion criteria is detailed in Supplemental Table 2.

Two researchers (W.B.S. and I.E.C.) conducted the selection after independently evaluating the studies for inclusion, based on predetermined criteria. After eliminating duplicates, the remaining results were screened according to title and abstract. The full texts of the potentially relevant studies were subsequently examined to confirm their eligibility. In cases where full texts were not readily available, efforts were made to contact the corresponding authors directly, but studies remained excluded if the necessary data could not be obtained. Abstracts that did not provide outcome information were excluded, as they could not provide data extraction. Any discrepancies between the two researchers were resolved through discussions with a third author (R.R.B.C.). Zotero Software version 7.0.15 was used to select the studies and eliminate duplicates.

Data analysis

After these procedures, a data extraction table was constructed based on the following variables: author, publication year, country, ASA status, surgery type, MS and Local Anesthetic (LA) dosages, patient count, mean age, and volume of the mixture utilized.

The revised Cochrane Risk-of-Bias tool for randomized trials 2[14] (RoB 2) was employed by two researchers (W.B.S. and I.E.C.) to assess the risk of bias independently. Risk of bias was classified as "low risk", "some concerns", or "high risk." Discrepancies were also resolved through discussion with a third researcher (R.R.B.C.).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[15] system was employed to evaluate evidence certainty. Evidence was subsequently classified as high, moderate, low, or very low using GRADEpro software.[16] Two researchers (W.B.S. and I.E.C.) independently performed this stratification and any disagreements were resolved through consultation with a third researcher (R.R.B.C.).

Statistical tests

Review Manager version 5.4 (Cochrane Collaboration)[17] and R software version 4.5.1[18] (PWR[19] and metafor[20] packages) were used to conduct statistical analyses of the meta-analysis. Cochran's *Q* test and I^2 statistics were employed to measure heterogeneity. For outcomes exhibiting high heterogeneity ($I^2 > 75\%$),[11] leave-one-out sensitivity analysis was performed. For continuous outcomes, Mean Differences (MD) or Standardized Mean Diferences (SMD) with 95% Confidence Intervals (95% CI) were calculated, whereas Risk Ratios (RR) with 95% CI were used for binary outcomes. Furthermore, Prediction Intervals (PI) were determined to assess the treatment effect in upcoming clinical studies.[21] Variables were examined using DerSimonian-Laird[22] random-effects model, with statistical significance set at $p < 0.05$. Power analysis of sample sizes was performed to determine whether sample sizes were adequate to detect clinically significant differences. To evaluate publication bias across all outcomes, a funnel plot analysis was employed, supplemented by Egger's regression[23] for outcomes with a minimum of ten studies.

Results

Our database search strategy retrieved 174 potentially relevant records that were published up to January 2025. Of these, 46 records were excluded after initial screening for duplicate work and another 94 were excluded after reading the title and abstract. Of the 34 studies fully reviewed, 2 only provided the abstract and 22 did not contain any outcome of interest. Ten full-text randomized trials[24-33] were included in the final analysis. In the study by Verma et al.,[32] the two intervention groups were evaluated as separate independent comparisons. Figure 1 represents the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram and summarizes the reasons for the exclusion of records. The GRADE summary of findings for each endpoint is presented in Supplemental Table 3, with the certainty of evidence for the outcomes rated as low to moderate.

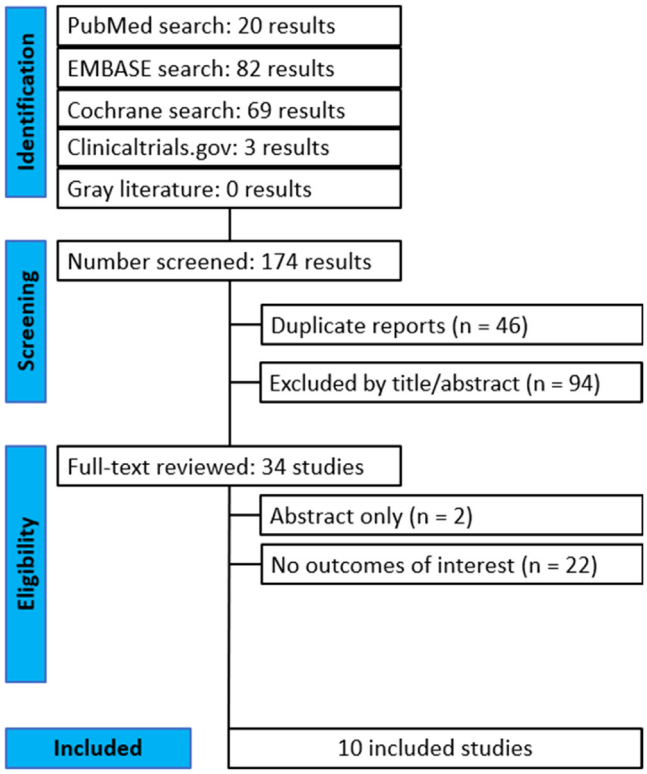

Figure 1 PRISMA flow diagram of study screening and selection.

Table 1 summarizes the baseline characteristics of the included studies. Data from 734 patients, including 367 in the MS group and 367 in the control group, were available for analysis. The peripheral blocking technique was anatomical (landmark) in one trial,[24] nerve stimulation in four trials[25,27-29] and ultrasound in five trials.[26,30-33] All trials used long-acting LAs (ropivacaine or bupivacaine) and the dose of MS varied between 125 and 250 mg.

Supplemental Figure 1 shows the risk of bias assessment for each primary outcome. The overall risk was classified as "high" in three studies,[24,25,33] "some concerns" in four studies[27,28,30,31] and "low" in the remaining three studies.[26,29,32] Most studies were either double- or triple-blind,[26-29,31,32] with the exception of one single-blind study.[30] However, three studies[24,25,33] did not provide a detailed account of the blinding methodology employed, and three other studies[27,31,33] reported participant attrition following randomization. The power analysis of sample sizes (power target: 0.8; significance 0.05) are available in Supplemental Table 4.

Block duration

The duration of sensory and motor blocks was reported in all ten studies,[24-33] totaling 734 patients. The results indicated that the group that used LA with the addition of MS presented a significantly longer sensory blockade time than the control group (Fig. 2), which used LA alone. The MD was 180.84 minutes (95% CI: [154.09, 207.59], 95% PI: [71.67,

Table 1 Baseline characteristics of included studies.

Study	Objectives	Patients, LA vs. MS	Country	Male, %, LA vs. MS	Age, y, LA vs. MS	ASA status	Regional anesthesia technique	LA, dose	MS, dose	Choice for rescue analgesia
Aggarwal 2022	To study the effect of adding magnesium as an adjuvant to ropivacaine in supraclavicular block.	40/40	India	55/47.5	44.8 ± 6.6 vs. 45.2 ± 7.7	I-II	Landmark	Ropi 0.5%	150 mg	Diclofenac sodium
Borgohain 2023	The advantage of using magnesium sulphate as an adjuvant to bupivacaine on the postoperative analgesia as well on the onset and the duration of sensory and motor blockade in the patients undergoing upper limb surgeries and to evaluate for any possible side effects or complications.	45/45	India	NA	36.15 ± 13.44 vs. 37 ± 14.78	I-II	Nerve stimulation	Bupi 0.5%	200 mg	–
Gupta	To compare the effectiveness of addition of $MgSO_4$ (150 mg) and fentanyl (50 micrograms) to 0.375% bupivacaine with placebo in supraclavicular brachial plexus block.	25/25	India	64/64	31.17 ± 11.91 vs. 36.00 ± 13.01	I-II	Ultrasound-Guided	Bupi 0.375	150 mg	Diclofenac sodium
Jalili 2024	To compare the effectiveness of adding Magnesium Sulfate (MS) and Low-Dose Dexamethasone (LDD) to ropivacaine in SCBPBs for elective upper extremity surgery.	15/15	Iran	73.3/80	42.73 ± 12.41 vs. 46.73 ± 13.30	I-II	Nerve stimulation	Ropi 0.5%	200 mg	Opioid
Kaur 2019	To evaluate the effect of $MgSO_4$ compared to ketamine when added to 0.5% ropivacaine for supraclavicular brachial plexus block, in terms of the duration of postoperative analgesia in adult patients undergoing upper limb surgery.	34/34	India	80/85.7	38.80 ± 14.37 vs. 45.22 ± 11.71	I-II	Nerve stimulation	Ropi 0.5%	250 mg	Diclofenac sodium
Mukherjee 2014	To test the hypothesis that magnesium when added as an adjuvant to ropivacaine in supraclavicular brachial plexus block may enhance the duration of sensory and motor block, duration of analgesia, and quality of block.	50/50	India	52/64	40.5 ± 13.2 vs. 44.9 ± 11.4	I-II	Nerve stimulation	Ropi 0.5%	150 mg	Diclofenac sodium
Patel 2023	To evaluate the efficacy of magnesium when added to ropivacaine in supraclavicular brachial plexus block.	30/30	India	56.7/43.3	37.13 ± 10.41 vs. 35.53 ± 9.98	I-II	Ultrasound-Guided	Ropi 0.5%	150 mg	Diclofenac sodium
Shukla 2021	To compare the efficacy of dexmedetomidine and $MgSO_4$ as an adjuvant to ropivacaine in ultrasound-guided supraclavicular brachial plexus block for upper limb surgeries in terms of onset, duration of sensory and motor blocks, and duration of analgesia.	19/19	India	73.3/68.4	35.90 ± 12.19 vs. 40.85 ± 11.20	I-II	Ultrasound-Guided	Ropi 0.5%	250 mg	Diclofenac sodium
Verma 2017	To evaluate the efficacy of $MgSO_4$ in two doses (125 mg and 250 mg) as an adjuvant to bupivacaine in USG-guided supraclavicular brachial plexus block.	30/30 (a) + 30 (b)	India	60/66.6	36.93 ± 12.12 vs. 38.37 ± 13.79	I-II	Ultrasound-Guided	Bupi 0.5%	125 and 250 mg	Diclofenac sodium
Youssef 2024	To evaluate the effectiveness of $MgSO_4$ and dexmedetomidine as adjuvants to ropivacaine in supraclavicular brachial plexus block.	49/49	Dubai	61.2/63.2	45.00 ± 10.50 vs. 44.00 ± 11.00	I-II	Ultrasound-Guided	Ropi 0.5%	250 mg	Parecoxib and paracetamol

ASA, American Society of Anesthesiologists; Bupi, Bupivacaine; MS, MS, LA, Local Anesthetics; NA, Not Available; Ropi, Ropivacaine.

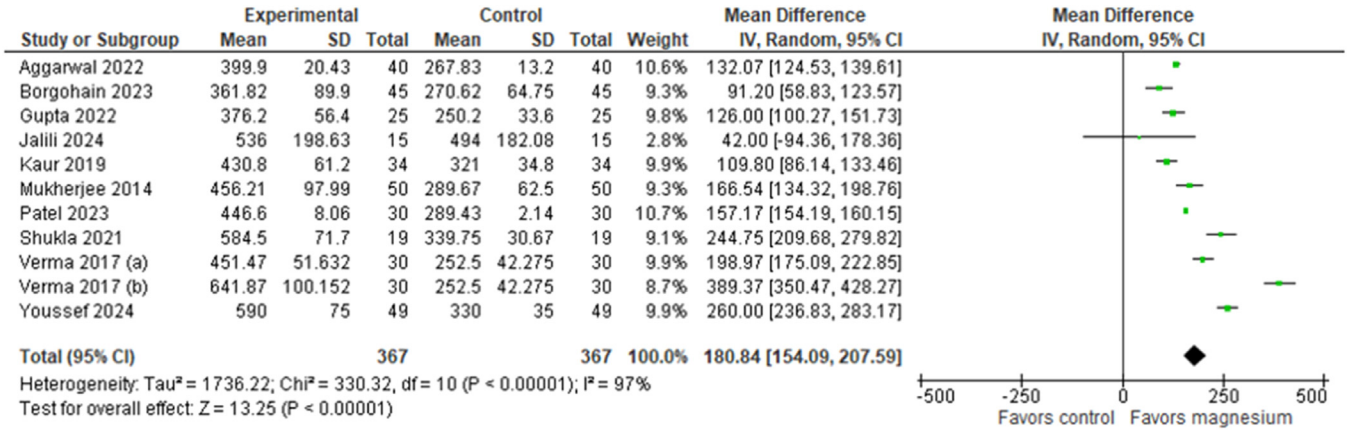

Figure 2 Duration of sensory block (minutes).

289.77], p < 0.00001, Egger's regression P = 0.4298, I^2 = 97%, GRADE moderate). Similarly, the use of MS as an adjunct to LA significantly improved motor block compared with the control group (Fig. 3). The pooled estimate of MD was 151.26 minutes (95% CI: [99.78, 202.74], 95% PI: [-23.12, 325.63], p < 0.00001, Egger's regression P = 0.7826, I^2 = 99%, GRADE low).

A subgroup analysis was performed to estimate the relationship between dose variations and block duration, in addition to increasing the robustness of the results presented (Supplemental Fig. 2 and 3). The results showed a statistically significant difference in all subgroups of both analyses, although it is possible to observe an important variation in the MD comparing the different doses.

Secondary outcomes

Similarly, the onset of sensory and motor blockade was reported in all included studies[24-33] (Figs. 4 and 5, respectively). Comparison of the time to onset of sensory blockade between the intervention group (MS + LA) and the control group (LA only) demonstrated a MD of 3.91 minutes (95% CI: 1.78, 6.05; 95% PI: -3.39, 11.22; Egger's regression P = 0.0038 I^2 = 99%, GRADE low), significantly favoring the intervention group. Similarly, comparing the onset of motor blockade, the analysis showed a MD of 4.73 minutes (95% CI: [1.99, 7.46]; 95% PI: [-4.53, 13.98]; Egger's regression P = 0.0029; I^2 = 99%, GRADE low), also favoring the intervention group. In the subgroup analysis (Supplemental Figs. 4 and 5), it is possible to observe a statistically significant difference favoring the MS group at doses of 200 and 250 mg in both figures.

Cumulative 24 h postoperative analgesic consumption was reported in four trials.[27,29,31,33] In these studies, rescue analgesia was quantified as the total amount of analgesic drug administered within the first 24 hours after surgery, expressed in milligrams of the specific drug used in each trial (opioids for Jalili et al.;[27] diclofenac sodium for Mukherjee et al.[29] and Shukla et al.;[31] parecoxib and paracetamol for Youssef et al.).[33] For meta-analysis, these continuous measures were standardized and pooled, resulting in a SMD of 0.96 (95% CI: [0.36, 1.57], 95% PI: [-2.19, 0.27], p < 0.00001, I^2 = 80%, GRADE moderate), indicating a statistically significant reduction in postoperative analgesic consumption in the intervention group compared with control.

Another outcome analyzed was the presence of nausea or vomiting during the postoperative period (Supplemental Fig. 7). There was no statistically significant difference between the groups, with a risk ratio of 1.39 (95% CI: [0.57, 3.38], 95% PI: [0.20, 9.76], p < 0.00001, I^2 0%, GRADE moderate).

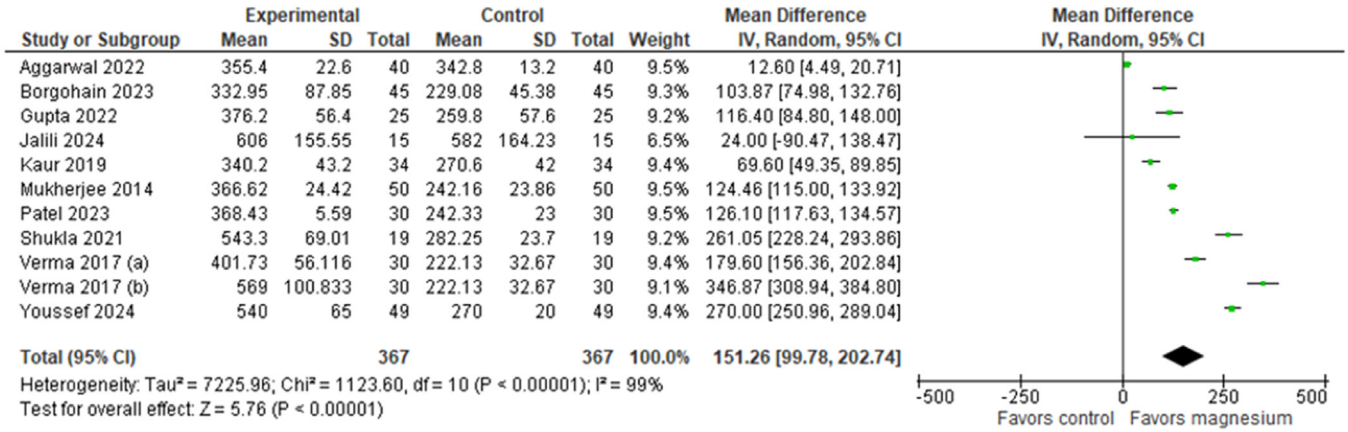

Figure 3 Duration of motor block (minutes).

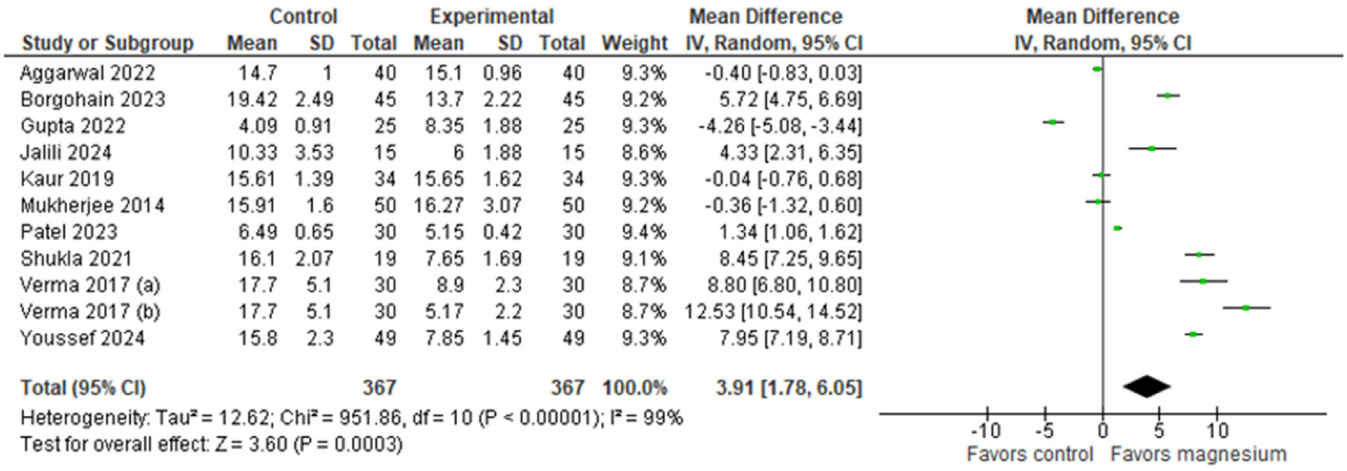

Figure 4 Onset of sensory block (minutes).

No significant hemodynamic changes were observed in the analyzed studies.

Heterogeneity

The observed asymmetry in the funnel plots (Supplemental Fig. 8 and 9), especially in the primary outcomes, indicates the potential presence of publication bias or other biases, such as methodological heterogeneity among the studies. Egger's test (Supplemental Fig. 10) yielded a p-value exceeding 0.05 for the primary outcomes, indicating minimal evidence of publication bias. Conversely, the outcomes related to the onset of sensory and motor blockade demonstrated a p-value less than 0.05, suggesting an elevated risk of publication bias.

A leave-one-out sensitivity analysis (Supplemental Fig. 11) was performed under a random-effects model for all outcomes with high heterogeneity, which was applied to all endpoints, except PONV. After analyzing each outcome, no single study was responsible for the observed high heterogeneity in most outcomes. However, for the outcome "total analgesic in 24 h", the study by Mukherjee et al.[29] substantially contributed to the heterogeneity.

Discussion

The main findings of our meta-analysis are as follows: 1) An extended duration of sensory and motor blockades; 2) A reduction in latency time for both motor and sensory blockades; 3) A decrease in analgesic consumption within the first 24 hours postoperatively, which in the included trials was measured as the total amount of the specific analgesic drug administered (opioid, diclofenac sodium, parecoxib, or paracetamol); and 4) No increase in PONV during the analyzed period.

The increased use of PNBs in surgeries has been a remarkable trend in recent years, with several studies highlighting the benefits of this approach compared to other anesthesia techniques.[34] This technique may offer numerous advantages, including effective analgesia, reduced opioid consumption, lower complication rates, and a more favorable recovery profile.[35,36]

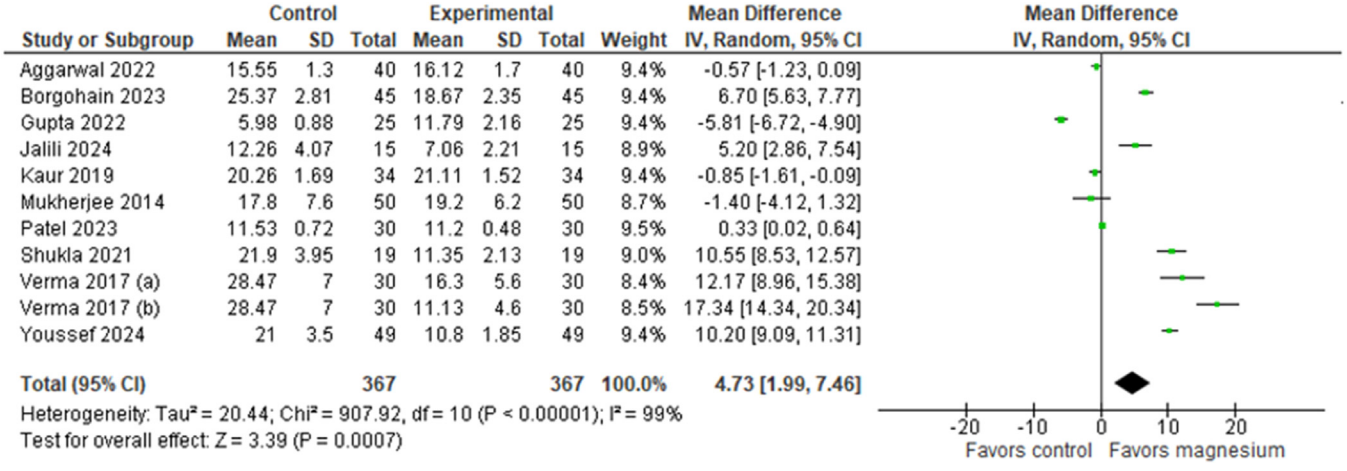

Figure 5 Onset of motor block (minutes).

