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# Brazilian Journal of ANESTHESIOLOGY 

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# Ultrasound-guided regional anesthesia: present trends and future directions 

> "The future depends on what you do today." Mahatma Gandhi

Regional anesthesia is not just the future, it is the present. Presently, we find ourselves amid what may be called as the golden era of regional anesthesia. ${ }^{1}$ This era is characterized by its rapid evolution, wherein novel blocks, techniques, and technological advancements are unveiled at a pace that may appear overwhelming to those who have not yet embraced this paradigm or are recently venturing into it. Herein, we explore several facets concerning the imperative dissemination of regional anesthesia, the emerging tools at our disposal for this purpose, and the forthcoming frontiers that beckon in the near future.

As ultrasound technology has advanced, fresh anatomical understanding and the capacity to safely access new targets have sparked an explosion in the description of novel blocks. Today, we have dozens of blocks described, which has inspired a lot of interest in new methods. However, this "enthusiasm-based" approach to medicine, where innovative and under-researched procedures are not validated, may paradoxically make it more difficult for patients to receive regional anesthesia. This might occur because just a small percentage of anesthesiologists will administer these blocks, while the majority will consider them to be too difficult and daunting. This is opposite to what we aim for, which is to have an increasing number of anesthesiologists practicing regional anesthesia; hence, a smaller list of Plan A blocks was proposed by Turbitt et al. ${ }^{2}$ This list would include the most common blocks, with the purpose to encourage more anesthesiologists to perform techniques that satisfy most of their daily needs. Obviously, after a period of time and experience, skills are acquired, and this list can be expanded and adapted to suit the requirements of each individual setting.

Now it appears that we face a new obstacle: distributing these skills to every anesthesiologist. Equipping all anesthesiologists with the necessary knowledge is yet to be achieved, and ultrasound-guided regional anesthesia is still underutilized. Many professionals in Brazil are geographically isolated
from major educational centers and struggle to gain access to high-quality information. Due to the COVID-19 pandemic of recent years, online teaching has become a part of daily life in all fields. Using online education tools is now one of the most obvious methods to spread this knowledge to a wider audience.

Today, major academic societies, such as the Brazilian Society of Anesthesiology (SBA) and the European and American Societies of Regional Anesthesia (ESRA and ASRA), offer widely accessible webinars and articles. Nevertheless, social media platforms are one of the most popular sources of information today. To name a few, on YouTube, renowned authors such as Ki Jinn Chin, ${ }^{3}$ Jeff Gadsden, ${ }^{4}$ and others upload block demonstrations, entire lectures, and high-quality educational videos; on X (former Twitter), research authors share their scientific articles and opinions ${ }^{5}$ and on Instagram, videos, slides, and interviews are shared regularly. ${ }^{6}$ Social media can ultimately provide curated content and direct networking with world experts. There are also widely used apps, such as NYSORA's, and other types of online platforms that provide a diverse range of formats and content. The most important point is to recognize valid sources and use them anywhere and at any time, with no geographical or temporal restrictions.

Regional anesthesia is an area of expertise that also requires manual skills. Anatomical interpretation and image acquisition are essential, yet hand-eye coordination is important as well. Consequently, it is evident that we must establish a theoretical basis, but the ultimate degree of competence is practical. Using increasingly useful and accurate simulators, we can currently circumvent the geographical issue, at least partially, in the present day. ${ }^{7}$

Simulators can be used to practice and develop the necessary competencies with increasing similarity to reality and they are likely to become ubiquitous in the coming years. ${ }^{8}$ This is particularly important in remote areas where access to in-person education is challenging. ${ }^{9}$

Another useful tool is the use of handheld ultrasounds, which facilitates the path to learning, as one can view an online video or course and practice the imaging anywhere,
largely independent of hospital resources or even patient access. ${ }^{10}$

Future technologies and artificial intelligence (AI) will facilitate regional anesthesia instruction and daily practice, making the technique simpler. The simpler the technique, the simpler it will be to increase the number of anesthesiologists capable of performing it. Color overlay software, which applies a color overlay to real-time ultrasound that highlights important anatomical structures, will reduce the learning curve for a new technique. ${ }^{11}$ Eye-tracking software is an additional Al technology that establishes visual fixation patterns during a regional anesthesia procedure, thereby assessing differences in practitioner expertise. The objective is to measure performance that cannot only distinguish between levels of proficiency but also help identify patterns that may be crucial to the evolution of abilities. ${ }^{12}$ Other types of simulators utilizing virtual reality trainer software with high-resolution motion capture and ultrasound imagery to teach cognitive-motor needling skills are being developed, and the trend over the next few years is to make all these tools more accessible. ${ }^{13}$

One could consider if the technology and Al will ultimately replace anesthesiologists. This is not the appropriate prism. The human decision-making process and experience remain irreplaceable.

For instance, a study evaluating the use of a DaVinci robot for robotic-assisted ultrasound-guided regional anesthesia yielded unsatisfactory results in a real-world setting. ${ }^{14}$ A second example is the use of certain software that still requires human intervention to determine the optimal settings. Al is only as good as the software behind it, and the software is only as good as the person who is interpreting.

A short list of blocks that are useful in most clinical situations, as opposed to dozens of blocks that only experts will perform; online resources from societies and social media; and current and future technology can help more anesthesiologists have access to regional anesthesia, which will directly translate into improved patient care and safety. These tools do not replace quality training in residencies, but they do help enhance skills, particularly for non-experts. And, most importantly, they enable access to knowledge for those who reside in more remote areas or who lack access to high-quality in-person training.

It is time for all of us to embrace digital learning and technology, as they have come to stay.

## Disclosures

Sara Amaral is the co-founder of the online regional anesthesia teaching company Blocker Gir ${ }^{\circledR}$.

Amit Pawa is the founder of an online teaching channel on YouTube, consulting for Pacira, and honoraria for GE Healthcare for teaching.

## Conflicts of interest

The authors declare no conflicts of interest.

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EDITORIAL

# Opioid administration and rescue dose: exploring the effects of opioid combinations 

Opioids have been used as analgesics since the isolation of the morphine molecule in 1804 by German pharmacist Friedrich Serturner. ${ }^{1}$ The analgesic ladder proposed by the World Health Organization in 1986 provided the grounds for the routine use of opioids according to pain intensity and, since then, its use has been discussed for specific pain syndromes. ${ }^{2}$ Prescribers should be familiar with the time required for onset of effect, duration of action, time to reach plasmatic steady-state concentration, and equivalent doses of opioids, besides explaining the risks to patients. It is essential to inform patients about common adverse effects (nausea, vomiting, constipation, pruritus, sedation, dysphoria), overdose, drug interaction, tolerance, hyperalgesia, misuse, abuse, and neurotoxicity, as they may interfere with treatment adherence. ${ }^{3,4}$ When initiating opioid treatment, practitioners must also determine patient risk stratification for addiction and be aware of local health surveillance policies. ${ }^{5}$

Morphine is considered the gold standard among opioids, therefore it deserves special consideration from the physician who, by respecting basic concepts of pharmacology, facilitates the understanding of proper prescription recommendations for this valuable and safe analgesic. Morphine steady state is attained approximately five half-lives after administration and is associated with full analgesic effect and potential adverse effects for the dose administered. Since the half-life of morphine is approximately four hours, notwithstanding the administration route, a steady state is only achieved roughly 24 hours after the dose is administered. ${ }^{6}$ This concept is critical for all opioids, given that the acknowledgment of half-life is required for assessing clinical efficacy and, if needed, making dose adjustments. Assessment of the intensity of residual pain is used to titrate dose increments. For mild intensity pain, an increase of approximately $25 \%$ of the dose is recommended; $50 \%$ for moderate pain; while for severe pain up to $100 \%$. ${ }^{7,8}$

Opioid tablets are dispensed in two preparations: immediate release (fast) and controlled release (slow). Immedi-ate-release tablets allow faster drug absorption to the bloodstream, can be associated with high plasmatic
concentration peaks, and, consequently, present a higher incidence of adverse effects. ${ }^{9}$ Conversely, controlledrelease tablets have the advantage of offering an analgesic concentration below toxic for a prolonged time (8, 12, or even 24 hours), presenting a more convenient dosage. ${ }^{10}$

Controlled-release morphine is an interesting and convenient formulation for pain management. The analgesic effect of the controlled-released morphine formulation available in Brazil lasts 12 hours. To calculate the required dose, it is imperative to administer immediate-release morphine in advance. The total daily dose of immediate-release morphine is calculated and divided by two. For example, a patient using 10 mg of immediate-release morphine every 4 hours totals 60 mg for 24 hours. Thus, the required dose of controlled-release morphine is 30 mg every 12 hours. ${ }^{11}$

When controlled-release morphine is used, the prescription of a rescue dose is required when breakthrough pain occurs. Thus, a fast-release morphine dose is used to cover the analgesic requirement due to greater nociceptive stimulus (dressings, mobilizations) or due to spontaneous variation in the plasma concentration drug toward a level below the therapeutic range. In this case, $5 \%$ to $15 \%$ of the total daily scheduled dose of morphine is prescribed routinely using immediate-release morphine. This dose can be repeated up to every hour, given that the maximum analgesic concentration is reached 1 hour after oral administration of immediate-release morphine. In the previous example, the adequate rescue dose would be approximately 5 mg of morphine in case of pain, administered every hour. ${ }^{12}$

In Brazil, controlled or transdermal release formulations are the only preparations available for oxycodone, tapentadol, fentanyl, and buprenorphine, and no immediate-release formulation of these drugs is available to be administered as a rescue dose (morphine is the only short-duration potent opioid available in the Brazilian market). This fact raises questions about which drug would be the best choice for a rescue dose since the basic principle of pain management is not to associate drugs with the same mechanism of action. For a comprehensive discussion, it is necessary to
understand concepts of opioid pharmacodynamics for establishing the rescue dose in patients presenting breakthrough pain and on routine use of opioids other than morphine.

Opioids can be classified according to their efficacy and receptor affinity. Intrinsic activity or efficacy is the ability of a substance to activate its receptor and produce the expected pharmacological effect. Intrinsic activity ranges from zero to one. Affinity, in turn, defines the strength of opioid binding with its specific receptor (described as $\mu, \kappa$, and $\delta$ ). Agonist drugs have both the aforementioned properties and must effectively interact with their receptors to produce a drug-receptor complex capable of triggering a full response. Conversely, antagonist drugs block receptors, as they have high affinity and low or absent efficacy. ${ }^{13}$

According to the interaction of opioids with $\mu$ receptors (mainly responsible for their analgesic effects), they can be classified into agonists (tramadol, codeine, morphine, fentanyl, methadone, oxycodone, and tapentadol); antagonists (naloxone, naltrexone); partial agonists (buprenorphine); and agonist-antagonists (nalbuphine). Agonists that produce intrinsic activity equal to 1 are called full agonists, as binding to all receptors produces a maximum response. When a drug shows intrinsic activity equal to zero, it is termed an antagonist, as it does not produce any effect, regardless of the receptors being bound. Partial agonist and agonistantagonist drugs show intrinsic activity ranging between 0 and $1 .{ }^{14}$

Following opioid receptor stimulation, the cAMP system is activated via the inhibitory $G$ protein, with consequent inhibition of adenylate cyclase and reduction of neuronal impulse transmission. ${ }^{15}$ Alternatively, several G protein-coupled receptors (GPCRs) are able to form dimers by combining two or more GPCRs. ${ }^{16}$ The $\mu-\delta$ heterodimers induce changes in ligand-receptor properties, modify cAMP regulation and signaling, and promote changes in the induction of MAPK phosphorylation. ${ }^{17}$ Patients chronically using opioids have shown a high number of $\mu-\delta$ heterodimers, contributing to the activation of several intracellular signaling pathways and the development of tolerance. ${ }^{18}$

Opioid-receptor interaction is complex and also involves activation of another signal translation pathway in addition to the G protein, the $\beta$-arrestin pathway, possibly related to opioid adverse effects. Opioids may possibly trigger both the G-protein pathway and the $\beta$-arrestin pathway, emphasizing that the aim when prescribing an opioid is analgesia without the occurrence of adverse effects. ${ }^{19}$

Opioid receptors are also subject to desensitization, downregulation, and internalization, all adaptation processes in response to agonist chronic administration. These processes produce progressive loss of the signaling translation that follows opioid receptor activation, with variable onset and duration, depending on the agonist or signaling pathway. ${ }^{20}$

Based on these considerations, how can two opioids with distinct pharmacokinetic properties and similar pharmacodynamics be combined? How should a rescue dose be used to treat a patient with a drug other than morphine?

Although the administration of two or more drugs with different mechanisms of action is an exciting strategy to improve the effectiveness of analgesia and reduce adverse effects, the combination of drugs from the same pharmacological group is controversial. Combining two potent opioids
can improve analgesia, avoid fast dose escalation of one of the drugs, and reduce the incidence of tolerance and adverse effects. ${ }^{21}$ This may be related to the interaction among subpopulations of $\mu$ receptors and it prompts the use of combinations of transdermal fentanyl with morphine or methadone with morphine. ${ }^{22}$ Also, the combination of oxycodone with morphine or transdermal fentanyl is based on the premise that oxycodone acts on $\kappa$ receptors promoting upregulation of $\mu$ receptor expression, synergistically increasing the clinical efficacy of the opioid, since analgesia will occur through both activation of $\kappa$ and $\mu$ receptors. ${ }^{23}$ On the other hand, the combination buprenorphine-morphine presumes that buprenorphine, by antagonizing $\kappa$ receptors, facilitates the action of morphine on $\mu$ receptors. ${ }^{24}$ Additionally, tramadol, by acting on the descending inhibitory system, could reduce the need for an excessive increase in the dose of strong opioids. ${ }^{25}$

The assumption that the association of two strong opioids is beneficial for patients suffering from acute or chronic pain does not have, however, a high level of clinical evidence. The systematic search for publications comparing opioid monotherapy versus combined opioid therapy using observational studies or clinical trials with adequate methodology has been disappointing. Thus, combined opioid therapy has not yet been validated in the literature and perhaps may be considered by experienced practitioners in the future. Alternatively, using a combination of potent or atypical opioids only as rescue medication cannot be regarded as evidencebased, despite some publications ${ }^{26-28}$ presenting satisfactory results regarding safety and clinical efficacy, especially due to methodological biases present in previous studies.

By combining, for example, oxycodone with morphine rescue, we could observe the following scenario. A hypothetical patient with pancreatic cancer uses 120 mg of oxycodone a day. If 10 mg of morphine every hour is ordered as a rescue dose for breakthrough pain relief, when the patient consumes six rescue doses per day ( 60 mg of morphine), we will have a total of 120 mg of oxycodone and 40 mg of the equivalent dose of oxycodone (considering the equianalgesic dose of oral morphine for oxycodone to be 1.5 times lower), or a total consumption of 160 mg of oxycodone per day. Alternatively, if we were to use $10 \%$ of the total daily dose of oxycodone for rescue dose calculation, we would prescribe 12 mg of oxycodone as a rescue dose (for routine use of 120 mg a day of oxycodone). Thus, using six rescue doses, the patient would receive a daily rescue dose of 72 mg and a total daily dose of 192 mg of oxycodone. In other words, the result is incompatible no matter how small the difference.

In this scenario, given immediate-release oxycodone is unavailable in Brazil, we currently prescribe morphine. By ordering 10 mg of morphine as a rescue dose, we are already: 1. using a subdose of rescue medication (an adequate dose would be 18 mg , since 12 mg of oxycodone multiplied by 1.5 results in 18 mg of morphine); 2 . facilitating the likelihood of competition for the same $\mu$-type pharmacological receptor; 3. promoting action on preferred signal translation pathways (bias) and facilitating the occurrence of more adverse effects; 4. possibly triggering heterodimer receptors involved in tolerance or hyperalgesia; 5. facilitating the plasma concentration peak of more than one substance and its active metabolites; 6. interfering with the receptor desensitization process; 7. inducing uneven
hysteresis curves. All these statements must be considered and questioned based on the complexity of the pharmacokinetics and pharmacodynamics of different opioids.

Therefore, when dealing with dose adjustments of a con-trolled-release opioid in the absence of immediate-release formulations of the same opioid, using two different opioids may result in unsatisfactory analgesia. Until we have access to well-designed studies regarding the association of drugs with supposedly the same mechanism of action, we should preferentially use a drug from another pharmacological group as a rescue dose, and, if we are not successful, we should increase the dose of the controlled-release opioid. In the absence of another potent immediate-release opioid, morphine remains the current option for rescue doses. We can conclude that, by prescribing morphine as a rescue dose when another opioid is prescribed simultaneously, there is no guarantee we are offering the best medical practice, and based on the current knowledge described above, we are exposing patients to potential risks. It is also crucial to emphasize that the use of opioids with a long half-life or a controlled-released formulation as a rescue dose is strictly contraindicated.

## Conflicts of interest

The authors declare no conflicts of interest.

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Sociedade Brasileira de Anestesiologia

## ORIGINAL INVESTIGATION

# Supra-inguinal fascia iliaca block in older-old patients for hip fractures: a retrospective study 

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## KEYWORDS

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#### Abstract

Background: Pain management in hip fracture patients is of great importance for reducing postoperative morbidity and mortality. Multimodal techniques, including peripheral nerve blocks, are preferred for postoperative analgesia. Older-old hip fracture patients with high ASA scores are highly sensitive to the side effects of NSAIDs and opioids. Our aim was to investigate the effectiveness of the recently popularized Supra-Inguinal Fascia Iliaca Block (SIFIB) in this population. Methods: Forty-one ASA III-IV patients who underwent SIFIB + PCA (G-SIFIB) or PCA alone (Group Control: GC) after general anesthesia were evaluated retrospectively. In addition to 24 -hour opioid consumption, Visual Analog Scale (VAS) scores, opioid-related side effects, block-related complications, and length of hospital stay were compared. Results: Twenty-two patients in G-SIFIB and 19 patients in GC were evaluated. The postoperative 24 -hour opioid consumption was lower in G-SIFIB than in GC ( $p<0.001$ ). There was a statistically significant reduction in VAS scores at the postoperative $1^{\text {st }}, 3^{\text {rd }}$, and $6^{\text {th }}$ hours at rest ( $p<0.001$ ) and during movement ( $p<0.001$ for the $1^{\text {st }}$ and $3^{\text {rd }}$ hours, and $p=0.02$ for the $6^{\text {th }}$ hour) in G-SIFIB compared to GC. There was no difference in pain scores at the $12^{\text {th }}$ and $24^{\text {th }}$ hours postoperatively. While there was no difference between the groups in terms of other side effects, respiratory depression was significantly higher in GC than in G-SIFIB ( $p=0.01$ ) , Conclusion: The SIFIB technique has a significant opioid-sparing effect and thus reduces opioidrelated side effects in the first 24 hours after hip fracture surgery in older-old patients. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


[^1]
## Introduction

Hip fracture is a serious problem affecting the elderly population due to osteoporosis. With the increasing life span of individuals, the frequency of this condition is increas-
ing, and it is an important socioeconomic problem globally. ${ }^{1}$ The elderly population can be chronologically categorized as "younger-old"' (aged 65 to 80 years) and "older-old"' (aged more than 80 years). The risk of hip fracture in the older-old group is 15 times higher than that in younger-old patients. ${ }^{2}$ Mortality and morbidity are higher among patients with hip fractures and older-old patients have worse outcomes and more in-hospital complications than younger-old patients. ${ }^{3,4}$

Early surgery can reduce postoperative complications and mortality by mobilizing the patient. ${ }^{5,6}$ In patients with hip fractures, effective pain management in addition to early surgery can positively affect the results. Effective pain management can prevent various undesired complications, such as impaired cognitive functions and delirium, and provides early mobilization, rehabilitation of the extremity and a more rapid recovery. It has been reported that the risk of developing delirium is nine times higher among hip fracture patients in whom adequate pain management cannot be achieved. ${ }^{7}$

Combined multimodal methods, in which opioids, paracetamol, NSAIDs, and peripheral regional anesthesia techniques are used, are preferred in postoperative pain management of hip fractures. However, pain management in geriatric patients is complicated by comorbidities, changed pharmacodynamics, and physiological changes in end-organ functions. ${ }^{8}$ Due to renal toxicity, coagulation disorders, and gastrointestinal side effects, NSAIDs are not preferred in geriatric patients. Opioids do not reduce dynamic pain and have side effects such as respiratory depression, sedation, nausea, and vomiting. Therefore, peripheral regional methods performed by ultrasonography (USG) can be employed to reduce the required opioid dose.

Fascia lliaca Block (FIB), which is widely used for postoperative analgesia in hip surgery, is a nerve block technique with proven efficacy. Hebbard et al. performed this block over the inguinal ligament and thus created a new technique: Supra-Inguinal Fascia Iliaca Block (SIFIB). ${ }^{9}$ Additional studies have revealed that this block is more effective than the classical (infra-inguinal) fascia iliaca block. ${ }^{10}$

Although the use of SIFIB in hip surgery has recently increased, to the best of our knowledge, patients with an advanced age with high ASA (American Society of Anesthesiologists) physical status scores have not been studied. In this retrospective study, our aim was to investigate the effectiveness of SIFIB in older-old patients.

## Methods

This retrospective study was approved by the Institutional Review Board of Baskent University (Project no: KA 21/29) and was funded by the Baskent University Research Fund. Patients who underwent surgery and were followed up due to femur fracture at Baskent University Adana Dr. Turgut Noyan Practice and Research Center between January 2019 and January 2021 were included in this study. Information regarding the patients was retrieved from the preoperative and intraoperative anesthesia record forms, patient files and the NUCLEUS electronic medical information system (Monad Software, Ankara, Turkey). Data collection and analysis were performed between January and February 2021.

Patients over 80 years of age with ASA physical status III and IV who refused other types of anesthesia or had a contraindication for neuroaxial anesthesia underwent general anesthesia for femoral nail surgery due to hip fractures (pertrochanteric femur fracture) were evaluated retrospectively. In our clinic, if patients receive general anesthesia, a nerve block is usually performed as part of analgesia. Patients who refused a nerve block were selected to the control group. Patients who had chronic pain for any reason and had chronic opioid use, patients who had undergone neuraxial anesthesia, had liver and kidney failure, had a $\mathrm{BMI}>35$, patients with multiple fractures, patients who were allergic to the drugs used in this study, and those who had dementia or other cognitive problems were excluded.

After the patients were taken to the operating room, standard anesthesia monitoring was performed with electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring. Anesthesia was induced with propofol ( 0.5 to $2 \mathrm{mg} . \mathrm{kg}^{-1}$ ) or thiopental sodium ( 2 to $5 \mathrm{mg} . \mathrm{kg}^{-1}$ ), rocuronium bromide ( $0.5 \mathrm{mg} . \mathrm{kg}^{-1}$ ), and fentanyl ( 0.5 to 1 $\mathrm{mcg} . \mathrm{kg}^{-1}$ ). Sevoflurane at $1 \%$ to $2 \%$ concentration in a $50 \%$ $\mathrm{N}_{2} \mathrm{O} / \mathrm{O}_{2}$ mixture was used for maintenance. We classified the patients into groups according to the presence of SIFIB due to refusal or acceptance of the nerve block. After endotracheal intubation, among the patients who planned to undergo SIFIB, the anterior superior iliac spine was identified by a high-frequency linear probe (SonoSite SLAx [6-13 MHz]; FUJIFILM Sonosite, Inc., Bothell, WA, USA) over the inguinal ligament in the parasagittal plane, following appropriate disinfection and draping of the patient in the supine position. Then, the probe was moved medially, and the internal oblique muscle in the cranial direction, the sartorius muscle in the caudal direction, the bow-tie shape formed by these muscles, the underlying iliacus muscle, and the fascia iliaca surrounding it were visualized. ${ }^{11}$ An $80-\mathrm{mm}$ peripheral nerve block needle was inserted from the caudal side, and the iliac fascia was passed. After identification of the correct area following 2 to 3 mL of hydrodissection, 40 mL of $0.25 \%$ bupivacaine was injected. The surgery was completed, and 1 g of paracetamol was administered intravenously to all patients during the closure phase. The neuromuscular block was antagonized with $0.05 \mathrm{mg} . \mathrm{kg}^{-1}$ neostigmine and $0.015 \mathrm{mg} . \mathrm{kg}^{-1}$ atropine, and the patients were extubated.

Patients were observed for 1 hour in the Postanesthesia Care Unit (PACU) and evaluated using a visual analog scale (VAS, $0=$ no pain, $10=$ worst pain) before being transferred to the ward. Patients were instructed in the use of the VAS scale and PCA (patient-controlled analgesia) device before the surgery. Fentanyl ( 10 mcg ) was administered to the patients with a VAS score $>4$. Fentanyl PCA was administered to all patients (no background infusion, $0.2 \mathrm{mcg} . \mathrm{kg}^{-1}$ bolus dose, $10-\mathrm{min}$ lockout interval, $4 \mathrm{mcg} . \mathrm{kg}^{-1} 4$-hour limit dose). When the patients' pain could not be controlled with the PCA under ward conditions, 50 mg of intravenous tramadol was used as an additional analgesic. The total opioid consumption was calculated by adding the equivalent dose of tramadol ${ }^{12}$ (tramadol $50 \mathrm{mg}=$ fentany 50 mcg ) that was used as an additional analgesic to the value obtained from the PCA administration of fentanyl.

In addition to the demographic data of the patients, postoperative 24 -hour fentanyl consumption, which is the primary outcome of this study, and the VAS scores at rest and


Figure 1 Study flow chart.
during movement at the $1^{\text {st }}, 3^{\text {rd }}, 6^{\text {th }}, 12^{\text {th }}$ and $24^{\text {th }}$ hours, as secondary outcomes, were recorded. Data were collected by our anesthesia technicians out of the study team. If the patient's record was missing data essential for the study, those patients were excluded from the data analysis.

In addition, the duration of surgery, analgesic methodrelated nausea-vomiting (absence/presence within 24 hours following the procedure), pruritus (acute itching after opioid administration without skin lesions), respiratory depression (defined as $\mathrm{SpO}_{2}<90$ when the patients were breathing room air), urinary retention (sudden inability to micturate during the study period), hematoma at the injection site for the nerve block, length of hospital stay, and adverse effects such as infection and systemic local anesthetic toxicity, were also investigated.

## Statistical analyses

SPSS 26.0 (SPSS Inc., IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM

Corp) was used for statistical analysis. Categorical variables are shown as numbers, whereas numerical variables are shown as the mean and standard deviation (as median and minimum-maximum when required). The Chi-Square test was used for a comparison of the categorical variables between groups. When comparing numerical variables between groups, normality was assessed. If the data did not have a normal distribution, the Mann-Whitney $U$ test was used; otherwise, Student's $t$-test was used; $p$-values less than 0.05 were considered significant.

## Results

Ninety-four patients over 80 years of age who underwent surgery due to pertrochanteric femur fracture were evaluated retrospectively. A total of four patients (one in the SIFIB group and three in the control group) had to be excluded from the study due to delirium in the PACU. Eventually, 53 patients were excluded from the study. Twenty-two patients in the SIFIB group and 19 patients in the control group were

Table 1 Demographic variables of the patients.

|  | Supra-inguinal fascia <br> iliaca block Group <br> $(\mathrm{n}=22)$ | Control Group $(\mathrm{n}=19)$ | $p$ |
| :--- | :--- | :--- | :--- |
| Age (years) | $85.31 \pm 4.53$ | $86.10 \pm 3.60$ | 0.48 |
| ASA (III/IV), n | $15 / 7$ | $13 / 6$ | 0.98 |
| Weight, mean $\pm$ SD (kg) | $72.54 \pm 13.41$ | $72.47 \pm 9.29$ | 0.32 |
| Height, mean $\pm$ SD $(\mathrm{cm})$ | $163.77 \pm 8.40$ | $165.63 \pm 7.02$ | 0.50 |
| Comorbidities, n |  | 12 | 0.05 |
| $\quad$ Diabetes mellitus | 12 | 17 |  |
| Cardiac disease | 20 | 8 |  |
| Lung disease | 5 | 7 | 0.79 |
| Kidney disease | 9 | 3 | 0.39 |
| Cerebrovascular event | 5 | $81.05 \pm 16.88$ | 0.83 |
| Sex (F/M), n | $13 / 9$ | $5(2-7)$ |  |
| Duration of surgery, mean $\pm$ SD (min) | $75.45 \pm 19.45$ |  |  |
| Length of hospital stay, median (range)(days) | $5(2-7)$ |  |  |

finally evaluated (Fig. 1). The patients' demographic data, comorbidities, duration of surgeries, and length of hospital stay were similar (Table 1).