The mechanism of action by which MS potentiates the analgesic effect of LAs remains not entirely clear,[37] although a meta-analysis has proven that the combination of MS and LAs in-nerve blocks could result in longer postoperative analgesia.[8] Magnesium acts as an antagonist of N-Methyl-D-Aspartate (NMDA) receptors and has been shown to raise the excitation threshold in peripheral nerves, particularly in myelinated Ab fibers, compared to unmyelinated C fibers. When administered perineurally, its mechanism of action may involve the influence of its positive divalent charge on the neuronal membrane, or its function as a physiological calcium antagonist.[2] Although its perineural use is still off-label and there are concerns about neurotoxicity, the available literature does not provide conclusive evidence of significant neurotoxic effects when MS is used as an adjunct in perineural applications.

The results showed that MS significantly increased the duration of sensory and motor blocks. These findings align with those of other studies indicating that MS, acting as an NMDA receptor antagonist, prolongs analgesic and anesthetic effects.[38,39] A study by Ramegowda et al.[40] reported similar results, with a significant increase in the sensory block duration in patients who received MS as an adjuvant. This effect can be attributed to the ability of MS to modulate nociceptive stimulus transmission and prolong neuronal block. The confidence interval exhibited considerable variance, alongside notably high reported effect sizes. The observed findings are likely attributable to the considerable heterogeneity across studies or perhaps to the variability in the temporal dynamics of MS when used as an adjunct. The subgroup analysis suggests a dose-dependent relationship between magnesium sulfate and anesthetic efficacy, particularly in sensory block duration. The 250 mg dose showed the greatest mean effect in both outcomes and was statistically superior to the 150 mg and 200 mg doses in prolonging sensory block ($p = 0.0003$). However, this trend did not reach statistical significance for motor block duration ($p = 0.10$), indicating the dose-response relationship varies across clinical parameters. The high heterogeneity observed may reflect methodological differences between studies – such as variations in block technique, anesthetic formulations, timing of assessment, or outcome definitions. While data suggest increased efficacy with higher doses, discrepancies across subgroups may be partially influenced by methodological limitations of the included studies.

Despite its benefits, motor block prolongation and phrenic nerve involvement remain important considerations with supraclavicular block. Phrenic nerve block following this technique occurs in 0–67% of cases in clinical trials.[41-46] This risk relates to the anatomical proximity of the brachial plexus to the phrenic nerve at the supraclavicular fossa and may be influenced by local anesthetic volume and technique. While healthy individuals tolerate transient hemidiaphragmatic paresis without significant symptoms, patients with respiratory disease, obesity, or reduced cardiopulmonary function may experience respiratory compromise.[47,48] In such cases, alternative approaches or modifications – such as reducing local anesthetic volume – may help minimize phrenic nerve involvement while maintaining effective analgesia.

Regarding onset time, the data indicate a significant reduction in the onset time of sensory and motor blocks with MS use. These findings are consistent with those in the literature, suggesting that MS enhances the effect of LAs, accelerating nerve blockade. Li et al.[6] also reported a significant reduction in block onset time in patients undergoing peripheral blocks with MS. This effect can be explained by the ability of the adjuvant to alter neuronal excitability and facilitate LA diffusion. In subgroup analysis, only the 150 mg dosage did not show a statistically significant difference favoring the intervention group. Subgroup analyses showed a consistent trend of increased clinical efficacy with higher doses of magnesium sulfate in accelerating motor and sensory block onset. Doses of 200 mg and 250 mg had statistically significant effects in both outcomes, whereas 150 mg did not. The subgroup difference tests were significant for both parameters ($p < 0.001$), suggesting a dose-dependent response. However, high heterogeneities were also observed in both analyses.

The analysis of the need for rescue analgesia within the first 24 h postoperatively revealed a significant difference favoring the group that received MS. This reduction in rescue analgesia reflects the prolonged analgesic effect of adjuvants. Previous studies, such as those by Wu et al.,[49] also observed lower opioid consumption postoperatively in patients receiving MS, reinforcing its role in multimodal analgesia. Regarding the need for long-term analgesia, the studies analyzed did not evaluate this topic.

The results showed no significant difference in the incidence of PONV between the groups. This finding suggests that MS does not directly affect the outcome. Although some studies have proposed that MS may reduce PONV incidence owing to its role in reducing opioid consumption,[50] our results do not support this hypothesis.

Our meta-analysis also revealed that magnesium as an adjuvant does not appear to be associated with significant unstable changes in hemodynamic parameters such as blood pressure and heart rate. Similar outcomes have been reported in recent studies conducted for infraclavicular brachial plexus nerve block,[51] axillary brachial plexus block[52] and laparotomy surgery.[53]

The potential neurotoxicity of MS as an adjuvant in PNBs is the subject of ongoing investigation. Cheng et al.[54] suggest that glutamate can increase the intracellular magnesium concentration, which may cause neurotoxicity. Animal studies have shown that the intrathecal administration of magnesium can cause nerve damage.[55,56] In a human study, Peng et al.[45] observed no such adverse effects after the administration of 400 mg of MS in the quadratus lumborum block. Moreover, a systematic review of neuraxial MS, which exhibits certain similarities with perineural applications, reported no significant neurological complications, although the risk has not been fully delineated.[57] In the studies included in our analysis, no adverse effects related to neurotoxicity were reported.

The methodological quality of the included studies varied considerably. Although some trials were rated as having a low overall risk of bias, several exhibited methodological concerns or a high risk of bias. For instance, studies by Aggarwal et al.,[24] Borgohain et al.,[25] and Youssef et al.[33] were classified as high risk due to the lack of blinding procedures. Jalili et al.,[27] Kaur et al.,[28] and Shukla et al.[31] showed risk of bias related to post-randomization attrition, while Patel et al.[30] presented "some concerns" due to the

implementation of only single blinding. When assessed using the GRADE approach, the certainty of evidence ranged from low to moderate across most outcomes. Downgrading was primarily due to risk of bias, imprecision (evidenced by wide confidence and prediction intervals), and inconsistency among study results. Although statistically significant MDs were observed, the heterogeneity and broad prediction intervals indicate a high degree of variability in the expected effects, suggesting that individual future studies could find no effect or even effects in the opposite direction. The presence of wide prediction intervals in several outcomes highlights the need for future high-quality, well-powered randomized trials with rigorous methodology and standardized outcome reporting to strengthen the evidence on the use of magnesium sulfate as an adjuvant in regional anesthesia. Such efforts are essential to confirm the observed dose-response relationship and to reduce the risk of overestimating the effects in future evidence syntheses.

The use of MS as an adjunct in supraclavicular brachial plexus block appears to be clinically applicable, particularly for prolonging the duration of analgesia and reducing postoperative pain and analgesic consumption. PNBs associated with MS represent a viable option for patients who are at elevated risk of experiencing respiratory depression, opioid addiction, or opioid-induced nausea and vomiting,[58] mainly in the context of upper limb surgeries, where a high incidence of postoperative pain is observed. When compared with other adjuvants, such as alpha-2 adrenergic agonists — concerns about hypotension and bradycardia —[59] our results did not observe such adverse effects with MS, although its use is still off-label.

Based on subgroup analyses, the 250 mg dose of MS showed statistically significant superiority in prolonging sensory and motor block duration and reducing onset time versus lower doses. This dose was not associated with clinically relevant adverse effects in the studies. These findings support recommending 250 mg as the optimal dose for enhancing supraclavicular brachial plexus blocks. The dose-dependent gradient and favorable safety profile reinforces this dosage's clinical viability in routine anesthetic practice, considering patient-specific factors.

Limitations

First, the overall methodological quality of the included trials was suboptimal, with most studies presenting some concerns or high risk of bias, particularly in randomization procedures and selective outcome reporting, as assessed by the RoB2 tool. Second, the certainty of evidence was rated as low to moderate using the GRADE approach, mainly due to serious risk of bias, inconsistency, and imprecision.

Second, high heterogeneity was observed in several outcomes, which suggests potential methodological differences among the studies. The observed differences can be attributed to several factors, including the type of surgery (such as forearm and upper limb procedures), the dosage of MS, the characteristics of local anesthetics (including types and volumes), the techniques employed for nerve blocks (such as anatomical, nerve stimulator, and ultrasound methods), and the scales utilized for outcome measurement. Despite these findings, no single study was responsible for the observed high heterogeneity in most of the outcomes (except Mukherjee et al.[37] in "total analgesic in 24 h"). In addition, some results report very wide confidence intervals, indicating variability in effect size estimates and possible inconsistencies.

Third, the individual trials had small sample sizes, ranging from 15 to 60 patients per group, which increased the risk of type I error and publication bias. However, after conduct a power analysis, we observed these sample sizes are adequate to detect clinically significant differences. Furthermore, our results are based on a limited number of studies (10).

Fourth, most of the studies were conducted in India, limiting generalizability. The findings of our research may have been influenced by ethnic or geographical commonalities.

Strengths

Our study possesses several notable strengths. We conducted a comprehensive literature search across major databases and trial registries, including gray literature sources, to minimize publication bias. The inclusion criteria were strictly limited to RCTs, which enhances the methodological rigor and validity of the findings. In addition, we performed subgroup analyses to explore potential sources of heterogeneity and improve the robustness of our conclusions. To further assess the risk of publication bias, we conducted both funnel plot inspection and Egger's regression asymmetry test, providing greater transparency in our synthesis. Methodologically, we applied the RoB2 tool to evaluate study quality in a structured, domain-based manner, and conducted a leave-one-out sensitivity analysis to determine the influence of individual studies on the pooled estimates. Finally, we used the GRADE approach to construct a summary of findings table and assess the certainty of evidence for each outcome, thereby enhancing the interpretability and clinical relevance of our results. These combined strategies support the internal validity of this meta-analysis.

Conclusion

Our meta-analysis supports the use of MS as adjuvant in supraclavicular block, with positive effects on several clinical outcomes, including prolonged block duration, faster onset time, and reduced need for rescue analgesia without important hemodynamic changes or increased PONV. The results endorse the suggestion of using a 250 mg dose as the most effective for improving supraclavicular brachial plexus blocks. However, for now, generalization of the results should be done with caution due to the high heterogeneity presented in our results.

Further studies are needed to explore variables, such as other surgical settings, different nerve block techniques, and their impact on outcomes. Standardized protocols will contribute to a broader clinical applicability and a better understanding of the safety and effects of perineural use of MS.

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.2025.844689.

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REVIEW ARTICLE

Ciprofol versus propofol for sedation in colonoscopy: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Ciprofol has emerged as a potential alternative sedative with improved safety and efficacy. However, comparative data for colonoscopy sedation remain limited.

Methods: A systematic search in PubMed, Embase, Cochrane Library, and Web of Science identified RCTs published through August 2025. Studies included patients undergoing colonoscopy using ciprofol or propofol, reporting relevant efficacy or safety outcomes. Risk Ratios (RRs) and Mean Differences (MDs) were calculated using the Mantel-Haenszel random-effects model and 95% Confidence Intervals. The heterogeneity was assessed with I^2 statistics and Cochrane Q test. Primary outcomes were procedure success rate and patient satisfaction (assessed on a 1-to-10 scale). Secondary outcomes included sedation onset time(s), respiratory depression, injection pain, and hemodynamic adverse events (hypotension and bradycardia). The statistical analyses were performed in *R* software (version 4.4.1.)

Results: Three RCTs with 645 patients were included. Colonoscopy success rates were similar between ciprofol and propofol (RR = 1.005; 95% CI 0.992—1.019). Ciprofol showed a lower risk of respiratory depression (RR = 0.24; 95% CI 0.08—0.71), injection pain (RR = 0.04; 95% CI 0.01—0.15), and hypotension (RR = 0.85; 95% CI 0.75—0.96). Patient satisfaction was slightly higher with ciprofol (MD = 0.18; 95% CI 0.08—0.29). No significant differences were found in sedation onset time (s) (MD = 2.49s; 95% CI -3.77—8.74) or bradycardia (RR = 0.88; 95% CI 0.44—1.77).

Abbreviations: ASA PS, American Society of Anesthesiologists Physical Status; CI, Confidence Interval; $GABA_A$, Gamma-aminobutyric acid type A; MD, Mean Difference; MH, Mantel-Haenszel; PACU, Post-Anesthesia Care Unit; PADSS, Post Anesthesia Discharge Scoring System; PROSPERO, International Prospective Register of Systematic Reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT, Randomized Controlled Trial; Rob2, Revised Cochrane Risk of Bias Tool for Randomized Trials; RR, Risk Ratio..

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Conclusion: Ciprofol provides comparable efficacy to propofol for colonoscopy sedation, with a lower incidence of respiratory depression, injection pain, and hypotension. Patient satisfaction was slightly higher with ciprofol, while bradycardia occurrence was similar. These findings suggest ciprofol as a promising alternative, though further large-scale studies are needed to confirm its clinical benefits.

Introduction

Colonoscopy is a cornerstone endoscopic procedure for the diagnosis, prevention, and treatment of colonic diseases, playing a pivotal role in the early detection of colorectal cancer – one of the leading causes of mortality worldwide.[1] Effective sedation is essential in this context, not only to ensure patient comfort but also to optimize procedural conditions, enhancing the quality and safety of the examination.[2] Propofol has long been the sedative agent of choice for endoscopic procedures, primarily due to its rapid onset of action, short duration, and favorable recovery profile, which are particularly advantageous in ambulatory settings.[3] However, its use is not without challenges, as it is associated with risks such as respiratory depression and hemodynamic instability, necessitating close monitoring and dosage adjustments to mitigate adverse effects.[4,5]

In the search for alternatives that combine efficacy with a potentially improved safety profile, ciprofol has emerged as a promising structural analog of propofol. Early studies suggest that ciprofol offers comparable – if not superior – sedative efficacy, with a reduced incidence of adverse events and faster recovery times.[6] Nevertheless, the variability in findings across clinical trials highlights the need for a robust quantitative analysis to consolidate the evidence and provide a nuanced understanding of the relative benefits and risks of each agent in the context of colonoscopy. Despite the widespread use of sedation in colonoscopies, the literature lacks a comprehensive comparative evaluation of the efficacy and safety profiles of ciprofol and propofol. While previous meta-analyses have compared ciprofol and propofol, their scope has been substantially broader, thereby limiting their applicability to this specific procedural context. For instance, existing reviews have aggregated data from diverse surgical and non-surgical procedures or focused on the induction and maintenance of general anesthesia rather than procedural sedation.[7,8] Consequently, a critical knowledge gap persists regarding the relative merits of these agents specifically for colonoscopy, a procedure with unique physiological demands and patient safety considerations.

Therefore, this meta-analysis aims to systematically assess and compare ciprofol and propofol in colonoscopy procedures, focusing on critical outcomes such as adverse event rates and recovery metrics. The findings will provide a comprehensive synthesis of the available evidence, offering valuable insights for clinical practice and guiding future research.

Methods

This systematic review and meta-analysis of the literature was performed and reported following the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement guidelines.[9,10] The review protocol was prospectively registered on International Prospective Register of Systematic Reviews (PROSPERO) in November 2024 under protocol CRD42024613088.

Eligibility criteria

Original studies were included in this review based on the following eligibility criteria: 1) Randomized Controlled Trial reports published in peer-reviewed journals; 2) Patients undergoing Colonoscopy; 3) Ciprofol and propofol comparison groups; 4) At least one safety or efficacy endpoint of interest. Non-randomized observational studies, non-English reports, literature reviews and conference abstracts were excluded from this study. No restrictions were applied regarding minimum sample size, patient age, or intervention dose range, provided that the studies fulfilled the inclusion criteria of randomized controlled design, colonoscopy patients, and a direct comparison between ciprofol and propofol. We acknowledge that the restriction to English-language reports, although commonly applied in systematic reviews, may have introduced language bias; however, this choice was made to ensure uniformity in data extraction and to minimize the risk of misinterpretation during the analysis.

Search strategy and data extraction

A systematic search was performed in PubMed, Embase, Cochrane Central Register of Controlled Trials and Web of Science databases from inception to August 2025 using the following search-key strategy: (Ciprofol OR HSK3486 OR Propofol) AND (Colonoscopy OR "Colonoscopy Procedure" OR "Colonoscopy Surgery" OR Colonoscop* OR Colonoscopic) AND (Sedation OR Anesthesia OR Anaesthesia OR Analgesia OR "Conscious Sedation" OR "Moderate Sedation" OR "Procedural Sedation"). Two independent authors (S.D and I.C.M) screened titles and abstracts for eligibility evaluation.

The included articles' data were independently extracted by two authors (S.D. and B.B.S) who reviewed the reports, supplementary materials and extracted the RCTs' characteristics and relevant information. The discrepancies were discussed and settled by another two authors (I.C.M and V.A.O)

Endpoints

The efficacy endpoints of this meta-analysis were (1) Patient satisfaction and (2) Onset time of sedation (s) and (3) Success rate of colonoscopy, and the safety outcomes were (4)

Bradycardia, (5) Hypotension, (6) Injection pain, (7) Respiratory depression. Patient Satisfaction was measured by different surveys on a scale of 1 to 10.

Quality assessment

The risk of bias in the included studies was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB-2). Two independent reviewers (V.A.O and I.C.M) conducted the evaluation based on the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[9,11] Any disagreements were addressed through discussion, and if a consensus was not reached, a third reviewer (S.D) was consulted for resolution.

The assessment covered various domains, including random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, completeness of outcome data, selective reporting of results, and additional potential sources of bias. Each domain was judged as "low risk of bias", "some concerns", or "high risk of bias", following the standardized RoB2 algorithm. To ensure transparency, domain-level judgments were combined to produce an overall risk of bias rating for each included trial. A study was classified as "low risk of bias" if all domains were rated as low risk, "high risk of bias" if at least one domain was judged high risk, and "some concerns" if one or more domains raised concerns without being rated high risk. The results of the risk of bias assessment were summarized in graphical format to facilitate interpretation and reproducibility.

Statistical analysis

We analyzed the endpoints using Risk Ratio (RR) for binary outcomes and Mean Difference (MD) for continuous outcomes, presenting them with 95% Confidence Intervals (95% CI). The Mantel-Haenszel (MH) method was applied with a random-effects model. To assess heterogeneity, we utilized the I^2 statistic and the Cochran Q test, considering heterogeneity significant when I^2 exceeded 40% and p-values were below 0.1.[9] We chose a more liberal p-value threshold ($p < 0.1$) for the Cochran Q test to enhance its sensitivity in detecting heterogeneity, particularly in meta-analyses with a small number of included studies, as this test is known to have low statistical power under these conditions. This approach helps to avoid Type II errors (falsely concluding homogeneity). For outcomes exhibiting significant heterogeneity ($I^2 \geq 40\%$), a leave-one-out sensitivity analysis was conducted to determine whether any single study disproportionately influenced the results. This approach also helped identify studies contributing most to the overall heterogeneity of those outcomes. All statistical analyses were performed using *R* software (version 4.4.1, R Foundation for Statistical Computing, Vienna, Austria).[12]

Results

Study selection

The initial search identified 4151 articles, with 572 from PubMed, 1825 from Embase, 1144 from Web of Science and 610 form Cochrane Central Register of Controlled Trials. After the removal of 1876 duplicates, 2275 articles underwent title and abstract screening. Of these, 16 were deemed eligible for full-text review. Among them, 13 were later excluded, with the reasons for exclusion detailed in the Prisma Flow Diagram, shown in Figure 1. Ultimately, a total of 3 RCTs were included.[13-15]

Characteristics of the included studies and patients

A total of three studies, RCTs conducted exclusively in China, including 645 patients (44% male) were analyzed.[13-15] Their clinical baseline features are shown in Table 1.

The three studies have similar inclusion criteria, with slight variations regarding age range, clinical parameters, and specific exclusion conditions. In Gao et al. (2024), patients aged $\geq$ 18 years, with an ASA physical status I—II and BMI between 18 and 30 $kg.m^{-2}$, were included. He (2024) adopted similar criteria but restricted the age range to 18—65 years and added a painless colonoscopy duration of $<$ 20 minutes as an inclusion criterion. Li (2022) included patients aged $\geq$ 18 and $<$ 65 years with a BMI between 18 and 30 $kg.m^{-2}$.[13-15]

Regarding exclusion criteria, Gao et al. (2024) and He et al. (2024) share criteria such as BMI $\geq$ 30 $kg.m^{-2}$, a history of substance abuse, allergies to anesthetics, and pregnancy or lactation. On the other hand, Li et al. (2022) presents stricter exclusion criteria, including contraindications for general and deep sedation, allergy to soybean- or egg-based products, recent use of propofol, benzodiazepines, opioids, or any analgesic-containing formulation within the past 72 hours. Additionally, Li (2022) excluded patients with neutropenia, thrombocytopenia, hepatic dysfunction, and renal insufficiency. Patients with uncontrolled hypertension (SBP $\geq$ 170 mmHg, DBP $\geq$ 105 mmHg), severe arrhythmias, heart failure, unstable angina, recent myocardial infarction, and advanced atrioventricular blocks were also excluded. He et al. (2024) further added arrhythmia and participation in pharmacological clinical trials within the last 3 months as exclusion criteria.[13-15]

Technical aspects of the colonoscopy procedure

Regarding monitoring, all studies assessed vital parameters such as blood pressure, heart rate, oxygen saturation, and ECG during the procedure. However, He et al. (2024) monitored Heart Rate Variability (HRV) and recorded data every 2 minutes for 20 minutes after induction. Oxygen supplementation also varied among the studies: Gao (2024) and He (2024) used a nasal cannula at 4 $L.min^{-1}$ and 5 $L.min^{-1}$, respectively, while Li et al. (2022) administered oxygen at 10 $L.min^{-1}$ via a face mask until the patient fully regained consciousness. Regarding pre-procedure preparation, all patients underwent standardized bowel preparation.[13-15]

For anesthetic induction, some studies administered fentanyl before ciprofol or propofol, but with differences in dosage and reinforcement regimens. He (2024) used 0.05 $\mu g.kg^{-1}$ of sufentanil, whereas Li et al. (2022) administered 50 μg of fentanyl. Induction was performed with ciprofol (0.4 $mg.kg^{-1}$) or propofol (2.0 $mg.kg^{-1}$) in Gao et al. (2024) and He et al. (2024), but in Li et al. (2022), the propofol dose was lower (1.5 $mg.kg^{-1}$). The criterion for initiating

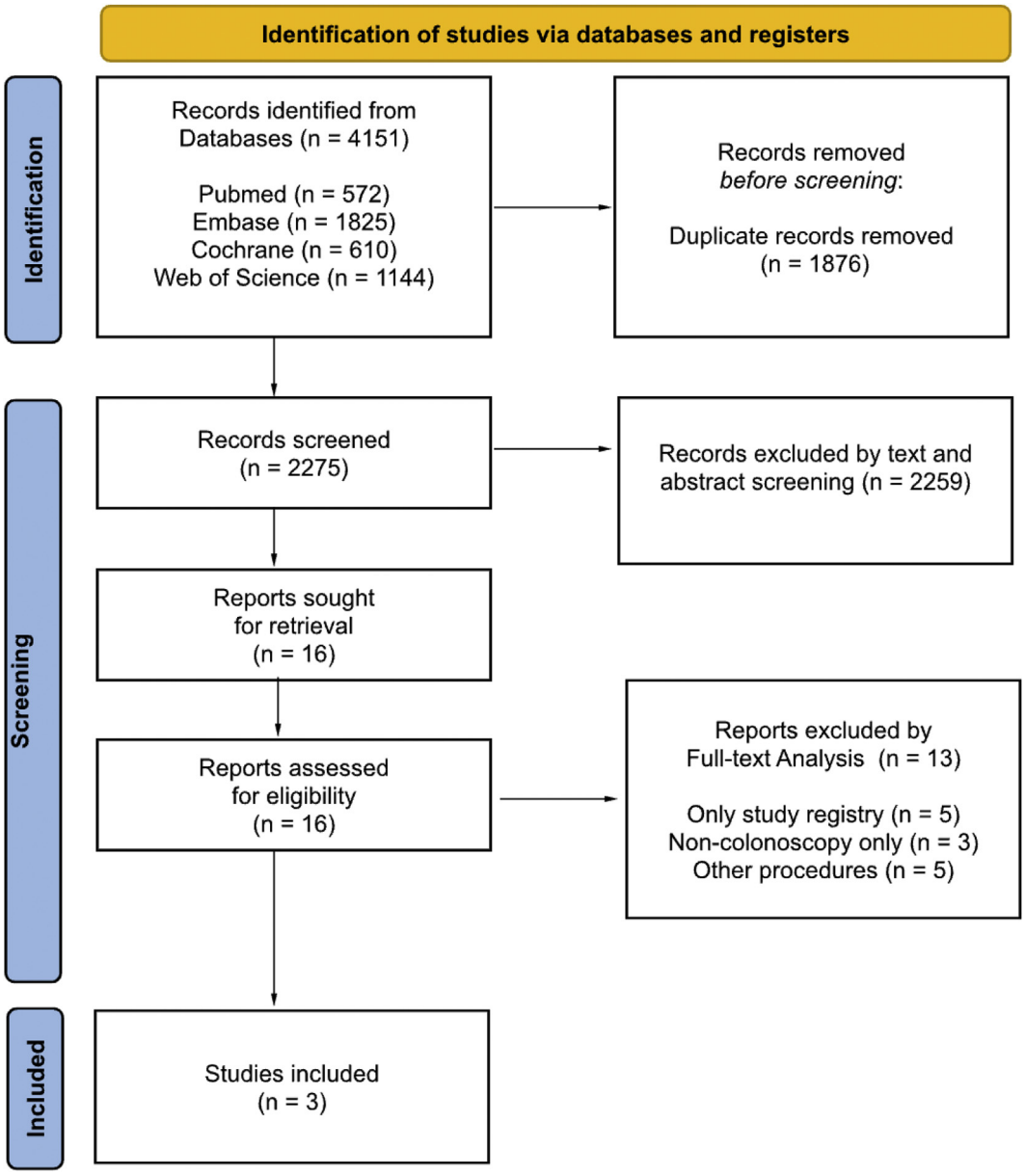

Figure 1 The prisma flow diagram.

colonoscopy was similar across all three studies, requiring a MOAA/S score of ≤ 1, assessed every 30 seconds during induction. However, the frequency of monitoring during the maintenance phase varied, occurring every 5 minutes in Gao et al. (2024) and every 2 minutes in Li et al. (2022) and He et al. (2024).[13-15]

During the sedation maintenance phase, the additional dosing regimen differed among the studies. Gao et al. (2024) and Li et al. (2022) administered reinforcement doses of 0.1 $mg.kg^{-1}$ for ciprofol and 0.5 $mg.kg^{-1}$ for propofol, while He et al. (2024) used supplementary doses equivalent to one-third of the initial dose. Sedation was considered ineffective if more than five additional doses were required within 15 minutes in all studies, in which case propofol was the only permitted alternative sedative.[13-15]

In the postoperative period, all patients were transferred to the Post-Anesthesia Care Unit (PACU), and discharge was based on standardized scoring systems. Gao et al. (2024) used the Post Anesthesia Discharge Scoring System (PADSS) with a discharge threshold of ≥ 9, while He (2024) and Li (2022) used the modified Aldrete score, with a discharge criterion of ≥ 9.[13-15]

Pooled analysis of included studies

Success rate of colonoscopy

In a meta-analysis of 3 studies, no significant difference was observed in the success rate of colonoscopy between ciprofol and propofol (RR = 1.005; 95% CI 0.992−1.019; I^2 = 0%; p = 0.4498; Fig. 2).

Onset time to sedation(s)

In a meta-analysis of 3 studies, the time to onset of sedation showed no statistically significant difference between ciprofol

Table 1 Baseline characteristics of the included studies.

Baseline clinical features	Li (2022)		He (2024)		Gao (2024)	
	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol
Patients (n)	129	130	110	112	82	82
Age (years)	43.8 ± 11.8	44.1 ± 11.3	48.0 ± 11.2	49.0 ± 9.7	54 ± 15.56	54 ± 14.07
Gender						
Male (%)	55 (38.2)	63 (43.4)	54 (49.1)	46 (41.1)	34 (41.5)	32 (40)
Female (%)	89 (61.8)	82 (56.6)	56 (50.9)	66 (58.9)	48 (58.5)	50 (40)
Height (mean ± SD, cm)	161.5 ± 8.2	163.1 ± 8.4	166.2 ± 9.0	165.2 ± 7.5	166 ± 8,89	165.5 ± 8.15
Weight (mean ± SD, kg)	60.0 ± 9.6	61.5 ± 9.7	65.9 ± 12.0	65.1 ± 10.3	63.5 ± 12.59	63.5 ± 12.59
BMI (mean ± SD, kg m^{-2})	23.2 ± 2.5	23.4 ± 2.6	23.7 ± 2.9	23.8 ± 2.7	23.4 ± 3.0	23.7 ± 3.0
ASA PS						
I (%)	115 (79.9)	118 (81.4)	29 (26.4)	36 (32.1)	16 (19.5)	20 (24.4)
II (%)	29 (20.1)	27 (18.6)	81 (73.6)	76 (67.9)	66 (80.5)	62 (85.6)
Objectives	Compare the deep sedation properties of ciprofol and propofol using an 8% non-inferiority margin in patients undergoing gastroscopy and colonoscopy.		Evaluate whether ciprofol provides greater hemodynamic stability than propofol during colonoscopy.		Assess differences in safety and efficacy between ciprofol and propofol for painless colonoscopy.	

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

and propofol (MD = 2.49; 95% CI -3.77—8.74; I^2 = 92.4%; p = 0.4356; Fig. 3).

Respiratory depression

In a meta-analysis of 3 studies, ciprofol was associated with a significantly lower risk of respiratory depression compared to propofol (RR = 0.24; 95% CI 0.08—0.71; I^2 = 0%; p = 0.01; Fig. 4).

Injection pain

In a meta-analysis of 2 studies, ciprofol significantly reduced the occurrence of injection pain compared to propofol (RR = 0.04; 95% CI 0.01—0.15; I^2 = 0%; p < 0.001; Fig. 4).

Hypotension

In a meta-analysis of 3 studies, ciprofol was associated with a lower risk of hypotension compared to propofol (RR = 0.85; 95% CI 0.75—0.96; I^2 = 44.4%; p = 0.010; Fig. 4).

Bradycardia

In a meta-analysis of 3 studies, no significant difference was observed in the incidence of bradycardia between ciprofol and propofol (RR = 0.88; 95% CI 0.44—1.77; I^2 = 0%; p = 0.718; Fig. 4).

Patient satisfaction

In a meta-analysis of 3 studies, ciprofol was associated with significantly higher patient satisfaction compared to propofol (MD = 0.18; 95% CI 0.07—0.29; I^2 = 0%; p < 0.01; Fig. 5).

Sensitivity analysis

To assess heterogeneity, a leave-one-out analysis was performed. For onset time to sedation(s), Li et al. (2022) was the primary contributor to heterogeneity. Its exclusion reduced I^2 to 0% and yielded MD = -1.13 (95% CI: -2.55 to 0.30; p = 0.1202), showing no significant difference. Omitting He et al. (2024) (MD = 4.64; I^2 = 83.8%) and Gao et al. (2024) (MD = 3.57; I^2 = 96.2%) did not resolve heterogeneity. The overall random-effects model showed MD = 2.49 (95% CI: -3.77 to 8.74; p = 0.4356) with high heterogeneity (I^2 = 92.4%; Supplementary Material 1).

For hypotension, removing Li et al. (2022) reduced I^2 to 0% (RR = 0.83 [0.73—0.94]), while excluding Gao et al. (2024) (RR = 1.09; I^2 = 70.2%) and He et al. (2024) (RR = 1.08; I^2 = 72.0%) maintained moderate heterogeneity. The random-effects model showed RR = 0.85 (95% CI: 0.75—0.96) with I^2 = 44.4%, favoring ciprofol over propofol in reducing hypotension risk (Supplementary Material 2).

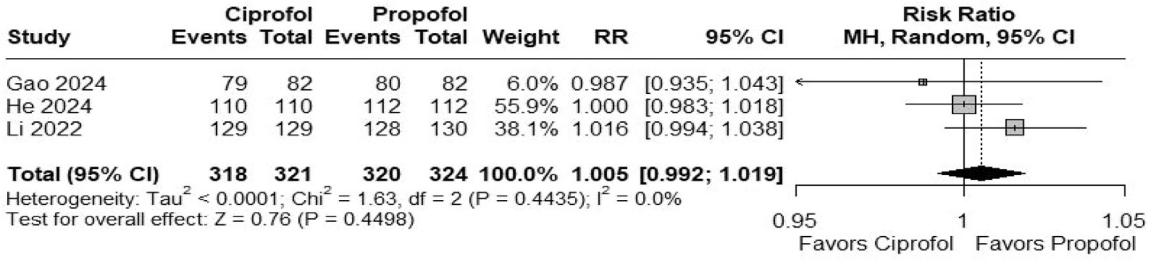

Figure 2 Forest plot showing no significant difference in success rate of colonoscopy between ciprofol and propofol.

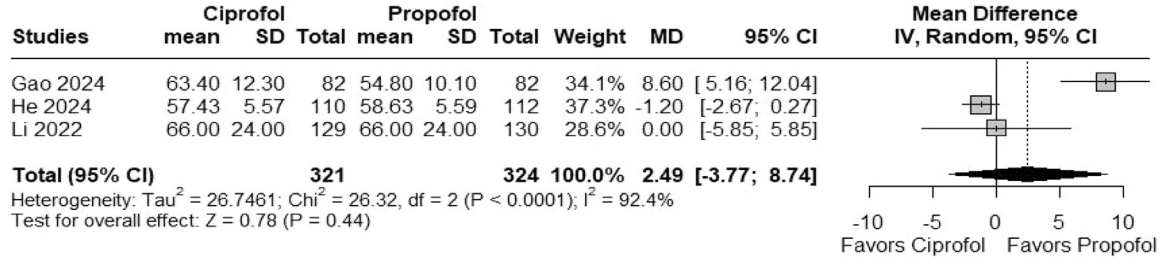

Figure 3 Forest plot showing no significant difference in onset time to sedation between ciprofol and propofol.

Risk of bias of included studies

All three included RCTs were considered to have a low risk of bias across all assessed domains.[13-15] The three (3/3; 100%) trials demonstrated low risk in relation to the randomization process, deviations from intended intervention, missing outcome data, measurement of outcomes, or selection of reported results. Detailed results of the RoB-2 assessment are provided in Supplementary Material 3.

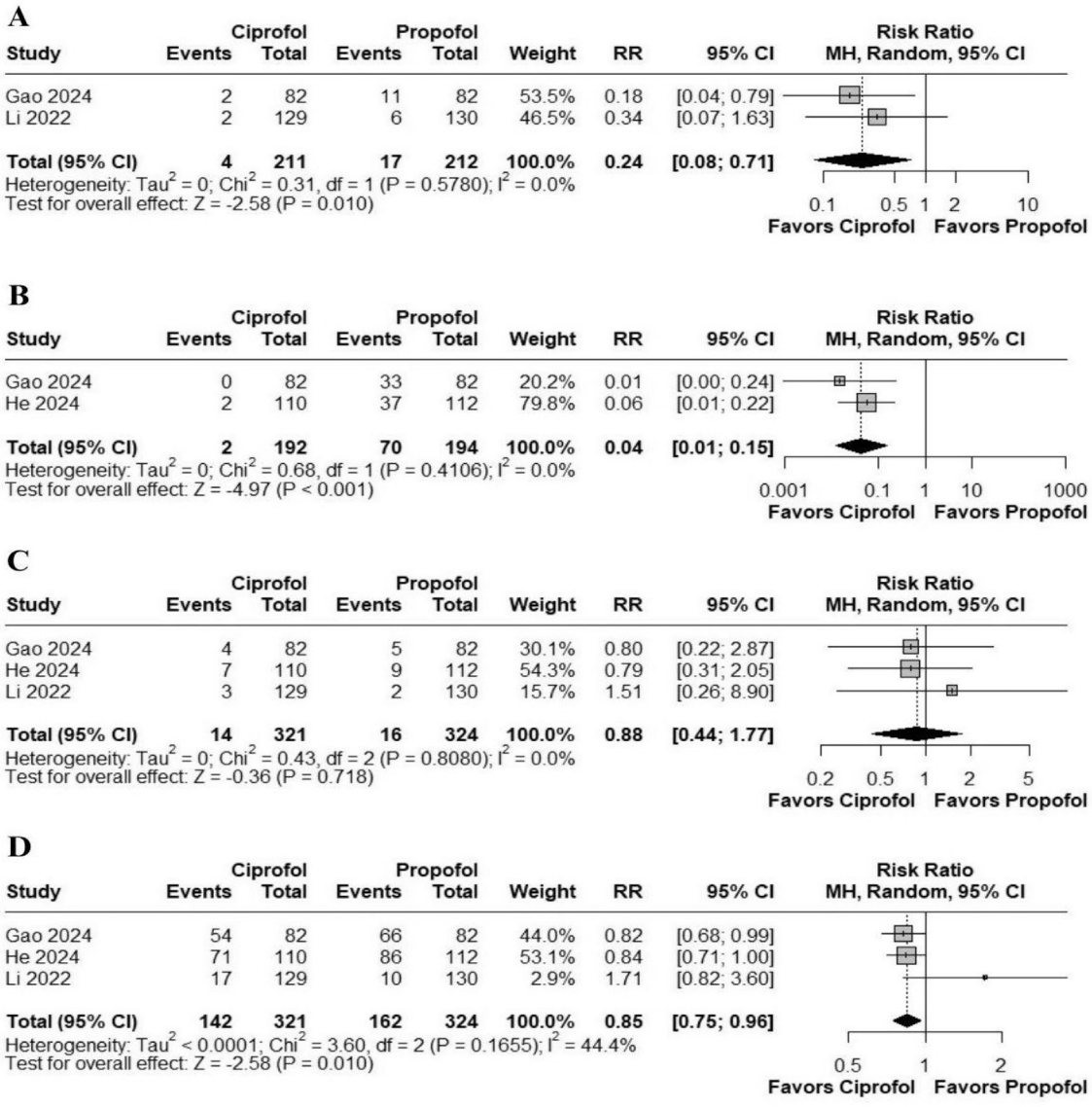

Figure 4 Forest plots of safety outcomes comparing ciprofol and propofol. Panel (A) shows the risk ratio for respiratory depression. Panel (B) shows the risk ratio for injection pain. Panel (C) shows the risk ratio for bradycardia. Panel (D) shows the risk ratio for hypotension.

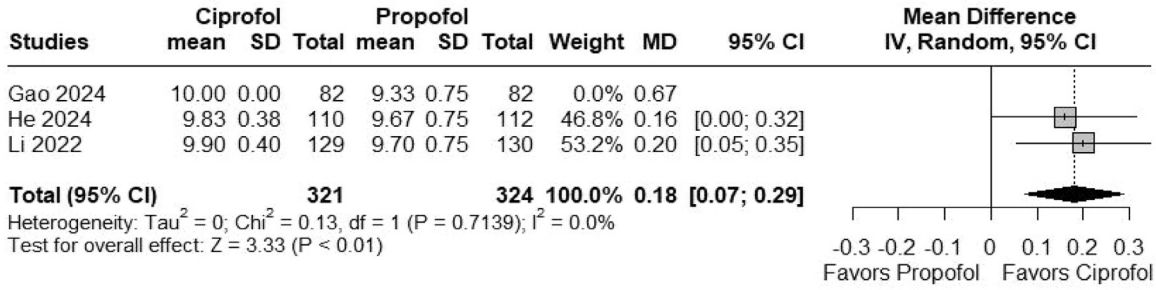

Figure 5 Forest plot showing a significant rise in patients' satisfaction between ciprofol and propofol.

Discussion

Clinical characteristics and outcomes of the novel compound known as ciprofol have been recently researched and compared with propofol in different medical procedures. This meta-analysis of three RCTs encompassing 645 patients was the first to compare the safety and efficacy between these two short-acting intravenous anesthetics in patients undergoing colonoscopy procedure. The results we found suggest that ciprofol administration was less likely to cause respiratory depression and hypotension than propofol. Patients undergoing colonoscopy with ciprofol had less injection pain and higher levels of procedure satisfaction when compared to those under the propofol effect. However, the procedure success rate, onset time to sedation(s) and bradycardia were not significantly influenced by the anesthetic compound choice. Clinically, this suggests that while efficacy remains similar, the improved safety profile of ciprofol could reduce the burden of managing hemodynamic instability during procedures, potentially lowering the need for immediate interventions such as vasopressors or supplemental oxygen.

Colonoscopy is a vital procedure for diagnosing and preventing colorectal diseases, enabling early detection and intervention for conditions like cancer and polyps. Sedation and analgesia are important in this exam but the pattern protocol for this procedure anesthesia is not well established, with hospitals adopting their own protocols according to their clinical experience and structure. Still, the use of benzodiazepines and opioids (alone or combined) are the most common pharmacological tools used in colonoscopy.[2,5,16-19] Propofol, the "Milk of Amnesia" used to maintain general anesthesia and/or sedation in invasive and non-invasive medical procedures, has been widely used in gastroscopy due to its rapid anesthetic effect and fast patient recovery, reducing long-time sedation adverse effects.[20] However, propofol administrations can cause hemodynamic adverse effects, like hypotension, bradycardia, respiratory depression and the rare and lethal Propofol-Related Infusion Syndrome (cardiovascular affections, metabolic acidosis, lactic acidosis, rhabdomyolysis, hyperkalemia, lipidemia, hepatomegaly and acute renal failure).[21-23]

Ciprofol (HSK3486), a novel-short acting intravenous anesthetic based on a propofol structural modification was developed and reported in China in 2017, aiming to improve efficacy and reduce adverse effects.[6] It presents the chemical structure "(R)-2-(1-cyclopropyl ethyl)-6-isopropylphenol" and acts as a gamma-aminobutyric acid type A ($GABA_A$) antagonist and positive allosteric modulator with higher potency and selectivity than propofol, allowing a lower dose pharmacological administration.[6,24] This molecule presents higher plasma protein binding, and faster distribution with hepatic metabolism via CYP2B6 and CYP2C19 followed by primary renal excretion, demonstrating a lower systemic accumulation, faster half-life elimination and consequently a rapid recovery.[6,24,25] This anesthetic has been recently tested alone or compared with propofol in RCTs, cohort studies and case reports from diverse medical areas with invasive and non-invasive procedures.[15,26-32]

In this study, no significant statistical difference was evidenced between propofol and ciprofol for the success rate of colonoscopy and the time from drug administration to sedation. Our findings about the procedure success rate are consistent with a meta-analysis of 19 RCTs with diverse surgical and non-surgical procedures by Saeed et al. (2024) which presented that ciprofol has an efficacy comparable to propofol for endoscopic procedure completion rate and anesthesia/sedation induction time.[7] However, a meta-analysis of six RCTs regarding the use of these two drugs for induction and maintenance of general anesthesia by Hudaib et al. (2024) reviewed the time to successful induction and highlighted a propofol advantage in comparison with the ciprofol dosage of 0.5 $mg.kg^{-1}$ and no advantage on 0.4 $mg.kg^{-1}$.[8] Ultimately, in a non-randomized phase II trial the colonoscopy was 100% successful in the ciprofol and propofol groups.[33] The literature and our results suggest that ciprofol is an effective compound like propofol for colonospic procedures and this might be explained because of their structure similarity.