An additional analgesic was used once each in two patients in the control group. The total postoperative 24hour opioid consumption was found to be significantly lower in the SIBIF group than in the control group ( $74.54 \pm 21.09 \mathrm{mg}$ vs. $155.78 \pm 33.55 \mathrm{mg} ; p<0.001$ ) (Fig. 2).

In the evaluation of the VAS scores at rest, a significant reduction was observed at the $1^{\text {st }}, 3^{\text {rd }}$, and $6^{\text {th }}$ postoperative hours in the SIFIB group in comparison to the control group ( $p<0.001$ ) (Fig. 3). No significant reduction was observed at the $12^{\text {th }}$ and $24^{\text {th }}$ hours postoperatively.

In the evaluation of the VAS scores during movement, a significant reduction was detected at the $1^{\text {st }}, 3^{\text {rd }}$, and $6^{\text {th }}$ postoperative hours in the SIFIB group in comparison to the control group ( $p<0.001$ for the $1^{\text {st }}$ and $3^{\text {rd }}$ hours, $p=0.02$ for the $6^{\text {th }}$ hour) (Fig. 4). There was no significant reduction in the pain scores at the $12^{\text {th }}$ and $24^{\text {th }}$ hours postoperatively.

Regarding the side effects related to opioid use, there was no difference between the groups in terms of nauseavomiting, pruritus, or urinary retention $(p>0.05)$ (Table 2). There was a significant difference between the groups in terms of respiratory depression. While no respiratory depression was observed in any patient in the SIFIB group, five patients required oxygen support due to respiratory depression in the control group ( $p=0.01$ ) (Table 2).

No complications, such as systemic local anesthetic toxicity, infection, or hematoma at the injection site related to the nerve block were observed in any of the patients.

## Discussion

We found that the application of SIFIB in patients over the age of 80 years with pertrochanteric femur fracture had reduced opioid consumption in the first 24 hours by $48 \%$ compared to patients who were given PCA alone. In addition, we found that the VAS scores at rest and during movement during the first six hours postoperatively were significantly lower in the SIFIB group than in the control group.

Postoperative pain and loss of function due to pain significantly affect clinical outcomes, complications, and mortality. This is of greater importance in older-old patients. In the guidelines published by the National Institute for Health Clinical Excellence for hip fracture, paracetamol administration every six hours, opioid administration if the patient's condition is suitable, and peripheral nerve block in the presence of trained staff is recommended. However, the use of NSAIDs is not recommended. ${ }^{13}$ Similarly, FIB is recommended as a part of multimodal analgesia within the ERAS (enhanced recovery after surgery) protocol in hip fracture patients. ${ }^{14}$

Peripheral nerve blocks alleviate postoperative pain by providing analgesia specific to the operation site and preventing complications and limitations created by central neuraxial blocks. Peripheral nerve blocks can be used as a part of light general anesthesia in cases of anticoagulant use where central neuraxial blocks are contraindicated and in cases where severe hypotension caused by a spinal block could create problems in very old patients with a high ASA physical status score. Nerve blocks can also reduce the need for opioids without causing hemodynamic instability. ${ }^{15}$

Fascia iliaca block is an effective and safe block used in pain management after hip and femur fracture surgery. ${ }^{8}$ This easily applicable technique can be considered an anterior approach to the lumbar plexus. SIFIB has a lower risk of nerve damage than the classical infra-inguinal method due to its distance from the femoral nerve. In addition, the close course of the nerves in the fascial plane over the inguinal ligament makes the block more effective when performed supra-inguinally. ${ }^{9}$ In our study, we applied the longitudinal supra-inguinal method used by Desmet et al. ${ }^{11}$ and, consistent with their findings, observed a $48 \%$ reduction in opioid consumption within the first 24 hours. While Desmet et al. reported a significant reduction in VAS scores within the first 4 postoperative hours using a 40 mL dose of $0.5 \%$ ropivacaine, we achieved a significant reduction in VAS scores within the first 6 hours using a $40-\mathrm{mL}$ dose of $0.25 \%$ bupivacaine in our study. This difference can be explained by the fact that the mean age of the patients in Desmet et al.'s study was 60 years, whereas the average age of the


Figure 2 Opioid consumption (mgr) within 24 hours ( ${ }^{*} p<0.001$ ).


Figure 3 Postoperative pain scores at rest at various time points. Data are expressed as means. VAS, Visual Analogue Scale (* $p<0.001$ ).


Figure 4 Postoperative pain scores with movement at various time points. Data are expressed as means.VAS, Visual Analogue Scale ( ${ }^{*} p<0.001, B p=0.02$ ).
patients in our study was 85 . With increasing age, loss of myelin in neural tissues and loss of mucopolysaccharide in perineural tissues changes the response of peripheral nerves to local anesthetics, causing greater exposure of neural tissue to local anesthesia. ${ }^{16}$ This may be the reason for the longer sensory block time and lower VAS scores in our study.

Although the VAS scores both at rest and during movement up to the $6^{\text {th }}$ hour in our study were significantly lower than those of the control group, the dynamic pain scores started to increase as the nerve block started to lose its effect at the $6^{\text {th }}$ hour, and VAS scores at the $12^{\text {th }}$ and $24^{\text {th }}$ hours were similar between the groups due to higher fentanyl consump-

Table 2 Comparison of the opioid-related side effects between the groups.

|  | Supra-inguinal fascia <br> iliaca block Group <br> $(\mathrm{n}=22)$ | Control Group $(\mathrm{n}=19)$ | $p^{\mathrm{a}}$ |
| :--- | :--- | :--- | :--- |
| Nausea/vomiting | 3 | 5 | 0.31 |
| Respiratory depression | 0 | 5 | 0.01 |
| Urinary retention | 1 | 2 | 0.46 |
| Pruritus | 1 | 3 | 0.23 |

a Significant $p$-values are written in bold.
tion in the control group. Desmet et al. reported that when the block was performed longitudinally and supra-inguinally, the obturator nerve, which has an important role in hip and femur innervation, was involved more frequently, thus increasing the success of the block. ${ }^{11}$

There are other studies in the literature showing that SIFIB, in line with our results, reduces opioid consumption. Kumar et al. compared SIFIB to the classical infra-inguinal technique in hip fractures and found a significant decrease in VAS scores in the first 6 hours in the supra-inguinal block group. ${ }^{10}$ The authors also reported that VAS scores were similar at the $12^{\text {th }}$ and $24^{\text {th }}$ hours and that total opioid consumption was much lower in the supra-inguinal fascia iliaca group. In another hip surgery study in which the control group was compared with the SIFIB group, both VAS scores and opioid consumption within the first 48 hours were found to be significantly lower in the fascia block group. ${ }^{17}$ In addition, the authors concluded that SIFIB accelerated recovery from general anesthesia by reducing the extubation time and the time spent in the PACU. The authors also commented that SIFIB combined with general anesthesia might be more appropriate as an anesthetic method in geriatric patients with a poor basal status. In contrast, in Shariat et al.'s study, the researchers performed FIB for hip surgery, and there was no difference in the 24 -hour opioid consumption and pain intensity in comparison to the sham group. ${ }^{18}$ However, in that study, the authors used a 30 mL dose of $0.5 \%$ ropivacaine, and the infra-inguinal technique was employed in the transverse plane. Performing the block in the transverse plane may have limited the cranial spread of the local anesthetic, and 30 mL of local anesthetic solution may have been insufficient. This study showed that infra-inguinal FIB performed in the transverse plane is not a favorable method.

In another study comparing SIFIB with periarticular infiltration, VAS scores, postoperative opioid need, and discharge times were found to be similar. ${ }^{19}$ However, in that study, a 60 mL dose of $0.5 \%$ ropivacaine was used. Although this volume was considered safe by the authors, Local Anesthetic Systemic Toxicity (LAST) is a serious complication that should be kept in mind during peripheral nerve block applications. In geriatric patients specifically, due to their decreased pharmacodynamics and organ functions, the clearance rate of local anesthetics decreases, and the risk of drug accumulation increases at higher doses. Therefore, the geriatric patient population is a very sensitive group in terms of LAST. ${ }^{20}$ Helayel et al. reported that the average local anesthetic volume required to create a sufficient FIB was $36 \mathrm{~mL} .{ }^{21}$ Since FIB is a compartment block that does not directly target the nerves and since our patients
were "older-old", we used 40 mL of local anesthetic at a concentration of $0.25 \%$, as has been used in many studies. In addition, real-time USG guidance increased the success of the block by ensuring the proximal spread of the local anesthetic, reducing the application time of the block, and preventing undesired vascular punctures.

In another study, in which the SIFIB applied for postoperative analgesia in hip surgery was compared with lumbar plexus block, no difference was found between the two groups in terms of cumulative morphine consumption, VAS scores or side effects. ${ }^{22}$ However, a more intense sensory block and a shorter length of hospital stay were achieved with SIFIB. In our study, there was no significant difference between the two groups regarding the length of hospital stay. This may be due to our patients' age and high ASA physical status scores. Consistent with the findings of our study, Kastanis et al. investigated the effect of the ASA physical status in hip fracture patients and reported that ASA III and IV patients received longer periods of medical care, and therefore, their length of hospital stay increased proportionally. ${ }^{23}$

Nausea-vomiting, sedation, urinary retention, pruritus, and respiratory depression are common side effects associated with opioid use. In our study, while there was no difference between the groups in terms of nausea-vomiting, urinary retention, or pruritus, five patients in the control group had respiratory depression that responded to oxygen using a face mask. We believe that this situation is related to the advanced age of our patients. Although low anesthetic drug doses were used in our study, it was based on intubated patients in terms of anesthesia techniques. However, hip fractures performed with deep sedation plus a fascia iliaca block without any airway intervention have also been reported in the literature. ${ }^{24}$

Our study had some limitations. The retrospective design of our study, the small number of patients, the fact that patient satisfaction was not evaluated, and the lack of evaluation of the motor and sensory innervation area of each nerve we thought could be affected by the fascia iliaca block are major drawbacks. Due to small sample size, multivariable regression analyses or other advanced statistical analyses could not be performed to determine the potential confounders and effect modifiers. This may also be addressed as bias since we accepted all performed SIFIBs as successful from the start, and patients in the SIFIB group may have stated more positive data about their VAS scores to please their physicians. Although we did not find a difference between the two groups regarding the length of hospital stay, prospective studies with a large number of
patients may reveal an effect of the block on the length of hospital stay and hospital costs. In addition, although we performed a single-dose block, the effect of continuous infusion techniques with catheters on early mobilization and on joint rehabilitation and limb function in the long term should be a subject of future studies.

## Conclusions

In conclusion, the SIFIB technique has a significant opioidsparing effect and thus reduces opioid-related side effects in the first 24 hours after hip fracture surgery in older-old patients. This technique may also be an important part of multimodal analgesia in patients with high ASA scores where opioid avoidance is especially important.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j. bjane.2021.08.008.

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Sociedade Brasileira de Anestesiologia

## ORIGINAL INVESTIGATION

# Efficacy of ultrasound-guided infiltration with levobupivacaine and triamcinolone for myofascial pain syndrome of the quadratus lumborum: a retrospective observational study 

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## KEYWORDS

Local anesthesia; Backache;
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#### Abstract

Introduction and objectives: Myofascial Pain Syndrome (MPS) of the Quadratus Lumborum muscle (QL) is a frequent cause of chronic low back pain. With this study, we aimed to assess the efficacy of ultrasound-guided infiltration with $0.25 \%$ levobupivacaine and 40 mg triamcinolone for MPS of the QL. Methods: Observational and retrospective study of participants submitted to ultrasound-guided infiltration of the QL muscle from January 1, 2015 to June 31, 2019. Pain intensity was assessed using the five-point pain Numeric Rating Scale (NRS): pre-intervention, at 72 hours, 1 month, 3 months and 6 months post-intervention. Additional data collected were demographic characteristics, opioid consumption, and adverse effects. Results: We assessed 90 participants with mean age of 55.2 years. Sixty-eight percent of participants were female. Compared to the pre-intervention assessment, there was an improvement in pain at 72 hours (Mean Difference [MD $=3.085$ ]; 95\% CI: 2.200-3.970, $p<0.05$ ), at the 1st month ( $M D=2.644 ; 95 \% \mathrm{CI}: 1.667-3.621, p<0.05$ ), at the $3^{\text {rd }}$ month ( $M D=2.017 ; 95 \% \mathrm{CI}$ : $0.202-2.729, p<0.05$ ) and at the $6^{\text {th }}$ month (MD $=1.339$; 95\% CI $0.378-2.300, p<0.05$ ), postintervention. No statistically significant differences in opioid consumption were observed. No adverse effects associated with the technique were reported. Conclusions: Ultrasound-guided infiltration of the QL muscle is a safe and effective procedure for the treatment of pain in the QL MPS within 6 months post-intervention. © 2021 Published by Elsevier Editora Ltda. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/ licenses/by-nc-nd/4.0/).


[^2]
## Introduction

Chronic low back pain is one of the main causes of work absenteeism, incapacity for work and early retirement in developed countries, being responsible for an increase in health service utilization. ${ }^{1,2}$ It is estimated that, in up to $80 \%$ of cases, Myofascial Pain Syndrome (MPS) is the cause of chronic low back pain and frequently its diagnosis is not established. ${ }^{3,4}$ MPS is defined as subacute or chronic pain, with autonomic, sensory and motor symptoms, generated from active Trigger Points (TrPs). TrPs are firm and highly irritable muscle spots, located in a tight muscle band, that under external pressure elicit a painful response. ${ }^{5}$ MPS originated at the QuadratL Muscle (QL) is a common cause of chronic low back pain and frequently observed in Chronic Pain Units (CPU). The QL is a posterior abdominal wall muscle that inserts inferiorly in the posteromedial iliac crest and superiorly in the inner border of the twelfth rib, as well as in the transverse processes of the four lumbar vertebrae. ${ }^{6}$ The diagnosis of MPS of the QL is essentially clinical, based on careful history taking and physical examination. The pain is usually described as deep and persistent, and it can be sharp upon movement. Some patients describe irradiation to the groin. The greater trochanter can become sensitive to pressure in such a way that the patient cannot tolerate lying on the ipsilateral side. Thus, actions such as turning, getting out of bed, standing, and walking are described as very painful. Pain is elicited whenever TrPs are stimulated by pressure, heat, cold, or movements that stretch the structure that contains the TrPs. Palpation of the TrPs will mimic or accentuate the pain described by the patient, causing them to withdraw in a reaction known as jump sign. ${ }^{7}$

Currently, there are several therapeutic strategies comprising non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, antidepressants, and muscle relaxants. Non-pharmacological strategies have also been used, such as physical exercise and physical therapy. More invasive treatment, for instance infiltration of the muscles involved, is recommended when the above-mentioned strategies fail. Infiltrations with local anesthetics and corticoids have been described as effective for MPS treatment and have been increasingly used in chronic pain clinics. A synergistic action has been suggested between the two drugs. ${ }^{6}$ Corticoids are supposed to selectively block the transmission of nociceptive fibers, and local anesthetics relax the TrPs and interrupt the cycle of pain and contracture. ${ }^{8}$ Several techniques are used to increase the safety and accuracy of the infiltration, comprising the use of fluoroscopy, CT scan, and ultrasound. ${ }^{6}$ Recently, ultrasound has gained a prominent role as it is a noninvasive, not expensive, and effective technique. ${ }^{9}$ However, there is not enough evidence supporting its broad recommendation due to the small number of participants and the quality of the studies published on ultrasoundguided Infiltration in the Quadratus Lumborum muscle (IQL) for patients presenting quadratus lumborum myofascial pain syndrome.

The primary objective of the study was to evaluate the efficacy and safety of triamcinolone and levobupivacaine in IQL.

## Methods

## Study design and participant selection

The study was observational, retrospective, and analytical. We selected patients seen at a Multidisciplinary Chronic Pain Unit for about 4 years (from January 1, 2015 to June 31, 2019), submitted to ultrasound-guided infiltration of the QL muscle for the management of myofascial pain refractory to conservative treatment. Each year, this unit performs roughly 130 invasive procedures, guided either by ultrasound, fluoroscopy, or CT scan.

The pain Numeric Rating Scale (NRS) was initially obtained. The diagnosis of QL MPS was established according to the concomitant presence of four of the following clinical criteria: pain on palpation below the $12^{\text {th }}$ rib and 5 cm lateral to the transverse process of L1, with pain referred to the iliac crest; pain on palpation of TrPs in the quadratus lumborum muscle; low back pain when walking, sitting and squatting; pain exacerbation during posture change while lying down; lower back pain associated with muscle stretching; pain on palpation of TrPs located at the level of the L4 vertebral body, 1 to 2 cm above the iliac crest, with pain referred to the greater trochanter. ${ }^{10}$

Patients submitted to simultaneous injections at different sites were excluded, with a total of 90 participants included.

Participants were assessed at several moments: preintervention, at 72 hours post-intervention by telephone contact, and by evaluation of the records of the clinical process and telephone contact at the first, third- and sixthmonth post-intervention.

## Procedure protocol

The procedure was carried out after antisepsis and under sterile conditions. The technique was performed only by two anesthesiologists following the same protocol. With the participant in lateral decubitus a low-frequency curvilinear probe was placed parallel to the iliac crest, in the midaxillary line, and oriented posteriorly to obtain the Lateral Interfascial Triangle (LIFT) image. Using an in-plane approach, a 22 G needle was oriented in the lateralmedial and posterior-anterior directions targeting the region between the erector spinae muscle and the posterior surface of the QL muscle (Fig. 1). Appropriate needle location was confirmed by hydro dissection with 2 to 3 mL of saline. A bolus injection of 40 mg triamcinolone diluted in 9 mL of $0.25 \%$ levobupivacaine was given, with 3 mL deposited intramuscular and 7 mL for the infiltration in the intermediate layer of the Thoracolumbar Fascia (TLF) adjacent to LIFT.

## Data collection

Data was collected from patient charts, regarding age, gender, marital status, occupation, incapacity for work, previous spinal surgery, psychiatric pathology, fibromyalgia, pain in other locations, previous physical therapy, prescribed


Figure 1 Ultrasound imaging of the quadratus lumbar muscle infiltration. (1) Intermediate layer of thoracolumbar fascia (posterior fascia quadratus lumbar muscle); (2) Intramuscular infiltration of the quadratus lumbar muscle.
analgesic drugs, pain characteristics, pain intensity assessed by NRS, complications and adverse effects resulting from the technique performed.

## Bias

The main existing bias was information bias since the study has a retrospective design that is highly dependent on data acquired from the medical charts of participants.

## Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences ${ }^{\circledR} 23$ program (SPSS ${ }^{\circledR}$ Inc., Chicago, IL, USA). A p < 0.05 value, corrected by Bonferroni when indicated, was considered statistically significant. Data were depicted as absolute (n), relative (\%), mean (standard deviation) or median (minimum and maximum values), when applicable. The normality of the data was verified by the Kolmogorov-Smirnov test. As pain intensity data represented by the NRS scores had a normal distribution during the various moments of assessment, parametric tests were used and the ANOVA test for repeated measures was applied. The model was adjusted to covariates that could interfere with NRS scores, so a mixed model for repeated measures was used to verify differences in NRS scores, using the number of drugs taken, psychiatric disorder and opioid consumption as factors. We used the Cochran's Q test, followed by three McNemar's tests with Bonferroni correction to compare opioid consumption between the three moments of evaluation, as the variables were qualitative dichotomous.

## Ethics committee and informed consent

The study was approved by the Ethics Committee for Health of the institution where the study was carried out. Informed consent was obtained from all participants. Anonymity and confidentiality of all participants were safeguarded by all authors.

## Conflicts of interest

The study was carried out with no commercial or monetary associated conflicts of interest.

## Results

The study included 90 participants with a mean age of 55.2 years, and 61 participants ( $68 \%$ ) were female. The social characteristics and medical history of the participants are shown in Table 1. Due to absence of records, NRS data was obtained only from 77. 78 and 71 participants, respectively, at 72 hours and first, third-, and sixth-month post-intervention.

Compared to the initial assessment, there was an improvement in the mean pain intensity, especially at 72 hours post-IQL (Table 2). Nevertheless, after performing the IQL we observed statistically significant improvement in pain 72 hours (MD = 3.085; 95\% CI 2.200-3.970, $p<0.05$ ), 1 month (MD $=2.644 ; 95 \% \mathrm{Cl} 1.667-3.621, p<0.05)$, 3 months (MD = 2.017; 95\% Cl 1.120-2.914, $p<0.05$ ) and 6 months (MD = 1.339; 95\% Cl 0.378-2.300, $p<0.05$ ). Table 3 describes the differences registered between the other moments of the study. Reduction $\geq 30 \%$ for NRS was observed in $55.8 \%$, $48.7 \%$ and $36.6 \%$ of participants in the first, third and sixth

Table 1 Sociodemographic and medical history of participants undergoing IQL.

|  | $\mathrm{n}=90(\%)$ |
| :--- | :---: |
| Gender |  |
| Female | $61(67.8 \%)$ |
| Male | $29(32.2 \%)$ |
| Profession |  |
| Specialists in intellectual and scientific professions | $2(2.2 \%)$ |
| Sales and services workers | $4(4.4 \%)$ |
| Farmers and skilled workers in agriculture and fishery | $5(5.6 \%)$ |
| Workers, craftsmen, and similar jobs | $16(17.8 \%)$ |
| Plant and machine operators and line assembly workers | $9(10 \%)$ |
| Non-qualified workers | $17(18.9 \%)$ |
| Retired | $16(17.8 \%)$ |
| Unemployed | $8(8.9 \%)$ |
| Unknown | $13(14.4 \%)$ |
| Retirement due to incapacity | $12(13.3 \%)$ |
| Presenting a CIT at the day of the procedure | $14(15.6 \%)$ |
| Presenting a CIT 6 months after procedure | $7(9.7 \%)$ |
| Past lumbar spinal surgery | $33(36.7 \%)$ |
| Other specialties follow-up | $25(27.8 \%)$ |
| Orthopedic | $38(42.2 \%)$ |
| Neurosurgery | $11(12.2 \%)$ |
| Orthopedic and neurosurgery | $33(36.7 \%)$ |
| Past lumbar spinal surgery |  |
| Pain characteristics | $24(26.7 \%)$ |
| Nociceptive | $66(73.3 \%)$ |
| Mix | $42(46.7 \%)$ |
| Presence of pain in other sites | $2(2.2 \%)$ |
| Fibromyalgia | $33(36.7 \%)$ |
| Psychiatric disorder | $39(43.3 \%)$ |
| Physical therapy before procedure | $13(33.3 \%)$ |
| Medications being taken at the day of the procedure | $44(48.9 \%)$ |
| Antidepressants | $56(62.2 \%)$ |
| Anticonvulsants | $81(90.0 \%)$ |
| Myorelaxants | $34(37.8 \%)$ |
| NSAlDs | $16(17.8 \%)$ |

IQL, Ultrasound Guided infiltrations in quadratus Lumbar for myofascial pain syndrome; CIT, Certificate of Temporary Disability; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

Table 2 Pain intensity over the various moments of assessment.

| NRS before <br> $(\mathrm{n}=90)$ <br> Mean (DP) | NRS 72 h <br> $(\mathrm{n}=77)$ | NRS 1 month <br> $(\mathrm{n}=77)$ <br> Mean (DP) | NRS 3 months <br> $(\mathrm{n}=78)$ | NRS 6 months <br> $(\mathrm{n}=71)$ |
| :---: | :---: | :---: | :---: | :---: |
| $6.600(0.1848)$ | $3.69(0.278)$ | $4.23(0.295)$ | $4.65(0.299)$ | Mean (DP) |

NRS, Numerical Rating Scale; SD, Standard Deviation.
month (Table 4). After controlling for number of medications being taken, presence of psychiatric disorder, and consumption of opioids, we registered a statistically significant improvement for NRS scores at 72 hours (MD $=3.294$; 95\% CI 1.520-5.067, $p<0.05$ ), 1 month (MD = 3.090; 95\% Cl 1.234-4.946, $p<0.05$ ), 3 months (MD = 2.832; 95\% Cl 1.191-4.472, $p<0.05$ ) and 6 months (MD $=3.111$; $95 \% \mathrm{Cl}$ $1.376-4.845, p<0.05$ ) compared to the initial NRS score (Table 5).

Regarding treatment, we observed that 43.3\% of participants underwent physical therapy prior to the technique, of which $33.3 \%$ reported pain improvement. At the time of the procedure, opioid was the drug class most used by the participants (90.0\%), followed by anticonvulsants (62.2\%) and antidepressants (48.9\%) (Table 1). It is noteworthy that $36.7 \%$ of participants had a concomitant psychiatric disorder. At the first and third months after the technique, despite an apparent decrease in opioid consumption the difference was

Table 3 Comparison of NRS between different moments.

|  | MD | $p$-value | $95 \% \mathrm{CI}$ |
| :--- | :---: | :---: | :---: |
| Difference between NRS pre and: |  |  |  |
| NRS $72 \mathrm{~h}(\mathrm{n}=58)$ | 3.085 | $<0.001$ | $2.200-3.970$ |
| NRS 3 months $(\mathrm{n}=58)$ | 2.017 | 0.001 | $1.120-2.914$ |
| NRS 6 months $(\mathrm{n}=58)$ | 1.339 | 1.000 | $0.378-2.300$ |
| Difference between NRS 72 h and: | -0.441 | 0.093 |  |
| NRS 1 month $(\mathrm{n}=58)$ | -1.068 | 0.001 | $-1.270-0.389$ |
| NRS 3 months $(\mathrm{n}=58)$ | -1.746 | 0.945 | $-2.227-0.091$ |
| NRS 6 months $(\mathrm{n}=58)$ | 0.008 | $-2.812--0.679$ |  |
| Difference between NRS 1 month and: | -0.627 | 0.330 | $-1.946-1.612$ |
| NRS 3 months $(\mathrm{n}=58)$ | -1.305 | $-2.387-0.223$ |  |
| NRS 6 months $(\mathrm{n}=58)$ | -1.083 | $-2.565-0.399$ |  |
| Difference between NRS 3 months and: |  |  |  |
| NRS 6 months $(\mathrm{n}=58)$ |  |  |  |

NRS, Numerical Rating Scale; MD, Mean Difference; CI, Confidence Interval.

Table 4 Efficacy of the IQL, considering an effective reduction in NRS $\geq 30 \%$.

|  | 1 month <br> $(\mathrm{n}=77)(\%)$ | 3 months <br> $(\mathrm{n}=78)(\%)$ | 6 months <br> $(\mathrm{n}=71)(\%)$ |
| :--- | :---: | :---: | :---: |
| Efficient | $43(55.8 \%)$ | $38(48.72 \%)$ | $26(36.6 \%)$ |
| Not efficient | $34(44.2 \%)$ | $40(51.22 \%)$ | $45(63.4 \%)$ |

IQL, Ultrasound-Guided Infiltrations in Quadratus Lumbar myofascial pain syndrome.

Table 5 Comparison of NRS between different moments, after controlling the number of drugs, existence of psychiatric disorder and opioid consumption.

|  | MD | $p$-value | $95 \% \mathrm{Cl}$ |
| :--- | :---: | :---: | :---: |
| Difference between NRS pre and: |  |  |  |
| NRS $72 \mathrm{~h}(\mathrm{n}=58)$ | 3.294 | $<0.001$ | $1.520-5.067$ |
| NRS 1 month $(\mathrm{n}=58)$ | 3.090 | $<0.001$ | $1.234-4.946$ |
| NRS 3 months $(\mathrm{n}=58)$ | 2.832 | $<0.001$ | $1.191-4.472$ |
| NRS 6 months $(\mathrm{n}=58)$ | 3.111 | 1.000 | $1.376-4.845$ |
| Difference between NRS 72 h and: | -0.203 | 1.000 | $-1.691-1.284$ |
| NRS 1 month $(\mathrm{n}=58)$ | 1.000 | $-2.548-1.624$ |  |
| NRS 3 months $(\mathrm{n}=58)$ | -0.462 | 1.000 | $-2.034-1.668$ |
| NRS 6 months $(\mathrm{n}=58)$ | 1.000 | $-2.138-1.621$ |  |
| Difference between NRS 1 month and: | -0.183 | 1.000 | $-1.953-1.994$ |
| NRS 3 months $(\mathrm{n}=58)$ | -0.259 | $-1.566-2.125$ |  |
| NRS 6 months $(\mathrm{n}=58)$ | 0.020 | -0.279 |  |
| Difference between NRS 3 months and: |  |  |  |
| NRS 6 months $(\mathrm{n}=58)$ |  |  |  |

NRS, Numerical Rating Scale; MD, Mean Difference; CI, Confidence Interval.

Table 6 Profile of opioid consumption at different times of assessment.

|  | 1 month <br> $(n=90)$ | 3 months <br> $(n=90)$ | 6 months <br> $(n=90)$ |
| :--- | :---: | :---: | :---: |
| Dosage increased | $6(6.7 \%)$ | $5(5.6 \%)$ | $12(13.3 \%)$ |
| Dosage decreased | $5(5.6 \%)$ | $9(10.0 \%)$ | $1(1.1 \%)$ |
| Opioid discontinued | $6(6.7 \%)$ | $7(7.8 \%)$ | $7(7.8 \%)$ |
| Opioid dose increment | $2(2.2 \%)$ | $2(2.2 \%)$ | $9(10.0 \%)$ |
| Dosage unchanged | $65(72.2 \%)$ | $57(63.3 \%)$ | $53(58.9 \%)$ |
| Total of participants consuming opioids | $78(86.7 \%)$ | $73(81.0 \%)$ | $75(83.3 \%)$ |

not statistically significant. Table 6 shows that at 6 months there was an increase, although not statistically significant, in the number of participants requiring increase in dosage of opioids or their introduction. At the time of the procedure, $46.7 \%$ of participants complained of pain in at least one site, in addition to the lumbar spinal site. However, 6 months after the technique, no statistically significant association was revealed between presence or absence of pain in other locations and opioid dose increments $(p=0.129)$ and addition of opioid ( $p=1.000$ ).

It is worth mentioning that the largest proportion of participants submitted to the IQL were unskilled workers (22.1\%).

No adverse effects associated with the technique were recorded in participants submitted to the technique.

## Discussion

To the best of our knowledge, this is the first study to demonstrate the efficacy of ultrasound-guided infiltration with $0.25 \%$ levobupivacaine and 40 mg triamcinolone for chronic low back pain due to QL MPS over 6 months post-treatment. Pain management in chronic low back pain caused by QL MPS is usually unsatisfactory, often leading to gradual increment of opioid dosage ${ }^{9}$ and superfluous diagnostic investigations. Although MPS pathophysiology ${ }^{11}$ is not entirely clear, it is known that the affected muscles and those with TrPs cease to function efficiently. Therefore, to compensate for this weakness, other muscles of the functional muscle unit chronically contract, making them susceptible to developing TrPs. Therefore, once MPS is established in the lumbar spine muscles, a vicious cycle is elicited, perpetuating muscle dysfunction and pain. ${ }^{12}$

IQL is a recent anesthetic technique, first described in $2007{ }^{13}$ and extensively used for postoperative analgesia in patients to be submitted to abdominal and retroperitoneal surgeries. ${ }^{14,15}$ The technique aims at injecting local anesthetic and/or corticosteroids in the site adjacent to the QL muscle. ${ }^{16}$ Although not yet fully understood, it is believed that the TLF plays a central role in its mechanism of action. ${ }^{17}$ The TLF is a fibrous tissue and component of the myofascial group that envelopes the lower trunk and plays an important role in posture, load transfer and lumbar spine stabilization. ${ }^{6}$ It is assumed that the action of local anesthetics on the existing TLF mechanoreceptors cause the therapeutic response of IQL, ${ }^{18}$ as well as the dispersion of the local anesthetics drug to the paravertebral space. Recently, several studies have revealed the effectiveness of IQL for postoperative analgesia in many surgical procedures. IQL action is well established for relieving acute postoperative pain, however, to date, there are no clinical studies showing its benefit for chronic pain management. There are studies assessing the efficacy of ultrasound-guided injections with local anesthetics and/or corticosteroids for treatment of chronic pain caused by MPS reporting controversial results. ${ }^{19}$

Gopinath Niraj ${ }^{20}$ evaluated the effect of transmuscular infiltration with 10 mL of $0.5 \%$ levobupivacaine and 60 mg of methylprednisolone of the quadratus lumborum muscle for abdominal MPS and reported pain improvement in $36 \%$ of patients undergoing the procedure, and that the effect was maintained for 12 weeks. Agreeing with the results obtained
by that author, the present study showed pain improvement at all evaluation times. Furthermore, approximately one-third of participants had a decrease of at least $30 \%$ of their initial pain when they were assessed at 6 months. It should be noted that the improvement reported at 6 months after treatment was not influenced by the number of drugs, the presence of psychiatric disorder or opioid consumption, which strengthens our conclusions.

Alternatively, the superiority of other treatments in relation to this technique has not been shown. Andrés et al. ${ }^{21}$ concluded that botulinum toxin infiltration is not more effective in reducing NRS compared to $0.25 \%$ bupivacaine for treatment of MPS involving iliopsoas and/or QL muscles. Similarly, Levesque A. et al. ${ }^{22}$ verified that there is no additional benefit with the infiltration of botulinum toxin combined with $0.2 \%$ ropivacaine compared to the isolated administration of $0.2 \%$ ropivacaine for pain relief in chronic pelvic MPS. They also concluded that both groups showed a decline in the analgesic effect 3 months after the intervention. However, Hong JO et al. ${ }^{23}$ reported that when compared to ultrasound-guided injection of TrP, shock wave therapy showed better pain control for patients presenting QL MPS. The study did not use local anesthetic or corticosteroids, which are believed to play a role in sustained pain relief.

In the present study, about a third of participants had already undergone lumbar spine surgery, suggesting that QL MPS may play an important role in postoperative pain of lumbar spine surgery. On the other hand, QL MPS may mimic other conditions, and its precise diagnosis is crucial to avoid unnecessary surgical interventions. ${ }^{24,25}$

In this study, it is worth underscoring capacity/functionality improvement, revealed by the $50 \%$ reduction of participants with incapacity for work 6 months after performing the IQL, which suggests a significant clinical improvement associated with the technique. However, given the small sample size, further studies are required to validate these results.

Ninety percent of participants were under treatment with opioids and still presenting uncontrolled pain. Thus, these data indicate that ultrasound-guided infiltration with $0.25 \%$ levobupivacaine and 40 mg triamcinolone may be an effective alternative to conservative therapy.

Based on this study, it is not possible to infer a positive impact on opioid consumption related to the procedure, conversely to what has been observed in other studies. ${ }^{26}$ Along the 6-month follow-up, we did not observe differences in opioid consumption. Our data reveal that $46.7 \%$ of participants had pain in at least one more site besides the lumbar spine, which may explain this finding. However, an association between opioid consumption and pain in another site has not been demonstrated.

The procedure is safe as there was no record of complications or adverse effects related to the technique, coinciding with previously published studies.

This study has some limitations. It was a retrospective study and, therefore, not controlled, and randomized. The sample size was relatively small, and the follow-up period short. It should also be noticed that it was not always possible to obtain the NRS records of the 90 participants assessed, reducing the number of participants with this variable studied. The diagnosis of QL MPS was presumptive, as it was
based on clinical criteria. Moreover, as the symptoms presented by the participants overlapped other musculoskeletal syndromes, false positives might have occurred. Since the follow-up was performed by telephone contact, we were unable to use scales other than NRS for pain scoring, as most of the scales are extensive or involve physical examination. In the future, it would be important to consider using other assessment tools, such as the Oswestry Disability Index. In this study, we only assessed pain at rest, so it would be important to understand the IQL impact on dynamic pain. In addition, the assessment of quality of life and symptoms of anxiety and depression should be considered.

## Conclusion

QL MPS is a common and often overlooked disorder that significantly impacts quality of life. This study revealed the efficacy and safety of ultrasound-guided infiltration with levobupivacaine $(0.25 \%)$ and 40 mg of triamcinolone for QL MPS along the 6-month post-intervention follow-up of patients with chronic low back pain refractory to conservative treatment, thus the technique can be considered as an alternative treatment. Prospective studies, with larger samples and standardized protocols, will be key to verify the results obtained in present study.

## Conflicts of interest

The authors declare no conflicts of interest.

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Sociedade Brasileira de Anestesiologia

# Effectiveness and safety of ultra-low-dose spinal anesthesia versus perineal blocks in hemorroidectomy and anal fistula surgery: a randomized controlled trial 

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## KEYWORDS

Anal fistula;
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#### Abstract

Background: Ultra-low-dose Spinal Anesthesia (SA) is the practice of employing minimal doses of intrathecal agents so that only the roots that supply a specific area are anesthetized. The aim of this study was to compare the effectiveness and safety of ultra-low-dose spinal anesthesia with that of Perineal Blocks (PB). Methods: A two-arm, parallel, double-blind randomized controlled trial comparing two anesthetic techniques (SA and PB) for hemorrhoidectomy and anal fistula surgery was performed. The primary outcomes were postoperative pain, complementation and/or conversion of anesthesia, and hemodynamic changes. Results: Fifty-nine patients were included in the final analysis. The mean pain values were similar in the first 48 h in both groups $(p>0.05)$. The individuals allocated to the SA group did not need anesthetic complementation; however, those in the PB group required it considerably (SA group, $0 \%$ vs. PB group, $25 \% ; p=0.005$ ). Hemodynamic changes were more pronounced after PB: during all surgical times, the PB group showed lower MAP values and higher HR values ( $p<0.05$ ). Postoperative urinary retention rates were similar between both groups (SA group 0\% vs. PB group 3.1\%, $p=0.354$ ). Conclusion: SA and PB are similarly effective in pain control during the first 48 h after hemorrhoidectomy and anal fistula surgery. Although surgical time was shorter among patients in the PB group, the SA technique may be preferable as it avoids the need for additional anesthesia. Furthermore, the group that received perineal blocks was under sedation with a considerable dose of propofol.


[^3]
## Introduction

Ambulatory surgery is a safe and economic approach to manage anorectal conditions. ${ }^{1}$ Hospital admissions occur in up to $17 \%$ of cases, ${ }^{2}$ and in up to $61 \%$ of cases undergoing hemorrhoidectomies. ${ }^{3}$ Major causes of morbidity for ambulatory anorectal procedures include pain, bleeding, urinary retention, and Postoperative Nausea and Vomiting (PONV). ${ }^{2}$

Neuraxial blocks are available in addition to other effective anorectal surgery methods. However, they have been traditionally associated with high postoperative urinary retention rates, ${ }^{1}$ although there is still conflicting evidence on this issue. ${ }^{1,2,4}$

General anesthesia, spinal anesthesia, and sedation are commonly associated with perineal block or infiltration during ambulatory hemorrhoidectomy. There is disagreement in the literature regarding the best technique for postoperative analgesia. ${ }^{3}$ Recently, local infiltration has shown lower analgesic efficacy than spinal anesthesia in hemorrhoidectomy. ${ }^{5}$

Spinal anesthesia causes longer hospitalization and recovery times in addition to urinary retention in anorectal surgeries ${ }^{1,4,6}$ and hemorrhoidectomy. ${ }^{3}$ However, local anesthesia (LA) decreases costs, anesthesia time, nausea, and increases patient satisfaction in anorectal surgeries. ${ }^{6}$

The incidence of general postoperative urinary retention is $2-3.8 \%$, after anorectal surgery it is $2048 \%$, ${ }^{4}$ and it also occurs more frequently after hemorrhoidectomy. ${ }^{1}$ Risk factors that vary according to the populations studied are as follows: age above 50-60 years, neuraxial anesthesia, operative time longer than 120 min , intravenous fluids higher than $750-2000 \mathrm{ml}$, laparoscopic surgery, anorectal and lower limb arthroplasty, neurological comorbidities, and specific pharmacological agents. ${ }^{4}$

The proposed mechanisms of anorectal surgery leading to postoperative urinary retention (POUR) are well established and include alpha-adrenergic activation, change in bladder position after surgery, and injury of autonomic nerves, despite the surgical approach. ${ }^{4}$

Spinal anesthesia results in blockage of the urination reflex, which lasts until the spinal anesthetic regresses to level S3, in that longer acting anesthetics result in greater urinary retention. ${ }^{4}$ Lower values of local anesthetic have been proposed, aiming at less pronounced motor and sensory block, and facilitating early discharge of the patient. Ultra-low-dose spinal anesthesia was defined as levobupivacaine or bupivacaine $\leq 5 \mathrm{mg}$ administered as a single injection of spinal anesthesia. ${ }^{7}$

Studies that address side effects of spinal anesthesia in hemorrhoidectomy in the outpatient setting have used different LA, with varying doses of LA and opioids. ${ }^{3}$

This study was based on the hypothesis that ultra-lowdose spinal anesthesia is effective in some specific types of ambulatory benign anorectal surgeries. The main objective of this study was to compare the effectiveness and safety of ultra-low-dose spinal anesthesia with that of perineal blocks.

## Methods

## Study design

A two-arm, parallel, double-blind (surgeons and patients) randomized controlled trial comparing two anesthetic techniques, ultra-low-dose spinal anesthesia and perineal blocks, for hemorrhoidectomy and anal fistula surgery was performed.

## Participants

Patients scheduled for hemorrhoidectomy, anal fistula surgery, or internal lateral sphincterotomy were included in this study. Each surgical intervention followed a technique with a higher level of evidence and/or was standardized ${ }^{10-12}$ so that there was no variation in the surgical technique among patients with the same clinical condition.

Inclusion criteria were as follows: 1) Grade III to IV external hemorrhoids, ${ }^{8}$ anal fissure, and anorectal fistula indicative of surgical treatment; 2) Age 18-65 years; and 3) American Society of Anesthesiologists (ASA) physical status of I-III. ${ }^{9}$

The exclusion criteria were as follows: 1) Contraindication of subarachnoid anesthesia and outpatient stay (absence of telephone contact, difficulty in locomotion, and residence outside the municipality where the anesthetic-surgical intervention took place); 2) Cognitive inability; 3) Decompensated clinical pathology; 4) Neurological pathology; 5) Diabetes mellitus; 6) Urge incontinence; 7) Previous prostate, renal, or urological surgery; and 8) Drug allergy.

After identifying eligible patients, they were contacted by the research team and were guided regarding the research protocol, followed by obtaining the informed consent form, inclusion of patients, and randomization.

## Sample calculation

The minimum sample size calculated per group was 28 patients assuming: $\alpha=5 \%$ and power $=80 \%$, for a difference of up to $30 \%$ in local anesthetic techniques versus conventional spinal anesthesia, predicting a reduction in the incidence of pain.

## Randomization, blinding, and allocation concealment

After inclusion, block randomization was performed using a computer-generated number list prepared by an independent researcher. Each individual was randomly assigned to receive ultra-low-dose Spinal Anesthesia (SA group) or Perineal Blocks (PB group) with the allocation rate of 1:1.

Opaque and sealed envelopes with identification of allocation were delivered to the anesthesiologist after each participant entered the operating room. Coloproctologists, data collection teams, and statisticians were blinded to the anesthetic technique. The surgeons and individuals from the
collection group were only allowed after anesthesia was performed and patients were positioned in a lithotomy position.

## Interventions

The interventions consisted of SA and PB performed by anesthesiologists. The intervention protocol for this study consisted of three phases.

The first phase, common to both groups, consisted of fasting for 8 hours before the beginning of surgery, spontaneous urinary disposal immediately before the procedure, supplemental oxygen, and restriction of intravenous fluids to 100 ml of $0.9 \%$ sodium chloride during surgery. Different anesthesiologists and surgeons performed the procedures, and all anesthesiologists were previously trained to perform these procedures.

The second phase consisted of the performance of different anesthetic techniques. The SA group received ultra-lowdose spinal anesthesia with $2.5 \mathrm{mg}(0.5 \mathrm{ml})$ of $0.5 \%$ hyperbaric bupivacaine and $20 \mu \mathrm{~g}(0.4 \mathrm{ml})$ of fentanyl. The technique was performed with the patient seated between L4 and L5 or L5 and S1 using a 25 G or 27G Quincke needle. After spinal anesthesia, the patient remained in the supine position with a $25^{\circ}$ cephaloaclive for eight minutes, in order to ensure sacral dispersion of the intrathecal drugs. Patients were sedated with midazolam 0.05 to $0.1 \mathrm{mg} . \mathrm{kg}^{-1}$.

The PB group consisted of bilateral blockades of the pudendal and anorectal nerves, with the patient in the lithotomy position. A bilateral nerve block was performed with 150 mg of ropivacaine ( 20 ml ) diluted in 20 ml of $0.9 \%$ NaCl . Half of the solution was used on each side through a $21 G 0.8 \times 100 \mathrm{~mm}$ (B. Braun Melsungen AG) isolated needle connected to a peripheral nerve stimulator (Stimuplex ${ }^{\circledR}$ ) regulated to release a square pulsatile current of 1 mA , with a frequency of 2 Hz , inserted transperineal, medial, and perpendicular to the sciatic tuberosity, at a depth of approximately $4-7 \mathrm{~cm}$, seeking contraction of the anal sphincter.

The anorectal block was performed with superficial and deep infiltration of $400 \mathrm{mg}(20 \mathrm{ml})$ of lidocaine with vasoconstrictor diluted in 10 ml of $0.9 \% \mathrm{NaCl}$ through a $25 \times 0.7 \mathrm{~mm}$ needle anterior, posterior, and lateral to the anus, making up its entire circumference. The patients were sedated with targeted controlled infusion of propofol. The preanesthesia target and the postanesthesia targets were $2-4 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ and $1 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$, respectively.

Ephedrine $5-25 \mathrm{mg}$ EV and atropine $(0.5 \mathrm{mg}) \mathrm{EV}$ (could be repeated) were standardized for the treatment of hypotension and symptomatic or important bradycardia, respectively.

Both interventions received drugs with prolonged analgesic action. Patients in the SA and PB groups received intrathecal fentanyl and ropivacaine, respectively. Intrathecal fentanyl in SA for anorectal surgery is associated with a better pain score in the first 6 hours and decreased use of analgesics in the postoperative period. ${ }^{13}$ Ropivacaine in perianal block for anorectal surgery is associated with reduced pain, opioid consumption, and faster recovery. ${ }^{14}$

The third phase, also common to both groups, consisted of management of complementation and/or conversion of anesthesia, analgesia, and prophylaxis of PONV.

Anesthetic complementation was implemented if there was any change after testing the incision area: complaint of
pain, verbalization or movement of the sedated patient, and acute hemodynamic repercussion (tachycardia or hypertension), through a complementary anorectal block with $200 \mathrm{mg} / 10 \mathrm{ml}$ of lidocaine with vasoconstrictor through a $25 \times 0.7 \mathrm{~mm}$ needle. Conversion to general anesthesia was performed if the alterations persisted.

Postoperative analgesia before discharge was performed with morphine $0.05 \mathrm{mg} . \mathrm{kg}^{-1}$ for mild pain and $0.1 \mathrm{mg} . \mathrm{kg}^{-1}$ for moderate to maximum pain, and the dose was repeated until resolution.

Intraoperative venous prophylaxis was performed for nausea and vomiting with 6 mg of dexamethasone and 8 mg of ondansetron, and for pain with 2 g of dipyrone and 30 mg of tenoxicam. Postoperative prophylaxis for pain was recommended orally, with 1 g dipyrone at $6 / 6 \mathrm{~h}$ for 3 to 5 days, 500 mg of paracetamol and 30 mg codeine at $6 / 6 \mathrm{~h}$ for 3 to 5 days, 100 mg of nimesulide at $12 / 12 \mathrm{~h}$ for 5 days, and topical with $50 \mathrm{mg} . \mathrm{g}^{-1}$ of polycresuline and $10 \mathrm{mg} . \mathrm{g}^{-1}$ cinchocaine hydrochloride at $8 / 8 \mathrm{~h}$ for 14 days.

## Data collection

Sociodemographic and clinical data were collected preoperatively. Surgical and anesthetic data were collected both intraoperatively and postoperatively. Standard intraoperative monitoring included noninvasive mean arterial pressure (NIMAP), peripheral oxygen saturation $\left(\mathrm{SpO}_{2}\right)$, and heart rate (HR) recorded every 5 min. Follow-up started during the intraoperative period at the end of surgery (TO), and continued in the postoperative periods 1 h (T1), 3 h (T3), 5 h (T5) in the anesthetic recovery room and 10 h (T10), 24 h (T24), 48 h (T48) through telephone contact at the exact time indicated after surgery.

## Outcome measures

Primary outcome measures
The primary outcome was the effectiveness and safety of SA compared to that of PB.

Effectiveness was evaluated through postoperative pain analysis and complementation and/or conversion of anesthesia.

Pain was assessed using the visual analog scale (VAS) and was quantified as follows: $0=$ No pain, 1 to $3=$ Mild pain, 4 to $6=$ Moderate pain, 7 to $9=$ Severe pain, and $10=$ Maximum pain. It was grouped into the following categories: absence of pain, minor pain in case of mild pain and major pain in case of moderate to maximum pain, for statistical analysis in order to understand the profile of analgesia techniques.

The safety of the techniques was evaluated through hemodynamic changes measured through MAP and HR variation analyses.

## Secondary outcome measures

The secondary outcomes were the incidence of side effects, interference of anesthesia in outpatient discharge, and user satisfaction.

The evaluated side effects were incidence of constipation, pain at first evacuation, average pain when first evacuating, strength limitation in the lower limbs, difficulty in walking, and incidence of POUR/PONV. POUR was diagnosed
using the following clinical criteria: presence of voiding desire and inability to empty the bladder spontaneously and adequately at any time during the first 24 h after the intervention. Constipation was defined as a delay in bowel movement for 48 h .

The interferences of anesthesia analyzed during outpatient discharge were the incidence of ambulatory discharge delay and unplanned hospital admission. Delay of outpatient discharge was defined as discharge from the medical service beyond 5 h after the end of the procedure.

User satisfaction was assessed using a form adapted from the lowa Satisfaction with Anesthesia Scale. Patients received a form containing five sentences: "I'd like to have the same anesthesia again", "I felt pain", "I felt safe", "I felt pain during surgery", and "I was satisfied with my anesthetic care". In each sentence, they had to mark only one of two options: agree or disagree. ${ }^{15}$

## Statistical analysis

The data were entered with double entry and verified with the "validate", Epi-info Program module, version 6.04 (WHO/CDC; Atlanta, GE, USA), to identify any inconsistencies. The Statistical Package for Social Sciences (SPSS) for Windows software, version 17.0 (SPSS Inc.; Chicago, IL, USA) was used for analyses.

Statistical analyses consisted of descriptive analyses using measures of central tendency and frequency, the Sha-piro-Wilk test to verify the normality pattern of continuous variables, Pearson chi-square test or Fischer's exact test, and $t$-test for independent samples; $p$-value below 0.05 was considered statistically significant.

## Ethics criteria

This Randomized Controlled Trial (RCT) was approved by the university ethics committee of Universidade Federal de Alagoas (Study number: 2,508,805). RCT Registration: https:// ensaiosclinicos.gov.br/rg/RBR-5fn873. This study was conducted between March 2018 and January 2019 at Hospita|*** and is in compliance with the Declaration of Helsinki. This trial was performed according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

## Financial statement

The research was carried out with the resources of the researchers themselves.

## Results

Seventy patients scheduled for ambulatory anorectal surgery were eligible for the study and were randomly allocated to the SA or PB groups. Only 59 patients were included in the final analysis, as demonstrated in Fig. 1.

## Characteristics of groups

Socio-demographic and clinical profiles did not vary between the groups. However, the surgical time was shorter in the PB group ( $p=0.000$ ) (Table 1).

## Primary outcomes

The mean pain values were similar in the first 48 h in both groups, even when analyzed by type of surgery, regardless of the hemorrhoid grade. The highest mean pain was after 24 $h(4.00 \pm 2.70)$ and $1 \mathrm{~h}(3.20 \pm 1.78)$ in the SA and PB groups, respectively (Table 2).

There was no difference in the incidence of pain in the first 24 h when the groups were subdivided into the following categories: absence of pain, major pain, and minor pain. However, there was a difference after 48 h (SA group: $85.2 \%$ without pain, $7.4 \%$ with minor pain, and $7.4 \%$ with major pain vs. PB group: $71.9 \%$ without pain, $28.1 \%$ with minor pain, $p=0.048$ ). It is noteworthy that major pain was found earlier in the PB group (after 1 h and 5 h ) compared to the SA group (after $10 \mathrm{~h}, 24 \mathrm{~h}, 48 \mathrm{~h}$ ). When the incidence of pain was analyzed according to the type of surgery, there was only major pain in hemorrhoidectomy, which was similar between the groups (Fig. 2).

The individuals allocated to the SA group did not need anesthetic complementation; however, those in the PB group required it considerably (SA group, 0\% vs. PB group, $25 \% ; p=0.005$ ). Nevertheless, the need for anesthetic conversion did not differ between the groups (SA group, $0 \%$ vs. PB group, $9.4 \% ; p=0.102$ ).

During all surgical times, the PB group showed lower MAP values (statistically significant after $5,10,15$, and 20 min ) and higher HR values (statistically significant after 5, 45, 50, and 55 min ). Even when these hemodynamic changes were analyzed by the type of surgery, we found the same pattern for NIMAP changes in both hemorrhoidectomy (statistically significant after $5,10,15$, and 20 min ) and anal fistula surgery (statistically significant after 5, 10, and 15 min ) (Fig. 3).

## Secondary outcomes

The frequency of constipation (SA group, $59.3 \%$ vs. PB group, $40.6 \% ; p=0.154$ ) and the incidence of pain at first evacuation (SA group, 54.5\% [6/11] vs. PB group, 57.9\% [11/19]; $p=0.858$ ) evaluated after ambulatory discharge were similar between the groups. Mean pain at the first evacuation was also similar (SA group, $5.33 \pm 2.33$ vs. PB group, $4.27 \pm$ 2.83; $p=0.447$ ). Pain was more frequent among those who evacuated later regardless of the allocated group.

Only the PB group showed force limitation in the lower limbs, which occurred after 1 h (SA group, $0 \%$ vs. PB group, $3.1 \% ; p=0.354)$. Patients with strength limitations were only able to move their knees (partial motor block). After 3 h and 5 h , no difference (SA group, $0 \%$ vs. PB group, $0 \%$ ) was observed. Difficulty in walking was only found in the PB group ( $9.4 \%, p=0.102$ ) because they were drowsy.

The incidence of POUR after 3 h of the procedure was similar between the groups (SA group, 0\% vs. PB group, 3.1\% [1/32]; $p=0.354$ ). In the PB group, one patient (female, 64 years old) underwent hemorrhoidectomy (surgical time of 25 min ), and partially emptied the bladder without needing catheterization. Besides this case, none of the patients presented with POUR.

The incidence of nausea (SA group $0 \% \times \mathrm{PB}$ group $6.3 \%$, $p=0.186$ ) and vomiting (SA group, $0 \%$ vs. PB group, $3.1 \%$; $p=0.354$ ) was similar between the groups throughout the


Figure 1 Flow diagram based on the Consolidated Standards of Reporting Trial (CONSORT) statement.
study, occurring only after 5 h . One patient who experienced nausea vomited.

The incidence of discharge delay (SA group, $0 \%$ vs. PB group, $3.1 \% ; p=0.354$ ) and unplanned hospital admission (SA group, $0 \%$ vs. PB group, $3.1 \%, p=0.354$ ) were similar between the groups. Both ambulatory discharge delay and unplanned hospital admission occurred because of bleeding related to patients' surgical condition. The results are summarized in Table 3.

Overall satisfaction with anesthesia was appropriate in both groups ( $>80 \%$ ) and no significant differences were found between them.

## Discussion

Ultra-low-dose spinal anesthesia and perineal blocks for anorectal surgeries can be performed in many ways using several drugs and in different amounts. The comparison presented in this RCT aimed for intense anesthetic reduction in the SA group and the association of blockades in the PB group to make the comparative analysis more equitable.