Although our results did not show a statistically significant difference in sedation onset time, the high heterogeneity (I^2 = 92.4%) identified for this outcome requires a more detailed analysis. Our leave-one-out sensitivity analysis demonstrated that the study by Li et al. (2022) was the primary contributor to this heterogeneity, as its exclusion reduced the I^2 to 0%.[15] A deeper evaluation of the included studies' characteristics reveals that methodological differences may be the cause. Specifically, the study by Li et al. (2022) used a lower propofol dose (1.5 $mg.kg^{-1}$) compared to the other studies (2.0 $mg.kg^{-1}$).[15] Furthermore, while Li et al. (2022) administered fentanyl as premedication, He et al. (2024) used sufentanil, which may have influenced the onset of sedation.[14,15] These variations in dosage and anesthetic technique, along with stricter patient exclusion criteria in the Li et al. (2022) study, may have impacted the results, making it an outlier in our analysis.[15] This similarity allows both drugs to act as positive allosteric modulators of $GABA_A$

receptors, leading to comparable sedative and anesthetic effects, including similar induction times and procedural success rates.[6]

Regarding ciprofol safety, our findings suggest that this drug is less likely to cause respiratory depression and hypotension than propofol, but bradycardia during the novel drug effect had no significant difference compared to the control group. In a meta-analysis of 7 RCTs, Zeng et al. (2024) demonstrated that patients undergoing surgery or painless examination under ciprofol administration had a significantly lower incidence of respiratory depression, consenting with the results of our study. Meanwhile, the incidence of hypotension was not statistically relevant compared to the patients under propofol.[34] Therefore, a prospective single-center cohort encompassing 200 patients undergoing painless colonoscopy registered 3 cases of respiratory depression, 2 occurrences of bradycardia and 76 hypotension registrations, representing that 38% of the sample had hemodynamic adverse events due to blood pressure.[35] In total, the cases registered of hypotension in our analysis have an approximate incidence of 44.2% in the ciprofol sample, but still less than 50% in the propofol population we included. From a clinical perspective, these safety advantages may translate into reduced requirements for intensive cardiopulmonary monitoring, shorter recovery room stays, and improved workflow efficiency in busy endoscopy centers. The respiratory depression reduction and lower incidence of hypotension in ciprofol administration might be explained by its higher potency and more stable plasma profile, leading to lower dose administration of this drug and consequently, a gentler modulating of $GABA_A$ receptors, preserving the respiratory drive and the hemodynamic stability.[24,36]

Ultimately, patient satisfaction levels were substantially significant in our study, followed by a considerably lower incidence of injection pain in the ciprofol group. Akhtar et al. (2024), in a meta-analysis of 1958 patients, registered a great lower incidence of injection pain during ciprofol administration in comparison with propofol for anesthesia induction.[37] Still, a study measured patient satisfaction and injection pain by comparing two cohorts, one for patients under ciprofol and the other for people under propofol, and the results were higher satisfaction and significantly lower pain injection in the ciprofol group.[38] The lower satisfaction of the anesthetic procedure might be related to the pain associated with propofol injections, due to its direct irritation of the venous endothelium, leading to the release of mediators like bradykinin, which increase vascular permeability and stimulate pain receptors. The reduced incidence of injection pain with ciprofol may be attributed to differences in its lipid emulsion formulation and pH, which could lead to less endothelial irritation compared to propofol.[6,39] Improved patient comfort and satisfaction are also clinically relevant, as they may encourage adherence to colorectal cancer screening programs that require repeated colonoscopies, ultimately contributing to better public health outcomes.

Overall, these findings indicate that ciprofol may be a suitable alternative to propofol for colonoscopy sedation, offering comparable efficacy with a potentially more favorable safety and tolerability profile. Specifically, its lower incidence of respiratory depression, hypotension, and injection pain, alongside higher patient satisfaction, are encouraging. However, these differences should be interpreted cautiously due to the small evidence base and limited geographic scope of available studies. While the pharmacological properties of ciprofol suggest clinical advantages, further research is needed to determine whether these translate into meaningful improvements such as reduced post-procedural complications, shorter recovery times, or decreased hospital admissions. The rapid recovery and short post-procedure stay, which were assessed through standardized scoring systems such as the PADSS and modified Aldrete scores, are key clinical benefits that further support ciprofol's use for colonoscopy.

Limitations

Despite providing valuable insights, this review has several limitations. First, the analysis included only three RCTs with relatively small sample sizes, which limits statistical power and increases susceptibility to heterogeneity. Second, all included studies were conducted in China, which may restrict the generalizability of our findings to broader and more diverse populations and healthcare systems. Third, the included patients were predominantly ASA PS I—II, restricting applicability to higher-risk populations. Fourth, the trials primarily assessed immediate procedural outcomes, while long-term safety and efficacy data remain unavailable. Fifth, potential publication bias and methodological heterogeneity (e.g., differences in propofol dosage and premedication protocols) cannot be excluded. Finally, only studies published in English were included, which may have introduced language bias. However, this decision was made to ensure accurate comprehension of the manuscripts and minimize the risk of misinterpretation during data extraction and analysis. Collectively, these limitations highlight the need for larger, multicenter, international RCTs to rigorously evaluate the short- and long-term safety, efficacy, and cost-effectiveness of ciprofol in colonoscopy.

Conclusion

This meta-analysis provides the most comprehensive comparison to date between ciprofol and propofol in colonoscopy sedation. The available evidence suggests that ciprofol may offer comparable efficacy to propofol, with similar procedure success rates and sedation onset times(s). In addition, ciprofol was associated with a lower risk of respiratory depression, injection pain, and hypotension, while patient satisfaction appeared slightly higher. No significant differences were observed regarding bradycardia occurrence. Nevertheless, these findings should be interpreted with caution due to the limited number of studies and their geographic concentration, which restrict generalizability. Future high-quality, multicenter RCTs are warranted to confirm these results and to further assess long-term safety, cost-effectiveness, and the potential role of ciprofol as an alternative sedative and anesthetic in colonoscopy.

Authors' contributions

Saul Dominici contributed to the conception and design of the study, data acquisition, drafting of the initial manuscript, critical revision, and supervision of the project.

Italo C. Martins contributed to data analysis, manuscript drafting, and critical revision.

Breno Dias L. Ribeiro contributed to data collection, manuscript drafting, and critical revision.

Victor Arthur Ohannesian contributed to data interpretation, data visualization, manuscript drafting, and critical revision.

Brunno Braga Sauaia contributed to data analysis, data visualization, manuscript drafting, and critical revision.

Abdias Rocha Santos contributed to study conception, project supervision, and critical revision.

Caio Márcio Barros de Oliveira contributed to project supervision, result validation, data interpretation, and critical revision.

Plinio da Cunha Leal contributed to project supervision, result validation, data interpretation, and critical revision.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Declaration of competing interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844710.

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REVIEW ARTICLE

Intranasal dexmedetomidine for procedural sedation in children: a systematic review and meta-analysis

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Meta-Analysis;
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Abstract
Background: Intranasal Dexmedetomidine (IN-DEX) is a promising agent for pediatric procedural sedation due to its non-invasive route and favorable safety profile. However, a comprehensive synthesis quantifying its clinical timeline and safety as monotherapy is lacking. This meta-analysis assesses the efficacy and adverse events of IN-DEX as a standalone sedative in children.
Methods: Following PRISMA 2020 guidelines and PROSPERO registration (CRD420250652456), this meta-analysis systematically searched PubMed, ScienceDirect, and SciELO for intranasal dexmedetomidine monotherapy in children under 18 years from January 1, 2003, to July 1, 2025. Key outcomes included sedation success, onset, and duration. Data were pooled using a random-effects model, with risk-of-bias assessed via RoB2. We performed sensitivity and subgroup analyses and evaluated evidence certainty using the GRADE approach.
Results: Twenty-eight RCTs were included. The overall pooled mean onset time was 18.9 minutes and duration was 60.3 minutes, though both had very low evidence certainty due to high heterogeneity ($I^2 > 99\%$). The overall success rate was 79.58%. Notably, in a subgroup of low-to-moderate risk-of-bias studies, a dose of [2, 3) mcg.kg^{-1} achieved an 84.04% success rate, supported by high-quality evidence (GRADE: High, $I^2 = 0\%$). The pooled proportions for key adverse events were hypotension (8.24%), bradycardia (5.08%), and desaturation (2.76%).
Conclusion: IN-DEX is an effective monotherapy for pediatric procedural sedation. Doses of [2, 3) mcg.kg^{-1} are associated with high success rates, supported by high-quality evidence. While IN-DEX demonstrates a favorable respiratory profile with low desaturation rates, its use requires vigilant hemodynamic monitoring due to the risks of hypotension and bradycardia.

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Introduction

Procedural sedation and premedication in the pediatric population represent a significant clinical challenge, requiring strategies that minimize anxiety and distress while ensuring patient safety and cooperation.[1] The ideal sedative should be effective, have a favorable safety profile with minimal respiratory depression, and be administered through a non-invasive route to avoid further distress.[2] In this context, needle-free options are particularly valuable.

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, has emerged as a promising agent for procedural sedation in ambulatory and emergency settings. Its pharmacological properties, providing anxiolysis, sedation, and analgesia without significant respiratory compromise, make it an attractive alternative to traditional sedatives.[3,4] Although its use for this indication in children is largely off-label, its Intranasal (IN) administration has gained popularity due to its ease of use and rapid systemic absorption through the nasal mucosa.[5]

The use of dexmedetomidine in the pediatric population has been the subject of several systematic reviews, although their focus has often been on specific clinical scenarios other than procedural sedation. For instance, meta-analyses have investigated its role in preventing perioperative respiratory adverse events during general anesthesia or have focused on direct comparisons against oral midazolam for the purpose of premedication.[6,7] While this body of work is valuable, a significant gap remains regarding the use of Intranasal Dexmedetomidine (IN-DEX) as a standalone sedative agent for procedural sedation. Specifically, a comprehensive meta-analysis that provides pooled, quantitative estimates for key clinical parameters, such as sedation onset time and duration of action, is currently lacking. Furthermore, prior reviews have not centered on quantifying the pooled incidence rates of key adverse events across a broad spectrum of pediatric procedures. Therefore, an updated synthesis focusing on IN-DEX as monotherapy is needed to provide clinicians with robust data on its clinical timeline and safety profile, stratified by dose and procedure type.

While prior reviews are valuable, they often focus on comparative efficacy (e.g., IN-DEX vs. other drugs) or its use in combination with other agents.[7] In contrast, a quantitative synthesis focused strictly on IN-DEX monotherapy, providing robust estimates of its intrinsic clinical variables (like onset time, duration, and safety) to aid clinical planning, is lacking. To our knowledge, this is the first review to address this gap and stratify these key outcomes by dose range to identify an optimal therapeutic window.

This study aims to assess the efficacy and adverse events associated with IN-DEX in pediatric patients, considering dose stratification and types of procedures.

Methods

Protocol and registration

This systematic review and meta-analysis was conducted and reported in accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The completed PRISMA checklist is provided in Appendix A. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO)[8] and is available in ID CRD420250652456.

Data sources and search strategy

A systematic search was conducted on PubMed, ScienceDirect, and SciELO, covering the period from January 1, 2003, to July 1, 2025. ScienceDirect was utilized as a search database for content hosted on its platform, in addition to its use for full-text retrieval (Fig. 1). The full, database-specific search strategies are provided in Appendix A. No language restrictions were applied.

Eligibility criteria

Studies were included if they met the following criteria: a) Study design: randomized clinical trial; b) Population: patients under 18 years of age; c) Intervention: at least one group receiving IN-DEX as monotherapy; d) Outcomes: studies reporting central tendency measures for at least one of the following outcomes – time to sedation onset, duration of sedation, or sedation success rate. Exclusion criteria were: a) Study design: reviews, observational studies, case reports, case series, letters to the editor; b) Population: studies including participants older than 18 years; c) Intervention: studies that did not include at least one group receiving IN-DEX as monotherapy; d) Outcomes: studies lacking primary outcome variables or failing to report measures of central tendency. In line with research integrity policies, all included studies were screened for retractions, expressions of concern, or serious methodological/ethical flags using the Retraction Watch and PubPeer databases (Figs. 2 and 3).

Study selection

Study selection was performed in two phases by independent reviewers (KOR, MMP). Titles and abstracts were manually screened for relevance, followed by full-text assessment of potentially eligible articles. Disagreements were resolved by a third reviewer (ERFAS).

Data extraction

Two reviewers (KOR, MMP) independently and manually extracted relevant data using a standardized Microsoft Excel 365 spreadsheet. Extracted information included study characteristics, patient demographics, intervention details, and outcome data. For multi-arm trials that included both monotherapy and combination therapy groups, only data from the IN-DEX monotherapy arm and its relevant comparator arm (e.g., placebo, another active drug) were extracted for inclusion in this meta-analysis.

Data synthesis and statistical analysis

Medians and interquartile ranges were converted to means and standard deviations using the Box-Cox method as described by McGrath et al. (2020), as this approach is more appropriate for non-parametric data distributions.[9] Age-

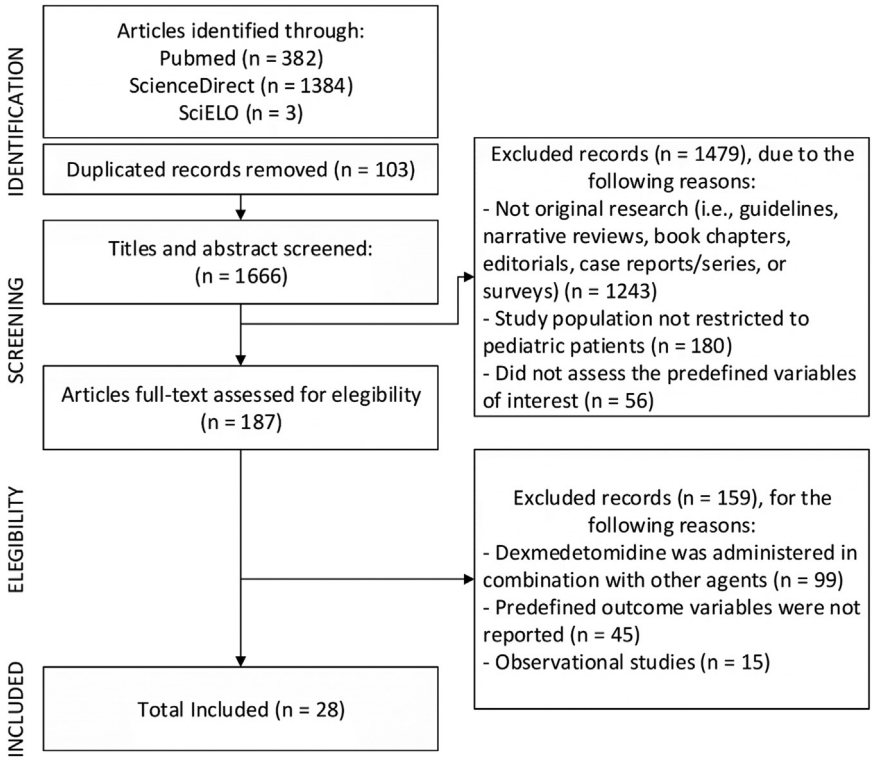

Figure 1 PRISMA flow diagram illustrating the study selection process.

related central tendency measures were normalized to a yearly scale. Weighted mean prevalence, overall mean and 95% Confidence Intervals (95% CIs) and 95% Prediction Intervals (PIs) were calculated using a random-effects model with the DerSimonian and Laird estimator, applying logit transformation to stabilize distributions.

Study heterogeneity was assessed using the I^2 statistic, which estimates the proportion of variability not attributable to sampling error. Heterogeneity was considered substantial when I^2 exceeded 50%. Publication bias was evaluated both subjectively through funnel plot inspection and objectively using Egger's test (Appendix A). Egger's test was applied only to outcomes reported in ten or more studies. All statistical analyses were performed in R using the meta package (version 7.0-0), with a type I error threshold of 5%.

Definitions

Success and adverse events

Success was defined as completing the procedure without the need for additional sedatives or repeated sedation dosing. Definitions for hypotension, bradycardia, and desaturation from each article were extracted and are presented in Appendix A.

Invasiveness categories

Procedures were classified into four levels of invasiveness based on the degree of physical contact, tissue penetration, and pain potential: (0) Non-invasive and painless: no direct contact with tissues or induction of pain (e.g., imaging exams, electroencephalogram, electrocardiogram); (1) Minimally invasive: light contact with minimal discomfort, without significant tissue penetration (e.g., ophthalmologic examinations); (2) Moderately invasive: superficial penetration with mild to moderate pain (e.g., venous cannulation); (3) Invasive with pain potential: deep tissue manipulation or procedures associated with significant pain (e.g., dental procedures).

Age strata

Studies were classified into pediatric strata based on the mean age of participants: Neonatal (0–28 days), Infant (0–1 year), Toddler (1–3 years), Preschooler (3–6 years), Child (6–12 years), and Adolescent (12–19 years). When the mean age clearly aligned with a specific stratum, that category was adopted. In cases of broad age ranges, the standard deviation was considered to identify the predominant concentration.

Assessment of risk of bias in included studies and risk of publication bias

Two authors (KOR, MMP) independently assessed the quality and risk of bias of the included studies using the Cochrane Risk of Bias 2.0 (RoB2) tool for randomized controlled trials (Appendix A).[10,11]

Sensitivity assessment and subgroup analysis

To assess the robustness of the primary outcome, pre-specified sensitivity analyses were conducted by repeating the

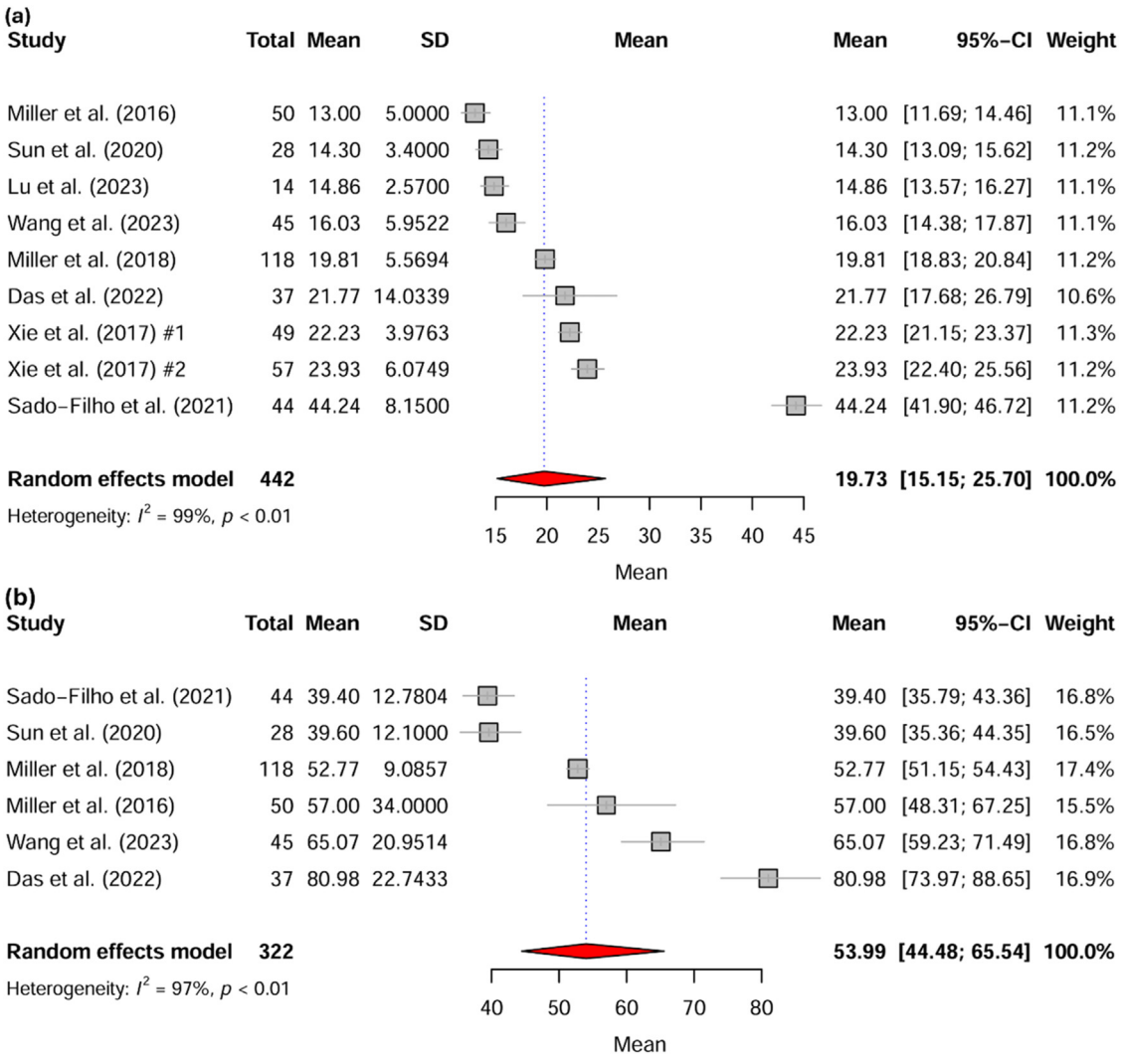

Figure 2 Forest plot of the weighted mean (a) onset time and (b) duration of IN-DEX at [2, 3) mcg.kg^{-1}/dose in pediatric patients, excluding studies rated as high-risk studies according to the RoB2 tool. Xie et al. (2017) presents two distinct groups, #1 with mucosal atomization device, #2 with serynge device.