The intense reduction in the amount of local spinal anesthesia was motivated by the high rates of POUR associated with this technique, which were published without anesthetic methodological descriptions. ${ }^{3}$

Table 1 Sociodemographic and clinical profiles.

|  | SA Group (27) | PB Group (32) | $p$-value |
| :---: | :---: | :---: | :---: |
| Age - mean $\pm$ SD | $46.4 \pm 10.5$ | $44.3 \pm 12.5$ | $0.489{ }^{\text {b }}$ |
| Sex, n (\%) |  |  | $0.197^{\text {a }}$ |
| Male | 66.7\% (18) | 50\% (16) |  |
| Female | 33.3\% (9) | 50\% (16) |  |
| Schooling - \% (n) |  |  | $0.530^{\text {a }}$ |
| Illiterate | 11.1\% (3) | 12.5\% (4) |  |
| Incomplete elementary | 22.2\% (6) | 21.9\% (7) |  |
| Complete elementary | 14.8\% (4) | 9.4\% (3) |  |
| Incomplete high school | 22.2\% (6) | 6.3\% (2) |  |
| Complete high school | 25.9\% (7) | 40.6\% (13) |  |
| Incomplete superior | 0\% | 3.1\% (1) |  |
| Complete superior | 3.7\% (1) | 6.3\% (2) |  |
| Types of Surgery - \% ( n ) |  |  | $0.832^{\text {a }}$ |
| Hemorrhoidectomy | 63\% (17) | 65.6\% (21) |  |
| Anal fistula surgery | 37\% (10) | 34.4\% (11) |  |
| ASA - \% ( n ) |  |  | $0.534^{\text {a }}$ |
| I | 66.7\% (18) | 71.9\% (23) |  |
| 1 | 33.3\% (9) | 25\% (8) |  |
| III | 0\% | 3.1\% (1) |  |
| BMI - mean $\pm$ SD | $26.11 \pm 5.41$ | $26.69 \pm 4.79$ | $0.668{ }^{\text {b }}$ |
| Surgical Time - Méd. $\pm$ DP | $43.2 \pm 14.1$ | $28.3 \pm 14.3$ | $0.000^{\text {b }}$ |

[^4]Although the techniques are equivalent in terms of analgesia, SA was more effective than PB for hemorrhoidectomy and anal fistula surgery because of the lower incidence of anesthetic complementation and hemodynamic changes (hypotension and tachycardia). The incidence of side effects (limitation of strength in the lower limbs, difficulty in walking, POUR, PONV, and constipation), interference of anesthesia in ambulatory discharge, and user satisfaction in both techniques were similar.

There are conflicting reports regarding the best technique (perineal block or traditional spinal anesthesia) for controlling immediate postoperative pain. ${ }^{3}$ In a previous study, local infiltration showed lower efficacy postoperative analgesia when compared to spinal anesthesia in hemorrhoidectomy surgery. ${ }^{5}$ Unlike this study, in our research, local anesthesia was performed with double blockade, and SA was performed with a dose of LA which was four times lower, consequently, analgesia was similar in both groups.

Even when potentiating LA in the PB group and reducing the anesthetic dose in the SA group, resulting in ultra-lowdose spinal anesthesia, the incidence of general pain and pain at the first evacuation was low and similar between the groups.

Anesthetic complementation occurred only in the PB group and was significant, indicating that anesthesia is not always efficient. The tendency for more pain to appear earlier in the PB group strengthens these findings. The absence of anesthetic complementation in the SA group demonstrated effective anesthesia and the tendency for major pain to appear late strengthens the need for optimization of postoperative analgesia.

Postoperative analgesics may cause pain interpretation bias. For ethical reasons, the same pain protocol was applied to both groups. The multimodal preventive association of analgesics at the end of surgery was used ${ }^{5}$ aiming to improve recovery after surgery (enhanced recovery after surgery). ${ }^{6}$

The absence of hemodynamic changes in the SA group resulted from the low dose of the local intrathecal anesthetic. The hemodynamic changes observed in the PB group can be due to the propofol infusion necessary to perform the blockade in an extremely innervated region. An additional contribution to this situation could arguably have been the absorption of local anesthetics. Although propofol does not have analgesic properties, those receiving high doses of this drug may experience a decrease in response to painful stimuli. Dose-dependent hypotension is the most common complication and occurs due to vasodilation (sympathetic activity decreases by direct effect on intracellular influx of calcium and sodium from smooth muscle and mediated by increased release of nitric oxide by the vascular endothelium). Propofol inhibits the baroreceptor reflex and, consequently, reduces the physiologic elevation of heart rate in response to hypotension. ${ }^{16}$ This may justify a statistically significant hypotension initially, when the vasodilator effect was maximum, and statistically significant tachycardia later, when the effect on baroreceptors may not have been strong.

Ultra-low-dose spinal anesthesia has been used in other studies of anorectal surgery. Intrathecal 2.5 mg hyperbaric levobupivacaine plus $12.5 \mu \mathrm{~g}$ or $25 \mu \mathrm{~g}$ fentanyl was used, which resulted in good quality anesthesia without motor block and the need for supplementary analgesia during

## Table 2 Average postoperative pain.




Figure 2 Incidence of pain (\%) subdivided into categories in all surgeries, in hemorrhoidectomy and in anal fistula surgery; $p$-value (Pearson Chi-Square). Minor pain: VAS $=1$ to 3. Major pain: VAS $=4$ to 10. VAS, visual analog scale.
surgery. ${ }^{17}$ In our study, we used equivalent doses of bupivacaine, which resulted in the absence of anesthetic complementation and residual motor block, and low incidence of POUR, which is the main side effect of benign anorectal surgeries (20-48\% in anorectal surgeries). ${ }^{4}$

The intense reduction in intrathecal bupivacaine associated with the described management of the technique (urinary disposal before the procedure, restriction of intravenous fluids, and supine position with $25^{\circ}$ cephaloaclive for eight minutes after spinal anesthesia) provided low




Figure 3 Average Mean Arterial Pressure - MAP $(\mathrm{mmHg})$ and Heart Rate - HR (bpm) in all surgeries, hemorrhoidectomy, and anal fistula surgery.

Table 3 Secondary results.

|  | SA Group (27) | PB Group (32) | $p$-value |
| :--- | :--- | :--- | :--- |
| Incidence of constipation | $59.3 \%(16 / 27)$ | $40.6 \%(13 / 32)$ | 0.154 |
| Incidence of pain at first evacuation | $54.5 \%(6 / 11)$ | $57.9 \%(11 / 190$ | 0.858 |
| Average pain when first evacuating | $5.33 \pm 2.33(6)$ | $4.27 \pm 2.83(11)$ | 0.447 |
| Strength limitation in LL - T1 | $0 \%$ | $3.1 \%(1 / 32)$ | 0.354 |
| Difficulty walking | $0 \%$ | $9.4 \%(3 / 32)$ | 0.102 |
| Incidence of POUR | $0 \%$ | $3.1 \%(1 / 32)$ | 0.354 |
| Incidence of nausea | $0 \%$ | $6.3 \%(2 / 32)$ | 0.186 |
| Incidence of vomit | $0 \%$ | $3.1 \%(1 / 32)$ | 0.354 |
| Ambulatory discharge delay | $0 \%$ | $3.1 \%(1 / 32)$ | 0.354 |
| Unplanned hospital admission | $0 \%$ | $3.1 \%(1 / 32)$ | 0.354 |

$p$-value (pearson's Qui-Square).
SA, Ultra-low-dose Spinal Anesthesia; PB, Perineal Blocks; LL, Lower Limbs; POUR, Postoperative Urinary Retention.
incidence of POUR by interfering with consecrated factors such as intrathecal amount/dispersion of local anesthetic ${ }^{17}$ and intravenous administration of fluids, associated with this side effect. ${ }^{2,4}$

Residual motor block after spinal anesthesia is a factor associated with urinary retention because detrusor blocks last longer than motor blocks. ${ }^{4}$ In our intervention, all patients presented with preserved strength in the lower limbs after 1 h and 3 h , full flexion of knees and feet, according to the Bromage classification. ${ }^{18}$ And all patients were able to walk after 3 h . This evidences a rapid return to the condition prior to anesthesia. However, $9.4 \%$ of patients in the PB group experienced difficulty walking due to drowsiness, taking longer to return to the condition prior to anesthesia. This was due to the slow redistribution of propofol to the highly fat-soluble peripheral compartment. ${ }^{19}$

Spinal anesthesia is associated with POUR in anorectal surgeries ${ }^{1,4,6}$ and hemorrhoidectomy. ${ }^{3}$ Our study found no statistically significant difference in the incidence of POUR between the groups.

Multiquadrant hemorrhoidectomy and multiple concomitant anorectal procedures have demonstrated consistently higher rates of urinary retention. ${ }^{2}$ Our study did not include a distinct analysis of quantitative quadrants treated with hemorrhoidectomy but identified higher levels of pain in patients with grade IV hemorrhoids at 5 h and 10 h , regardless of the allocated group ( $p>0.05$ ).

The adoption of a preoperative urination routine and transoperative water restriction due to the proposed intervention in SA may have led to the misdiagnosis of POUR, since there could be no time for bladder filling and consequent diuresis. In addition, ultrasound diagnosis is more accurate in estimating bladder volume. ${ }^{4}$ However, even with the adoption of such measures, SA did not differ from PB regarding the incidence of POUR.

Although ambulatory discharge delay can be defined as a delay of more than 12 h after a medical intervention, the purpose of this study was not to justify the permanence of patients in a health service longer than this time, in addition to being followed by telephone contact.

The literature points out that local anesthesia in anorectal surgery is associated with a decrease in postoperative nausea, reduced constipation rate, and increased patient satisfaction with spinal anesthesia. ${ }^{6}$ In our study, the incidence of constipation, PONV, and degree of satisfaction did
not differ between the groups. The intense reduction of LA in the SA group avoids hypotension, often found after conventional spinal anesthesia, and the consequent PONV and poor satisfaction, which may justify these findings. ${ }^{20,21}$

This study had a few limitations. Firstly, the absence of analysis of intravenous opioid consumption for rescue analgesia in the postoperative period until discharge. Secondly, the clinical diagnosis of POUR is less accurate than when performed via ultrasound technique. Thirdly, the control group received a large infusion of propofol. Fourthly, the mean surgical time values were different between the groups. The shorter surgical time in the PB group can be explained by the fact that the surgeries were performed by different surgeons during this study on effectiveness and safety, which could influence pain-related outcomes as prolonged surgeries can be related to worse pain outcomes. Since the surgical time was longer in the SA group, the difficulty in controlling pain among these patients was probably higher. In the future, further RCTs addressing these issues would help in precisely establishing the magnitude of the effect of the SA technique.

## Conclusion

Ultra-low-dose spinal anesthesia and perineal blocks are similarly effective in pain control during the first 48 hours after hemorrhoidectomy and anal fistula surgery. Although surgical time was shorter among patients in the PB group, the SA technique may be preferable as it avoids the need for additional anesthesia. Furthermore, it is worth noting that the group that received perineal blocks was under sedation with a considerable dose of propofol. Further research addressing this issue may help to identify additional advantages of the SA technique.

## Clinical trial number

This randomized clinical trial - RCT was approved by the ethics committee of the Federal University of Alagoas and the study number was $2,508,805$. After the inclusion of new election criteria, it was approved by the same committee and the study number was $2,857,891$. RCT Registration: https://ensaiosclinicos.gov.br/rg/RBR-5fn873.

## Declaration of Competing Interest

## The authors declare no conflicts of interest.

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# Dexmedetomidine versus sufentanil as adjuvants to bupivacaine for brachial plexus block during upper extremity surgery: a randomized clinical trial 

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## KEYWORDS

Brachial plexus block; Bupivacaine; Dexmedetomidine; Sufentanil;
Local anesthesia;
Ultrasonography


#### Abstract

Background: Brachial plexus block (BPB) has been accepted as a reliable alternative for general anesthesia in upper limb surgeries. Adding adjuvant drugs like dexmedetomidine and sufentanil has been shown to have clinical and pharmacologic advantages. In this randomized parallel clinical trial, we aim to compare the effects of these two adjuvants for bupivacaine in BPB. Methods: In this double-blinded study, by using computer-assisted block randomization, 40 patients ranged from 20 to 65 years old and scheduled for elective upper limb surgeries were assigned to two equal study groups ( $\mathrm{n}=20$ ), receiving 1 mL of $5 \mu \mathrm{~g} . \mathrm{mL}^{-1}$ sufentanil (group S ) or 1 mL of $100 \mu \mathrm{~g} . \mathrm{mL}^{-1}$ dexmedetomidine (group D) in adjunction to 30 mL of $0.5 \%$ bupivacaine for supraclavicular BPB under the guidance of ultrasonography. Characteristics of local anesthesia and postoperative analgesia were evaluated ( $\mathrm{n}=40$ ). Results: The duration of blocks significantly improved in group S (sensory: estimated median difference (EMD) [95\%CI] = 100.0 [70.0~130.0], $p<0.001$; motor: EMD [95\%CI] = 120.0 [100.0~130.0], $p<0.001$ ). Group $S$ also had significantly longer postoperative analgesia and lower opioid consumption within 24 hours after the surgery (EMD [95\%CI] = 4.0 [3.0~7.0], $p<$ 0.001 ; EMD $[95 \% \mathrm{CI}]=-5.0[-5.0 \sim-5.0], p<0.001$; respectively). None of the patients showed adverse effects concerning vital signs, nausea, or vomiting. Conclusion: Our study showed that during ultrasound-guided supraclavicular BPB, sufentanil is a fairly better choice than dexmedetomidine as an adjuvant for bupivacaine and can provide preferable sensory and motor blocks. No significant side effects were seen in either of the study groups. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


[^5]
## Introduction

As a reliable alternative to general anesthesia, peripheral nerve blockade has attracted acceptance among specialists. Brachial plexus block (BPB) has been commonly performed for patients undergoing upper limb surgeries. ${ }^{1}$ Regarding its less adverse effects, BPB has been considered an ideal choice for patients with underlying cardiopulmonary diseases. ${ }^{2}$

There are various approaches to perform BPB, depending on the patient's condition and the medical team's expertise. ${ }^{3}$ The supraclavicular approach is an efficient and acceptable method for BPB. ${ }^{4}$ Given the ease of procedure, high success rates, fast blockade onset time, ${ }^{2}$ and high single-shot efficient blockade rates, the supraclavicular approach under ultrasound guidance is a suitable choice for BPB.

The addition of various drugs as adjuvants to the local anesthetic has been shown to have clinical and pharmacologic merits. ${ }^{5-7}$ Prolonged duration of analgesia, faster blockade onset, and decreased total anesthetic usage, thus an extended safety margin of the block, are among the advantages. ${ }^{8}$

Alpha-2 adrenoreceptor agonists and opioids have been widely studied as adjuvant drugs. ${ }^{9-11}$ Bupivacaine (known widely by its brand name, Marcaine ${ }^{\circledR}$, Pfizer) is a local anesthetic that blocks $\mathrm{Na}^{+}$influx and thereby depolarization of nerve cells and has been widely used for peripheral nerve blockade. In this study, we aim to compare the effects of dexmedetomidine, an $\alpha-2$ agonist, with sufentanil, a synthetic opioid, as adjuvants for bupivacaine. The onset and the duration of sensory and motor blocks and postoperative analgesia were evaluated and analyzed.

## Material and methods

The ethics committee of the university approved the study protocol before the initiation of the study, and it was registered under the same code in the National Committee for Ethics in Biomedical Research, which is the official registry for the clinical trials of medical universities in the country. This study was registered retrospectively on the German Clinical Trials Register (DRKS) under the ID number DRKS00024182. Before obtaining written informed consent, the study protocol was described to each patient, and we answered their questions. Subsequently, written consent was obtained from all the individuals. None of the patients revoked their consent during or after the study.

This randomized, double-blinded, parallel (1:1), monocenter clinical trial was performed during October and November 2019. Forty patients aged 20 to 65 years and scheduled for elective upper limb surgeries were included. Their physical status was equivalent to the American Society of Anesthesiologists (ASA) I or II. Patients with prior brachial plexus injury or a history of allergic reactions to the study drugs were previously excluded.

Using computer-generated random numbers, one research assistant allocated the patients in blocks of 4 participants. Another assistant was separately responsible for enrolling the patients into blocks. A third assistant was responsible for assigning the patients to either of the
study groups: S, receiving 1 mL of $5 \mu \mathrm{~g} .1 \mathrm{~mL}^{-1}$ sufentanil added to 30 mL of $0.5 \%$ bupivacaine; or D, receiving 1 mL of $100 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ dexmedetomidine added to 30 mL of $0.5 \%$ bupivacaine. The groups were initially named A and B, and the names $S$ and $D$ were assigned to the groups after the data collection. The volume of the solutions was equal in both groups. The drug type was masked from the patients and the anesthesia assistant who prepared the study drugs. One anesthesiologist performed nerve blocks and data registrations in the entire study. The drug type was also masked from the anesthesiologist. None of the patients experienced an unsuccessful block, and all of the enrolled patients were included in the analysis. The enrollment process was designed according to the CONSORT guideline, and flow diagram of the study is shown in Figure 1.

Before entering the operation room (OR), patients were medicated with 2 mg of midazolam using an intravenous (IV) line obtained from the non-injured upper limb. They were told to fast eight hours before surgery. Upon their arrival to the OR, patients' standard monitoring, including noninvasive measurement of peripheral O 2 saturation ( O 2 sat), heart rate (HR), respiratory rate (RR), and noninvasive mean arterial pressure (MAP) was initiated. The registration of vital signs began at the anesthetic injection time and repeated 5,15 , and 30 minutes after the injection (start of surgery), and every 15 minutes until the end of surgery.

As sufentanil and dexmedetomidine have sedative characteristics, no intraoperative sedative was administered to the patients. However, if the administration of the sedative was indicated, $100 \mu \mathrm{~g}$ fentanyl would be injected intravenously, and the patient would be excluded.

The patients underwent nerve blockade under ultrasound guidance (SonoAce ${ }^{T M}$ R5 Ultrasound Machine [Samsung] with LN5-12/40@ Linear Probe [Samsung]) while their head was rotated at an angle of $45^{\circ}$ to the opposite of the operation side in the supine position. After proper sterilization of the skin and anesthetization of the cutaneous tissue by injecting 3 ml of $2 \%$ lidocaine, brachial plexus was spotted in the supraclavicular fossa using ultrasound guidance. Delivery of the anesthetic solution was performed via a single injection to the brachial plexus using a 22 G needle.

Sensory block was described using the pinprick test. Compared with the non-operative upper limb, the pinprick test has three scores: 2, indicating the normal sensation, 1, indicating the sensation loss to pinprick, and 0 , indicating the sensation loss to fine touch. Achieving the score of 0 in the innervated regions of the five main branches of the brachial plexus (axillary, median, radial, musculocutaneous, and ulnar nerves) was considered a complete sensory block. Motor block was evaluated using modified Lovett's rating scale, which consists of 6 scores: 0 for complete paralysis, 1 for almost total paralysis, 2 for substantial movement impairment, 3 for slight movement impairment, 4 for a reduction in muscular force, and 5 for normal muscular force. The complete motor block was defined as reaching a score of 0 in the primary motor nerves of the upper limb innervated areas. The time interval between the completion of injection and the resultant complete block was defined as the onset of block. The time interval between the initiation of the complete block and its full restoration to the normal state was defined as the duration of the block.


Figure 1 The CONSORT flow of the study.

Patients' MAP, HR, RR, and 02 saturation were recorded up to the end of surgery. In the recovery room, patients were observed for 30 minutes regarding postoperative side effects including itching, nausea, or vomiting.

Pain levels were evaluated before, during, and after the surgery using the Visual Analog Scale (VAS), that ranges from 0 , indicating no pain, to 10 , reflecting the worst pain possible. The patients were familiarized with the scale before entering the OR. Pain levels were recorded at 30, 15, 10, and 5 minutes before, once during, and $6,12,18$, and 24 hours after the surgery. The VAS score at 30 minutes before surgery was registered concurrently with the injection time. For postoperative VAS score more than $4,5 \mathrm{mg}$ of IV morphine sulfate was administered. Also, the first opioid (IV morphine sulfate) request time (FORT) and total postoperative opioid consumption in the first 24 hours (TPOC24)
were recorded using patients' folders and nursing notes. The mean TPOC24 value in each group was determined as the primary indicator of postoperative analgesia. If the patient requested opioids after the first 24 hours, the time would be registered, and the total opioid consumption would be considered zero.

Finally, patients were asked about their satisfaction with the surgery. Overall satisfaction rates were evaluated using a scale from 1 , meaning a terrible experience, to 5 , which showed an excellent experience.

The primary outcome of this study was sensory block duration. The secondary outcomes included the onset of blocks, the duration of motor block, FORT, TPOC24, VAS scores, and patients' vital signs. The null hypothesis was that there would be no difference between the groups concerning the sensory block duration.

Based on the values taken from a study conducted by Farooq et al., ${ }^{12}$ the sample size was calculated $\mathrm{n}=20$ for each group using PASS® 11 software. The level of statistical significance throughout the data analysis was assumed $p<0.05$ for a two-sided $t$-test. Type 1 and type 2 errors were assumed 0.05 and 0.20 , respectively. The primary outcome, sensory block duration, was treated as a continuous variable. The difference that was expected to be detected between the means of the two groups was 47.4.

Data analysis was performed using IBM ${ }^{\circledR}$ SPSS ${ }^{\circledR}$ Statistics version 25 . Given the small sample size of the study groups, the Mann-Whitney $U$ test was used and summary statistics are presented as median and interquartile range (IQR). Besides, categorical variables are reported as absolute and relative frequencies, and the Chi-square test was performed to compare them. Vital signs' data were analyzed using a Linear Mixed Model (LMM). For each vital sign variable, a maximum of 13 timepoints, including 30 (baseline), 25, and 15 minutes before, at the beginning, and every 15 minutes up to the end of the surgery (maximum surgery time $=135$ minutes) were extracted. Due to different surgery durations, a LMM analysis was performed to compare these values. Regarding the small sample size, restricted maximum likelihood (REML) was chosen for LMM. All of the variables were modeled by using the Unstructured covariance type. Ultimately, due to multiple comparisons, the Holm-Bonferroni (HB) method was used for the correction of the family-wise error rate of 0.05 .

## Results

Demographic information and ASA classifications of both groups are summarized in Table 1. They were comparable between the groups. In the sufentanil group ( S ), the sensory and motor block duration was significantly longer compared to the other group. After adjustment of the study's $\alpha$ level by applying the HB method, significant differences between the onset of the blocks were ultimately revealed to be insignificant. The difference between the medians of the onset of sensory and motor blocks was approximately 1 minute and can be considered clinically irrelevant. Study groups were comparable regarding the duration of surgery. Detailed results for these variables are depicted in Table 2.

As presented in Table 2, there were significant differences in the patients' postoperative FORT and TPOC24 levels. The patients in group S had significantly lower TPOC24 levels, thus, a longer period of analgesia. Besides, the patients in group $S$ had also significantly longer FORT values.

Regarding the VAS scores, there was a small but statistically significant difference at various timepoints. However, after applying HB method, the initial statistically significant differences at 15 and 10 minutes before surgery and 18 hours post-surgery were corrected to insignificant ( $p=$ $0.014\left[0.002^{1} p=0.026\left[0.002^{\circ}\right]\right.$, and $p=0.041\left[0.003^{\circ}\right]$, respectively). As shown in Figure 2, VAS was slightly, but significantly lower in group $S$ at 12 hours post-surgery, and roughly the same at the rest of the timepoints.

[^6]There was no incidence of nausea or vomiting in either of the groups.

In LMM for the vital signs, type III tests of fixed effects showed no statistically significant difference among the groups. Further details are depicted in Figure 3.

Moreover, patients' overall satisfaction rate was comparable among the groups ( $p=0.054$ ).

## Discussion

The popularity of peripheral nerve blockade is rising. With fewer complications and more feasibility, it is an outstanding replacement to conventional general anesthesia during limb surgery. The supraclavicular approach under the guidance of ultrasound is among the most reliable and successful methods.

Like most local anesthetics, various drugs have been studied as adjuvants for bupivacaine. Dexmedetomidine is a well-known $\alpha-2$ adrenoreceptor agonist and eight times more selective than clonidine for $\alpha 2 / \alpha 1$ receptors. ${ }^{8}$ Many studies have evaluated both its intravenous ${ }^{13}$ and local ${ }^{11,2,8,12,14,15}$ effects on regional nerve block. Sufentanil, a semi-synthetic fentanyl analog, is believed to be 5 to 15 times more potent than fentanyl and has been used in various types of anesthesia, including as an adjuvant to local anesthetics. ${ }^{11,16-18}$ Sufentanil has been shown to prolong the duration of local analgesia when used as an adjuvant, ${ }^{10,11}$ however, some studies suggest otherwise. ${ }^{19}$ Since a limited number of studies have been done a head-to-head comparison of dexmedetomidine and sufentanil as adjuvants for local anesthetic during BPB, we compared these two drugs in our study. It is noteworthy that the use of ultrasonography can reduce not only the likelihood of supraclavicular BPB side-effects including phrenic nerve palsy but also the probability of intravenous or intra-arterial bolus injection of the anesthetic solution. Moreover, as elderly patients are more likely to benefit from BPB, probable bradycardia resulted from IV or intra-arterial dexmedetomidine, ${ }^{20,21}$ or a clinically significant decrease in O 2 saturation following intravenous sufentanil injections could be catastrophic. 22

In our study, the duration of surgery was comparable between the study groups. Similar findings were observed in previous studies. ${ }^{23-25}$ The duration of sensory and motor block was significantly improved in the sufentanil group. However, the onset of sensory and motor blocks was roughly similar among the groups. There were statistically significant differences concerning both TPOC24 and FORT, indicating better postoperative analgesia in the sufentanil group. Moreover, using VAS at various timepoints before and after the surgery, we observed significantly lower pain levels in the sufentanil group 12 hours after the surgery. Although it is plausible to assume that the considerable difference in TPOC24 levels might be due to the significant difference of VAS levels at 12 hours post-surgery, further follow-up data on the postoperative opioid consumption would be more helpful to establish a clearer understanding. Overall, the adjunction of sufentanil to the anesthetic solution seems to lower the postoperative pain slightly more than dexmedetomidine. This observation probably can be explained by the immense analgesic potency and the rapid onset of action of sufentanil. In this study, comparing the vital signs among

Table 1 Description of demographics and ASA classification among the groups.

| Parameter |  | Groups |  | Total |
| :---: | :---: | :---: | :---: | :---: |
|  |  | D ( $\mathrm{n}=20$ ) | $S(\mathrm{n}=20)$ |  |
| Sex (n\%) | Male | 13 (65\%) | 15 (75\%) | 28 (70\%) |
|  | Female | 7 (35\%) | 5 (25\%) | 12 (30\%) |
| Median age (IQR ${ }^{\text {a }}$ ) (years) |  | 38.00 (13) | 41.00 (17) | 40.00 (13.00) |
| Median height (IQR ${ }^{\text {a }}$ ( cm ) |  | 178.00 (13) | 175.50 (12) | 176.00 (13) |
| Median weight ( $\mathrm{IQR}^{\mathrm{a}}$ ) ( kg ) |  | 74.50 (12) | 75.00 (15) | 75.00 (14) |
| Median BMI (IQR ${ }^{\text {a }}$ ) |  | 23.46 (1.15) | 23.09 (2.25) | 23.16 (1.21) |
| ASA (n\%) | 1 | 13 (65\%) | 13 (65\%) | 26 (65\%) |
|  | 11 | 7 (35\%) | 7 (35\%) | 14 (35\%) |

ASA, American Society of Anesthesiologists physical status.
a Interquartile range.

Table 2 Description and comparison of onset and duration of blocks (minutes), First Opioid Request Time after the surgery (h), and Total Postoperative Opioid Consumption within $24 \mathrm{~h}(\mathrm{mg})$ among the groups.

| Parameter | Groups |  | The estimate of Median Difference ${ }^{\text {a }}$ | 95\% Confidence Interval ${ }^{\text {² }}$ |  | Two-tailed $p$-value ${ }^{b}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | D ( $\mathrm{n}=20$ ) | $S(\mathrm{n}=20)$ |  | Lower | Upper |  |
| Median sensory block onset (IQR) | 16.00 (1) | 14.00 (1) | -1.0 | -2.0 | 0.0 | 0.005 |
| Median sensory block duration (IQR) | 530.00 (65) | 647.50 (45) | 100.0 | 70.0 | 130.0 | < 0.001 |
| Median motor block onset (IQR) | 18.00 (0) | 17.00 (2) | -1.0 | -2.0 | 0.0 | 0.033 |
| Median motor block duration (IQR) | 470.00 (38) | 590.00 (18) | 120.0 | 100.0 | 130.0 | < 0.001 |
| Median duration of surgery (IQR) | 60.00 (30) | 67.50 (56) | 0.0 | -15.0 | 15.0 | 0.813 |
| Median FORT (IQR) | 16.00 (4) | 20.00 (4) | 4.0 | 3.0 | 7.0 | < 0.001 |
| Median TPOC24 (IQR) | 10.00 (0) | 5.00 (5) | -5.0 | -5.0 | -5.0 | < 0.001 |

[^7]Median of VAS scores


Figure 2 Description and comparison of VAS (interquartile range) at specific time intervals among the groups.


Figure 3 Comparison of mean vital sign variables between the groups using a Linear Mixed Model ( $p$-values are the significancy for Type III Tests of Fixed Effects of Timepoint.

* Study group by using the Unstructured covariance type. Error bars represent $\pm$ SD).
the groups did not render significant differences. There were no incidences of cardiopulmonary complications among the patients. No patient reported itching, nausea, or vomiting. Besides, patients' satisfaction rates were comparable between the groups.

It has been shown that both the concentration and volume of the anesthetic solution are influential to attain desirable local anesthesia. ${ }^{26}$ Although there were studies with lower concentrations of local anesthetic, ${ }^{14,23}$ given the nature of dexmedetomidine and the potency of sufentanil, studying low concentrations of bupivacaine could hypothetically alter the effects of sufentanil or dexmedetomidine in an unbalanced fashion. Hence, we chose $0.5 \%$ bupivacaine concentration.

Farooq et al. conducted a randomized trial on 105 patients undergoing supraclavicular brachial plexus block. They compared three groups of patients receiving either normal saline added to $3 \mathrm{mg} . \mathrm{kg}^{-1}$ of $0.75 \%$ ropivacaine, 1 $\mu \mathrm{g} . \mathrm{kg}^{-1}$ of fentanyl added to $3 \mathrm{mg} . \mathrm{kg}^{-1}$ of $0.75 \%$ ropivacaine, or $1 \mu \mathrm{~g} . \mathrm{kg}^{-1}$ of dexmedetomidine added to $3 \mathrm{mg} . \mathrm{kg}^{-1}$ of $0.75 \%$ ropivacaine. Their results showed better onset and duration of blocks in the fentanyl group. They reported no significant difference between the groups concerning postoperative analgesia and observed no side effects in the groups. ${ }^{12}$

Dharmarao and Holyachi showed that the addition of 1 $\mu \mathrm{g} . \mathrm{kg}^{-1}$ of dexmedetomidine compared with the addition of $1 \mu \mathrm{~g} . \mathrm{kg}^{-1}$ of fentanyl to $0.5 \%$ ropivacaine during the ultrasound-guided supraclavicular BPB does not make a significant difference regarding the onset of blocks. On the other hand, the duration of blocks was significantly longer in the dexmedetomidine group. While they concluded that the postoperative analgesia was longer in the dexmedetomidine
group, they report no significant difference concerning the administered rescue analgesics. Interestingly, even though they used $1 \mu \mathrm{~g} . \mathrm{kg}^{-1}$ of dexmedetomidine, the researchers reported more sedation, bradycardia, nausea, and vomiting incidences in the dexmedetomidine group that was statistically insignificant. ${ }^{27}$

In separate studies, Kaur et al. and Hamed et al. found that dexmedetomidine significantly improves the onset and duration of sensory and motor blocks with significantly longer postoperative analgesia compared with fentanyl. ${ }^{2,28}$

Hamed et al. compared three groups of patients receiving either $1.5 \mathrm{mg} . \mathrm{kg}^{-1} 0.5 \%$ bupivacaine, the same dose of bupivacaine plus $1 \mathrm{mg} . \mathrm{kg}^{-1}$ dexmedetomidine, or the same dose of bupivacaine plus $1 \mathrm{mg} . \mathrm{kg}^{-1}$ fentanyl. Despite their reported statistically significant differences between the groups regarding HR and MAP variables, they concluded that dexmedetomidine is a better adjuvant for bupivacaine without substantial adverse effects. ${ }^{2}$

Kaur et al. compared $1 \mu \mathrm{~g} . \mathrm{kg}^{-1}$ of dexmedetomidine with $1 \mu \mathrm{~g} . \mathrm{kg}^{-1}$ of fentanyl as adjuvants for $25 \mathrm{~mL} 0.5 \%$ levobupivacaine. They reported no statistically significant side effects in the study except for grade 2 sedation in the dexmedetomidine group. ${ }^{28}$

Dexmedetomidine is shown to be more effective than morphine on the onset and duration of sensory and motor block in epidural anesthesia. ${ }^{29}$ Moreover, regarding a study by Barzin et al., as an adjuvant to local anesthetic during BPB, sufentanil is significantly more effective on postoperative analgesia than morphine and buprenorphine. ${ }^{10}$ It is noteworthy that the addition of fentanyl to local anesthetic has been shown to increase the duration of sensory block. ${ }^{30}$ A similar result showing prolonged analgesia with sufentanil
is reported in a study by Antonucci. ${ }^{16}$ Since sufentanil is an analgesic 5 to 15 times more potent than fentanyl, ${ }^{17,18}$ the discrepancy of the results between our study and the mentioned studies on dexmedetomidine and fentanyl is possibly due to this considerable difference in drugs' potency. The difference in the dosage of the drugs between the current and the previously mentioned studies is yet another possible factor. However, due to the lesser sample size of our study, there might be no adequate material for challenging those findings.

A relatively low number of subjects was a noticeable limitation of our study. Due to logistic constraints, we had limited postoperative monitoring of the patients and no follow-up for the patients' analgesic consumption after their discharge. Further studies with larger sample sizes, different study groups, and better patient monitoring are mandatory for a better understanding of the subject.

## Conclusion

In summary, our study showed that during ultrasound-guided supraclavicular brachial plexus block, the addition of sufentanil as an adjuvant for bupivacaine can provide more desirable sensory and motor block than dexmedetomidine. In this study, no significant side effects were observed.

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## Conflicts of interest

The authors declare no conflicts of interest.

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Sociedade Brasileira de Anestesiologia

## ORIGINAL INVESTIGATION

# Perineural low dexamethasone dose as adjuvant in supraclavicular brachial plexus block for arteriovenous fistula creation in end stage renal disease: a randomized controlled trial 

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## KEYWORDS

Arteriovenous fistula; Brachial plexus block; Dexamethasone; Anesthetics, local


#### Abstract

Background and aims: Dexamethasone as adjunct to local anesthetic solution improves the quality of brachial plexus block (BPB). However, evidence for its efficacy at low doses (<4 mg) is lacking. This study was designed to evaluate the duration of analgesia attained with low dose dexamethasone as adjuvant to local anesthetic for creation of arteriovenous fistula (AVF) under BPB. Methods: Sixty-six patients scheduled for AVF creation were randomly allocated to receive either saline (control) or 2 mg dexamethasone, together with $0.5 \%$ ropivacaine and $0.2 \%$ lignocaine. The primary outcome was duration of analgesia, defined as time from performing the block to the first analgesic request. The secondary outcomes were time from injection to complete sensory block, time from injection to complete motor block, duration of motor block, postoperative analgesic consumption, and fistula patency at three months. Results: All the blocks were effective. In the group that received dexamethasone, the time to first analgesic request was significantly delayed ( $432 \pm 43.8$ minutes vs. $386.4 \pm 40.2$ minutes; $p$ $<0.01$ ). The onset of sensory and motor blockade occurred faster in dexamethasone group and overall analgesic consumption was also reduced. However, dexamethasone addition did not prolong the duration of motor block. There was no statistically significant difference in the patency of fistulas between the two groups at three months. $(p=0.34)$.


[^8]
#### Abstract

Conclusion: Addition of low-dose perineural dexamethasone to local anesthetic solution significantly prolonged the duration of analgesia. Further trials are warranted to compare the adverse effects between dexamethasone doses of 4 mg and lower. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/ 4.0/).


## Introduction

There has been a considerable evolution in the practice of regional anesthesia over the past few decades. Regional anesthesia improves the quality of perioperative pain management. Although the single-injection regional anesthesia technique is easy to perform and requires fewer resources and manpower during postoperative management, its benefits may be offset by its limited duration of analgesia. This limitation of the single-injection technique can be overcome by the use of adjuvants along with local anesthetics, which may serve the purpose of prolonging the postoperative analgesia. Furthermore, a good quality postoperative analgesia ensures patient satisfaction, decreases duration of hospital stay, and decreases the occurrence of chronic pain and its related complications.

The efficacy of dexamethasone as a perineural adjunct to local anesthetics in prolonging the duration of analgesia has been validated by several prior systematic reviews and meta-analyses. ${ }^{1-5}$ Various doses of dexamethasone have been used in studies ranging from 4 mg to 10 mg , without a clear rationale for using a particular dose. The use of dexamethasone may also result in complications like hyperglycemia, immunosuppression, infection, suppression of hypothalamic-pituitary axis, impaired wound regeneration, neurotoxicity, amongst others - which may be dose-dependent in nature. ${ }^{6}$ Furthermore, there is lack of evidence to suggest that higher perineural doses of dexamethasone are more efficacious compared to lower doses. ${ }^{7}$

In contrast to this, a recent meta-analysis by Kirkham et al. ${ }^{5}$ showed a ceiling dose of 4 mg for perineural administration. Few authors have studied perineural dexamethasone administration at doses lower than 4 mg , and therefore robust evidence for doses less than 4 mg is lacking.

The objective of this randomized controlled trial was to evaluate the duration of analgesia attained with 2 mg dexamethasone as an adjuvant to local anesthetic solution in ultrasound guided brachial plexus block (BPB) in patients with chronic kidney disease (CKD) undergoing arteriovenous fistula (AVF) creation. We hypothesized that a lower perineural dose of dexamethasone also significantly prolongs the duration of analgesia of supraclavicular BPB.

## Methods

This prospective, double-blind, randomized study was conducted after obtaining approval by the Institutional Ethics Committee (IEC 9606/PG 2Trg/2013/14301). Written informed consent was obtained from the patients enrolled in the study. Sixty-six patients of either gender, aged 18 -60 years, belonging to American Society of Anesthesiologists (ASA) physical status II and III, and scheduled for
arteriovenous fistula (AVF) creation were studied from June 2014 to November 2016. Non-inclusion criteria were: uncooperative patients or patient refusal, clinically significant coagulopathy, presence of upper extremity peripheral neuropathy/neurological disorder, presence of local site infection, history of known allergy to local anesthetics, body mass index less than 18 or more than 25 , revision of previously blocked AVF, contraindication for brachial block like anatomical deformities, history of cephalic vein or central vein occlusion, and brachial or radial artery stenosis.

The enrolled patients were randomly allocated by a com-puter- generated sequence into two groups - group RL and group RLD. Sealed opaque envelopes with the group allocation were opened by an anesthesiologist not involved in the study, who prepared the drug solutions for the block. Patients allocated to group RL $(\mathrm{n}=33)$ received BPB using $0.5 \%$ ropivacaine (Ropin, Neon Laboratories Ltd., Mumbai, India) $1 \mathrm{mg} . \mathrm{kg}^{-1}$, $2 \%$ lignocaine (Lox, Neon Laboratories Ltd, Mumbai, India) $2 \mathrm{mg} . \mathrm{kg}^{-1}$, and 2 mL normal saline. Patients in group RLD $(\mathrm{n}=33)$ received BPB using $0.5 \%$ ropivacaine ( $1 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ ), $2 \%$ lignocaine ( $2 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ ) and 2 mg preserva-tive-free dexamethasone diluted in 2 mL normal saline.

The patients were evaluated prior to surgery and were explained about the anesthetic procedure. Monitoring consisted of standard ASA monitors - electrocardiography, noninvasive blood pressure, pulse oximetry, and temperature. Pre-procedural vitals were recorded. Using strict aseptic precautions, a sterile $6-13 \mathrm{MHz}$ linear US (ultrasound) transducer (SonoSite; M-Turbo; SonoSite; Bothell, Washington, USA) was used to visualize the brachial plexus in supraclavicular region. Brachial plexus was recognized by its characteristic "honeycomb appearance" in the region lateral to the subclavian artery. After infiltrating the skin with local anesthetic, a 22G, 50-mm, insulated needle (Stimuplex A; B Braun, Melsungen, Germany) was inserted in an "in plane technique" to reach the lateral corner of the subclavian artery and above the first rib. A small volume of local anesthetic solution ( $0.5-1 \mathrm{~mL}$ ) was injected initially to hydrodissect the fascial sheath and perineural structures. With the needle tip near the brachial plexus, drug solution was injected in aliquots with intermittent aspiration until the entire plexus was encircled by the solution. Sensory block was evaluated by a blunt-tipped needle every five minutes at $5,10,15$, and 20 minutes after injection in the region of distribution of the following nerves as: median (palmar aspect of the second finger), ulnar (fifth finger), radial (dorsum of the hand between the thumb and second finger), musculocutaneous (lateral forearm), and medial cutaneous nerve of the forearm (medial forearm). A validated 3-point scale was used: $0=$ no block (patient has normal sensation); 1 = patient can feel pin prick, but the sensation is reduced compared with the unblocked side; and 2 = complete anesthesia. The combined score of sensory blockade of the 5
nerves was calculated. The patient was considered to have a satisfactory sensory block when a minimal score of 9/10 was achieved. Motor blockade was evaluated by the modified Bromage score ${ }^{8}$ for upper limb: $0=$ normal motor function with full extension and flexion of elbow, wrist, and fingers; 1 = decreased motor strength, with ability to move only fingers; 2 = complete motor block with inability to move elbow, wrist, and fingers. A successful block was one with adequate sensory blockade and the patient being able to tolerate a simulated surgical stimulus. The need to give additional local anesthetic infiltration or general anesthesia constituted a failed block. Intraoperative hemodynamics were recorded every five minutes.

Visual Analog Scale (VAS) was used by a blinded investigator to assess postoperative pain at 1, 2, 4, 6, 8, 12, and 24 hours after surgery. Oral paracetamol 500 mg was administered when VAS score exceeded 4. If the pain was not relieved with a repeat dose of paracetamol, then patients were administered tablet tramadol 100 mg per oral. The analgesic doses given were recorded. Time to return of motor power was assessed by the patient's ability to abduct the shoulder. Any adverse events like hypotension (a 20\% decrease in relation to the baseline value), bradycardia (HR $<50$ beats per min ), hypoxemia ( $\mathrm{SpO}_{2}<90 \%$ ), nausea and vomiting, vascular puncture, inadvertent IV (intravenous) injection, significant eye drooping (Horner syndrome), hematoma formation, local anesthetic toxicity, pneumothorax, and dyspnea were recorded. The patients were discharged home after 24 hours and interviewed by telephone after 48 hours for the presence of any complications.

During a follow-up visit after three months, the patency of AV fistula was assessed by placing a Doppler probe over the target vessels and observing for blood flow. The measurements of blood flow through the vessels were recorded only after stabilization of signal for at least 30 seconds. Minimum of two readings were obtained.

The primary outcome was the duration of analgesia, defined as the time from performing the block to the first analgesic request. The secondary outcomes were time of onset of sensory block (defined as the time from injection to
complete sensory block); time of onset of motor block (defined as the time from injection to complete motor block); duration of motor block (injection to full ability to abduct the shoulder); overall postoperative analgesic consumption; and AVF patency at three months as assessed by Doppler ultrasound.

All observations were recorded in a standardized data collection sheet and analyzed statistically using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). Qualitative or categorical variables were described as frequencies, percentages and proportions. The association of categorical data with the two groups was analysed using Chi-square test or Fisher's exact test, whichever applicable. The normality of quantitative data was assessed using Kolmogorov-Smirnov test of normality. Quantitative variables were described in terms of mean and standard deviation when normally distributed and median and quartiles if non-normally distributed. For normally distributed quantitative data, Student's $t$-test (unpaired) was applied to compare two group means. For skewed data, Mann-Whitney U Test was applied to compare the distributions of two groups. For time related comparisons within groups, repeated measure ANOVA test was used, followed by post hoc multiple comparisons test (Bonferroni correction). The duration of analgesia was analysed by the Kaplan-Meier survival analysis. A $p$-value $<0.05$ was considered as significant.

The calculated sample size was 23 patients per group based on expected improvement of analgesia duration by $30 \%$ at $p<0.05$ and power goal of $90 \%$. With a dropout rate of $40 \%$, the minimum number of patients to be studied came out to be 33 patients in each group.

## Results

Sixty-six patients were enrolled and randomized out of 70 patients who were assessed for the study (Fig. 1). All the patients completed the study. The data was analyzed and


Figure 1 CONSORT flow diagram of participants enrolled in the study.

Table 1 Patient characteristics.

|  | Group RL <br> $n=33$ | Group RLD $n=33$ |
| :--- | :--- | :--- |
| Age (years) | $46.1 \pm 15.7$ | $46.2 \pm 12.2$ |
| Gender (male/female) | $18 / 15$ | $21 / 12$ |
| Height (cm) | $161.5 \pm 5.1$ | $162.1 \pm 4.9$ |
| Weight (kg) | $63.6 \pm 6.4$ | $64.3 \pm 4.7$ |
| Duration of surgery <br> $\quad(\mathrm{min})$ | $90.8 \pm 19.4$ | $99.1 \pm 17.1$ |
| Duration of anesthesia <br> $\quad(\mathrm{min})$ | $258.5 \pm 76.4$ | $263.6 \pm 74.6$ |

All results are expressed as mean $\pm$ SD.

Table 2 Blockade characteristics.

|  | Group RL | Group RLD | $p$-value |
| :--- | :--- | :--- | :--- |
| Time to onset of <br> sensory <br> block | $6.2 \pm 1.1 \mathrm{~min}$ | $5.3 \pm 1.0 \mathrm{~min}$ | $<0.01^{\mathrm{a}}$ |
| Time to onset of <br> motor block <br> Duration of sen- <br> sory block | $6.7 \pm 1.4 \mathrm{~min}$ | $386.4 \pm 40.2 \mathrm{~min}$ | $432 \pm 43.8 \mathrm{~min}$ |
| Duration of <br> motor block | $236.5 \pm 32.4 \mathrm{~min}$ | $250.0 \pm 37.8 \mathrm{~min}$ | 0.07 |

All the values are expressed as mean $\pm$ SD.
${ }^{\text {a }} p<0.05$.
the baseline characteristics were found to be comparable between the two groups (Table 1).

The addition of low dose dexamethasone to a combination of ropivacaine and lignocaine resulted in a faster onset of sensory blockade $(5.3 \pm 1.0 \mathrm{~min}$ vs. $6.2 \pm 1.1$

Table 3 Postoperative pain scores (VAS) at different time points.

| Time | Group RL | Group RLD | $p$-value |
| :--- | :--- | :--- | :--- |
| VAS 1 h | $0(0,0)$ | $0(0,0)$ | 1.00 |
| VAS 2 h | $0(0,0)$ | $0(0,0)$ | 0.32 |
| VAS 4 h | $1.06(1,0)$ | $0.82(1,1)$ | 0.18 |
| VAS 6 h | $2.88(3,2)$ | $2.12(2,2)$ | $0.002^{\mathrm{a}}$ |
| VAS 8 h | $3.27(3,1)$ | $2.76(3,1)$ | $0.016^{\mathrm{a}}$ |
| VAS 12 h | $1.58(2,1)$ | $1.42(1,1)$ | 0.19 |
| VAS 24 h | $1.06(1,0)$ | $1.0(1,0)$ | 0.71 |

All the values are expressed as median (IQR).
${ }^{\text {a }} p<0.05$.
$\min ; p<0.01$ ). Dexamethasone also hastened the onset of motor blockade ( $3.2 \pm 0.9 \mathrm{~min}$ vs. $6.7 \pm 1.4 \mathrm{~min}$; $p<0.01$ ). (Table 2)

The duration of analgesia was also prolonged with the addition of dexamethasone ( $432 \pm 43.8 \mathrm{~min}$ vs. $386.4 \pm 40.2$ min ) which was statistically significant ( $p<0.01$ ). The painfree probability with time after performing the block was significantly higher in the dexamethasone group (log rank test, $p<0.001$ ) (Fig. 2). However, dexamethasone did not prolong the duration of motor blockade significantly (250.0 $\pm 37.8 \mathrm{~min}$ vs. $236.5 \pm 32.4 \mathrm{~min} ; p=0.07$ ). (Table 2 )

The pain (VAS) scores of the two groups were comparable up to four hours postoperatively after which lower VAS scores were observed in the RLD group compared to RL group (Table 3). The VAS score was significantly less in RLD group compared to RL group at 6 hours ( $p<0.01$ ) and 8 hours ( $p=0.02$ ) postoperatively.

In the RLD group, 7 patients did not request for any postoperative rescue analgesic, 26 patients requested for rescue analgesic once, and no patient required a second dose of rescue analgesic. In the RL group, all patients requested for postoperative rescue analgesia out of which 28 patients


Group RL- Ropivacaine, lignocaine and normal saline
Group RLD- Ropivaciane, lignocaine and dexamethasone
Figure 2 Duration of analgesia: Kaplan-Meier survival curve depicting the cumulative pain-free probability as a percentage in both groups after performing the block.
requested only once while 5 patients requested second dose of rescue analgesia. No patient in either of the groups requested for a second rescue analgesic. There was statistically significant difference regarding overall analgesic consumption between the two groups $(p=0.01)$. However, addition of dexamethasone had no impact on the outcome of the fistula and the difference in the flow in the fistula between the two groups was not statistically significant ( $p=0.34$ ).

## Discussion

The results of this prospective, randomized study concluded that the addition of low dose dexamethasone to a combination of ropivacaine and lignocaine hastened the onset of sensory and motor blockade while simultaneously prolonging the duration of analgesia in AVF construction surgery. This study also demonstrated better postoperative pain relief and lesser postoperative rescue analgesic consumption in the group which received dexamethasone.

Supraclavicular brachial plexus block provides rapid, dense, and predictable anesthesia of the entire upper extremity in a very consistent manner. Ultrasound guidance for supraclavicular block reliably reduces the procedure time and improves the safety profile of the technique. ${ }^{7}$ Occasionally, a single-shot technique for peripheral nerve block may prove inadequate to provide pain relief in postoperative period. Perineural catheters have been used to extend the duration of analgesia, but these may be associated with problems like difficulty in catheter placement, catheter migration, infection, anesthetic drug leakage, or pump malfunction requiring complex logistic organization, especially following ambulatory surgery. ${ }^{9}$ This led to the use of various adjuvants to prolong the duration of analgesia administered by a single-shot technique thereby avoiding the use of continuous perineural infusions. ${ }^{10-12}$

Corticosteroids like dexamethasone have been used routinely for chronic pain management by administration into the epidural space for treating radicular pain with a reliably acceptable side effect profile. ${ }^{13}$ There are various theories regarding the mechanism of action of dexamethasone as an adjuvant to local anesthetics in regional anesthesia. Steroids induce a degree of vasoconstriction, so one theory is that the drug acts by reducing local anesthetic absorption. ${ }^{14} \mathrm{~A}$ more attractive theory holds that dexamethasone increases the activity of inhibitory potassium channels on nociceptive C-fibers (via glucocorticoid receptors), thus decreasing their activity. ${ }^{15}$ Due to concern of adverse physiochemical effects from perineural dexamethasone, certain authors have recommended against its use as an adjuvant to LA or have suggested that alternative routes of administration (IV) are preferable. ${ }^{16}$ Several studies have used varying doses of dexamethasone ranging from 4 mg to 10 mg , hence an optimum dosing regimen remains undefined. Despite the concern surrounding the "off-label" use of perineural adjuvants, the safety profile of dexamethasone is promising.

The current study demonstrated prolongation of duration of analgesia in patients receiving 2 mg perineural dexamethasone as adjunct to local anesthetic. Previous studies have also successfully demonstrated that lower doses of dexamethasone ranging from $1-4 \mathrm{mg}$ are equally effective as
analgesics in the perioperative period. ${ }^{17-20}$ We found a similar duration of motor blockade in dexamethasone and control groups, in contrast to the findings of Liu ${ }^{17}$ and Albrecht et al. ${ }^{19}$ They may have observed a different duration of motor blockade possibly due to various reasons. Firstly, the patients studied by Liu and Albrecht et al. underwent shoulder arthroscopy and required shoulder immobilization in the postoperative period, which may probably compromise the motor function recovery evaluation. Secondly, the motor function was evaluated by a telephonic call to the patient at home in the above-mentioned studies. This subjective assessment of motor function recovery may be inaccurate due to recall bias. The prolonged analgesia without prolongation of motor blockade is desirable in our patient population since AVF construction is performed as an ambulatory surgery in our center. It is beneficial for the patient, surgeon, as well as the anesthesiologist since it allows early discharge and reduces hospital costs and wastage of manpower. Our study also revealed better pain-related outcomes in patients receiving dexamethasone in the form of lower postoperative pain scores and lesser requirement of rescue analgesia. Our study demonstrated longer time to first analgesic request in dexamethasone group, which was similar to the findings of Woo et al. ${ }^{18}$ However, a few other studies were unable to detect any clinically significant difference in postoperative pain scores and analgesic requirement in patients receiving dexamethasone. ${ }^{17,19,20}$ This may be attributed to the heterogeneity in type, volume, and dose of local anesthetic drugs as well as the level of blocks administered in the studies.

Although the difference in duration of analgesia between the two groups in our study was statistically significant, the actual difference in duration was less than 1 hour. The percentage difference was $15 \%$, which was much less than the expected difference of $30 \%$ used in our sample size calculation. In their systematic review and meta-analysis of nine randomized trials, Choi et al. ${ }^{1}$ found that higher doses of perineural dexamethasone in the range of $4-10 \mathrm{mg}$ when mixed to the long-acting local anesthetics could prolong the duration of analgesia by almost 9 to 10 hours. The use of lower doses like $1-3 \mathrm{mg}$ has shown varying results by prolonging the analgesia duration by a wide range of 2.5 -11 hours. ${ }^{17-19}$ The use of lower doses may not always provide a clinically significant effect, sometimes it may only provide a subtle and marginal benefit, similar to what was observed in our study. The prolongation of analgesia provided by perineural dexamethasone seems to be dose dependent. Since Kirkham et al. ${ }^{5}$ found that perineural dexamethasone reaches a ceiling effect after a 4 -mg dose, it may be preferable to use $4-\mathrm{mg}$ dose as deemed effective in their metanalysis. The systemic adverse effects of dexamethasone, like hyperglycemia, immunosuppression, and neurotoxicity, were not assessed in our study. If the use of doses $<4 \mathrm{mg}$ has similar incidence of adverse effects, it would be better to use a standard dose of 4 mg as it guarantees a longer analgesic duration. On the contrary, if lower doses produce fewer adverse effects, the anesthesiologist may weigh the risk-benefit ratio of administering lower dexamethasone doses in this susceptible patient population.

We found that both groups had similar low VAS scores throughout the 24 hours of assessment. Although we found a statistically significant difference in VAS scores at 6- and 8-
hour intervals, this may or may not be clinically relevant since the absolute difference in VAS pain scores was less than 1 point between the groups. The absolute value of the minimal clinically important difference in pain severity continues to be debatable, but values varying between 0.9 and 1.1 on VAS scale have been reported to be clinically significant. ${ }^{21,22}$ We chose to use the VAS scale as it is practical, reproducible, and sensitive to treatment effects. Even though small differences in scores may reach statistical significance during analysis, statistical significance cannot be equated with clinical significance. For the clinicians, it is the actual clinical impact on patients' pain that is more important.

Predicting the factors that contribute to maturation of AVF remains challenging. This is due to the heterogeneity of ESRD patients studied, and also due to the varied etiologies of ESRD. AVF maturation may also be influenced by several other factors, like patient's comorbid illnesses including but not limited to - peripheral vascular disease and diabetes mellitus, which occur concurrently in patients with chronic kidney disease. ${ }^{23}$ As concluded by Reynaud et al. in their study, BPB leads to significant intraoperative forearm vasodilation, but does not result in improved distal AVF prevalence or outcomes when compared to the conventional techniques. ${ }^{24}$ In our study, there was no statistically significant difference on adding dexamethasone to the flow characteristics of the fistulae. Also, of all the 66 patients recruited in the study, all the fistulas except one were patent at the three months follow up. The good outcome may be attributed to the meticulous preoperative site selection using ultrasound, which was done for all the patients enrolled in the study. It may also be attributed to the administration of BPB, which has shown to improve AVF outcomes. ${ }^{25,26}$ A larger sample size is, however, warranted to evaluate the long-term clinical benefits of addition of dexamethasone. It may also be advisable to follow these patients for a longer time to accurately assess the patency of fistula before drawing conclusions about the long-term patency.

There were some limitations in the study. Firstly, the sample size may be inadequate to decide if the perineural dexamethasone as an adjuvant in brachial plexus block can actually affect the fistula outcome. Secondly, the three months follow-up period may be insufficient to conclude whether the intervention actually resulted in a meaningful outcome. Longer follow-up periods are desired to achieve more definitive results. Thirdly, although the fistulas were created by surgeons with at least five years of surgical experience, surgeries performed by different surgeons or by different operative technique may have an impact on the outcome of the fistula. Fourthly, the maturation of the fistulas is also affected by patient-related factors like underlying comorbidities which were not assessed. ${ }^{27,28}$ Another possible limitation of this study is that it is possible for the patients to have late-onset neuropathy with the use of perineural dexamethasone, which was not assessed as the patients were not followed beyond three months postoperatively. For future investigations, it is suggested to follow up these patients for longer durations using survey questionnaires or telephonic interviews to detect such complications.