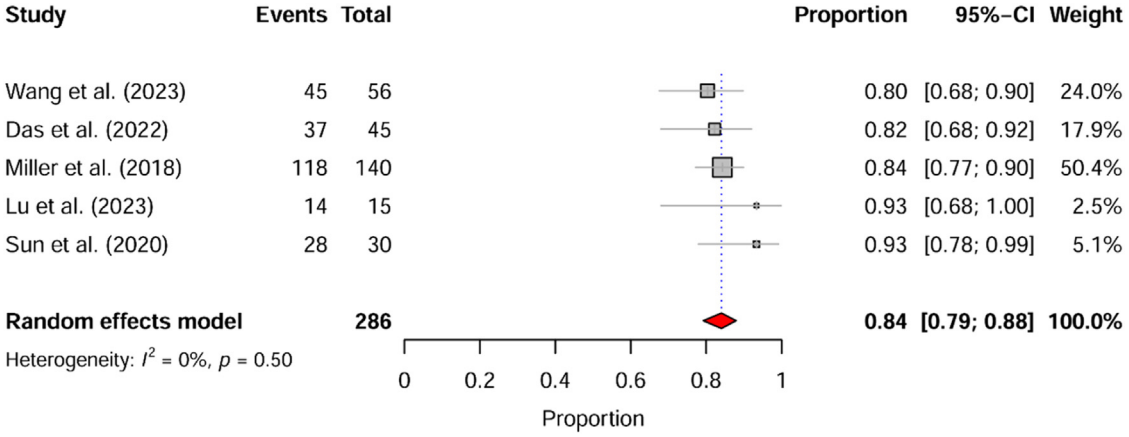

Figure 3 Forest plot of the weighted success proportion in pediatric patients receiving IN-DEX at (2, 3] mcg.kg^{-1}/dose, excluding studies rated as high-risk studies according to the RoB2 tool.

main analysis while sequentially excluding studies with a high risk of bias and studies conducted in China. The results were considered robust if the direction and statistical significance of the pooled effect estimate did not change substantially.

Quality of evidence

Evidence certainty for each primary outcome was independently assessed by two authors using the GRADE approach. Starting from a 'high' rating for randomized trials, certainty was downgraded based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Final ratings were classified as high, moderate, low, or very low.

Results

Descriptive analysis

In the 28 clinical trials analyzed (Table 1), a geographical concentration of studies in Asia was observed, with the majority being conducted in China (κ = 12; n = 922) and India (κ = 8; n = 249), followed by the United States (κ = 3; n = 207). The pediatric population in these trials was mainly composed of preschoolers (κ = 10; n = 503) and toddlers (κ = 9; n = 678). Regarding the clinical context, IN-DEX was predominantly used for non-invasive and painless procedures (κ = 13; n = 921) but was also applied in scenarios with potential for pain (κ = 8; n = 338), moderately invasive (κ = 5; n = 209), and minimally invasive procedures (κ = 2; n = 161). The dosage stratification for these trials revealed a predominance of doses in the [2, 3) mcg.kg^{-1} range (κ = 17; n = 830). Higher doses, $\geq$ 3 mcg.kg^{-1}, were also frequently investigated (κ = 9; n = 668), while lower doses in the [1, 2) mcg.kg^{-1} range were less common (κ = 4; n = 131).

Inferential assessment

Onset time

The analysis for sedation onset time included 34 distinct groups with 1,609 participants. The overall pooled mean onset time was 18.9 minutes (95% CI: 16.6–21.4; 95% PI: 8.7–41.1; I^2 = 99%; GRADE: Very low). A sensitivity analysis restricted to 16 distinct groups (897 participants) with low or moderate risk of bias yielded a mean onset time of 20.5 minutes (95% CI: 17.3–24.3; 95% PI: 9.7–43.5; I^2 = 97.5%; GRADE: Low). A further sensitivity analysis did not improve the heterogeneity, as shown in Table 2. Excluding Chinese clinical trials, which included 18 study groups (687 participants), we found a mean onset time of 18.9 minutes (95% CI: 15.0–23.8); I^2 = 99.5%; GRADE: Very low). In a meta-regression analysis restricted to studies with low or moderate risk of bias, both procedural invasiveness (p = 0.009) and IN-DEX dosage (p = 0.01) were significantly associated with an increase in sedation onset time, as shown in Appendix A.

Duration

The analysis of sedation duration time included 28 study groups (1,368 participants), yielding a pooled mean duration of 60.3 minutes (95% CI: 52.7–69.1; 95% PI: 28.3–128.4; I^2 = 99.3%; GRADE: Low), as shown in Table 2. Sensitivity analysis restricted to studies with low or moderate risk of bias (11 groups, 674 participants) found a mean duration of 54.6 minutes (95% CI: 47.8–62.4; 95% PI: 32.6–91.6; I^2 = 97.2%; GRADE: Low). A separate sensitivity analysis restricted to non-Chinese clinical trials (16 groups, 630 participants) yielded a similar mean duration of 58.0 minutes (95% CI: 50.4–66.7; I^2 = 98.7%; GRADE Very low). A meta-regression, limited to studies not classified as high risk of bias, identified that sedation duration significantly increased with the mean age of participants (expB = 1.06; p = 0.018; I^2 = 95.5%; R^2 = 37.2%), while procedural invasiveness (p = 0.118) and dexmedetomidine dose (p = 0.446) were not significant predictors.

Success

The following analysis of procedural success was restricted to studies defining this outcome as the ability to complete the intervention without administering supplemental sedatives or repeating the initial sedation dose. The overall success rate, evaluated across 17 clinical trial groups (1,132 participants), yielded a pooled proportion of 79.58% (95% CI: 73.56–84.52; 95% PI: 51.17–93.55; I^2 = 77.33%; GRADE: Low). A sensitivity analysis excluding studies with a high risk of bias (12 groups, 893 participants) resulted in a success rate of 78.23% (95% CI: 70.31–84.51; 95% PI: 45.08–94.02; I^2 = 81.4%; GRADE: Low). In the overall analysis, the subgroup with a dose of [2, 3) mcg.kg^{-1} had a success rate of 82.45% (95% CI: 77.46–86.52; 95% PI: 70.66–90.16; I^2 = 25.12%; GRADE Moderate). When restricted to low- and moderate-risk studies, this same dose range demonstrated a success rate of 84.04% (95% CI: 79.21–87.91; 95% PI: 75.70–89.90; I^2 = 0%; GRADE: High). Evidence certainty was rated High as this finding was based on low-risk studies, demonstrated no inconsistency (I^2 = 0%), and yielded a precise effect estimate. A multivariable meta-regression did not find a significant correlation between the success rate and mean age, procedural invasiveness, dexmedetomidine dose, or RoB2 score (p > 0.05 for all variables).

Hypotension

The overall proportion of hypotension across 9 study groups (597 participants) was 8.24% (95% CI: 5.06–13.16; I^2 = 55.81%; GRADE: very low). A sensitivity analysis excluding studies with a high risk of bias (5 groups, 477 participants) yielded a similar proportion of 8.61% (95% CI: 4.59–15.57; 95% PI: 1.00–46.71; I^2 = 72.07%; GRADE: very low) (Table 3). The highest quality of evidence emerged from this subset of low and moderate-risk studies for hypotension defined as a SBP decrease of 20% from baseline; this event occurred in 6.94% of participants (95% CI: 4.68–10.20), with no heterogeneity and a moderate quality of evidence (I^2 = 0%; GRADE: moderate). A primary multivariable meta-regression of the full dataset identified both mean age (p = 0.013) and the Risk of Bias score (RoB2) (p = 0.021) as significant predictors of hypotension. However, in a subsequent meta-regression restricted to studies without a high risk of bias, mean age remained the sole significant predictor (ExpB = 0.298; p = 0.014), with younger age associated with a higher proportion of hypotension. Procedural invasiveness,

Table 1 Overview of pediatric studies using intranasal dexmedetomidine.

Author (year, country)	Description of the study population	DEX doses	Device	Sedation scale – criteria for success	Definitions for adverse events	Risk of bias
Xie et al. (2017, China)[11]	106 ASA I–II children for eye surgery; evaluated sedation via spray or syringe drops	2 mcg.kg^{-1}	Atomizer and Drops by Syringe	FLACC – Conclusion of the procedure.	SpO_2 < 94%	Low
Wang et al. (2024, China)[12]	105 infants with cleft lip/palate for CT scan; compared dexmedetomidine alone vs. combo with midazolam	2 mcg.kg^{-1}	Atomizer	RSS – Conclusion of the procedure.	HR < 60 bpm, SpO_2 < 90%	Low
Li et al. (2019, China) [13]	275 ASA I–II autistic children for CT/ABR; received intranasal dexmedetomidine alone or with buccal midazolam	3 mcg.kg^{-1}	Not specified	UMSS – Conclusion of the procedure.	HR < 20% from baseline, SBP < 20% from baseline, SpO_2 < 94%	Moderate
Chandrasekar et al. (2023, India)[14]	195 ASA I–II children scheduled for MRI; compared triclofos, midazolam, and dexmedetomidine sedation	3 mcg.kg^{-1}	Not specified	PSSS ≤ 3	SBP < 20% from baseline, SpO_2 < 92%	High
Qiao et al. (2017, China)[15]	135 ASA I–II children (2–6 yrs) for eye surgery; received dexmedetomidine, ketamine, or both	2.5 mcg.kg^{-1}	Not specified	Sedation Scale (SS-5) – Conclusion of the procedure.		High
Patel et al. (2018, India)[16]	44 ASA I uncooperative children (4–9 yrs) for dental care; compared dexmedetomidine doses/routes	2 to 2.5 mcg.kg^{-1}	Not specified	SS-5 ≥ 3 and SpO_2 ≥ 90%		High
Ibrahim et al. (2014, Egypt)[17]	63 ASA I–II children (4–10 yrs) for MRI; compared intranasal dexmedetomidine and ketamine + IV midazolam	3 mcg.kg^{-1}	Not specified	RSS – Conclusion of the procedure.	HR < 20% from baseline, SBP < 20% from baseline, SpO^2 < 92%	High
Panda et al. (2021, India)[18]	100 ASA I–II children (< 3 yrs) for echocardiography; compared intranasal dexmedetomidine vs. midazolam	2 mcg.kg^{-1}	Drops by Syringe	RSS ≥ 3	HR < 20% from baseline, SpO_2 < 92%	High
Yuen et al. (2012, China)[1]	116 ASA I–II children (7–17 kg) for elective surgery; grouped by age and hospital	1 mcg.kg^{-1} and 2 mcg.kg^{-1}	Drops by Syringe	SS-5 ≥ 3		High
Li et al. (2016, China) [19]	279 ASA I–III children for echocardiography; received dexmedetomidine via atomizer or drops	3 mcg.kg^{-1}	Atomizer and Drops by Syringe	UMSS ≥ 2	HR < 20% from baseline, SBP < 20% from baseline, SpO_2 < 92%	Low
Yuen et al. (2017, China)[20]	196 ASA I–II children for CT scan; received oral chloral hydrate or intranasal dexmedetomidine	3 mcg.kg^{-1}	Atomizer	UMSS ≥ 2	HR < 20% from baseline, SpO_2 < 94%	Low

Table 1 (*Continued*)

Author (year, country)	Description of the study population	DEX doses	Device	Sedation scale – criteria for success	Definitions for adverse events	Risk of bias
Janiani et al. (2024, India)[21]	15 ASA I children with negative dental behavior; underwent molar pulpectomy	1 mcg.kg^{-1}	Atomizer	RSS – Conclusion of the procedure.	$SpO_2 < 94\%$	High
Azizkhani et al. (2020, Iran)[22]	162 children in emergency room for CT; randomized to Dexmedetomidine or midazolam sedation	3 mcg.kg^{-1}	Atomizer	RSS ≥ 3		High
Gupta et al. (2017, India)[23]	60 ASA I–II children for elective brain MRI; received midazolam or dexmedetomidine	1 mcg.kg^{-1}	Drops by Syringe	MOAA/S ≤ 3	$SpO_2 < 94\%$	High
Miller et al. (2018, USA)[24]	280 infants (3–24 months) with heart disease for echocardiography; received dexmedetomidine or oral pentobarbital	2.5 mcg.kg^{-1}	Atomizer	RSS > 3	HR < 80 bpm, SBP < 70, $SpO_2 < 92\%$	Low
Qian et al. (2020, China)[25]	63 ASA I–II children (3–7 yrs) for tonsillectomy; received intranasal dexmedetomidine or dexmedetomidine + ketamine	2 mcg.kg^{-1}	Not specified	MOAA/S ≤ 3		High
Das et al. (2022, India) [26]	90 ASA I–III children (3–6 yrs) with cancer; 21 radiotherapy sessions with dexmedetomidine or oral midazolam + ketamine	2 mcg.kg^{-1}	Not specified	RSS = 3	SBP $< 20\%$ from baseline	Low
Sado-Filho et al. (2021, Brazil)[27]	88 ASA I–II children (1–7 yrs) with poor dental behavior; treated with dexmedetomidine or dexmedetomidine + ketamine	2.5 mcg.kg^{-1}	Not specified	OSUBRS $> 50\%$	$SpO_2 < 88\%$	Low
Surendar et al. (2014, India)[28]	84 ASA I children (4–14 yrs) uncooperative in dental care; received one of four intranasal sedation protocols	1 mcg.kg^{-1} and 1.5 mcg.kg^{-1}	Not specified	SRSB > 2 and $SpO_2 > 90\%$	SBP $< 20\%$ from baseline, $SpO_2 < 90\%$	High
Chen et al. (2019, China)[29]	100 ASA I–II children with congenital cataracts for ophthalmologic exams	2 mcg.kg^{-1} and 3 mcg.kg^{-1}	Not specified	MOAA/S ≤ 3	$SpO_2 < 94\%$	High
Lu et al. (2023, China) [30]	40 hospitalized burn patients (5–45 months); received dexmedetomidine drops or chloral hydrate enema for Peripherally Inserted Central Catheter	2 mcg.kg^{-1}	Drops by Syringe	RSS ≥ 3		Low

Table 1 (*Continued*)

Author (year, country)	Description of the study population	DEX doses	Device	Sedation scale – criteria for success	Definitions for adverse events	Risk of bias
Miller et al. (2016, USA)[31]	150 infants (3–36 months) with heart disease; received dexmedetomidine 2 μg.kg^{-1}, 3 μg.kg^{-1}, or oral chloral hydrate	2 mcg.kg^{-1}	Drops by Syringe	RSS $\geq$ 3	HR < 80 bpm, SpO_2 < 92%	Moderate
Ghai et al. (2017, India)[32]	59 ASA I–II children (1–6 yrs) for CT; received oral midazolam or intranasal dexmedetomidine 2.5 μg.kg^{-1}	2.5 mcg.kg^{-1}	Drops by Syringe	RSS $\geq$ 4		High
Reynolds et al. (2016, USA)[33]	85 children (6 months–8 yrs, 5–25 kg) for ABR; excluded prior sedation failure and comorbidities	3 mcg.kg^{-1}	Not specified	Own adapted scale – Conclusion of the procedure.	SpO_2 < 90%	Moderate
Cao et al. (2017, China) [34]	141 ASA I–II children (3–36 months) with cataracts; received intranasal dexmedetomidine or oral chloral hydrate	2 mcg.kg^{-1}	Not specified	RSS – Conclusion of the procedure.	HR < 60 bpm, SpO_2 < 94%	High
Sun et al. (2020, China) [35]	60 ASA I–II infants (1–36 months) with heart disease; received dexmedetomidine alone or dexmedetomidine + ketamine	2 mcg.kg^{-1}	Drops by Syringe	MOAA/S $\leq$ 3	SpO_2 < 90%	Low
Nikula et al. (2024, Sweden) [3]	148 healthy Swedish children (3–15 yrs) with fractures or burns < 4%; treated in emergency room	2 mcg.kg^{-1}	Drops by Syringe	RSS $\geq$ 2	HR < 20% from baseline, SpO_2 < 94%	High
Tug et al. (2015, Turkey) [36]	60 ASA I–II healthy children (1–10 yrs) for MRI; received 3 or 4 μg.kg^{-1} dexmedetomidine with recovery and side effect tracking	3 mcg.kg^{-1} to 4 mcg. kg^{-1}	Not specified	RSS = 5	HR < 60 bpm, SpO_2 < 94%	Moderate

ASA, American Society of Anesthesiologists; CT, Computed Tomography; EEG, Electroencephalogram; MRI, Magnetic Resonance Imaging; HR, Heart Rate; SBP, Systolic Blood Pressure; FLACC, Face, Legs, Activity, Cry, Consolability Scale; RSS, Ramsay Sedation Scale; OSUBRS, Ohio State University Behavioral Rating Scale; SRSB, Sedation Rating Scale for Behavior; MOAAS, Modified Observer's Assessment of Alertness/Sedation Scale; UMSS, University of Michigan Sedation Scale; PSSS, Pediatric Sedation State Scale.
For studies with multiple intervention arms, only data from the intranasal dexmedetomidine monotherapy group were extracted for this analysis.

Table 2 Sensitivity assessment of onset time across clinical trial publications — restricted to studies without high risk of bias according to RoB2.

Onset Time					
Variables	K (Events / N)	Mean (95% CI) [95% PI]	I^2	Ajusted Mean (95% CI)	GRADE
Onset Time General (high-risk included)	34 (34/1609)	18.9 (16.6 – 21.4) [8.7 – 41.1]	99.3	15.5 (13.6 – 17.8)	Very low
High-risk of bias excluded	16 (16/897)	20.5 (17.3 – 24.3) [9.7 – 43.5]	98.6	22.4 (19.0 – 26.4)	Low
Infant	2 (2/146)	16.9 (12.3 – 23.2) [–]	97.4	–	Very low
Toddler	7 (7/489)	17.4 (15.2 – 20.0) [10.6 – 28.7]	95.3	17.4 (15.2 – 20.0)	Low
Preschooler	6 (6/217)	28.0 (20.8 – 37.5) [9.5 – 82.6]	98.6	29.2 (22.3 – 38.3)	Very low
Non-invasive and painless	12 (12/733)	19.2 (17.1 – 21.5) [12.1 – 30.3]	95.3	18.6 (16.5 – 20.8)	Low
Moderately invasive	2 (2/106)	23.0 (21.4 – 24.7) [–]	67.1	–	Low
Invasive with potential for pain	2 (2/58)	25.7 (8.8 – 74.7) [–]	99.7	–	Very low
Dose: [2, 3) mcg.kg^{-1}	9 (9/442)	19.7 (15.1 – 25.7) [7.3 – 53.7]	99.1	24.2 (18.8 – 31.2)	Very low
Dose: ≥ 3 mcg.kg^{-1}	7 (7/455)	21.4 (18.2 – 25.0) [12.1 – 37.7]	95.7	18.8 (15.9 – 22.2)	Low
Duration					
Variables	**K (Events / N)**	**Mean (95% CI) [95% PI]**	**I^2**	**Ajusted Mean (95% CI)**	**GRADE**
Duration time general (high-risk included)	28 (28/1368)	60.3 (52.7 – 69.1) [28.3 – 128.4]	99.3	60.3 (52.7 – 69.1)	Low
High-risk of bias excluded	11 (11/674)	54.6 (47.8 – 62.4) [32.6 – 91.6]	97.2	49.0 (42.6 – 56.2)	Low
Infant	2 (2/146)	46.0 (34.7 – 60.9) [–]	95.6	–	Very low
Toddler	4 (4/372)	51.0 (40.9 – 63.6) [17.7 – 147.4]	97.3	44.8 (34.6 – 58.0)	Very low
Preschooler	4 (4/111)	61.9 (42.8 – 89.7) [10.4 – 369.6]	97.5	49.3 (33.7 – 72.1)	Very low
Non-invasive and painless	10 (10/630)	56.5 (49.1 – 64.9) [33.4 – 95.6]	97.2	50.0 (43.4 – 57.7)	Very low
Dose: [2, 3) mcg.kg^{-1}	6 (6/322)	54.0 (44.5 – 65.5) [26.5 – 110.0]	96.9	54.0 (44.5 – 65.5)	Low
Dose: ≥ C3 mcg.kg^{-1}	5 (5/352)	55.5 (44.6 – 69.1) [23.9 – 129.2]	97.4	45.9 (36.6 – 57.5)	Very low
Success Rates					
Variables	**K (Events / N)**	**Proportion (95% CI) [95% PI]**	**I^2**	**Ajusted Proportion**	**GRADE**
Success general (high-risk included)	17 (897 / 1132)	79.58% (73.56 – 84.52) [51.17 – 93.55]	77.33	76.54% (70.21 – 81.88)	Low
High-risk of bias excluded	12 (697 / 893)	78.23% (70.31 – 84.51) [45.08 – 94.02]	81.4	75.02% (66.81 – 81.76)	Very low
Infant	2 (146 / 170)	87.08% (75.16 – 93.76) [–]	35.94	–	Low
Toddler	6 (439 / 562)	79.96% (71.02 – 86.66) [45.69 – 94.98]	77.97	76.64% (67.22 – 83.99)	Very low
Preschooler	3 (67 / 105)	62.53% (29.44 – 86.97) [0.00 – 100.00]	89.57	62.53% (29.44 – 86.97)	Very low
Non-invasive and painless procedure	11 (683 / 878)	77.48% (69.29 – 83.99) [43.58 – 93.87]	82.52	74.98% (66.58 – 81.84)	Very low
Dose: [2, 3) mcg.kg^{-1}	5 (242 / 286)	84.04% (79.21 – 87.91) [75.70 – 89.90]	0	83.30% (77.95 – 87.57)	**High**
Dose: ≥ 3 mcg.kg^{-1}	7 (455 / 607)	73.05% (60.78 – 82.58) [28.60 – 94.83]	86.78	73.05% (60.78 – 82.58)	Very low

All variables following "High-risk of bias excluded" refer specifically to studies classified as having low or moderate risk of bias.
General: overall group encompassing all event subgroups definitions.
K, Distinct Subgroups.
Adjusted proportions represent the estimated values following correction using the *trim and fill* method in groups showing evidence of publication bias.

Table 3 Evaluation of the weighted proportion of key adverse events associated with IN-DEX, restricted to studies assessed as low or moderate risk of bias by the RoB2 tool.