To conclude, there is no randomized controlled trial conducted to assess the efficacy of low-dose dexamethasone as
an adjuvant to local anesthetic agent for creation of an arteriovenous fistula to the best of our knowledge. The lower dose of dexamethasone seems to provide a subtle and marginal prolongation of duration of analgesia and may improve patient comfort and satisfaction in the postoperative period. However, it may be prudent to use dexamethasone doses < 4 mg only if it has lower incidence of adverse effects compared to doses of 4 mg and higher, as lower doses may be accompanied by the disadvantage of clinically insignificant pain relief in the postoperative period. Hence, future studies aimed at comparing the incidence of adverse events between perineural dexamethasone doses of 4 mg and 2 mg may resolve this existing conundrum for the anesthesiologist.

## Conflicts of interest

The authors declare no conflicts of interest.

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# Safety and efficacy of target-controlled infusion versus intermittent bolus administration of propofol for sedation in colonoscopy: a randomized controlled trial 

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## KEYWORDS

Colonoscopy;
Deep sedation; Intravenous anesthetics;
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#### Abstract

Background: Our objective was to compare the safety and efficacy of Target-Controlled Infusion (TCI) versus intermittent bolus of propofol for colonoscopy sedation. Methods: We conducted a randomized (1:1), single-blind, parallel-group superiority trial with fifty ASA I or II patients, both sexes, aged 18 to 65 years, Body Mass Index $\leq 30 \mathrm{~kg} . \mathrm{m}^{-2}$, undergoing colonoscopy, allocated to receive propofol by TCl (effect-site, $2 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ plus $0.5 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ until unconsciousness and as necessary for agitation) or intermittent bolus ( $1 \mathrm{mg} . \mathrm{kg}^{-1}$ plus $0.5 \mathrm{mg} . \mathrm{kg}^{-1}$ every 5 minutes or as above). The primary safety outcome was the need for airway maneuvers and the primary efficacy outcome was the need for interventions to adjust the level of sedation. Secondary outcomes included incidence of agitation, propofol dose, and time to recovery. Results: The median (IQR) number of airway maneuvers and interventions needed to adjust sedation was $0(0-0)$ vs. $0(0-0)(p=0.239)$ and $1(0-1)$ vs. $3(1-4)(p<0.001)$ in the TCl and control groups, respectively. Agitation was more common in the intermittent bolus group - 2 ( $0-2$ ) vs. $1(0-1), p<0.001$. The mean $\pm$ SD time to recovery was $4.9 \pm 1.4$ minutes in the TCI group vs. $2.3 \pm 1.6$ minutes in the control group ( $p<0.001$ ). The total propofol dose was higher in the TCI group ( $234 \pm 46 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ vs. $195 \pm 44 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}(p=0.040)$ ). Conclusions: During colonoscopy, TCI is as safe as intermittent bolus of propofol while reducing the incidence of agitation and the need for dose adjustments. However, intermittent bolus administration was associated with lower total propofol dose and earlier recovery. © 2022 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/ 4.0/).


[^9]
## Introduction

Colonoscopy is indicated for diagnostic and therapeutic purposes in several colorectal disorders. ${ }^{1}$ However, colonoscopy is considered an invasive procedure and is associated with discomfort. The patient's fear of experiencing pain can result in anxiety and uncooperativeness. ${ }^{2}$ Therefore, the use of intravenous sedation is widely recommended. Although a combination of a benzodiazepine and an opioid may be used, propofol is usually the agent of choice, as it is associated with rapid arousal, shorter postanesthetic recovery time, and higher patient satisfaction. ${ }^{3}$

The conventional technique for propofol sedation in colonoscopy involves manual administration of intermittent boluses. This leads to fluctuations in plasma concentration of the anesthetic agent and may therefore be associated with undesirable effects such as agitation and respiratory depression ${ }^{4}$ due to insufficient and excessive depths of anesthesia, respectively. Conversely, in target-controlled infusion regimens, the dose is automated to reach and maintain a pre-set concentration, ${ }^{5}$ which can be titrated according to the patient's response, reducing the fluctuations associated with the conventional technique. Target-controlled infusion is now a well-established technique for administering total intravenous anesthesia in the operating theatre, ${ }^{6}$ but can also be useful for outpatient procedures requiring sedation. Research has shown that the target-controlled infusion of propofol increases the safety of sedation for outpatient procedures by reducing the incidence of respiratory depression. ${ }^{7}$ However, few studies have compared target-controlled infusion with the conventional intermittent bolus technique in colonoscopy.

The present study was thus designed to compare the safety and efficacy of target-controlled propofol infusion versus the intermittent manual bolus technique for sedation during colonoscopy. The hypothesis was that target-controlled infusion would result in less need for interventions (such as dose adjustments and airway maneuvers), reduced agitation, and no increase in respiratory depression during the procedure.

## Methods

## Study design

Randomized (1:1), single-blind, parallel-group superiority trial.

## Inclusion criteria

Inclusion criteria were age between 18 and 65 years, ASA (American Society of Anesthesiologists) physical status I and II, Body Mass Index less than or equal to $30 \mathrm{~kg} . \mathrm{m}^{-2}$, scheduled for elective colonoscopy. Patients with a known allergy to any of the drugs used for sedation were excluded, as were those with a history of chronic alcohol, benzodiazepine, or opioid use. The clinical phase of the trial was carried out in a tertiary hospital in Cuiabá, Mato Grosso, Brazil, first from October 2017 to February 2018 and, subsequently, in September and October 2020.

## Interventions

Ethical approval for this study (Plataforma Brasil certificate $\mathrm{n}^{\circ} 58452416.0 .0000 .8055$ ) was provided by the Ethical

Committee of the Federal Institute of Education, Science and Technology of Mato Grosso (IFMT), Cuiabá, MT, Brazil (chairperson Marilu Lanzarin) on August 11, 2017, and registered in the Brazilian Registry of Clinical Trials with accession number RBR-2dxshp (https://ensaiosclinicos.gov.br/rg/ RBR-2dxshp). The provisions of the CONSORT statement were followed throughout. After ethical approval had been obtained, 50 patients were selected and allocated randomly (1:1) by one member of the care team using the sealed opaque envelope method into two groups, depending on the sedation regimen: target-controlled infusion (experimental group) or intermittent manual bolus (control).

During the preanesthetic evaluation, patients scheduled to undergo colonoscopy were informed of the study and invited to participate; those who agreed then signed an informed consent form. In the endoscopy suite, patients were placed on multi-parameter monitoring (ECG, pulse oximetry, noninvasive blood pressure) and received oxygen via a nasal cannula ( $2 \mathrm{~L} . \mathrm{min}^{-1}$ ). Peripheral venous access was established with a 22G cannula. Due to the substantial differences between the two sedation techniques, blinding the anesthesiologist responsible for patient care was impossible.

Patients in the target-controlled infusion group were sedated with a single bolus of intravenous (IV) fentanyl, $1 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1}$, followed by target-controlled infusion of propofol with an initial target of $2 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ and titrated in $0.5 \mu \mathrm{~g}$. $\mathrm{mL}^{-1}$ increments until loss of responsiveness to tactile stimulation, corresponding to a score of 1 on the Observer's Assessment of Alertness/Sedation (OAA/S) Scale. ${ }^{8}$ (Table 1). Colonoscopy was begun once the target level of sedation had been achieved. If the patient developed agitation at any time during colonoscopy, additional $0.5 \mu \mathrm{~g} \cdot \mathrm{~mL}^{-1}$ target adjustments were performed. The target-controlled infusion was based on the Schnider et al pharmacokinetic model ${ }^{9,10}$ which provides for effect-site targeting. In the control group, patients were sedated with fentanyl $1 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \mathrm{IV}$, followed by propofol $1 \mathrm{mg} . \mathrm{kg}^{-1} \mathrm{IV}$. Additional $0.5 \mathrm{mg} . \mathrm{kg}^{-1}$ boluses of propofol were administered as needed to achieve the loss of responsiveness to tactile stimuli ( $\mathrm{OAA} / \mathrm{S}=1$ ), and colonoscopy was begun. To maintain sedation in the control group, $0.5 \mathrm{mg} . \mathrm{kg}^{-1}$ propofol boluses were repeated every 5 minutes, or in case of agitation or patient movement. In both groups, if the peripheral oxygen saturation fell below $90 \%$, ventilatory assistance with a jaw-thrust maneuver and noninvasive ventilation with $100 \%$ oxygen via face mask was provided; in the target-controlled infusion group, the target was reduced by $0.5 \mu \mathrm{~g} . \mathrm{mL}^{-1}$ as well. Given obese subjects were not included in our study, we used total body weight-

Table 1 Observer's Assessment of Alertness/Sedation (OAA/S) Scale.

| Responsiveness | Score |
| :--- | :--- |
| Responds readily to name spoken in normal tone <br> Lethargic response to name spoken in normal | 5 |
| $\quad$ tone |  |$\quad 40$

based regimens for the bolus dose and the target-controlled infusion. Upon completion of the procedure, patients were observed until they were responsive to the sound of their names ( $O A A / S=4$ ) and then transferred to the postanesthesia care unit. All data were collected or supervised by the same investigator (first and second authors).

## Outcomes

The primary outcome was designed to test the hypothesis of superiority of the target-controlled infusion method in controlling the level of sedation by reducing the need for anesthesiologist interventions during colonoscopy compared to the control group. Interventions were defined as propofol dose adjustments, whether additional boluses or target corrections (primary efficacy outcome), as well as maneuvers to ensure airway patency and assist ventilation if necessary (primary safety outcome).

Additional analyses were carried out for the incidence of agitation, defined as any movement made by the patient in reaction to endoscope manipulation; time to arousal after completion of colonoscopy; total dose of propofol administered during sedation; and the predicted effect-site Concentration (Ce) of propofol at loss and at the recovery of consciousness.

## Sample size calculation

Considering an average colonoscopy duration of 20 minutes ${ }^{11}$ and the need to repeat manual propofol boluses every 5
minutes to maintain sedation in the control group (four interventions), we estimated that a reduction of at least one intervention would occur in the target-controlled infusion group (i.e., three interventions would be required), with a standard deviation of one intervention. To detect this difference at a significance level of $5 \%$ and statistical power of $90 \%$, a minimum sample size of 24 patients in each group was established. Considering possible losses, we approximated the sample size upward to 50 patients. A two-tailed means comparison test for two samples was used for this calculation.

## Statistical analysis

Kolmogorov-Smirnov test and Levene's test of variances were used for evaluating the assumptions of normality and homoscedasticity of the studied variables, respectively. Pearson's Chi-Square test was used to compare proportions. Student's $t$-test for independent samples and the MannWhitney U test were used to compare means between the groups as appropriate. Pearson's correlation test was used to analyze the correlation between the Ce of propofol at loss and recovery of consciousness. Statistical significance was accepted at $p<0.05$.

## Results

Of 133 eligible subjects, we included 50 . Fourteen refused to participate, and 69 did not meet the inclusion criteria. The CONSORT flow diagram of the study is shown in Figure 1.


Figure 1 CONSORT flow diagram of patient inclusion.

Table 2 Demographic characteristics of patients and duration of the procedure. Values are given as numbers (percentage) or mean $\pm$ Standard Deviation.

| Parameter | Group |  |
| :---: | :---: | :---: |
|  | Targetcontrolled infusion $(n=25)$ | Intermittent bolus $(\mathrm{n}=25)$ |
| Sex |  |  |
| Male | 8 (32\%) | 12 (48\%) |
| Female | 17 (68\%) | 13 (52\%) |
| Age (years) | $45.4 \pm 14.1$ | $43.4 \pm 11.5$ |
| Weight (kg) | $68.5 \pm 11.6$ | $70.8 \pm 11.6$ |
| Height (m) | $1.66 \pm 0.08$ | $1.67 \pm 0.09$ |
| Body mass index, $\mathrm{kg} \cdot \mathrm{m}^{-2}$ | $24.6 \pm 3.2$ | $25.1 \pm 2.8$ |
| Duration of procedure, minutes | $13.1 \pm 3.4$ | $12.7 \pm 4.1$ |

Table 2 presents the demographic characteristics and duration of colonoscopy in the groups. There was no significant difference in the duration of colonoscopy.

Table 3 describes the detailed results on the variables of interest. The Target-Controlled Infusion (TCI) group required fewer dose adjustments and had a lower incidence of agitation during colonoscopy. There was no between-group difference in safety, i.e., the number of airway maneuvers performed secondary to hypoxemia. There was also no significant difference between groups in the number of patients who experienced respiratory depression during sedation. The total dose of propofol was significantly higher in the TCI group. The time required to achieve the desired level of sedation and recovery was significantly longer with TCI.

In the TCI group, the mean (standard deviation) predicted effect site concentrations for loss and recovery of consciousness were $3.6(0.7) \mu \mathrm{g} \cdot \mathrm{mL}^{-1}$ and $1.6(0.5) \mu \mathrm{g} \cdot \mathrm{mL}^{-1}$, respectively. Figure 2 illustrates the analysis of the observed values for these variables. Despite the significant difference, a positive correlation (49\%) was observed between the predicted effect-site concentration of propofol at loss and
recovery of consciousness with Schnider's pharmacokinetic model (Fig. 3).

## Discussion

Our study demonstrated that target-controlled infusion of propofol for sedation during colonoscopy is safe and effective. Compared to the intermittent manual bolus technique, target-controlled infusion reduced agitation during sedation without increasing the incidence of respiratory depression, requiring less interventions by the anesthesiologist. Although propofol is the drug of choice for sedation in gastrointestinal endoscopy, its use may result in complications. High doses are often necessary to provide ideal conditions for the examination, which can result in intercurrent events such as respiratory depression. Keeping the patient still and breathing spontaneously is usually the greatest challenge during this procedure, in which adequate sedation not only provides patient comfort but can also optimize diagnostic potential. ${ }^{12}$

Satisfactory control of the degree of sedation depends on maintaining adequate effect-site concentration in the central nervous system of propofol in balance with plasma levels, and target-controlled infusion is considered the best method to achieve this. ${ }^{13}$

Campbell et al. reported on the use of patient-controlled sedation with target-controlled propofol infusion for colonoscopy. ${ }^{14}$ They concluded that the method was well tolerated by patients; however, sedation was titrated to target plasma levels, and patients took quite a long time to reach an adequate depth of sedation ( 15 to 20 minutes). Plasma targeting of infusion rates has several limitations; among them, the clinical response is always delayed in relation to the predicted plasma concentration, which probably contributed to the delay in inducing sedation in the aforementioned study. Plasma targeting of infusion is the only option for the Marsh model with "slow" blood-brain equilibration rate constant $\mathrm{k}_{\mathrm{e} 0}$ value ( $0.26 \mathrm{~min}^{-1}$ ).

In our study, sedation was titrated with effect-site targeting, and we observed an accordingly faster induction of sedation, with an average time of approximately 4 minutes to loss of consciousness and lack of responsiveness to tactile stimuli $(O A A / S=1)$. Effect-site targeting is more practical

Table 3 Clinical variables. Values are given as mean $\pm$ Standard Deviation, median (interquartile range) or number (percentage).

| Parameters | Groups |  | $p$-value |
| :---: | :---: | :---: | :---: |
|  | Target-controlled infusion ( $\mathrm{n}=25$ ) | Intermittent bolus $(\mathrm{n}=25)$ |  |
| Total interventions ${ }^{\text {a }}$ (number of interventions) | 1 (0-1) | 3 (1-4) | <0.001 |
| Dose adjustments (number of adjustments) | 1 (0-1) | 3 (1-4) | <0.001 |
| Airway maneuvers ${ }^{\text {b }}$ (number of maneuvers) | 0 (0-0) | 0 (0-0) | 0.239 |
| Respiratory depression (number of patients) | 3 (12\%) | 6 (24\%) | 0.269 |
| Agitation (number of episodes) | 1 (0-1) | 2 (0-2) | < 0.001 |
| Time to induction ${ }^{\text {c }}$ (minutes) | $3.8 \pm 1$ | $1.6 \pm 1$ | < 0.001 |
| Total propofol dose ( $\mu \mathrm{g} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ ) | $234 \pm 46$ | $195 \pm 44$ | 0.040 |
| Time to recovery (minutes) | $4.9 \pm 1.4$ | $2.3 \pm 1.6$ | <0.001 |

[^10]

Figure 2 Predicted effect-site Concentration (Ce) of propofol for sedation ( $\mathrm{OAA} / \mathrm{S}=1$ ) and arousal $(\mathrm{OAA} / \mathrm{S}=4)$. Values are given as mean and standard deviation ( $p<0.001$ ).
and logical, considering that pharmacological action correlates better with predicted concentrations at the site of action (Ce) than in plasma (Cp). ${ }^{15,16}$ Effect-site targeting should also allow faster achievement of a given depth of anesthesia or sedation, so that subsequent titration of the level of anesthesia could also be easier.

Stonell et al. ${ }^{17}$ investigated patient-maintained, targetcontrolled sedation in colonoscopy, comparing it with the intermittent bolus method. The authors found similar results on patient satisfaction, endoscopist satisfaction, and operating conductions. Although it has been studied for decades, ${ }^{18-20}$ patient-controlled sedation has yet to enter widespread use, and its benefits are still controversial. In
our study, the target-controlled infusion was assisted by the anesthesiologist, while in the control group, the intermittent bolus method was chosen because it is the standard technique used in our digestive endoscopy service. A standardized regimen consisting of a loading dose of $1.0 \mathrm{mg} . \mathrm{kg}^{-1}$ followed by intermittent boluses of $0.5 \mathrm{mg} . \mathrm{kg}^{-1}$ has been recommended for sedation in colonoscopy. ${ }^{21}$ According to our pharmacokinetic simulations in Tivatrainer ${ }^{\circledR}$ software, this protocol leads to peak concentrations at the effect site of 3 to $4 \mu \mathrm{~g} \cdot \mathrm{ml}^{-1}$, which are close to the mean values observed for loss of consciousness in the experimental group of our study.

The two main pharmacokinetic models used for targetcontrolled infusion of propofol in clinical practice are those proposed by Marsh et al. ${ }^{22}$ and Schnider et al. Although there is no evidence of superiority of one over the other, our choice of the Schnider model was based on several reasons. First, because it provides for effect-site targeting of the infusion, which allows a more appropriate and rapid titration. Furthermore, unlike in the Marsh model, Schnider includes additional covariables besides weight, such as age, sex, and height; this is appropriate, as the pharmacokinetics of propofol are not influenced solely by weight. ${ }^{23}$ Finally, because its equilibrium constant $\left(\mathrm{k}_{\mathrm{e} 0}\right)$ and all other parameters have been derived from a single study, in our opinion, this model offers a more robust option for effect-site targeting.

Propofol sedation blunts the ventilatory response to hypoxemia, ${ }^{24}$ and combined administration of opioids, although common in clinical practice, potentiates respiratory depression. ${ }^{25}$ Therefore, supplemental oxygen is mandatory. In our study, low-flow oxygen ( $2 \mathrm{~L} . \mathrm{min}^{-1}$ ) was given via a nasal cannula to make oxygen saturation more sensitive to respiratory depression, thus allowing easier detection of any difference between the groups; high-flow oxygen via facemask was


Figure 3 Statistically significant ( $p=0.013$ ) correlation between predicted effect-site concentration (Ce) of propofol for sedation $(O A A / S=1)$ and arousal (OAA/S = 4).
reserved for cases of hypoxemia. Although not statistically significant, we consider the twofold occurrence of hypoxemia in the intermittent bolus group to be clinically relevant. Perhaps a larger sample size could provide more conclusive results on safety.

We observed a higher total propofol dose and time to recovery in the target-controlled infusion group. We attribute this finding to the decision to maintain the same propofol target throughout colonoscopy as long as there was no need for correction, and to stop the infusion only at the end of the procedure. However, there is less discomfort during endoscope withdrawal, which should allow a reduction of the infusion target. Moerman et al reported faster recovery reducing the propofol infusion rate near the time of procedure completion. ${ }^{26}$ Despite the significant between-group difference in time to arousal, we do not consider it clinically relevant. The difference was minor, of only a few minutes, and did not impair patient flow within the unit. Furthermore, there were no reports of any complications in the postanesthesia care unit with either technique.

We observed that arousal occurred at significantly lower effect-site concentrations of propofol than at the time of loss of consciousness. Despite this difference, there was a positive correlation between the two. A similar result was obtained by Simoni et al with the modified Marsh model. ${ }^{27}$ We did not find any publications that investigated this correlation with the Schnider model.

The present study has many strengths that contribute to the literature on the role of target-controlled infusion in sedation for gastrointestinal endoscopy, but it also has some limitations that need to be discussed. First, we did not use a depth-of-anesthesia monitor. Nevertheless, propofol was titrated during sedation induction according to clinical response measured by the OAA/S scale, which correlates well with the bispectral index ${ }^{28}$ and can be used to assess the hypnotic effect of anesthetic drugs.

Second, our study is single-blinded because there are important differences between infusion techniques. Although the intermittent bolus could have been administered by a third assistant using a syringe pump, so that the anesthesiologist who recorded the data would have been blinded, we proposed to replicate in the control group the reality of most anesthesiologists, which we believe is the administration of propofol by a manual intermittent bolus.

Third, the hemodynamic response was not evaluated as a primary safety outcome. Propofol causes dose-related cardiovascular depression and its use is associated with hypotension, but adverse respiratory effects, such as hypoxemia, may be more frequent. ${ }^{29}$ Although hemodynamics were not formally evaluated, we did not record any significant adverse changes in the hemodynamic pattern requiring intervention or treatment in either group.

Finally, a possible limitation would be the narrow criteria for patient inclusion in the study. However, Marsh and Schnider's pharmacokinetic models have been validated for a selected population that includes young, healthy, and nonobese adults, a group in which the models show good accuracy, with the difference between measured and predicted plasma concentrations being less than $25 \% .{ }^{30}$ Thus, the inclusion of patients with other characteristics could affect the performance of the infusion system and bias the results.

We conclude that target-controlled infusion of propofol for sedation during colonoscopy is as safe as the intermittent manual bolus technique in terms of adverse respiratory effects (hypoxemia) and is superior in terms of reducing the incidence of agitation/patient movement and the need for dose adjustments by the anesthesiologist. Nevertheless, intermittent manual boluses are associated with faster recovery after completion of the procedure and a lower total propofol dose.

## Conflicts of interest

The authors declare no conflicts of interest.

## Links

Institutional Research Board Approval: https://plataformab rasil.saude.gov.br/visao/publico/indexPublico.jsf

CAAE: 58452416.0.0000.8055
Study Registry: https://ensaiosclinicos.gov.br/rg/RBR2dxshp

DATA repositor: https://data.mendeley.com/datasets/ m4drb6wbt6/draft?a=b732d073-66fb-4202-a186e2d9e40e5d02

## Presentation

Partial results of this study were presented at the $65^{\text {th }}$ Congresso Brasileiro de Anestesiologia (Belém do Pará, 2018) and at the European Anaesthesiology Congress - Euroanaesthesia 2019 (Vienna, Austria, 2019).

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## ORIGINAL INVESTIGATION

# Rider sitting position widens lumbar intervertebral distance: a prospective observational study 

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## KEYWORDS

Anesthesia, spinal;
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#### Abstract

Background: Reduced lumbar lordosis may make the process of identifying the intervertebral distance easier. The primary aim of this study was to measure the L3-L4 intervertebral space in the same patients undergoing spinal anesthesia in three different sitting positions, including the classic sitting position (CSP), hamstring stretch position (HSP) and rider sitting position (RSP). The secondary aim was to compare ultrasonographic measurements of the depth of the ligamentum flavum and intrathecal space in these three defined positions. Methods: This study is a single-blinded, prospective, randomized study. Ninety patients were included in final analysis. the patients were positioned on the operating table in three different positions to perform ultrasonographic measurements of the spinal canal. The intervertebral distance (IVD), the distance between the skin and the ligamentum flavum (DBSLF) and the intrathecal space (IS) were measured in the L3-L4 intervertebral space in three different positions. Results: The RSP produced the largest mean distance between the spinous processes. The RSP yielded a significantly larger IVD than did the CSP ( $p<0.001$ ) and HSP ( $p<0.001$ ). The DBSP was larger in the CSP than in the HSP $(p=0.001)$. The DBSLF was significantly larger in the RSP than in the HSP $(p=0.009)$. Conclusions: Positioning the patient in the RSP significantly increased the intervertebral distance between L3-L4 vertebrae compared to the CSP and HSP, suggesting easier performance of lumbar neuraxial block.


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[^11]
## Introduction

Lumbar spinal or epidural anesthesia is frequently administered in various surgeries to provide anesthesia and postoperative analgesia. The most important factor affecting success during spinal and epidural interventions is the patient's positioning. ${ }^{1}$ Reduced lumbar lordosis may facilitate the palpation of vertebral spinous processes and identification of intervertebral distance. ${ }^{2,3}$

Anesthesia textbooks outlined two regular patient positions as the lateral decubitus position and the sitting position ${ }^{4}$ however there are several trials comparing different modified sitting positions. ${ }^{1,2,5}$ Tashayod et al. described a modified sitting position named as hamstring stretch position and Manggala et al. described crossed leg sitting position in Asian population. ${ }^{6}$ All authors describing these modified sitting positions have the same purpose of achieving the optimal flexed position to reduce the lumbar lordosis and open the intervertebral space. In addition to these positions described in the literature, another sitting position that we call "the rider sitting position"' is commonly applied during spinal epidural anesthesia in our clinic. This position has not been previously described in the literature. However, anecdotal evidence in our experience suggested that induction of spinal anesthesia with the patients positioned on the table like they were riding a horse with the knees flexed 90 degrees and the feet swinging freely, legs placed on the table, make spinal puncture easier.

The use of ultrasonography (US) to increase success during neuraxial block applications has gained popularity among anesthesiologists in recent years. Ultrasound imaging for vertebral canal can display the spine of vertebra, the optimal needle insertion point and can identify the soft tissue acoustic window between vertebral laminas and also can measure the intervertebral distance and the extent of the ligamentum flavum. ${ }^{7-9}$ The optimal position for lumbar punctures to figure out maximal intervertebral distance has been assessed in pediatrics and adults by using ultrasonography and radiography. ${ }^{10-12}$ However, none of these studies include the position defined as the rider sitting position in our clinic.

The primary aim of this study was to measure the acoustic target (defined as the visualized L3-L4 intervertebral space) of the same patients undergoing spinal anesthesia in three different sitting positions, defined as classical sitting position (CSP), hamstring stretch position (HSP), and rider sitting position (RSP). The secondary aim was to compare ultrasonographic measurements of the depth of ligamentum flavum and intrathecal space at these three defined positions.

## Methods

This observational study was approved by Mugla Sitki Kocman University Training and Research Hospital Biomedical Research Ethics Committee on September 17, 2019 and registered at anzctr.org.au (Trial ID: ACTRN12619001753145) and conducted in accordance with the current Declaration of Helsinki. The study adheres to CONSORT guidelines. After obtaining written informed consents from the participants, patients who underwent surgery under spinal anesthesia were considered for the study. Patients between 18-45 years
old with American Society of Anesthesiologists (ASA) physical status I-III and scheduled for spinal anesthesia were prospectively included in the study. The exclusion criteria were patients with history of previous lumbar vertebral surgery, significant spinal anatomical abnormalities, allergy to ultrasound gel, those whose body mass index (BMI) > $30 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ or those who presented a language barrier. Subjects who did not want to participate were excluded. The age, height, weight, and BMI of all the participants were recorded. Participants were sequentially enrolled to the study.