Variables	K (Events / N)	Proportion (95% CI) [PI 95%]	I^2	Ajusted Proportion	GRADE
Hypotension general	5 (45 / 477)	8.61% (4.59 – 15.57) [1.00 – 46.71]	72.07	13.80% (7.79 – 23.28)	Very low
SBP < 20% from baseline	4 (23 / 359)	6.94% (4.68 – 10.20) [2.89 – 15.79]	0	7.21% (4.88 – 10.52)	**Moderate**
Bradycardia general	9 (31 / 629)	4.78% (1.97 – 11.12) [0.36 – 41.02]	72.57	11.71% (4.87 – 25.55)	Very low
HR < 20% from baseline	4 (14 / 386)	1.56% (0.09 – 21.22) [0.00 – 99.98]	86.38	11.83% (1.14 – 60.90)	Very low
Desaturation general	14 (11 / 846)	3.07% (1.90 – 4.92) [1.80 – 5.19]	0	4.02% (2.24 – 7.14)	**Moderate**
SpO_2 < 92%	4 (9 / 401)	2.98% (1.01 – 8.45) [0.05 – 64.27]	50.18	3.89% (1.24 – 11.59)	Very low
SpO_2 < 90%	3 (2 / 112)	3.28% (1.06 – 9.72) [0.00 – 98.37]	0	5.13% (1.96 – 12.77)	Very low

CI, Confidence Interval; PI, Prediction Interval; General, Overall group including all event definitions; K, Distinct subgroups; SBP, Systolic Blood Pressure; HR, Heart Rate.
Adjusted proportions represent estimates corrected using the trim-and-fill method in groups with evidence of publication bias.

IN-DEX dose, and the RoB2 score were not significant in this stricter model.

Bradycardia

The overall proportion of bradycardia across 13 study groups (839 participants) was 5.08% (95% CI: 2.61–9.67; 95% PI: 0.36–41.02), with a high degree of heterogeneity and a very low quality of evidence (I^2 = 66.73%; GRADE: very low). When the analysis was restricted to studies with a low or moderate risk of bias (9 groups, 629 participants), the proportion was 4.78% (95% CI: 1.97–11.12), with the quality of evidence remaining very low (I^2 = 72.57%; GRADE: very low). No subgroup analysis for bradycardia, including specific definitions like a Heart Rate (HR) decrease of 20% from baseline, achieved a moderate or high quality of evidence. A multivariable meta-regression analysis did not find a significant correlation between the proportion of bradycardia and mean age, procedural invasiveness, IN-DEX dose, or the risk of bias score.

When the analysis was restricted to non-Chinese clinical trials (7 groups, 347 participants), the proportion of bradycardia was 9.12% (95% CI: 6.34–12.95). Notably, this finding was supported by a moderate quality of evidence and demonstrated no heterogeneity among studies (I^2 = 0%; GRADE: moderate). A further sensitivity analysis within this non-Chinese subset, which excluded studies with a high risk of bias (4 groups, 198 participants), yielded a similar proportion of 9.73% (95% CI: 6.21–14.94). This more restricted analysis also showed no heterogeneity and was supported by a moderate quality of evidence (I^2 = 0%; GRADE: moderate). Details are shown in Appendix A.

Desaturation

The overall proportion of desaturation across 25 study groups (1,289 participants) was 2.76% (95% CI: 1.87–4.06; 95% PI: 1.80–5.19), a finding supported by moderate quality of evidence with no heterogeneity among studies (I^2 = 0%; GRADE: moderate). This result remained robust across multiple sensitivity analyses. When restricted to studies with a low or moderate risk of bias, the proportion was 3.07% (95% CI: 1.90–4.92), with the evidence of quality remaining moderate (I^2 = 0%; GRADE: moderate). Similarly, in an analysis of non-Chinese trials, the proportion was 3.92% (95% CI: 2.51–6.07), also with moderate quality of evidence and no heterogeneity (I^2 = 0%; GRADE: moderate). A multivariable meta-regression did not find any significant correlation between the proportion of desaturation and mean age, procedural invasiveness, dexmedetomidine dose, or the risk of bias score.

Risk of bias assessment

The methodological quality of the included studies was assessed using the RoB2 tool for randomized controlled trials. Overall, 9 studies (32.1%) were classified as having a low risk of bias, 4 (14.3%) raised some concerns, and 15 (53.6%) were deemed to have a high risk of bias. The domain concerning bias arising from the randomization process showed the lowest risk, with all 28 studies (100%) assessed as low risk. In contrast, the highest risks were identified in the domains of bias in selection of the reported result, where 16 studies (57.1%) were rated as high risk, and bias due to missing outcome data, where 12 studies (42.9%) were rated as high risk. A significant number of studies, 7 (25%), were also classified as high risk for bias due to deviations from intended interventions.

Discussion

This meta-analysis yields three principal findings that clarify the clinical effects of Intranasal Dexmedetomidine (IN-DEX) in the pediatric population. First, the overall success rate, defined as a single application without the need for adjuvant

sedatives, was approximately 80%. Notably, a dose of [2, 3) mcg.kg^{-1} was associated with an 84% success rate, supported by high-quality evidence. Second, the temporal profile of sedation was characterized by a mean onset time of approximately 20 minutes and a mean duration of about 60 minutes, although both outcomes exhibited substantial heterogeneity. Third, IN-DEX demonstrated a favorable respiratory profile with a low and consistent incidence of desaturation (∼3%). The most common adverse events were hemodynamic, including hypotension (∼8%) and bradycardia (∼5%), with hypotension being more frequent in younger patients.

The pooled overall success rate of approximately 80% identified in this meta-analysis is broadly consistent with the existing literature, yet it also highlights the significant variability in efficacy reported by individual observational studies, with rates ranging from 57% to 100%. A primary driver of this heterogeneity appears to be the diverse definitions of 'successful sedation' and the wide array of procedures performed. For instance, studies on minimally stimulating procedures like echocardiography or EEG reported success rates exceeding 95%, whereas studies involving longer and more stimulating procedures like MRI reported much lower efficacy for IN-DEX as a sole agent.[12-15] The criteria for success varied substantially, from achieving a specific score on a sedation scale (e.g., MOAA/S $\leq$ 3 or Ramsay $\geq$ 3), as seen in the studies by Li et al. and Saudek et al., to a more pragmatic endpoint of completing the entire procedure without the need for rescue sedatives, a common definition in studies on EEG and ABR.[16-19] Therefore, the pooled estimate of 80% provides a more clinically representative benchmark, averaging the effects across different procedural contexts and outcome definitions, and underscores the reliable efficacy of IN-DEX for a general pediatric population undergoing non-painful procedures.

While acknowledging the significant heterogeneity for temporal outcomes, this meta-analysis establishes a clinically relevant benchmark profile for IN-DEX, with a mean sedation onset of approximately 20 minutes and a duration of about 60 minutes. This variability in onset is complex; the meta-regression indicated that onset is prolonged by procedural invasiveness and likely higher patient anxiety, given that a heightened state of sympathetic arousal directly counteracts the central sympatholytic effect of dexmedetomidine. Furthermore, the analysis revealed that onset may be paradoxically delayed by higher doses, a finding attributable to several factors, including a potential dose-dependent vasoconstrictor effect or unmeasured confounders like varying drug concentrations.[20] Despite this high variability, the pooled mean onset of approximately 20 minutes positions IN-DEX as significantly faster than older oral agents like triclofos sodium and generally faster than, or at least comparable to, oral chloral hydrate.[19,21,22] This onset is predictably slower than that of other intranasal agents such as midazolam or ketamine, which typically take effect in under 15 minutes.[23-25]

Conversely, the key advantage of IN-DEX lies in its more sustained duration of action. While intranasal midazolam's effect is often brief, sometimes lasting less than 20 minutes, the pooled estimate of a ∼60-minute duration highlights IN-DEX's suitability for procedures that exceed a very short timeframe.[26] This profile represents a favorable clinical trade-off: in exchange for a slightly longer waiting period for onset compared to some alternatives, clinicians achieve a more stable and prolonged plane of sedation, potentially reducing the need for redosing. An important nuance to this finding, however, comes from our meta-regression, which revealed that duration significantly increases with patient age. This is likely a pharmacokinetic phenomenon tied to body composition: as children age, their proportion of adipose tissue increases, enlarging the volume of distribution for lipophilic dexmedetomidine and prolonging its clinical effect.[27] Furthermore, while combining IN-DEX with agents like ketamine or midazolam can shorten onset, this often comes at the cost of significantly prolonged recovery and discharge times, reinforcing the efficiency of IN-DEX monotherapy for procedures of moderate length.[18,28]

Regarding safety, the findings from this meta-analysis reinforce the characteristic profile of IN-DEX, which is marked by a notable dissociation between its respiratory and hemodynamic effects. The low pooled incidence of oxygen desaturation (∼3%) is a key finding, underscoring its reputation for respiratory stability. This is consistent with data from numerous comparative trials where IN-DEX demonstrated a similar or often superior respiratory safety profile compared to agents like oral chloral hydrate, midazolam, and ketamine.[29-31] This respiratory-sparing effect is a direct consequence of its α2-adrenergic agonist mechanism, which differs fundamentally from GABAergic or opioid agents.

In contrast, the most frequently observed adverse events were hemodynamic, with pooled incidences of approximately 8% for hypotension and 5% for bradycardia. Given the low certainty of the evidence, these numbers should be viewed with caution, as estimates that may change with more rigorous future research. Beyond the issue of generalizability, the significant geographic concentration of studies raises potential pharmacogenomic concerns. Dexmedetomidine is primarily metabolized by hepatic cytochrome P450 enzymes, particularly CYP2A6, which is known to have genetic polymorphisms that vary in prevalence across different ethnic populations.[32] These genetic variations can influence drug clearance, potentially affecting the incidence of adverse events. Therefore, the safety profile identified in this meta-analysis may not be directly applicable to all pediatric populations. While these effects are pharmacologically expected, it is crucial to note that the vast majority of these events reported in the literature were transient, mild, and self-resolving, rarely requiring clinical intervention.[3,21,26,30,33] Furthermore, IN-DEX was associated with a lower incidence of other troublesome side effects, particularly vomiting, when compared to traditional agents like chloral hydrate.[29,34] This overall safety profile suggests that while vigilant hemodynamic monitoring is essential during IN-DEX sedation, its advantages in respiratory stability and reduced gastrointestinal side effects make it a highly favorable option for pediatric procedural sedation.

Limitations

This meta-analysis has several important limitations. First, substantial heterogeneity was observed for temporal outcomes like sedation onset and duration ($I^2 > 85\%$), likely stemming from diverse administration techniques and patient populations; therefore, these pooled estimates

should be interpreted as an average value. Second, the evidence base is constrained by a significant geographic concentration in Asia, primarily China, and a high proportion of studies with a high risk of bias (57.4%). While our sensitivity analyses confirmed the robustness of the primary efficacy outcomes after excluding these respective study groups, the geographic bias may limit the generalizability of safety findings, and the overall poor quality of the primary evidence warrants a cautious interpretation. Finally, the statistical power to draw firm conclusions for certain subgroups was limited, particularly for lower doses in the [1, 2) $mcg.kg^{-1}$ range and for patients undergoing more invasive procedures, meaning these specific findings must be considered exploratory.

Conclusion

In conclusion, this meta-analysis provides high-quality evidence that IN-DEX, at doses of [2, 3) $mcg.kg^{-1}$, is highly effective for non-painful procedural sedation in the pediatric population. Although the evidence for its temporal profile is of low quality, the pooled estimates for sedation onset and duration still serve as a useful framework for clinical planning. However, every case must be individualized. The use of IN-DEX carries a non-negotiable requirement for adequate hemodynamic monitoring, including regular assessment of blood pressure and heart rate. Ultimately, clinicians must be prepared to manage its potential adverse effects to ensure patient safety.

Data availability statement

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

Study registration

This study is a systematic review and meta-analysis of published data and, therefore, does not require institutional review board approval for its conduct. It was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the ID CRD420250652456

AI assistance disclosure

No AI tools were used in the preparation or analysis of this manuscript. The authors take full responsibility for the content.

Authors' contributions

Kelvin Oliveira Rocha: Study conception, search strategy, initial screening, risk of bias assessment, statistical analysis, data interpretation, manuscript writing, and revision.

Ellen Renata Ferreira de Araújo Santos: Resolution of screening discrepancies, critical revision of the manuscript.

Mariana Madureira Pombeiro: Initial screening, risk of bias assessment, critical revision of the manuscript.

Márcia Nayara da Silva Leite Fidelis: Critical revision of the manuscript and contribution to clinical expertise.

Fabiana Maria Kakehasi: Overall supervision, critical revision of the manuscript.

Daniela Caldas Teixeira: Overall supervision, critical revision of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

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Florentino Fernandes Mendes

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LETTER TO THE EDITOR

Preoperative pulmonary ultrasound: a valuable tool for managing post-COVID-19 sequelae

Dear Editor,

Lung Ultrasound (LUS) has emerged as a valuable diagnostic tool for evaluating residual lung injuries in patients recovering from SARS-CoV-2 infection. While LUS has gained recognition in critical care and emergency settings over the past two decades, its full potential as a preoperative risk assessment tool, especially in post-COVID-19 patients, remains largely unexplored. Originally described by Lichtenstein et al. in 1997 for the detection of alveolar-interstitial syndrome via ultrasound artifacts like the comet-tail sign, LUS has evolved into a cornerstone of pulmonary imaging in the Intensive Care Unit (ICU).[1] Its appeal lies in its non-invasiveness, bedside applicability, absence of radiation, and low cost, demonstrating its superiority over physical examination and conventional chest X-Ray in detecting pleural and parenchymal abnormalities.[2,3]

The emergence of portable ultrasound devices has further enabled its application in various settings – from operating rooms to pre-hospital environments. Despite these advantages, the integration of LUS into the routine practice of non-radiologist physicians is limited, often due to a lack of training and institutional barriers to access.[4] With the advent of the COVID-19 pandemic, the need for point-of-care imaging became more pressing than ever. In just the initial months of the pandemic, millions were infected, and tens of thousands of lives were lost globally. Brazil was among the severely affected nations, reporting over 40,000 confirmed cases and more than 2500 deaths within the first months of 2020,[5] which have grown exponentially to the present days. The virus posed not only an acute challenge to global health systems but also left a growing population of patients with persistent pulmonary complications, whose long-term management is still being defined.

It is well established that chest CT imaging in COVID-19 patients reveals typical peripheral and bilateral lung lesions, often described as “ground-glass” opacities. These findings are most frequently located in the posterior and lower lobes. While CT remains the gold standard for diagnosing such lesions, LUS has proven to be a reliable, real-time, bedside alternative, particularly for detecting superficial, pleura-associated abnormalities seen in Acute Respiratory Distress Syndrome (ARDS) and COVID-19.[6,7]

Our prospective observational study aimed to detect persistent pulmonary sequelae in post-COVID-19 patients during the convalescence phase and to assess their potential impact on preoperative risk stratification. Therefore, 31 adult patients recovering from SARS-CoV-2 infection were evaluated. All patients included in the study agreed and signed a written informed consent form (CAAE: 37,658,720.4.0000.0087). The patients underwent lung ultrasound between 4 and 6 weeks after symptom onset as part of their post-recovery assessment. All had been hospitalized, and many had required intensive care. We specifically excluded mild COVID-19 cases and those with pre-existing chronic lung disease to isolate findings associated with acute SARS-CoV-2 infection. Lung ultrasound was conducted using a standardized image acquisition protocol recommended by the Italian LUS-COVID expert team.[8] Their lungs were evaluated by a physician with at least three years of experience performing focused LUS. Fourteen lung regions (three posterior, two lateral and two anterior) were examined for 10 s each per patient using either convex or linear probes, and images were scored based on pleural line appearance and presence of B-lines or consolidations (Figure 1).

The results showed that 100 % of patients had some degree of lung consolidation, and 67.7 % exhibited abnormalities scored as 2 or 3. The most frequent findings included pleural thickening (64.5 %) and pleural effusion (19.4 %). These structural changes were detected well into the convalescence period and affected not only the clinical perception of recovery but also preoperative risk. In addition to pulmonary alterations, a significant portion of patients reported lingering emotional and physical sequelae, including depression (54.8 %), memory loss (80.6 %), muscle weakness (77.4 %), and hair loss (32.3 %) (Figure 1). Notably, three patients died following their post-COVID recovery period despite having undergone LUS evaluation beforehand. These outcomes underscore the critical need for robust perioperative risk stratification tools in this population.

Although CT imaging remains superior in terms of anatomical resolution, its practical limitations – radiation exposure, cost, lack of portability – make it less ideal for bedside risk assessment prior to surgery. LUS, on the other hand, provides dynamic, real-time insights into lung aeration,

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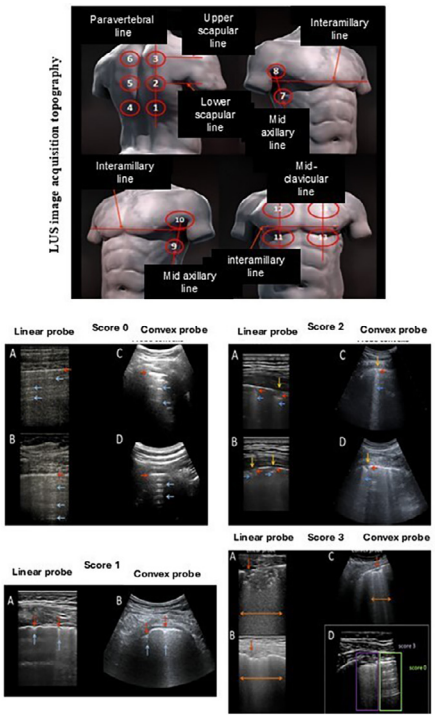

Variable	Category	n	%	Variable	Category	n	%	Variable	Category	n	%
		Value				Value				Value	
Sex	Male	15	48	Trach	No	26	83.9	MP	No	24	77.4
	Female	16	52		Yes	5	16.1		Yes	7	22.6
	Total	31	100		Total	31	100		Total	31	100
				LUS	Yes	31	100				
Htn	No	21	67.7		Total	31	100	ML	No	6	19.4
	Yes	10	32.3	Consol	No	31	100		Yes	25	80.6
	Total	31	100		Total	31	100		Total	31	100
DM	No	27	87.1	PT	No	11	35.5	HL	No	21	67.7
	Yes	4	12.9		Yes	20	64.5		Yes	10	32.3
	Total	31	100		Total	31	100		Total	31	100
Death	No	28	90.3	PE	No	25	80.6	ACT	No	28	90.3
	Yes	3	9.7		Yes	6	19.4		Yes	3	9.7
	Total	31	100		Total	31	100		Total	31	100
CVA	No	29	93.5	At least 1 LUS alteration	No	10	32.3	RRT post-covid	No	29	93.5
	Yes	2	6.5		Yes	21	67.7		Yes	2	6.5
	Total	31	100		Total	31	100		Total	31	100
DVT post-covid	No	29	93.5	DD	No	14	45.2	Weak	No	7	22.6
	Yes	2	6.5		Yes	17	54.8		Yes	24	77.4
	Total	31	100		Total	31	100		Total	31	100

Figure 1 **Epidemiological and clinical history data.** Qualitative data of 31 participants were evaluated; data were presented as percentage (%). LUS images for each score, obtained with a linear probe (A) and a convex probe (B). Score 0: continuous and regular pleural line (red arrows); horizontal artifacts — A lines (blue arrows). Score 1: indented pleural line (red arrows); sparse B lines present (blue arrows). Score 2: pleural line with interruptions (yellow arrows); below the pleural line interruption points, small areas of consolidation are present (red arrows), associated with areas of coalescent vertical artifacts (B lines) (blue arrows). Score 3: pleural line with extensive interruptions; Below the points of discontinuity of the pleura, extensive pulmonary consolidations can be found (red arrows), associated with generalized areas of "white lung" (orange arrows). Htn, Hypertension; DM, Diabetes Mellitus; CVA, Cerebral Vascular Accident; DVT, Deep Vein Thrombosis; Trach, Tracheostomy; LUS, Lung Ultrasound; Consol, Consolidation; PT, Pleural Thickening; PE, Pleural Effusion; DD, Depression disorder; MP, Muscle Pain; ML, Memory Loss; HL, Hair Loss; ACT, Anticoagulation; RRT, Renal Replacement Therapy; Weak, Body Weakness.

interstitial involvement, and pleural integrity. Importantly, it can be conducted by trained clinicians in non-radiology specialties, expanding its utility in both inpatient and outpatient settings.

Currently, no widely adopted protocols incorporate lung ultrasound into preoperative evaluations of post-COVID-19 patients. Our study supports the argument that they should be included. Approximately two-thirds of patients in our cohort exhibited persistent pulmonary abnormalities detectable via LUS, so anesthesiologists and surgical teams would benefit from incorporating this tool into standard evaluation protocols. Doing so could allow for individualized ventilation strategies, perioperative respiratory therapy, and fluid management, ultimately improving outcomes. We also note that interobserver agreement in LUS interpretation was high in our study, affirming that with appropriate training, the technique yields reproducible and clinically relevant results. Such reliability bolsters its potential for broader adoption across healthcare teams.

In conclusion, LUS is a promising, underutilized modality for detecting pulmonary sequelae in post-COVID-19 patients. It is simple, affordable, and can be performed at the bedside without the logistical and financial burden of more complex imaging.[9] Given the persistent and often underestimated respiratory complications in COVID-19 survivors, particularly those requiring ICU admission, the incorporation of lung ultrasound into preoperative assessments may represent an important evolution in perioperative care. We urge healthcare institutions and surgical teams to consider routine use of lung ultrasound in post-COVID patients, particularly those undergoing procedures requiring anesthesia. Future multicenter studies should explore the correlation between LUS findings and postoperative complications to further validate its role in perioperative medicine.

Data availability statement

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

Authors' contributions

LARL, VRSO, CSD: Wrote and prepared the manuscript. LARL, LHNL, RML: Conceptualized and collected data.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

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LETTER TO THE EDITOR

Feasibility of early rapid sequence induction and intubation training and the role of a cognitive aid on-demand reader in medical students: lessons from a pilot randomized study

Dear Editor,

Rapid Sequence Induction and Intubation (RSII) is a key part of safe airway management in emergency and perioperative care. Since its initial description by Stept and Safar in 1970,[1] RSII has been recognized as a time-sensitive procedure that demands careful preparation, proper drug sequencing, and effective team coordination. In Brazil and other developing countries, newly graduated physicians often take on responsibilities for airway management in emergency departments immediately after medical school, often without specialized anesthesia training.[2] This situation highlights the need for developing effective, scalable, and early educational strategies to ensure that future physicians can safely perform life-saving procedures, such as RSII. Recent evidence emphasizes the importance of preparing medical students with anesthesia-related skills to support the global surgery agenda and to reduce disparities in access to safe anesthesia care.[2]

We briefly report a pilot study aimed at assessing the feasibility of incorporating RSII training into the medical school curriculum shortly after students develop basic skills in tracheal intubation. Additionally, we sought to evaluate the potential impact and logistical considerations of providing a cognitive aid "reader" to assist students during simulation.[3]

We conducted a prospective, randomized simulation study with 44 medical students from the 3rd to 6th year of medical school. The institutional research ethics committee approved the study (Certificate of Presentation for Ethical Consideration [CAAE: 58,776,122.6.0000.0121]), and participants signed written informed consent before enrolling. Participants completed an online preparatory module covering indications for RSII, preoxygenation, pharmacology of induction agents and neuromuscular blockers, and a step-by-step checklist of 17 essential tasks. Students were then randomized to perform a standardized RSII scenario with or without the presence of a trained cognitive aid reader, who followed the checklist and was available to read steps upon the students' prompts. Procedures were video-recorded, and performance was evaluated by blinded assessors using the 17-item checklist as the primary outcome. Secondary outcomes included adherence to the correct sequence, number of technical errors, time to completion, and overall performance rating.

The median number of checklist items completed was 17 (IQR 16–17) in the reader group and 16 (IQR 15–17) in the control group ($p = 0.11$). No statistically significant differences were observed between groups regarding adherence to the correct sequence, technical errors, or overall scenario duration. Reader activation occurred in approximately 22 % of steps, most commonly during drug administration and preparation for intubation. Both groups reported high satisfaction with the training and increased perceived preparedness for airway management.

In our study, having a cognitive aid reader did not significantly boost performance in a simulated RSII scenario. This indicates that combining structured preparatory materials with simulation exposure might be enough for students to perform at a high level early in their training. These findings match previous research showing that cognitive aids are more helpful in less structured, crisis-like situations or for participants facing high cognitive load, rather than for learners who have just undergone focused training.[4]

The study was conducted at a single institution with a relatively small sample size, which limits its generalizability. Students from various academic years were intentionally included, which may have introduced variability in baseline knowledge and confidence; however, this was not tested due to the small sample size. We used a medium-fidelity manikin, which cannot replicate all clinical cues of a real RSII; however, the choice reflects the reality of most medical schools in Brazil and other developing countries, where high-fidelity simulators are not routinely available. This makes our results more realistic for similar settings. Additionally, readers were instructed to follow the cognitive aid script exactly, simply reading each item as written, without changing timing or phrasing. This consistent approach ensured reliability but may have limited the flexibility of the intervention.

Despite these limitations, this pilot study demonstrates the feasibility of introducing RSII training soon after tracheal intubation instruction in the regular medical curriculum. The results also suggest that including a cognitive aid reader may not provide measurable benefits in this context, raising essential considerations about the logistics and cost-effectiveness of deploying readers as part of routine RSII training.

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In conclusion, early RSII training is feasible and effective when supported by structured preparation and simulation-based education. The addition of a cognitive aid reader did not produce measurable performance improvement, indicating that resources might be better spent on ensuring high-quality pre-simulation preparation and structured debriefing.

Future studies should investigate whether cognitive aids become more relevant under stress conditions, with multiprofessional teams, or in more complex airway scenarios, and whether repeated exposure throughout medical school translates into improved clinical performance after graduation.

Data availability statement

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

Declaration of AI use

During the preparation of this work, the authors used Grammarly and ChatGPT to improve grammar, clarity, readability, and aid in rephrasing sentences for conciseness and flow. After using these tools, the authors carefully reviewed and edited the content to ensure accuracy, scientific integrity, and compliance with journal guidelines, and they take full responsibility for the content of the published article.

Authors' contributions

Getúlio Rodrigues de Oliveira Filho helped with the study's conception, supervision, manuscript writing, and final version approval.

Miguel A. Fabrin helped with the study's conception, manuscript writing, and final version approval.

Victor M. Benincá helped with the study's conception and the approval of the final version of the manuscript.

Ian N. Quadri helped with the study's conception and the approval of the final version of the manuscript.

Gabriel R. G. da Silva helped with the study's conception and the approval of the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Correlation between impostor phenomenon and burnout syndrome in medical residents: a single-center study

Dear Editor,

Since the 1970s, two psychological constructs have been described: Impostor Phenomenon (IP), defined as the psychological experience of intellectual and professional fraudulence[1] and Burnout Syndrome (BS), which is defined as the psychological syndrome that emerges in response to prolonged exposure to work stressors, characterized by three dimensions described as Emotional Exhaustion (EE), Depersonalization (DP) and decreased Personal Achievement (PA).[2] For healthcare professionals, specifically physicians in training, the frequency of IP has been reported to be as much as 30%[3] and the rate of BS from 25% to 75%. The failure to recognize and assess IP and BS can limit the career development process. Given the negative impact of IP and BS on healthcare professionals, we evaluated both constructs in a population of residents from all medical specialty programs, starting from the second year onwards, at the General Hospital of Zone 1 Aguascalientes of the Mexican Institute of Social Security, a second-level general hospital, to determine the frequency and correlation of IP and BS among the participants.

The study, approved by the Local Ethics and Research Committee (Registry Number R-2024-101-119), was an observational, descriptive, prospective, and single-center study. All participants provided duly informed consent.

A total of 56 second- and third-year medical residents from all medical specialty programs in the 2024—2025 academic year were selected. Demographic and academic data were obtained through a self-administered questionnaire, assessing six variables: age, gender, academic program, academic year, duty hours and rest hours. The Clance Impostor Phenomenon Scale (CIPS) was administered to all participants. The CIPS is a psychometrically validated instrument composed of 20 items rated on a 5-point Likert scale. CIPS Scores are categorized as follows: scores of 40 or below reflect a few characteristics of IP; scores between 41 and 60 indicate a moderate level; scores from 61 to 80 suggest frequent impostor-related experiences; and scores of 81 or above correspond to intense manifestations of the IP. For this study, the presence of IP was defined as CIPS $\geq$ 60 and we use an instrument validated in Spanish.[4] We also use the Maslach Burnout Inventory (MBI) including three dimensions analysis (emotional exhaustion, depersonalization and personal achievement). The instrument assesses burnout prevalence in the target population through 22 items rated on a 7-point frequency scale. The questionnaire yields three numerical variables with the following cut-off points: Emotional Exhaustion (EE) is classified low ($\leq$ 18), moderate (19–26), or high ($\geq$ 27); Depersonalization (DP) as low ($\leq$ 5), moderate (6–9), or high ($\geq$ 10); and Personal Achievement (PA) as low ($\leq$ 33), moderate (34–39), or high ($\geq$ 40). Burnout was identified when the following criteria were simultaneously met across the three dimensions of MBI; EE with a score $\geq$ 27, DP with a score $\geq$ 10, and PA with a score $\leq$ 33. We use an instrument validated in Spanish.[5]

We conducted descriptive statistical analyses of the variables included in the information questionnaire. We calculated the Pearson correlation coefficient to evaluate the association between the scores of the CIPS and the three dimensions of the MBI. We applied a logistic regression model to assess the relationship between the variables and the scores of the CIPS and the three dimensions of the MBI. All analyses were performed using Microsoft Excel® and GNU Operating System PSPP® version 2.0.1 for Windows®. A p-value < 0.05 was considered significant for hypothesis testing.

The age distribution of medical residents ranged from 25 to 40 years (mean = 30, SD = 2.86-years), including 38 females (68%) and 18 males (32%). Regarding the academic program, 39 residents (70%) were enrolled in Anesthesiology, while 17 residents (30%) were enrolled in Emergency Medicine. They reported duty time of 75.79 $\pm$ 23.78 hours per week and rest time of 26.8 $\pm$ 18.91 hours per week. Participants who scored in the frequent or intense IP range were considered to have IP, resulting in an overall IP prevalence of 45%. We observed an SB prevalence of 29% (16 participants with high EE and DP and low AP simultaneously) (Table 1).

In the analysis of association between IP and BS, a moderate non-causal correlation was obtained between EE and IP (95% CI 0.39–1.15; F = 16.67); a strong non-causal correlation between DP and IP (95% CI 0.98–2.46; F = 21.8); and a strong non-causal negative correlation between PA and IP (95% CI -1.75 to -0.28; F = 7.69) ($p < 0.05$). We obtained a strong non-causal correlation between the three dimensions of BS and IP (95% CI -0.88 to -2.255; F = 8.14) (Table 1),

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Table 1 Frequency of Impostor Phenomenon and Burnout Syndrome and Pearson Correlation Coefficient of the participants.

Variable	Categories	Number of participants Total (n = 56)
CIPS score	Few	9 (16%)
	Moderate	22 (39%)
	Frequently	18 (32%)
	Intense	7 (13%)
IP Percentage Variable		**Total (n = 25)**
Gender	Male	7 (28%)
	Female	18 (72%)
Academic program	Anesthesiology	16 (64%)
	Emergency Medicine	9 (36%)
Academic year	Second	13 (52%)
	Third	12 (48%)
MBI Score		**Total (n = 56)**
Emotional Exhaustion	Low (≤ 18)	10 (18%)
	Moderate (19–26)	13 (23%)
	High (≥ 27)	33 (59%)
Despersonalization	Low (≤ 5)	15 (27%)
	Moderate (6–9)	13 (23%)
	High (≥ 10)	28 (50%)
Personal achievement	Low (≤ 33)	21 (38%)
	Moderate (34–39)	26 (46%)
	High (≥ 40)	9 (16%)
BS Percentage Variable		**Total (n = 16)**
Gender	Male	8 (50%)
	Female	8 (50%)
Academic program	Anesthesiology	10 (62%)
	Emergency Medicine	6 (38%)
Academic year	Second	8 (50%)
	Third	8 (50%)

Pearson correlation matrix of variables of interest (values refer to correlation coefficients *r*)

	EE MBI	**DP MBI**	**PA MBI**	**CIPS**
EE MBI	1	–	–	–
DP MBI	0.646167[a]	1	–	–
PA MBI	-0.509819[a]	-0.578983274[a]	1	–
CIPS	0.4825796[a]	0.536297465[a]	-0.3530322[a]	1

[a] $p < 0.05$.

BS, Burnout Syndrome; CIPS, Clance Impostor Phenomenon Scale; DP, Depersonalization; EE, Emotional Exhaustion; IP, Impostor Phenomenon; MBI, Maslach Burnout Inventory; PA, Personal Achievement.

confirming the association between IP and the three dimensions of the BS which, to the best of our knowledge, has not been reported in this form in previous studies. There is a statistically significant correlation between the female gender and IP, as well as the depersonalization dimension of the MBI for BS. Additionally, a statistically significant correlation between the academic level and IP, as well the personal achievement dimension of the MBI for BS.

We identified the intense and frequent levels of IP among participants in this sample. When combined with a stressful and high-demand work environment, these factors necessitate the use of coping mechanisms such as perfectionism and overexertion, ultimately leading to BS. We report a higher prevalence of IP in the early stages of an academic career, associating a greater risk of IP with fewer years of practice. This suggests that increased work experience and the attainment of an academic degree, by reinforcing perceived competence, may help mitigate IP symptoms as part of a broader coping strategy.[6]

Among the three BS dimensions, PA is the one that best explains the BS score in our sample. Our population exhibited higher personal accomplishment scores, which served as a protective factor in reducing the frequency of BS diagnoses. PA can function as a coping mechanism that lowers the overall MBI score and, consequently, the BS diagnosis. It may also mask high exhaustion and depersonalization scores within the studied population.

Our findings suggest that the IP and BS are two interrelated mental health conditions that significantly affect medical residents enrolled in postgraduate academic programs. The statistical association observed between both

constructs underscores the need for integrated approaches to their identification and management.

Given their strong link to work-related factors, we included variables such as the number of hours residents spent in hospital-based training activities. The reported weekly workload was consistent with findings from previous studies. However, we were unable to compare the self-reported rest hours with existing literature, likely due to the lack of standardized or validated instruments. Despite this limitation, our data highlight the importance of rest as a contributor to residents' overall quality of life.

This study was limited by its single-center design and inclusion of only two medical specialties, which restricts generalizability. Future studies should expand the range of specialties evaluated and incorporate validated tools for time-use assessment. Moreover, future research should explore the influence of personal, occupational, and motivational factors on the development of IP and BS, which may exert a greater effect than demographic characteristics alone. A deeper understanding of these variables could inform the development of targeted interventions to reduce the prevalence and impact of these conditions among medical trainees.

Data availability statement

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

Authors' contribution

Cristina González Ramírez: Conceived and planned the study, carried out the observational study; designed the experimental study; processed the experimental data, performed the analysis, wrote and drafted the manuscript and designed the figures.

Rocío Pérez Bocanegra: Supervised the project; contributed to the interpretation of the results; provided critical feedback and helped shape the research, analysis and manuscript.

Carlos Armando Sánchez-Navarro: Responsible for all communications with the journal; conceived and planned the study, carried out the observational study; supervised the project; supervised the experimental data, performed the analysis; provided critical feedback and helped shape the research, analysis and manuscript.

All authors discussed the results and contributed to the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Effect of preoperative clear carbohydrate beverage on emergence delirium in children – a randomized controlled trial☆

Dear Editor,

Preoperative carbohydrate loading has been shown to attenuate insulin resistance, maintain euglycemia and improve recovery in pediatric patients.[1] Children are particularly vulnerable to perioperative glucose fluctuations due to limited metabolic reserves. Both hypoglycemia and hyperglycemia have been linked to cognitive dysfunction and delirium.[2,3] Despite these associations, the effect of carbohydrate loading on Emergence Delirium (ED) remains underexplored. This study investigates whether preoperative carbohydrate drink administration reduces ED in children, focusing on fasting duration and blood glucose levels as potential mediators.

This prospective, randomized, assessor-blinded study included ASA I–II children aged 2–6 years scheduled for elective ocular surgery. Standard fasting guidelines were followed (> 6h for solids and > 2h for clear liquids). Participants were randomly allocated into:

- Group CD (Carbohydrate Drink): Received 3 mL.kg^{-1} (max 150 mL) of a commercially available clear carbohydrate beverage 2h preoperatively.
- Group C (Control): Received an equivalent volume of plain water at the same time interval.

A nurse uninvolved in the study administered the intervention. The same commercial brand of a flavored sweetened beverage (glucose content 12.9 gm/100 mL) was used to ensure uniformity of carbohydrate load, palatability, and voluntary intake among participants. Studies in children using serial magnetic resonance imaging have confirmed that 3 mL.kg^{-1} of such beverages return to baseline gastric volumes within an hour, making this volume a safe choice.[4] No premedication was given. Anxiety was assessed using modified Yale Preoperative Anxiety Scale (mYPAS). Thirst was assessed using a binary scale. All patients underwent standardized inhalational induction with sevoflurane and nitrous oxide. Compliance during induction was evaluated using Induction Compliance Checklist (ICC). After induction, intravenous fentanyl (1–2 μg.kg^{-1}) was administered, followed by laryngeal mask insertion. Blood glucose levels were measured at induction – Fasting Blood Glucose (FBG) and before emergence. Maintenance anesthesia was with sevoflurane in oxygen/nitrous oxide and Ringer lactate fluid infusion. Upon completion, sevoflurane was discontinued, and 100% oxygen was administered. Intravenous ondansetron (0.1 mg.kg^{-1}) and paracetamol (15 mg.kg^{-1}) were given. After awake removal of the airway device, patients were transferred to the Post-Anesthesia Care Unit (PACU). ED was evaluated every 5 minutes for 30 minutes using the Pediatric Anesthesia Emergence Delirium (PAED) scale. ED was defined as PAED score > 10.[5] Pain was assessed using Face, Legs, Activity, Cry, Consolability (FLACC) scale. Vital signs were continuously monitored. The primary outcome of the study was incidence of ED in first 30 min in PACU. The secondary outcomes were a) Association of fasting and emergence blood glucose levels with ED and b) Correlation between preoperative fasting duration and FBG level.

SPSS Version 23.0 was used to analyse the data. The normality of data was checked using Shapiro-Wilk test. Independent *t*-tests and Mann-Whitney *U*-tests were used as appropriate. Categorical variables were compared using Chi-Square or Fisher's exact test. Spearman's correlation assessed relationships between fasting duration and FBG values. Significance was set at $p < 0.05$. Based on prior ED incidence (~44.4%) in children undergoing ocular surgery,[6] a sample size of 39 per group (allowing for 10% dropout) was calculated to detect a 30% reduction in ED with 80% power ($\alpha = 0.05$).

Seventy-eight children were randomized (39 per group). The Table 1 depicts the patients' demographic and clinical characteristics. Eleven (28.2%) patients in group CD and 9 (23.1%) patients in group C exhibited postoperative ED ($p = 0.60$, OR = 1.31; 95% CI: 0.47, 3.63). Children who developed ED had lower mean FBG and emergence glucose values compared to those without ED, but these differences were not statistically significant ($p = 0.29$ and 0.10, respectively). No significant correlation was found between clear fluid fasting duration and FBG (Spearman's $p = 0.16$, $p = 0.17$). A multivariable logistic regression analysis was performed to adjust for potential confounders including age, fasting duration, preoperative anxiety, quality of induction and duration of anesthesia. In the adjusted logistic regression model, clear fluid fasting duration was independently associated

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Table 1 Demographic and clinical characteristics of the studied patients.

	Carbohydrate drink group (n = 39)	Control group (n = 39)	p-value[†,§]
Age (years)	3.87 ± 1.45	3.73 ± 1.63	0.55
Gender: Male/Female	19 (48.7) / 20 (51.3)	15 (38.5) / 24 (61.5)	0.36
Weight (kg)	15.88 ± 3.95	15.46 ± 4.13	0.80
Type of admission: Out-patient / In-patient	23 (59.0) / 16 (41.0)	28 (71.8) / 11 (28.2)	0.23
Fasting for clear fluids (hours)	3.09 ± 0.83	5.23 ± 3.04	0.004
ASA Status I	39 (100)	39 (100)	1.00
Duration of procedure (minutes)	58.74 ± 4.55	58.41 ± 7.04	0.44
Discharge from PACU readiness (minutes)	60.00 ± 15.73	59.49 ± 14.68	0.89
Preoperative thirst	25 (64)	26 (67)	0.81
Preop mYPAS score	26.67 (23.33–41.67)	28.33 (23.33–41.67)	0.48
ICC score	0 (0–1)	1 (0–2.5)	0.31
FLACC score	0 (0–2)	0 (0–3)	0.39
Fasting blood glucose ($mg.dL^{-1}$)	80 (76–87)	83 (79–86.5)	0.3
Blood glucose at emergence ($mg.dL^{-1}$)	82 (77.5–86)	79 (76–84)	0.21

PACU, Postanesthesia Care Unit; ASA, American Society of Anesthesiologists; mYPAS, modified Yale Preoperative Anxiety Scale; ICC, Induction Compliance checklist; FLACC score, Face, legs, activity, cry and consolability score.
[†] Values are expressed as numbers (percentage), mean ± SD or median (IQR).
[§] Independent *t*-tests and Mann-Whitney *U* tests were used as appropriate.

with a higher likelihood of ED (OR = 1.87, 95% CI: 1.10–3.18, p = 0.02). The other factors were not statistically significant predictors in this model.

Our study found no difference in the incidence of ED between the intervention and control group. Several factors may explain this finding. First, the volume of carbohydrate beverage administered may have been insufficient to produce a measurable physiological or behavioural effect. Previous studies using larger volumes (6–15 $mL.kg^{-1}$) of preoperative oral fluids have reported reduction in preop irritability among children.[7,8] Second, ED is a multifactorial phenomenon – despite standardized anesthesia protocols, individual variations in baseline anxiety levels, drug dosages, anesthetic agents, anesthesia depth, emergence conditions or postoperative pain may have influenced outcomes. However, the absence of significant differences in FLACC scores between children with and without ED suggests that pain was not a major contributing factor to the observed emergence behaviors. Third, the study population – healthy children undergoing short-duration elective surgery – might inherently have a lower baseline ED risk, reducing the likelihood of detecting a treatment effect. Finally, only the outcome assessors were blinded-introducing a risk of potential performance bias.

Glucose plays a key role in supporting neurotransmitter activity and cognitive function, and fluctuations in glycemia have been associated with agitation and impaired emergence behaviors.[2] By maintaining euglycemia, carbohydrate loading may offer partial neurobehavioral protection during emergence, addressing one component of the complex ED pathophysiology. In our study, children who developed ED had lower mean fasting and emergence glucose levels, but the differences were not statistically significant. These findings align with prior studies that suggest a potential but not definitive link between perioperative hypoglycemia and behavioral disturbances.[8] The limited sample size along with the modest glycemic differences observed may have been insufficient to elicit a clinically meaningful effect.

The lack of a statistically significant correlation between preoperative fasting duration and FBG levels indicates considerable interindividual variability owing to factors such as patients' age, nutritional status, carbohydrate type and content of foods and drinks ingested in preoperative period, baseline metabolic rate and hormonal regulation modulating perioperative glycemic responses independently of fasting duration.

Despite standardized preoperative instructions, a variability in actual fasting durations was observed among participants in both groups. This discrepancy is likely attributable to practical scheduling constraints, operating room logistics, and variability in surgery start times-common challenges in pediatric surgical settings. While we aimed to adhere strictly to the fasting protocol, such deviations reflect the real-world clinical environment, where delays or early scheduling changes can extend or shorten fasting periods unpredictably. Longer fasting duration was found to be independently associated with higher odds of ED.