After the enrolled patients arrived at the operating room, standard monitoring procedures per ASA were applied. Before the administration of spinal anesthesia, patients were positioned on the operating table in three different positions, respectively. All patients were approached to twist forward and curve out their back maximally. The patients were told to sit in the CSP for the measurements of lumbar spinal canal, then move to the HSP when the measurement was over, and sit in the RSP after the 2nd measurement of spinal canal. At the CSP, the knees were flexed approximately 90 degrees, the hip was on abduction, and the feet were on a stool support (Fig. 1A). At the HSP, the patients were seated with the legs totally supported by the operating table and were asked for knee extension and hip adduction (Fig. 1B). At the RSP, patients were positioned on the table like they were riding a horse with the knees were flexed 90 degrees and the feet were swinging freely (Fig. 1C). For every position on the same patient, ultrasonographic measurements of spinal canal were performed by the same anesthesiologist (M.K.T) with at least 50 patient experience in ultrasonography in neuraxial blocks and images were recorded. The ultrasonographic evaluation was performed with a curvilinear 52 MHz US probe (SonoSite MTurbo; FUJIFILM SonoSite, Bothell, WA). In all three positions, curvilinear ultrasonography probe was applied on the longitudinal paramedian position, $1-2 \mathrm{~cm}$ lateral to the spinous process, initially articular process view had been obtained. Then the probe was slightly tilted medially to beam the lamina of L3, L4, and L5 vertebrae, saw-like image of the lumbar vertebra was recognized as Chin et al. defined in their study. ${ }^{13}$ First the intervertebral spaces and then the targeted L3-L4 intervertebral space were identified. The ligamentum flavum (LF) was determined as an echogenic structure inside the intervertebral space. These displays were recorded to the ultrasound own memory. All recorded ultrasonography images evaluated by a different anesthesiologist (B.A.) who was blinded to the positions. The intervertebral distance between the L3-L4 laminae (IVD), the distance between the skin and the ligamentum flavum (DBSLF), and the distance between anterior and posterior dura defined as intrathecal space (IS) were measured in the paramedian sagittal plane in L3-L4 intervertebral place using in built-in calipers (Fig. 2). The specific point on the spinous process was determined by a method that was described in a previous study. ${ }^{14}$ The acoustic shadows of the L3 and L4 lamina was determined. The IVD was measured as the distance between the apexes of the acoustic shadows of the L3 and L4 lamina. The IVD, DBSLF and the diameter of IS were recorded in three positions for every participant (three measurement for every position), thus there were 9 measurements for every subject.


Figure 1 A, The volunteer at the classical sitting position; B, The volunteer at the hamstring stretch position; C, The volunteer at the rider sitting position.


Figure 2 Paramedian longitudinal oblique ultrasonographic view of the lumbar spine at the level of the lamina showing the L3-4 and L4-5 interlaminar spaces. Red arrow: intervertebral distance; Yellow arrow: intrathecal space; L3: Lamina of L3 vertebrae; L4: Lamina of L4 vertebrae.

## Statistical analysis

The sample size of the study was calculated using the G*Power program (v3.1.9.2). We conducted a pilot study with 15 patients in our clinic. According to this pilot study, the mean difference of 0.15 cm with the standard deviation 0.02 cm between CSP and RSP in the IVD measurement accepted as clinically significant. Assuming $\alpha$-error $=0.01$ (two-tailed), and $\beta$-error $=0.10$ with a power of $90 \%$, at least 76 patients were needed in total. Considering a $20 \%$ drop-out, we decided to include 92 patients in total.

Suitability for the normal distribution of the measured variables of IVD, DBSLF, and IS were examined using ShapiroWilk test. For parametric distributions, data were detailed with mean $\pm$ standard deviation and analyzed using analysis of variance test. Taking steps further with Anova, post-hoc tests were performed using least significant difference for pairwise comparisons. Analyses were performed using Statistical Package for Social Science (SPSS) version 25 (made by SPSS Incorporated, located in Chicago, Illinois, USA). A $p$-value of $<0.05$ was considered as statistically significant.

## Results

The statistical analysis included 90 patients (Fig. 3). Patient recruitment and enrollment was made in December 2019.

Table 1 Patient demographics.

| Demographics |  |
| :--- | :--- |
| Age (years) | $44.73 \pm 11.5$ |
| Weight $(\mathrm{kg})$ | $74,1 \pm 10$ |
| Height (cm) | $169,8 \pm 7,2$ |
| BMI | $25,6 \pm 2,3$ |
| Gender | $43(47.8 \%)$ |
| Female | $47(52.2 \%)$ |
| Male | $27 / 56 / 7(30 \% / 62 \% / 8 \%)$ |
| ASA (I/IIIII) |  |

Data are expressed as the mean $\pm$ SD or as the number and percentage of patients.
BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status.

The mean $\pm$ standard deviation (SD) age of the participants was $44.73 \pm 11.5$ years, their mean height was $169.8 \pm 7.2$ cm , their mean weight was $74.1 \pm 10 \mathrm{~kg}$ and their mean BMI was $25.6 \pm 2.3 \mathrm{~kg} . \mathrm{m}^{-2}$ (Table 1).

The L3-L4 intervertebral space of 90 participants were identified in three different positions. The mean $\pm$ standard deviation and median of IVD, DBSLF, and IS measurement for each position are shown in Table 2.

The mean differences of the IVD, DBSLF and IS between three positions was calculated with a $95 \%$ confidence interval. The mean differences were figured out with pairwise comparisons providing adjusted $p$-values (Table 3 ). The RSP position produced the largest mean distance between spinous processes. The RSP significantly increased the IVD comparing to CSP $(p<0.00)$ and HSP ( $p<0.001$ ). Also, the DBSP was higher at the CSP comparing to HSP $(p=0.001)$.

When the DBSLF measurements were taken into consideration, the DBSLF significantly increased at the RSP comparing to HSP $(p=0.009)$. Although the RSP decreased the DBSLF comparing to CSP, the difference of the means was not significant ( $p=0.223$ ). The RSP resulted in the largest mean IS comparing to CSP $(p=0.223)$ and HSP $(p=0.009)$.

## Discussion

In this study we measured the intervertebral space at L3-L4, the distance between the skin to ligamentum flavum, and the intrathecal space in different positions with ultrasonography. We demonstrated that with the rider sitting position, the intervertebral distance at L3-L4 interlaminar


Figure 3 Flowchart of the study.
space identified with the preinsertion lumbar ultrasonography increased, and this extend was significant compared to CSP and HSP. The distance between the skin and the ligamentum was similar in both the CSP and the RSP. This study also demonstrated the benefits of the RSP compared to HSP by achieving the decreased DBSLF and increased IS.

Sandoval et al. compared the three different positions for lumbar puncture to identify the widest interspinous dis-
tance with US at the emergency department. ${ }^{10}$ The mean of intervertebral L4-L5 space of their 16 volunteers were reported between 1.91 cm to 2.02 cm in three different positions. In our study the mean of the L3-L4 intervertebral space in three different positions were approximately $50-60 \%$ wider comparing to their results. We assumed that performing our measurements at the longitudinal paramedian approach instead of sagittal approach and using the

Table 2 Means and Medians of the intervertebral distance, the distance between skin to ligamentum flavum, intrathecal space in each position.

| Measurements | Classical sitting position | Hamstring stretch position | Rider sitting position |
| :--- | :--- | :--- | :--- |
| IVD $(\mathrm{cm})$ |  |  |  |
| Mean $\pm$ SD | $3,39 \pm 0,37$ | $3,19 \pm 0,36$ | $3,61 \pm 0,41$ |
| Median [IQR] | $3.35[3.14-3.65]$ | $3.15[2.94-3.5]$ | $3.58[3.25-3.87]$ |
| DBSLF $(\mathrm{cm})$ | $5,04 \pm 0,47$ | $5,14 \pm 0,46$ | $4,95 \pm 0,5$ |
| Mean $\pm$ SD | $5.17[4.63-5.45]$ | $5.3[4.7-5.54]$ | $5.1[4.47-5.36]$ |
| Median [IQR] |  |  |  |
| IS $(\mathrm{cm})$ | $1,3 \pm 0,12$ | $1.28 \pm 0,11$ | $1,45 \pm 0,13$ |
| Mean $\pm$ SD | $1.28[1.22-1.35]$ | $1.41[1.37-1.49]$ |  |
| Median [IQR] |  |  |  |

IVD, intervertebral distance; DBSLF, difference between skin to ligamentum flavum; IS, Intrathecal space; SD, standard deviation.

Table 3 Pairwise comparisons of the measured parameters.

|  |  | $95 \% \mathrm{CI}$ |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- |
| Parameter |  | Mean Difference | Lower | Upper | $p^{\text {a }}$ |
| IVD (cm) | CSP minus HSP | 0.20 | 0.09 | 0.31 | 0.001 |
|  | CSP minus RSP | -0.21 | -0.33 | -0.10 | 0.000 |
|  | HSP minus RSP | -0.41 | -0.53 | -0.30 | 0.000 |
|  | CSP minus HSP | -0.10 | -0.24 | 0.04 | 0.159 |
|  | CSP minus RSP | 0.09 | -0.05 | 0.23 | 0.223 |
| IS (cm) | HSP minus RSP | 0.19 | 0.05 | 0.33 | 0.009 |
|  | CSP minus HSP | 0.00 | -0.24 | 0.04 | 0.159 |
|  | CSP minus RSP | -0.15 | -0.05 | 0.23 | 0.223 |
|  | HSP minus RSP | -0.16 | 0.05 | 0.33 | 0.009 |

CI , confidence interval; IVD, intervertebral distance; DBSLF, difference between skin to ligamantum flavum; IS, intrathecal space.
Anova models for IVD, DBSLF, IS are at $p=0.000, p=0.032$, and $p=0.000$, respectively.
a Obtained with posthoc test with LSD.
apexes of the acoustic shadows of two lamina as a reference point caused this difference. They reported that the sitting and the feet supported position produced the widest interspinous space. In their study, sitting and the feet supported position was the same as classical sitting position in our study. However, the compared sitting and the feet unsupported position was not the same as RSP in our study. At the RSP, the hips were abducted on the operating table in our study and we believe that the hip abduction in that position makes the patient more comfortable for reducing the lumbar lordosis.

Abo et al. determined the different sitting and lateral recumbent positions of children under 12 years at which position the intervertebral space maximized for lumbar punctures. ${ }^{12}$ They included 28 patients and recommended the sitting position with flexed hips for maximally increased interspinous space. In their study, they classified sitting positions as sitting or sitting with maximal flexion of the hips and at the sitting with flexed position they measured the maximal interspinous space. The sitting with maximal flexion of the hips matched the CSP in our study but they did not define the RSP as our study because the sitting position did not match the RSP in our study. When we applied the RSP, we told our patients to take their waist out like a scared cat. So, the sitting position with the maximal flexion of the hips may match the RSP in our study.

The comparison of spinal needle bone contact by reducing lumbar lordosis with different positions had been the objective of several studies. Fisher et al. determined scheduled the number of needle bone contact was similar in both traditional sitting position (TSP) and HSP groups on 406 pregnant patients. ${ }^{2}$ Similarly, Mohammadi et al. compared the number of spinal needle-bone contacts and ease of needle insertion at TSP, HSP and squatting position (SP). ${ }^{1}$ They found no statistical difference between the TSP, HSP, and SP regarding. However, there were no studies determining the measurements of intervertebral space with ultrasonography before spinal anesthesia and comparing the differences between different positions. Also, to the best of our knowledge this is the first study to evaluate the effect of rider sitting position to intervertebral space. In our study, the IVD at the CSP and HSP was significant and greater at the CSP however at the above studies there were no differences of the number of needle bone contacts and the ease of needle insertion at the two-position knowing the TSP matched the CSP in our study. Although according to our study the IVD widen at the CSP as 0.20 cm , because experienced anesthetists perform neuraxial anesthesia in the study of both Fisher ${ }^{11}$ and Mohammadi ${ }^{1}$ may have led to this result.

When it is determined that the greatest distance between L3-L4 laminae reached at the RSP, the close look to the hip during three positions is essential.

In our study, the common point of all three positions was hip flexion, while the hip was adducted in the CSP and HSP, whereas the hip was abducted in the RSP. Although we could not find any evidence about the hip abduction reduces lumbar lordosis, in our opinion at hip abducted position patients flexed their vertebral column more easily.

Previous studies demonstrated a good correlation between US guided skin to ligamentum flavum distance and definite needle depth. ${ }^{8,15,16}$ In the current study, the DBSLF which is important in overweight, obese, and pregnant patients did not differ significantly between CSP and RSP. Although at the RSP the DBSLF reached to the shortest measure, it was only significant when compared with the HSP.

The intrathecal space demonstrated and measured as an anechoic space between the posterior and anterior complexes of the intervertebral space. The RSP and CSP reached the greatest diameter of IS compared to the HSP. The local anesthetic drugs are administered to the IS during spinal anesthesia. The engorgement of IS would be practical in dehydrated patient for free flow of cerebrospinal fluid.

Grau et al. analyzed the transverse, median longitudinal and paramedian longitudinal approaches of vertebral US and compared the quality of monitoring and concluded their study as the paramedian longitudinal window was excellent. ${ }^{17}$ We performed US imaging through the paramedian longitudinal approach in our patients.

The strength of our study was that the recorded images were evaluated by a blinded anesthesiologist. The single blinding supported our results.

One limitation of this study was that it evaluated only patients with normal BMI or overweight. So, the results may not be applicable to the obese patients. Another limitation was that we did not compare any success rate of neuraxial anesthesia, number of needle bone contacts, or easiness of neuraxial anesthesia. Thus, clinical studies with these positions will be required for confirmation.

## Conclusion

In conclusion, positioning the patient in the RSP significantly increased the L3-L4 intervertebral distance compared to the CSP and HSP, suggesting easier performance of lumbar neuraxial block.

## Conflicts of interest

The authors declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j. bjane.2021.03.010.

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Sociedade Brasileira de Anestesiologia

# Association between telomere length in the DNA of peripheral blood leukocytes and the propofol dose in anesthesia induction: an observational study 

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## KEYWORDS

Telomere length; Propofol dose; Anesthesia safety; Perioperative
complications


#### Abstract

Introduction: Propofol is a widely used anesthetic and its dose is closely related to aging. Telomere length (TL) is a unique heritable trait, and emerging as a biomarker of aging, health and disease. Telomerase RNA component (TERC) plays an important role in maintaining TL. We proposed a hypothesis that propofol dose in general anesthesia can be predicted by measuring TL before operation, which greatly reduced the risk of anesthesia, especially the elderly. Methods: The association between the propofol dose in anesthesia induction and: TL in the DNA of peripheral blood leukocytes; body weight; sex; difference of the Bispectral Index (BIS) before and after anesthesia induction in patients was evaluated by multivariable linear regression analyses. The mutation at the 5'end or 3'end of TERC was detected. We recruited 100 patients of elective surgery. Results: We found that propofol dose in anesthesia induction was clearly correlated significantly with $\operatorname{TL}(r=0.78, p<0.001)$, body weight ( $r=0.84, p=0.004$ ), $\operatorname{sex}(r=0.83, p=0.84, p=0.004)$, sex ( $r=0.83, p=0.004$ ), and difference of BIS before and after anesthesia induction ( $r=0.85$, $p=0.029$ ). By comparing the absolute values of standardized regression coefficients ( $0.58,0.21$, 0.19 , and 0.12 ) of the four variables, it can be seen that TL contributes the most to the propofol dose in anesthesia induction. However, the mutation at the $5^{\prime}$ end or 3 ' end of TERC was not found.


[^12]Conclusions: These findings provide preliminary evidence that the propofol dose in anesthesia induction was clearly correlated with genetically determined TL. TL may be a promising predictor of the propofol dose, which is beneficial to improve the safety of anesthesia and reduce perioperative complications.
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## Introduction

The elderly constitutes the most important population within the general population with regard to complications and deaths from anesthesia and surgery as the older population grows. ${ }^{1}$ Tolerance to intravenous general anesthesia decreases gradually with age in humans. ${ }^{2}$ To date, there are no precise criteria for assessing the change in tolerance of the body to anesthetic drugs. Telomeres are specialized protein-bound DNA repetitive sequences at the end of eukaryotic chromosomes. They regulate the replication and proliferation of cells, avoid chromosome fusion during mitosis, and maintain genomic stability. ${ }^{3}$ Telomerase RNA component (TERC) serves as a template and synthesizes DNA telomere repeats to maintain telomere length (TL). TL is a unique heritable trait, and has emerged as a biomarker of aging, health and disease. TL in leukocytes shortens in a divinable way with age by approximately 20-40 base pairs (bp) per year. ${ }^{4}$ The aging and subsequent death of cells often happens if the mean TL reaches a critical value. ${ }^{5}$

We proposed a hypothesis that propofol dose can be predicted by TL before operation, which greatly reduced the risk of anesthesia, especially the elderly. Hence, we designed a study to evaluate the association between TL in the DNA of peripheral blood leukocytes (PBLs) and propofol dose in the induction of general anesthesia.

## Methods

## Ethical approval of the study protocol

This study was approved by Ethics Committee of Guangzhou General Hospital of Guangzhou Military Command and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03429309, Principal investigator: WeiFeng Tu, Date of registration: February 9, 2018)

## Exclusion criteria

We excluded people: with known cardiac, hepatic, pulmonary, or renal disease; hearing disorders, neurologic diseases, or diabetes mellitus; consuming > 20 g of alcohol daily; with a body mass index ( $18 \mathrm{~kg} \cdot \mathrm{~m}^{-2}>\mathrm{BMI}>30 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ ).

## Research cohort and indicators

The number of observations should be more than 20 times the number of independent variables in multivariable lin-
ear regression analyses. We used four independent variables (TL; Body weight; sex and difference of BIS before and after anesthesia induction) in the study. Therefore, we recruited 100 patients of Chinese Han population aged from 18 to 80 years, with American Society of Anesthesiologists (ASA) physical status I-II. Testing took place in the morning after an overnight fast. Patients were scheduled for elective surgery.

## Anesthesia induction

After arrival in the operating theatre, a peripheral venous catheter was inserted for infusion of fluids and drugs. The heart rate, peripheral oxygen saturation, noninvasive blood pressure and Bispectral Index (BIS) were monitored continuously. Also, 100\% oxygen was given for 3 minutes by face mask.

The induction of anesthesia was started by infusion of propofol (Fresenius Kabi, Bad Homburg vor der Höhe, Germany) using an intravenous syringe pump (B. Braun Melsungen, Germany) at $30 \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~h}^{-1}$. Recording began before propofol infusion was started.

When patients had a BIS of 70, they were asked loudly to "open their eyes". This command was repeated up to three times, and the eyelash reflex was examined at $15-\mathrm{s}$ intervals until they became unconscious (i.e., lost response to a verbal command, no spontaneous movements and loss of the eyelash reflex) by the anesthetist. Recording of the heart rate, noninvasive blood pressure, and BIS was done when patients were awake (baseline) until propofol induced unconsciousness. The propofol dose and time taken for consciousness to disappear were recorded after propofol administration. Patients were instructed not to open their eyes, talk, or move during recording of the heart rate, noninvasive blood pressure, and BIS before propofol infusion. The sedation level was assessed until the patient became unconscious.

## TL measurement

The quantitative Real Time polymerase chain reaction (qRT$P C R$ ) technique is the method used most frequently by investigators for measuring TL. Blood samples were obtained from 100 patients during surgery. TL of DNA in PBLs pretreatment was assessed by qRT-PCR, as literature described previously. ${ }^{6,7}$ Total PBLs were separated using Red Blood Cell Lysis Buffer (C3702; Beyotime Institute of Biotechnology, Beijing, China). Genomic DNA was extracted from PBLs using a DNA Blood kit (Shanghai Majorbio Pharmaceutical Technology, Shanghai, China). qRT-PCR was done in a 7500 Real Time

Table 1 Demographic data.

| Research indicators | Characteristics |
| :--- | :--- |
| Patients | $\mathrm{n}=100$ |
| Age (years) | $18-80$ |
|  | $(49.66 \pm 15.99)$ |
| Difference of BIS before | $(33.43 \pm 18.83)$ |
| $\quad$ and after anesthesia |  |
| $\quad$ induction | $40-87$ |
| Body weight (kg) | $(63.13 \pm 10.52)$ |
|  | $30>$ BMI $>18$ |
| BMI (kg.m |  |
|  | $(23.31 \pm 3.02)$ |
| Sex (female, male) | female $=44$, |
|  | male $=46$ |

PCR system (Applied Biosystems, Foster City, CA). The relative ratio of telomere-repeat copy number to single-copy number (T/S ratio) was calculated. Samples were compared with a reference DNA sample.

## Detection of mutation at the 5'end or 3'end of TERC

TERC provides instructions for making one component of the enzyme telomerase.
qRT-PCR was used to detect gene mutation at the 5 'end or 3'end of TERC, as literature described previously. ${ }^{8}$ The reference gene $\beta$-globin was used for calculation of the copy number of TERC. An amplicon of size 1190 bp extending from 433 bp at the 5'end flanking to $306-\mathrm{bp}$ downstream of TERC was amplified for TERC sequencing. Genomic DNA was obtained with a SYBR ${ }^{\text {TM }}$ Premix Ex Taq kit (AK6006; TaKaRa Biotechnology, Shiga, Japan). The individual copy number of TERC at the 5'end or 3'end was calculated as the ratio of TERC/ $\beta$-globin of each sample using the comparative CT method ( $\left.2^{-\Delta \Delta C T}\right) .{ }^{8}$

## Statistical analyses

Multivariable linear regression analyses were undertaken to assess the relationship between the: propofol dose in anesthesia induction, and TL; sex; Body weight; difference of BIS before and after anesthesia induction, $p<0.05$ was considered significant. The propofol dose and TL correlation were measured with Pearson. Descriptive data were analyzed by mean $\pm$ standard deviation. Analyses were done using SPSS v21.0 (IBM, Armonk, NY, USA).

## Results

Demographic data are presented in Table 1.

## Association between the propofol dose and other factors

Telomere length in PBLsis $1.11 \pm 0.41$. The propofol dose in anesthesia induction ( $118.84 \pm 27.58 \mathrm{mg}$ ) was clearly correlated significantly with TL ( $r=0.78, p<0.001$ ); body weight

Table 2 Statistical results of the relationship between five variables (Coefficients ${ }^{\text {a }}$ ).

| Model | Standardized <br> coefficients <br> Beta | t | Sig. |
| :--- | :--- | :--- | :--- |
| (Constant) | 0.578 | 2.450 | 0.016 |
| Tel | 0.206 | 2.977 | 0.000 |
| Body weight | 0.189 | 2.953 | 0.004 |
| Sex | 0.124 | 2.215 | 0.004 |
| BIS |  |  |  |

${ }^{a}$ Dependent Variable: Propofol Dose.
( $r=0.84, p=0.004$ ); sex ( $r=0.83, p=0.004$ ); and difference of BIS before and after anesthesia induction ( $r=0.85$, $p=0.029$ ). By comparing the absolute values of standardized regression coefficients $(0.58,0.21,0.19$, and 0.12 ) of the four variables (Table 2), it can be seen that TL contributes the most to the propofol dose in anesthesia induction.

## Linear correlation scatter/dot between the propofol dose and other factors

The propofol dose in anesthesia induction was positively correlated with TL; body weight; difference of BIS before and after anesthesia induction from the scatter diagram (Fig. 1).

## Mutation at the 5'end or 3'end of TERC

Mutation at the 5'end or 3'end of TERC was not found in 100 participants.

## Discussion

We found a positive association between TL in DNA in PBLs and the propofol dose in anesthesia induction. Also, the propofol dose decreased with shorter TL (Fig. 1). Our study could reveal a closely association between the propofol dose and age-related outcomes by TL. This strategy could allow us to apply TL to assess changes in tolerance of the body to propofol as people get older. However, the mutation at the 5'end or 3'end of TERC (a ribonucleoprotein that contains the RNA template in telomerase) was not found in 100 patients, which showed that telomere in these patients was relatively stable. Hence, we inferred that tolerance of the body to propofol showed strong associations with the inherent genetic factors TL of aging. TL may be a promising predictor of the propofol dose, which is beneficial to individualization of the propofol dose and reduction in the risk of anesthesia.

In addition to TL, although we observed that the propofol dose in anesthesia induction was strongly correlated with body weight, sex, and difference of BIS before and after anesthesia induction in 100 participants (Fig. 1), it can be seen that TL contributes the most to the propofol dose by comparing the absolute values of standardized regression coefficients ( $0.58,0.21,0.19$, and 0.12 ) of the four variables (Table 2). In other words, TL may have the greatest influence on the propofol dose in several factors. It may be possible to


Figure 1 Linear correlation scatter/dot.
use TL association with external disease factors of aging to determine the propofol dose in the future, which can greatly reduce perioperative complications.

This was the first study showing a direct association between the tolerance of the body to the propofol dose and TL as a biomarker. TL has been recognized as a strong and informative biomarker of aging. Several studies have shown that TL in PBLs has an inverse association with age and a robust association with mortality risk score. ${ }^{9}$ In particular, Dean et al. ${ }^{10}$ observed a strong relationship between shorter TL and increased overall mortality. TL can be used to predict aging-related health outcomes. ${ }^{9,11}$ In our study, TL demonstrated associations with propofol dose, which may be helpful for determining the propofol dose during aging as well as improving the safety of anesthesia.

Telomere length and structure may be modulated by genetics, epigenetics, environment and behavioral attitudes. ${ }^{12}$ TERC was reported to be ubiquitously expressed in different types of normal tissues, and play a vital role in regulating TL. Over-expression of TERC increased TL. Mutations in TERC are associated with human diseases. Gradual attrition of telomeres occurs during each cell division. The cells become senescent (at least in part), cell-cycle arrest and apoptosis, and cannot divide further when telomeres become very short. ${ }^{13}$ Hence, telomeres play a major part in cellular senescence and might contribute significantly to the inherited background of human aging and longevity. ${ }^{14}$ Telomere shortening in one tissue may cause systemic effects. ${ }^{15}$ Age-matched elderly people with short telomeres in DNA in PBLs have been shown to have worse survival. ${ }^{16} \mathrm{TL}$ is a predictor of the extent of biological aging and lifespan, or specific for certain biological systems throughout the lifespan. Telomeres shorten with age. The propofol dose decreases with age. ${ }^{17}$ The three conform to the dialectical relationship. Aging results from a dynamic, complex, and multifactorial processes related to a decreased propofol dose by gradual accumulation of different types of cellular and molecular damage. ${ }^{18,19}$ Given this information, we can infer that TL of inherent heredity factors can reflect the sensitivity of the body to propofol, and may interact with many other relevant factors.

TL dynamics change constantly over a lifespan, but the rate of telomere change may depend upon genetics, environmental and lifestyle-related factors, stochastic factors, and the genetic mutations of telomerase. Previous research has found a significant association between
longer TL and better self-rated general health. ${ }^{20}$ TL may be an informative biomarker of healthy aging and overall immune competence. Short TL in leukocytes is a cause of impaired immune competence, and has been associated with a higher risk of hospitalization due to infectious disease and infection-related death. ${ }^{21}$ Senescence heterogeneity induced by telomere shortening, depends on the initial variance in TL. ${ }^{22}$ Hence, TL may be a promising predictor of the propofol dose combined with the physiological status of the body.

However, markers of biological aging may change over a lifespan, and a single biomarker may not be sufficient to reflect aging across various biological systems. It is also clear that many mysteries around telomeres and their function remain. In my study, a key question is to what extent the association between TL and the propofol dose observed in our study was causal. We did not know whether this phenomenon exists among other ethnicity. We did not consider the additional factors, which may have confounded our analyses. Clearly, further studies are needed to evaluate the extent to which TL influences the propofol dose with increasing age. How TERC affect telomere length is also our future research direction.

## Conclusions

We found a positive association between TL in DNA in PBLs and the propofol dose in anesthesia induction. Also, the propofol dose decreased with shorter TL. This strategy could allow us to apply TL to assess changes in tolerance of the body to propofol as people get older. Hence, TL may be a promising predictor of the propofol dose, which is beneficial to individualization of the propofol dose and reduction in the risk of anesthesia.

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## Conflict of interest

## The authors declare no conflict of interest.

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## ORIGINAL INVESTIGATION

# The effects of positive end-expiratory pressure (PEEP) application on optic nerve sheath diameter in patients undergoing laparoscopic cholecystectomy: a randomized trial 

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## KEYWORDS

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#### Abstract

Background: Positive end-expiratory pressure (PEEP) can overcome respiratory changes that occur during pneumoperitoneum application in laparoscopic procedures, but it can also increase intracranial pressure. We investigated PEEP vs. no PEEP application on ultrasound measurement of optic nerve sheath diameter (indirect measure of increased intracranial pressure) in laparoscopic cholecystectomy. Methods: Eighty ASA I-II patients aged between 18 and 60 years scheduled for elective laparoscopic cholecystectomy were included. The study was registered in the Australian New Zealand Clinical Trials (ACTRN12618000771257). Patients were randomly divided into either Group C (control, PEEP not applied), or Group P (PEEP applied at $10 \mathrm{cmH}_{2} 0$ ). Optic nerve sheath diameter, hemodynamic, and respiratory parameters were recorded at six different time points. Ocular ultrasonography was used to measure optic nerve sheath diameter. Results: Peak pressure (PPeak) values were significantly higher in Group P after application of PEEP $(p=0.012)$. Mean respiratory rate was higher in Group $C$ at all time points after application of pneumoperitoneum $(p<0.05)$. The mean values of optic nerve sheath diameters measured at all time points were similar between the groups ( $p>0.05$ ). The pulmonary dynamic compliance value was significantly higher in group $P$ as long as PEEP was applied ( $p=0.001$ ). Conclusions: During laparoscopic cholecystectomy, application of $10 \mathrm{cmH}_{2} \mathrm{O}$ PEEP did not induce a significant change in optic nerve sheath diameter (indirect indicator of intracranial pressure) compared to no PEEP application. It would appear that PEEP can be used safely to correct


[^13]respiratory mechanics in cases of laparoscopic cholecystectomy, with no significant effect on optic nerve sheath diameter.
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## Introduction

Laparoscopic surgical procedures are widely used with laparoscopic cholecystectomy being one of the most frequently applied.