In summary, oral carbohydrate preloading did not significantly reduce the incidence of ED in this population. Further studies are warranted to explore optimal carbohydrate composition, volume, and timing, and potentially examine additional outcomes such as parental satisfaction, perioperative stress markers, and neurocognitive recovery.

Ethical approval, CTRI registration and consent to participate: Ethical approval for the study was obtained from Intramural Institutional Ethics Committee (NK/7926/MD/547) on 25 November 2021. The study was prospectively registered with Clinical Trial Registry of India (CTRI/2021/12/038688). [Registered on: 16/12/2021]. Informed written consent from the parents was obtained for inclusion in the study.

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The contents of the article have not been published elsewhere and the paper is not being submitted elsewhere. The manuscript has been read and approved by all co-authors. We hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal.

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844698.

Associate Editor

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LETTER TO THE EDITOR

Association between troponin and NT-proBNP levels, cytokines, and clinical outcomes in early sepsis response: a cohort study

Dear Editor,

N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) and troponin are well-established biomarkers indicative of the severity of cardiac injury. An increase in preload stimulates ventricular myocytes to synthesize and release NT-proBNP. Troponin is frequently evaluated in critically ill patients with sepsis, with its release attributed to various mechanisms, including supply-demand mismatch and direct myocardial inflammation. Additionally, both biomarkers exhibit impaired renal clearance. They are associated with cardiomyocyte stress and myocardial inflammatory response and may be elevated in various inflammatory conditions affecting the heart.[1] The dysregulated inflammatory response to infection in sepsis often leads to unfavorable clinical outcomes.[2] Accordingly, elevated NT-proBNP and troponin levels have been correlated with worse outcomes, as well as with increased Sequential Organ Failure Assessment (SOFA) scores, reflecting more severe multiorgan injury and unresolved inflammation. Interleukin (IL)-6, IL-1β, IL-10, and C-Reactive Protein (CRP) are important markers of an early dysregulated inflammatory response in sepsis and are prognostic biomarkers of poor outcomes.[3,4] Additionally, the release of IL-1β and IL-6 during endotoxemia can lead to myocardial depression, suggesting that they may lead to myocardial damage.[5] Nonetheless, the relationship between the early elevation of interleukins and the levels of serum troponin and NT-proBNP has not been sufficiently investigated. Therefore, the main objective of this study is to evaluate the association between myocardial injury markers and pro- and anti-inflammatory ILs in the initial response of sepsis, as well as the association between these levels and early improvement in sepsis response.

We performed a post-hoc study derived from a cohort study that prospectively evaluated consecutive patients who had been admitted to four different ICUs (Grupo Hospitalar Conceição, Porto Alegre, Brazil). The original cohort was described previously.[6] This study was approved by the local ethics committee (Plataforma Brazil number 66240017.0.0000.5530).

We included adult patients admitted to the ICU with sepsis and persistent hypotension. Sepsis and persistent hypotension were defined according to the current guidelines.[7] Patients were excluded if they presented with known mitochondrial disease, pregnancy, refusal of the patient or next of kin to sign the informed consent, imminent death, withholding or withdrawing treatment, or acute coronary syndrome concomitant with a sepsis diagnosis.

The epidemiological characteristics were prospectively recorded, including the Simplified Acute Physiology Score (SAPSIII), SOFA score at admission to the ICU, and SOFA score on day-3. We measured NT-proBNP, troponin, IL-1β, IL-6, IL-10, and C-reactive protein (CRP) levels upon the diagnosis of sepsis. The primary objectives are to assess the correlation between troponin and NT-proBNP levels with ILs. The secondary objectives involve evaluating the correlation between NT-proBNP and troponin levels and clinical, hemodynamic, and CRP levels. Clinical variables are presented in Table 1.

Patients with ischemic cardiomyopathy (n = 16) did not have significantly increased troponin levels as compared to those who did not have ischemic cardiomyopathy (n = 60): 75 ng.L^{-1} (56—360) vs. 59 ng.L^{-1} (28—114), p = 0.18; and NT-proBNP levels: 3143 pg.mL^{-1} (1003—10369) vs. 3503 pg.mL^{-1} (2224—10643), p = 0.49. In addition, patients with heart failure (n = 15) did not have significantly increased troponin levels as compared to those who did not have heart failure (n = 61): 119 ng.L^{-1} (47—280) vs. 62 ng.L^{-1} (33—111), p = 0.10; as well as NT-proBNP levels: 7390 pg.mL^{-1} (1719—19865) vs. 3455 pg.mL^{-1} (1004—7732), p = 0.24.

Seventy-eight patients had CRP measurements, and 64 patients had IL-6, IL-10 and IL-1β measurements. Troponin levels were not associated with interleukin or CRP levels at the same time. The Pearson's coefficients were -0.02 (95% CI -0.24 to 0.29, p = 0.84) for IL-6; 0.01 (95% CI -0.25 to 0.28, p = 0.90) for IL-10; -0.14 (95% CI -0.39 to 0.13, p = 0.30) for IL-1β; and -0.02 (95% CI -0.25 to 0.21, p = 0.87) for CRP. Remarkably, there was an association between NT-proBNP and IL-6 levels, with a Pearson's coefficient of 0.3 (95% CI 0.03 to 0.52, p = 0.03), as well as between NT-proBNP levels and IL-10 levels, with a Pearson's coefficient of 0.34 (95% CI 0.07 to 0.56, p = 0.01). Furthermore, NT-proBNP levels were not associated with IL-1β levels (Pearson's coefficient 0.04 [95% CI -0.23 to 0.30]; p = 0.78) or CRP levels (Pearson's coefficient 0.02 [95% CI -0.21 to 0.26]; p = 0.83). In an analysis using a general linear model, we found an interaction

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Table 1 Clinical and laboratory variables associated with 28 days mortality.

Variable	Survivors (n = 48) Mean/ median (sd/iqr) or ratio	Non-survivors (n = 42) Mean/median (sd/iqr) or ratio	MD (95% CI), Median difference (95% CI), OR (95% CI), p-value
Age	64.1 (15.5)	67 (16.6)	MD -2 (-8 to 4), p = 0.64
SAPS3	73 (12)	79 (12.8)	MD -7 (-12 to -2), p = 0.03
CRT	4 (2 — 4)	4.5 (3 — 7)	Median Difference -1 (-2 to -1), p = 0.02
Cumulative fluid balance day-1	2650 (1151 — 4469)	4375 (2025 — 5857)	Median Difference -1241 (-2466 to -35), p = 0.04
NE maximum day-1	0.18 (0.1 — 0.3)	0.35 (0.19 — 0.61)	Median Difference -0.15 (-0.27 to -0.04), p < 0.01
Mottling score day-1	0 (0 — 0)	0 (0 — 2)	Median Difference 0 (0 to 0), p < 0.01
SOFA	7 (6 — 9)	9 (7 — 11)	Median Difference -2 (-3 to -1), p ≤ 0.01
IL-6	63 (30.2 — 195.2)	122.9 (32.7 — 217)	Median Difference -9 (-94 to 25), p = 0.58
IL-10	174.9 (125.8 — 224.9)	200 (168.4 — 246.7)	Median Difference -30 (-76 to 6), p = 0.1
IL-1β	23.6 (13.9 — 458.4)	56.3 (17.8 — 738.7)	Median Difference -23 (-163 to 4), p = 0.14
CRP	156 (79 — 212)	206 (112 — 290)	Median Difference -50 (-101 to -1), p = 0.04
Hemodialysis	6/48	23/42	OR 8.47 (2.96 — 24.2), p < 0.01
MV	37/48	40/42	OR 5.94 (1.23 — 57.65), p = 0.01
Male sex	30/48	20/42	OR 0.54 (0.23 — 1.26), p = 0.2
Malignancy	10/48	9/42	OR 1.03 (0.37 — 2.85), p = 1
COPD	7/48	5/42	OR 0.79 (0.23 — 2.71), p = 0.76
Diabetes	15/48	10/42	OR 0.68 (0.27 — 1.75), p = 0.48
Hypertension	17/48	15/42	OR 1.01 (0.42 — 2.4), p = 1
Ischemic cardiomiopathy	10/48	7/42	OR 0.76 (0.26 — 2.21), p = 0.78
Heart failure	11/48	5/42	OR 0.45 (0.14 — 1.43), p = 0.27
Troponin	58 (25 — 120)	71 (36 — 138)	Median difference 12 (-15 to 40), p = 0.36
NT-proBNP	2413 (976 — 8169)	4409 (1851 — 17750)	Median difference 1079 (-717 to 3621), p = 0.28

COPD, Chronic Obstructive Pulmonary Disease; CRP, C-Reactive Protein; CRT, Capillary Refill Time; IL, Interleukin; MD, Mean Difference; MV, Mechanical Ventilation; NE, Norepinephrine; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; OR, Odds Ratio; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

between NT-proBNP levels and IL-6 levels (β-coefficient 0.34 [95% CI 0.08—0.6], p = 0.01) and IL-10 levels (beta-coefficient 0.37 [95% CI 0.11—0.62], p < 0.01). This interaction was independent of heart failure or ischemic cardiomyopathy status. We analyzed the maximum Norepinephrine (NE) dose as a marker of hemodynamic dysfunction during sepsis. Troponin was not associated with the maximum NE dose: Pearson's coefficient -0.01 (95% CI -0.24 to 0.21, p = 0.88); but NT-proBNP was: Pearson's 0.3 (95% CI 0.07 to 0.49, p = 0.01).

We conducted a multivariate analysis of troponin and NT-proBNP and their association with 28-day mortality, adjusted for potential confounders: diagnosis of ischemic cardiomyopathy, diagnosis of heart failure, the cumulative fluid balance at day-1, the maximum NE dose at day-1, SAPS3 score, SOFA score at day-1, sex and CRP levels at day-1. In this modeling, troponin (OR = 1.0, 95% CI 0.99—1.0) and NT-proBNP (OR = 1.0, 95% CI 0.98—1.0) were not associated with the outcome.

Patients with an improved SOFA score (n = 51) on day-3 had lower troponin levels than those who did not improve SOFA score on day-3 (n = 25): 49 ng.L^{-1} (22—85) vs. 113 ng.L^{-1} (72—334), respectively; Mean Difference (MD) 53 ng.L^{-1} (95% CI 19—90), p < 0.01. Patients who improved their SOFA score (n = 50) on day-3 did not display lower NT-proBNP levels than those who did not improve their SOFA score on day-3 (n = 23): 2861 pg.mL^{-1} (1036—7532) vs. 5834 pg.mL^{-1} (1509 —21163), MD = 1256 pg.mL^{-1} (95% CI -724 to 5441), p = 0.26.

Early response in patients with sepsis shows increased troponin and NT-proBNP levels, and our data reiterate these findings.[8] Our results indicate distinct responses of troponin and NT-proBNP in the early stages of sepsis. Higher NT-proBNP levels were correlated with increased IL-6 and IL-10 expression and more severe hemodynamic instability during the acute phase, suggesting a similar acute profile between inflammatory and cardiac biomarkers. Because this kind of interaction, these associations may merely represent different indicators of patient severity. Nonetheless, troponin was associated with an improvement in the SOFA score, an important marker of clinical improvement in sepsis.[9] Elevated troponin and NT-proBNP levels in critically ill non-cardiac patients are associated with disease severity,[10] but were not associated with mortality. The small sample size limits definitive conclusions regarding these associations. Also, we performed multiple analyses of several variables and outcomes addressed in the study, but we did not correct the p-value for multiple interactions. Our study was designed

to be hypotheses-generating, and our findings necessitate validation through adequately powered, prospectively designed studies that incorporate serial biomarker sampling and account for potential confounding variables that may affect cardiac biomarker measurements.

Data availability statement

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

AI assistant disclosure

The authors used Paperpal to polish the language. The authors reviewed all suggested changes, and the authors retain full responsibility for the resulting content.

Declaration of competing interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Moving toward a standardized regional anesthesia approach in clavicle surgery

Dear Editor,

Over the past few years, we have closely followed the ongoing debate regarding the optimal regional anesthesia technique for clavicle surgery. Here, we would like to share our clinical experience and outline the technical details of a combined supraclavicular nerves and C5 root block that we have implemented in our institution.

The routine use of peripheral nerve blocks in this context remains controversial due to the complex innervation of the clavicle, which involves both the cervical and brachial plexuses.[1-3] Typically, surgical treatment of these injuries is performed under general anesthesia with systemic opioid-based analgesia, and establishing a standardized approach for peri- and postoperative pain management in clavicle fractures and acromioclavicular (AC) joint dislocations remains challenging. Considering the proven benefits of regional anesthesia, such as superior analgesia, reduced opioid consumption, and enhanced postoperative recovery, optimizing its application for clavicle injuries is both necessary and clinically valuable.[4]

To address this gap, we conducted a randomized controlled trial (German Clinical Trial Register, DRKS00017286) evaluating the analgesic potential of a combined selective blockade of the supraclavicular nerves and the C5 nerve root compared with single C5 root blockade and systemic analgesia alone. The study protocol and detailed results are available in the German Clinical Trials Register and have been published as a preprint (https://doi.org/10.1101/2025.09.22.25336305). A total of 56 patients were randomized into three groups. The first group received general anesthesia with a combined nerve block of the supraclavicular nerves and the C5 root (n = 19), the second group received general anesthesia only with a C5 root block (n = 18), and the third group had general anesthesia with systemic analgesia (control group, n = 19). Primary outcomes were postoperative pain scores (Numeric Rating Scale, NRS) and opioid consumption within 24 hours. Secondary outcomes included diaphragmatic excursion measured by M-mode ultrasound and oxygen saturation to assess phrenic nerve function. Patients with a combined blockade of the supraclavicular nerves and the C5 nerve root reported no pain during the first postoperative hour, significantly less than the C5-only and the control group. No additional opioid was required, which was also significantly lower compared with the C5-only and the control group. Phrenic nerve palsy was more frequent in the group with a combined blockade of the supraclavicular nerves and the C5 root, although oxygen saturation remained unaffected. By performing a selective blockade technique using a limited volume of local anesthetic, we initially aimed to avoid phrenic nerve involvement. However, these patients showed a significant reduction in diaphragmatic excursion during the first postoperative hour, with an average decline of about 50% compared with baseline values. Despite this decrease in diaphragmatic movement, no oxygenation impairment was observed. Nevertheless, our findings may not apply to patients with pre-existing pulmonary disease or obesity, in whom compensatory capacity may be reduced. Given that clavicle injuries predominantly affect athletic individuals with few comorbidities, this technique appears to be safe in this population. Based on these findings, combined selective regional anesthesia of the supraclavicular nerves and the C5 root may represent an effective approach for reducing postoperative pain and opioid consumption. Therefore, this approach has been adopted routinely for clavicle and AC joint surgeries in our department, where it is currently performed in approximately 100 cases per year.

The nerve block is performed preoperatively in awake patients, who are placed in the supine position with the head of the bed elevated by approximately 15° to 30°. The head is turned about 45° to the contralateral side and slightly elevated from the surface using a small head ring, identical to the standard positioning used for the interscalene brachial plexus block. The block is performed using an ultrasound-guided in-plane technique with a linear probe and a 50 mm needle through a single skin puncture (Fig. 1). The supraclavicular nerves are identified anterior to the prevertebral fascia and middle scalene muscle, embedded in the cervical fascia. For effective blockade, 5 mL of local anesthetic (2.5 mL ropivacaine 0.75% + 2.5 mL prilocaine 1%) is injected to ensure fascial spread. The needle is then advanced under ultrasound guidance to the C5 nerve root in the interscalene gap, where an additional 5 mL of the same anesthetic mixture is administered. In our experience, this technique is straightforward, safe, and can be completed within a few minutes by

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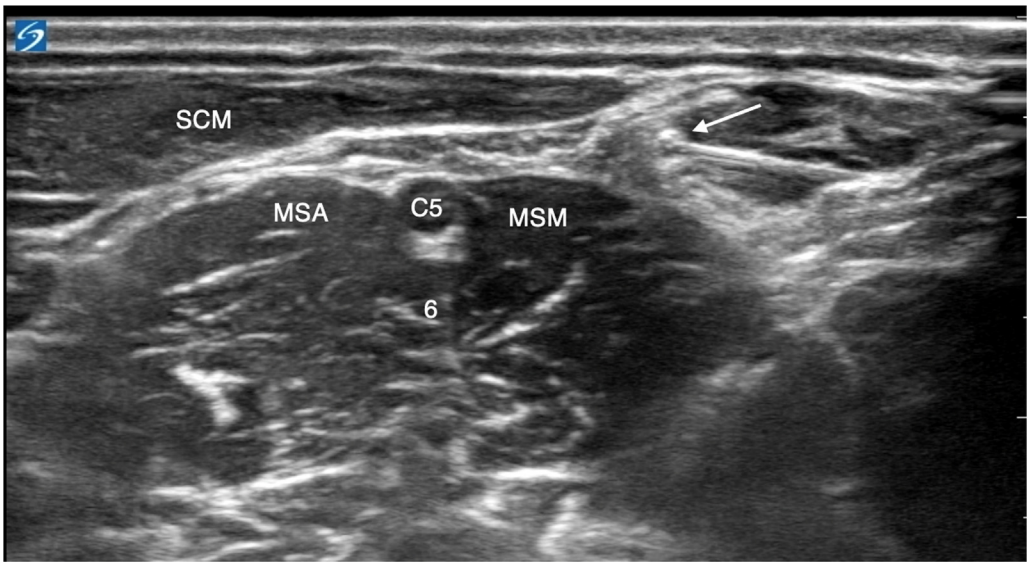

Figure 1 Selective blockade of the supraclavicular nerves and the C5 root. Arrow, Needle positioning at the level of the supraclavicular nerves; C5, C5 nerve root; (6), C6 nerve root; SCM, Sternocleidomastoid Muscle; MSA, Anterior Scalene Muscle; MSM, Middle Scalene Muscle.

an anesthesiologist experienced in ultrasound-guided nerve blocks.

We acknowledge the methodological limitations of our study, including its small sample size, open-label design, and short follow-up, which may limit the strength and generalizability of the results. As noted previously, our study did not include patients with significant comorbidities or severe pulmonary diseases. These factors should be taken into careful consideration when interpreting the findings of this blockade technique that may be associated with changes in phrenic nerve function. Nevertheless, the consistent clinical effectiveness and ease of reproducibility of this approach in daily practice are encouraging and suggest that it may serve as a model for wider adoption. Further well-designed randomized trials are warranted to evaluate its efficacy and safety and to support broader standardization. Future research should also explore its potential as a sole anesthetic technique without additional general anesthesia and its possible impact on faster postoperative recovery. With advances in ultrasound-guided regional anesthesia, approaches such as the clavipectoral fascial plane block have also emerged as promising alternatives for postoperative analgesia and merit further investigation.[5]

Trial registration

German Clinical Trial Registry DRKS ID: DRKS00017286, https://drks.de/search/en/trial/DRKS00017286/entails, date of registration May 20, 2019.

Ethics committee approval

Ethical Commission Westfalen-Lippe, Gartenstrasse 210–214, Münster/Germany, protocol number 2018-645-f-S, date of approval: March 14, 2019, chairperson Univ.-Prof. Dr. med. W.E. Berdel.

Data availability statement

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

AI assistance disclosure

No AI tools were used in the preparation of this manuscript. The authors take full responsibility for the content.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Letter to the Editor regarding lateral versus posterior quadratus lumborum block in children undergoing open orchiopexy: a double-blind randomized clinical trial

Dear Editor,

We read with great interest the recent article by Mutlu et al. comparing lateral and posterior Quadratus Lumborum Block (QLB) in children undergoing orchiopexy (Mutlu ÖPZ, Kendigelen P, Tutuncu AC. Braz J Anesthesiol. 2025;75:844661). This well-conducted double-blind randomized trial addresses an important gap in pediatric regional anesthesia, given the paucity of direct head-to-head comparisons of QLB approaches in children.[1] I commend the authors for their methodological rigor and adherence to CONSORT guidelines.

However, several aspects warrant further discussion. First, while both QLB approaches demonstrated equivalent efficacy, the study did not include a control group (e.g., caudal block or systemic analgesia), which would have contextualized the clinical advantage of QLB over more traditional techniques. Previous systematic reviews indicate that QLB reduces pain scores and opioid consumption compared to caudal blocks in children. Including such a comparator could have strengthened the translational impact of the findings.[2]

Second, the authors highlighted the limitation of not assessing the sensory block level intraoperatively. This omission makes it difficult to correlate anatomical spread with clinical outcomes. Recent imaging and cadaveric studies suggest that the extent of injectate dispersion in QLB can be highly variable. Without dermatomal mapping, it remains unclear whether inadequate coverage of scrotal innervation contributed to the requirement for rescue analgesia in nearly one-third of patients in both groups.[3]

Third, the reliance on parental reporting using Wong-Baker scores after discharge raises concerns about inter-rater reliability. Although pragmatic for outpatient surgery, this method introduces subjectivity. Combining objective pain assessment with validated observer-based tools tailored for different age groups may yield more robust data.[4]

A final consideration pertains to block selection in clinical practice. While the authors conclude that lateral QLB may be technically simpler, the choice of approach may also depend on patient positioning, anesthesiologist expertise, and potential spread patterns. It would be valuable if future studies incorporated long-term outcomes (e.g., incidence of chronic post-surgical pain) and stratified analysis by age groups, given that anatomical fascial characteristics differ significantly between infants and older children.[5]

In conclusion, Mutlu et al. provide valuable evidence that both lateral and posterior QLB yield comparable perioperative analgesia in pediatric orchiopexy. Future trials incorporating control groups, standardized sensory mapping, and extended follow-up are essential to refine the role of QLB approaches in pediatric pain management.

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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None.

Authors' contributions

Himanshu Shekhar: Conception and design; final review; conceptualization.

Parth Aphale: Data acquisition; writing the manuscript.

Shashank Dokania: Analysis; interpretation.

Declaration of competing interest

The authors declare no conflicts of interest.

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