Application of pneumoperitoneum (PP) in laparoscopic surgeries causes changes in respiratory mechanics. ${ }^{1,2}$ Due to the creation of pneumoperitoneum, intra-abdominal pressure increases and the expandability of the diaphragm decreases. Pulmonary compliance (PC), functional residual capacity (FRC), and vital capacity (VC) decrease due to the increase in intrathoracic pressure, and as a result an increase in alveolar partial pressure of carbon dioxide $\left(\mathrm{PaCO}_{2}\right)$, atelectasis, ventilation/perfusion (V/Q) mismatch and hypoxemia may occur. ${ }^{1,2}$

Positive end-expiratory pressure (PEEP) applied at a level of $10 \mathrm{cmH}_{2} \mathrm{O}$ to overcome the changes due to pneumoperitoneum and patient position, have been shown to have positive effects on respiratory compliance and resistance. ${ }^{3}$

The increase in intra-abdominal pressure and application of PEEP also increases intracranial pressure through various physiological mechanisms. ${ }^{4}$ Using ultrasound to measure optic nerve sheath diameter is a non-invasive imaging method that provides indirect measurement of an increase in intracranial pressure. There are reports of increased optic nerve sheath diameter in patients with increased intracranial pressure, such as head trauma and cerebrovascular disease, ${ }^{5,6}$ but, thus far, there are no studies investigating the effect of pneumoperitoneum and PEEP applications on optic nerve sheath diameter in laparoscopic cholecystectomies.

Our aim was to investigate whether PEEP application at $10 \mathrm{cmH}_{2} \mathrm{O}$, in patients undergoing laparoscopic cholecystectomy, alters the diameter of the optic nerve sheath compared with conditions where PEEP is not applied.

## Methods

A total of 80 ASA (American Society of Anesthesiologists) physical status I-II patients who were scheduled for laparoscopic cholecystectomy between June 2017 and October 2017 were included in the study. Informed consent forms were obtained from all patients, and the study was approved by the local ethics committee ( 15 May 2017, 38/05). Two patients from both groups were excluded as their surgery was ultimately performed as an open procedure. The study was registered in the Australian New Zealand Clinical Trials (ACTRN12618000771257).

Patients with acute or chronic eye disease, uncontrolled hypertension, asthma and known lung disease, any neurological disease, body mass indices (BMI) above $35 \mathrm{~kg} .\left(\mathrm{m}^{2}\right)^{-1}$, patients using drugs known to affect intracranial pressure, and those patients who refused to participate in the study
after giving their informed consent were excluded from the study.

This study was a non-blind, randomized, placebo-controlled trial. Patients included in the study were divided into two groups using the random numbers method. In the control group (Group C) PEEP was not applied during the procedure, while in the PEEP group (Group P), PEEP was applied at a level of $10 \mathrm{cmH}_{2} \mathrm{O}, 10$ minutes after creation of pneumoperitoneum. Standard monitorization procedures; electrocardiography (ECG), measurements of peripheral oxygen saturation ( $\mathrm{SpO}_{2}$ ), noninvasive arterial blood pressure, and end-expiratory $\mathrm{CO}_{2}\left(\mathrm{EtCO}_{2}\right)$, were performed during the procedure. In addition, patients' depth of anesthesia was monitored using the bispectral index (BIS). Propofol ( $2-3 \mathrm{mg}$. $\mathrm{kg}^{-1}$ ), fentanyl ( $1 \mathrm{mcg} \cdot \mathrm{kg}^{-1}$ ), rocuronium ( $0.6 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ ), and lidocaine ( $1 \mathrm{mg} . \mathrm{kg}^{-1}$ ) were used intravenously (IV) for the induction of anesthesia. Endotracheal intubation was performed with a cuffed endotracheal tube with an internal diameter of $7.0-8.5 \mathrm{~mm}$, under the guidance of direct laryngoscopy after adequate muscle relaxation was achieved. For the maintenance of anesthesia, inhalation of a mixture $40 \% \mathrm{O}_{2}, 60 \% \mathrm{~N}_{2} \mathrm{O}$, and $2 \%$ sevoflurane was used. All patients underwent volume-controlled mechanical ventilation at a respiratory rate of $12 /$ minute, with a tidal volume of 8 mL . $\mathrm{kg}^{-1}$, and an inspiration/expiration ratio of 1:2. During surgery, the frequency was adjusted to be within the range of $35-40 \mathrm{mmHg} \mathrm{EtCO}_{2}$. PEEP was applied at a level of 10 $\mathrm{cmH}_{2} \mathrm{O}$ to the patients in Group P, 10 minutes after creation of pneumoperitoneum and elevation of the patient's head.

Heart rate, mean arterial blood pressure, $\mathrm{SpO}_{2}$, airway peak pressure (Ppeak), dynamic lung compliance values, tidal volume (TV), respiratory rate (RR), minute volume (MV), $\mathrm{EtCO}_{2}$, and optic nerve sheath diameters (ONSD) were measured and recorded at six different time points, i.e., at baseline (after the patient was brought into the operation room and monitored, but before induction of anesthesia) ( t 1 ), after intubation and initiation of mechanical ventilation (t2), 10 minutes after creation of pneumoperitoneum ( t 3 ), 10 minutes after application of PEEP ( t 4 ), 5 minutes after desufflation (t5), and five minutes after extubation (t6) (Table 1).

Table 1 Diagram of timeline for data measurement.
t1 Baseline (after the patient was brought into the operation room and monitored, but before induction of anesthesia) After intubation and initiation of mechanical ventilation
t3 10 minutes after creation of pneumoperitoneum
t4 10 minutes after application of PEEP
t5 5 minutes after desufflation
t6 5 minutes after extubation

Table 2 Distribution of general characteristics of all patients ( $n=76$ ) (mean $\pm$ SD and percentage).

|  | Group $C(n=38)$ | Group $P(n=38)$ | $p$ |
| :--- | :--- | :--- | :--- |
| Age (year) | $49 \pm 11$ | $44 \pm 11$ | 0.082 |
| Gender (F/M) | $67 / 33$ | $65 / 35$ | 0.813 |
| ASA (I/II) | $78 / 22$ | $85 / 15$ | 0.39 |
| BMI $\left(\mathrm{kg} . \mathrm{m}^{-2}\right)$ | $25.53 \pm 2.82$ | $25.58 \pm 2.24$ | 0.93 |

F, female; M, male; ASA, American Society of Anesthesiologists physical status; BMI, body mass index.

Once the surgery was complete, tramadol ( $1 \mathrm{mg} . \mathrm{kg}^{-1}$, IV) was administered for postoperative analgesia. Dexketoprofen trometamol ( 50 mg , IV) was administered to those patients needing additional analgesia. For the prophylaxis of postoperative nausea and vomiting, ondansetron ( $4 \mathrm{mg}, \mathrm{IV}$ ) was also administered post-surgery. On completion of the procedure, sevoflurane and $\mathrm{N}_{2} \mathrm{O}$ inhalation were discontinued, the neuromuscular block was relieved with neostigmine ( $0.04 \mathrm{mg} . \mathrm{kg}^{-1}, \mathrm{IV}$ ) and atropine ( $0.01 \mathrm{mg} . \mathrm{kg}^{-1}$, IV), and the patient was extubated when his/her spontaneous breathing was at a sufficient level. Any drugs used during surgery were recorded. Patients were taken out of the operating room and sent to the ward when their Aldrete scores reached 9 -10 points in the recovery unit.

Patients whose intraoperative heart rates were raised more than $20 \%$ from their preoperative values received fentanyl ( $1 \mathrm{mcg} . \mathrm{kg}^{-1}$, IV bolus doses), as the depth of anesthesia was inadequate. Hypotension was considered if mean arterial pressure was below 60 mmHg , and when BIS values were between $40-60$, ephedrine ( 5 mg , IV) was administered. In addition, if BIS values were between 40 and 60, and the heart rate was $20 \%$ below baseline values, then atropine ( $0,5 \mathrm{mg}$, IV) was administered.

Measurement of the optic nerve sheath diameter was performed by the anesthesiologist following application of ultrasound gel to the upper eyelid of the left eye while the patient was in the supine position. The linear ultrasound probe (Sonosite $M$-Turbo, Bothell, USA) operating at 7.5 MHz was placed on the gel in a transverse plane to capture the most appropriate image between the retrobulbar echogenic fat tissue and the vertical hypoechoic band. The optic nerve sheath diameter was measured 4.5 mm behind the optic disc. Single measurements were performed at six time points and data were recorded.

Dynamic lung compliance was calculated using the following formula: Dynamic Lung Compliance = Tidal volume (VT)/peak airway pressure (Ppeak-PEEP).

## Statistical analysis

In a study by Dip F et al., ${ }^{7}$ the optic nerve sheath diameters during laparoscopic procedures were found to be $4.8 \pm$ 1.0 mm at baseline, $5.5 \pm 1.1$ at 15 minutes, and $5.9 \pm 1.0$ at 30 minutes. A power analysis was performed using this information, and the alpha error was calculated to be 0.05 , the effect size to be 0.70, and the minimum number of patients required to achieve a statistical power of $80 \%$ was calculated to be 34 patients per group and 68 patients in total. A total of 80 patients per group were included in our study, taking into account possible losses during the study period.

Statistical analysis of the data was performed using the SPSS for Windows 11.5. package program. For intergroup comparisons of qualitative and quantitative variables the chi-square and Student's $t$-test were used, respectively. For the comparison of time-dependent changes in quantitative variables in groups, the paired sample $t$-test was used. On repetitive samples, the two-way ANOVA test was employed to determine the effects of both groups and time on the variables.

The statistical significance was accepted as $p=0.05$.

## Results

Two patients from each study group were excluded, resulting in a total of 76 patients included in the study.

No statistically significant differences were found between the two groups in terms of demographic data ( $p>$ 0.05) (Table 2).

No statistically significant differences were detected between the groups in terms of mean arterial pressure and heart rate values ( $p>0.05$ ).

Peak airway pressure values were significantly higher in Group Pat time point t4 ( $p=0.012$ ).

Mean $\mathrm{EtCO}_{2}$ values did not differ statistically significantly between the groups ( $p>0.05$ ).

Minute respiratory volume (MV) values were significantly higher in Group C compared to Group P at time points t3 and t4 ( $p=0.05$ and $p=0.023$, respectively). The mean respiratory rates ( RR ) measured at $\mathrm{t} 3, \mathrm{t} 4$, and t 5 were found to be significantly higher in Group C compared to Group P ( $p=0.007, p=0.007$, and $p=0.007$, respectively) (Table 3).

Although there was a statistically significant difference in intragroup referring to the baseline values (t1) (Fig. 1), no

Table 3 Minute respiratory volume (MV) (L. $\mathrm{min}^{-1}$ ), and respiratory rate (RR) (breaths/min) values for both groups (mean $\pm$ SD).

| MV RR | Group C <br> $(\mathrm{n}=38)$ | Group P <br> $(\mathrm{n}=38)$ | $p$ |
| :--- | :--- | :--- | :--- |
| MV (t3) | $6.97 \pm 0.73$ | $6.56 \pm 1.06$ | $0.05^{\mathrm{a}}$ |
| MV (t4) | $7.03 \pm 0.74$ | $6.55 \pm 1.09$ | $0.023^{\mathrm{a}}$ |
| MV (t5) | $7.08 \pm 0.85$ | $6.7 \pm 1.16$ | 0.091 |
| RR (t3) | $12.13 \pm 0.46$ | $11.85 \pm 0.43$ | $0.007^{\mathrm{a}}$ |
| RR (t4) | $12.13 \pm 0.46$ | $11.83 \pm 0.5$ | $0.007^{\mathrm{a}}$ |
| RR (t5) | $12.13 \pm 0.46$ | $11.83 \pm 0.5$ | $0.007^{\mathrm{a}}$ |

[^14]

Figure 1 Average optic nerve sheath diameter (OND, cm) values for the two patient groups (PEEP applied and no PEEP applied). *Intragroup difference according to baseline values.
clinically significant difference in intergroup was detected in mean optic nerve sheath diameters among all measurements (Table 4).

Mean dynamic lung compliance values were significantly higher in Group P at time point $\mathrm{t} 4(p=0.001)$ (Table 5).

## Discussion

In this study we observed that application of PEEP in hemodynamically stable patients who underwent laparoscopic cholecystectomy did not cause a significant increase in the optic nerve sheath diameter, and thus in intracranial pressure.

The creation of pneumoperitoneum in laparoscopic cholecystectomies and other laparoscopic surgeries is known to increase intracranial pressure. ${ }^{8,9}$ Increases in intra-abdominal and intrathoracic pressures due to pneumoperitoneum prevent systemic venous return and cerebral venous blood flow, which lead to an increase in intracranial pressure. ${ }^{8}$ In addition, diffusion of $\mathrm{CO}_{2}$ gas from the peritoneum into the vascular system during pneumoperitoneum causes reflex arterial vasodilation in the central nervous system, further increasing intracranial pressure. ${ }^{10,11}$ Although invasive

Table 4 Mean optic nerve sheath diameter (ONSD) values for both patient groups (mean $\pm$ SD) at various time points.

| ONSD | Group C <br> $(\mathrm{n}=38)(\mathrm{cm})$ | Group P <br> $(\mathrm{n}=38)(\mathrm{cm})$ | $p$ |
| :--- | :--- | :--- | :--- |
| ONSD (t1) | $0.5 \pm 0.09$ | $0.5 \pm 0.11$ | 0.755 |
| ONSD (t2) | $0.49 \pm 0.09$ | $0.49 \pm 0.1$ | 0.982 |
| ONSD (t3) | $0.54 \pm 0.08$ | $0.53 \pm 0.1$ | 0.906 |
| ONSD (t4) | $0.54 \pm 0.08$ | $0.57 \pm 0.1$ | 0.212 |
| ONSD (t5) | $0.51 \pm 0.08$ | $0.52 \pm 0.1$ | 0.882 |
| ONSD (t6) | $0.53 \pm 0.08$ | $0.52 \pm 0.1$ | 0.672 |

[^15]methods are used in the measurement of intracranial pressure, noninvasive methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), are also frequently used. However, a real-time intracranial pressure measurement cannot be accurately performed using these imaging modalities. These methods also take a considerable amount of time and it is not possible to repeat these imaging methods within a short period of time. ${ }^{12,13}$ Thanks to the use of noninvasive ocular ultrasonography, which measures the optic nerve sheath diameter, intracranial pressures can be more frequently evaluated and the results have been shown to have a high degree of consistency and accuracy when compared to intracranial pressure measurements using intraventricular or intraparenchymal devices. ${ }^{14,15}$

A pressure change in the subarachnoid space is reflected in the diameter of the optic nerve sheath surrounded by dura mater and cerebrospinal fluid (CSF), and changes in intracranial pressure can be monitored by measuring the diameter of the optic nerve sheath. ${ }^{16}$ In previous studies where gold standard measurement methods of optic nerve sheath diameter and intracranial pressure were compared, optic nerve sheath diameter values over 5.8 mm were shown to be associated with a $96 \%$ increase in intracranial pressure of $20 \mathrm{mmHg} .{ }^{17}$ These data were obtained from centers where laparoscopic surgery, with the aid of carbon dioxide

Table 5 Mean dynamic lung compliance values (Cdyn) of both patient groups ( $\mathrm{mL} . \mathrm{cm}^{-1} \mathrm{H}_{2} \mathrm{O}$ ) (mean $\pm \mathrm{SD}$ ).

| Cdyn | Group C <br> $(\mathrm{n}=38)$ | Group P <br> $(\mathrm{n}=38)$ | $p$ |
| :--- | :--- | :--- | :--- |
| Cdyn (t2) | $38.98 \pm 9.4$ | $37.83 \pm 9.4$ | 0.587 |
| Cdyn (t3) | $24.88 \pm 4.63$ | $26.43 \pm 5.77$ | 0.19 |
| Cdyn (t4) | $25.35 \pm 5.8$ | $36.50 \pm 9.84$ | $0.001^{\text {a }}$ |
| Cdyn (t5) | $37.95 \pm 9.25$ | $37.45 \pm 9.86$ | 0.816 |

[^16]pneumoperitoneum, was performed on $86 \%$ of their patients on an outpatient basis. In our study, the difference between optic nerve sheath diameters measured at baseline and after application of pneumoperitoneum was not statistically significant. This may be because a laparoscopic cholecystectomy is performed within a short time, and, as such, the duration of pneumoperitoneum in our study did not exceed 20 minutes. The difference may be observed more clearly in longer surgical procedures. However, Dip et al. ${ }^{7}$ showed significant increases in optic nerve sheath diameter, and therefore intracranial pressures, at 15 and 30 minutes after creation of pneumoperitoneum.

Respiratory mechanics dependent on pneumoperitoneum are also negatively affected, as mentioned above. These negative effects of pneumoperitoneum can be increased with the effect of general anesthesia. The use of PEEP, which is one of the recruitment maneuvers, is widely used to overcome the worsening pulmonary functions observed during this surgery. However, there are reports that intracranial pressure may increase due to the use of PEEP. ${ }^{11}$ While PEEP application increases intrathoracic pressure, it partially blocks venous return from the sagittal sinus. We observed that application of $10 \mathrm{cmH}_{2} \mathrm{O}$ PEEP in hemodynamically stable patients, aided the maintenance of lung function within normal range, and did not cause a significant increase in the optic nerve sheath diameter.

In a recent study performed by Bedirli et al. ${ }^{18}$ on pigs, the authors reported that PEEP pressure at $10 \mathrm{cmH}_{2} \mathrm{O}$ maintained the intracranial pressure and brain perfusion pressure in laparoscopic surgery performed with the aid of pneumoperitoneum. In their study, PEEP pressures of $15 \mathrm{cmH}_{2} \mathrm{O}$ and $20 \mathrm{cmH}_{2} \mathrm{O}$ were shown to increase intracranial pressure and significantly decrease brain perfusion pressure. We used $10 \mathrm{cmH}_{2} \mathrm{O}$ PEEP and are thus unable to comment on the applications of PEEP at the higher values of 15 and $20 \mathrm{cmH}_{2} 0$.

Verdonck et al. ${ }^{19}$ demonstrated that pneumoperitoneum and Trendelenburg position did not change the diameter of the optic nerve sheath in laparoscopic prostatectomy patients, in stark contrast with other studies showing that pneumoperitoneum and Trendelenburg position in laparoscopic surgeries significantly increased the diameter of the optic nerve sheath. ${ }^{20,21}$ The increase in intracranial pressure due to the Trendelenburg position and pneumoperitoneum is thought to be due to the increase in intrathoracic and cerebral venous pressures. ${ }^{22,23}$ In contrast to laparoscopic prostatectomy, in laparoscopic cholecystectomy, as in our study, the reverse Trendelenburg position is preferred. While the cardiopulmonary effects of this position are generally well tolerated, their effects on optic nerve sheath diameter and intracerebral physiology are not clearly demonstrated. ${ }^{24,25}$

Chin et $\mathrm{al}^{5}$ compared optic nerve sheath diameters in patients who had and had not undergone PEEP applications at $8 \mathrm{cmH}_{2} \mathrm{O}$ during laparoscopic prostatectomies. They determined that optic nerve sheath diameter increased significantly when PEEP was applied before creation of pneumoperitoneum.

When pneumoperitoneum was applied, it was reported that the diameter of the optic nerve sheath increased in both groups compared to the baseline and time points of PEEP applications, but it did not cause a significant increase in the optic nerve sheath diameter in the group of $8 \mathrm{cmH}_{2} \mathrm{O}$
of PEEP compared to the group without PEEP. Kwak et al. ${ }^{26}$ reported that PEEP application did not cause an increase in intracranial pressure and suggested that the lack of any increase in intracranial pressure following PEEP application was due to a decrease in dynamic lung compliance related to creation of pneumoperitoneum (which limits the intracranial effects of PEEP). Similarly, Caricato et al ${ }^{27}$ also demonstrated that application of PEEP in patients with decreased lung compliance exerted minimal effects on intracranial pressure.

In our study, since we applied PEEP following creation of pneumoperitoneum, we could not examine the effect of PEEP application on the optic nerve sheath diameter before creation of pneumoperitoneum. We showed that dynamic lung compliance values decreased in both groups due to pneumoperitoneum, relative to baseline values. The decrease in lung compliance due to creation of pneumoperitoneum that we observed may mask the potential adverse effects of PEEP on intracranial pressure, therefore optic nerve sheath diameter may not be affected. This seems to be consistent with the theory proposed by Caracito et al. ${ }^{27}$

Since there is no consensus regarding the normal and upper limit of normal values of the optic nerve sheath diameter, a comparison of the baseline values of all patients as well as intergroup comparisons were made, and the impact of pneumoperitoneum, position of the patient, and PEEP on the optic nerve diameter were examined. In our study, the diameter of the optic nerve sheath increased with applications of pneumoperitoneum and PEEP, but this increase was not statistically and clinically significant. Maude et al. ${ }^{28}$ identified the mean baseline optic nerve sheath diameter to be $4.41 \mathrm{~mm}(4.25-4.7)$ in 136 normal individuals, while Dip et al. ${ }^{17}$ determined it to be 4.81 mm . In our study, the mean baseline optic nerve sheath diameter in both groups was 5.0 mm . It can be argued that this difference between studies makes it difficult to achieve standardization of values.

We also measured and recorded heart rate, mean arterial blood pressure, $\mathrm{SpO}_{2}$, airway peak pressure (Ppeak), dynamic lung compliance values, tidal volume (TV), respiratory rate (RR), minute volume (MV), and $\mathrm{EtCO}_{2}$ at six different time points, and we were thus able to follow the hemodynamic and respiratory parameters of the patients during this period. There was no observed hemodynamic instability or respiratory distress that would have affected the optic nerve sheath diameter.

In our study, $\mathrm{ETCO}_{2}$ levels were continuously monitored and maintained within a constant interval by adjusting respiratory frequency during the operation, thus preventing an increase in $\mathrm{ETCO}_{2}$, which might otherwise have led to an increase in intracranial pressure. None of the patients had signs and symptoms related to increased intracranial pressure before and after surgery.

The use of ocular ultrasonography is an important method in this study because it is a practical, fast, realtime, and noninvasive means to measure intracranial pressure. It shows the change in the diameter of the optic nerve sheath and guides us in estimating the intracranial pressure.

The limitation of this investigation was that a blind study design could not be achieved since application of PEEP could not be concealed from the researcher measuring the diameters of the optic nerve sheaths.

Future studies are needed to determine the effect of higher PEEP values on optic nerve sheath diameter, particularly for those patient groups where PEEP values higher than $10 \mathrm{cmH}_{2} \mathrm{O}$ may be required to control respiratory mechanics, such as obese patients.

In conclusion, the data we obtained suggest that PEEP application used to assist in the maintenance of normal lung function in hemodynamically stable patients, does not cause a significant increase in the optic nerve sheath diameter, and therefore in intracranial pressure, and that PEEP application can be used safely in laparoscopic cholecystectomy operations.

## Conflicts of interest

## The authors declare no conflicts of interest.

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# Investigating preoperative myoglobin level as predictive factor for acute kidney injury following cardiac surgery with cardiopulmonary bypass: a retrospective observational study 

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## KEYWORDS

Acute kidney injury; Coronary artery bypass graft surgery; Myoglobin; Valve surgery


#### Abstract

Background: Early identification of patients at risk of AKI after cardiac surgery is of critical importance for optimizing perioperative management and improving outcomes. This study aimed to identify the association between preoperative myoglobin levels and postoperative acute kidney injury (AKI) in patients undergoing valve surgery or coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass. Methods: This retrospective study included 293 patients aged over 17 years who underwent valve surgery or CABG with cardiopulmonary bypass. We excluded 87 patients as they met the exclusion criteria. Therefore, 206 patients were included in the final analysis. The patients' demographics as well as intraoperative and postoperative data were collected from electronic medical records. AKI was defined according to the Acute Kidney Injury Network classification system. Results: Of the 206 patients included in this study, 77 developed AKI. The patients who developed AKI were older, had a history of hypertension, underwent valve surgery with concomitant CABG, had lower preoperative hemoglobin levels, and experienced prolonged extracorporeal circulation (ECC) times. Multivariate logistic regression analysis revealed that preoperative myoglobin levels and ECC time were correlated with the development of AKI. A higher preoperative myoglobin level was an independent risk factor for the development of cardiac surgery-associated AKI. Conclusions: Higher preoperative myoglobin levels may enable physicians to identify patients at risk of developing AKI and optimize management accordingly. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


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## Introduction

Acute kidney injury (AKI) is a common complication in patients who have undergone cardiac surgery. ${ }^{1}$ Postoperative AKI is a major cause of prolonged intensive care unit stay and increased operative mortality. ${ }^{2}$ Morgan et al. reported an $18.7 \%$ incidence of AKI after cardiac surgery, while Hobson et al. reported an incidence rate between $5 \%$ and $42 \%$. ${ }^{3,4}$ In another study, cardiac surgery-associated AKI augmented the mortality rate to over $60 \%{ }^{5}$

Grams ME et al. noted that early identification of patients with cardiac surgery-associated AKI is of critical importance in optimizing perioperative management and improving the outcomes of patients undergoing cardiac surgery. ${ }^{3,6}$ The risk factors and predictors of cardiac surgery-associated AKI include older age, female sex, obesity, valve replacement surgery, history of myocardial infarction within 30 days of surgery, intraoperative diuretic administration, transfusion of blood products, low cardiac output, history of heart failure, hypertension, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. ${ }^{6-9}$

The mechanisms underlying the development of cardiac surgery-associated AKI are complex, multifactorial, and have not been elucidated. ${ }^{10}$ Nevertheless, epidemiologic studies on cardiac surgery-associated AKI are important because they allow for early diagnosis of AKI and facilitate the implementation of more effective strategies to prevent this complication, decreasing its subsequent morbidity and mortality. ${ }^{11}$ This study aimed to determine the risk factors, protective factors, and incidence of AKI in patients undergoing valve surgery or coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass.

The mechanisms underlying the development of cardiac surgery-associated AKI are complex, multifactorial, and have not been elucidated. ${ }^{10}$ The traditional risk factors of cardiac surgery-associated AKI include older age, female sex, obesity, valve replacement surgery, history of myocardial infarction within 30 days of surgery, intraoperative diuretic administration, transfusion of blood products, low cardiac output, history of heart failure, hypertension, diabetes, and chronic obstructive pulmonary disease. ${ }^{6-9}$ Preoperative biomarkers have been studied to predict cardiac surgery-associated AKI ${ }^{12-14}$ because early identification of patients with cardiac surgery-associated AKI facilitates the optimization of pre- and postoperative management to improve outcomes for patients undergoing cardiac surgery. ${ }^{6}$

However, to the best of our knowledge, much as myoglobin is a commonly measured biomarker, few reports have presented its potential as a predictive factor of cardiac surgery-associated AKI.

This study aimed to identify the association between preoperative myoglobin levels and postoperative AKI in patients undergoing valve surgery or CABG with cardiopulmonary bypass.

## Methods

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2019AS0064). Informed consent was not required because of the retrospective study design. This study included elective surgery
patients over the age of 17 years who underwent valve surgery or CABG with cardiopulmonary bypass at Korea University Ansan Hospital between March 2008 and December 2019. The surgical procedures included valve surgery, CABG, and combined valve surgery and CABG. The exclusion cri-
 end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, and incomplete data. The patients' demographics as well as intraoperative and postoperative data were collected from an electronic medical records database of the hospital.

Postoperative AKI was defined according to the Acute Kidney Injury Network criteria: a postoperative increase of > $0.3 \mathrm{mg}_{\mathrm{dL}}{ }^{-1}$ in serum creatinine ( SCr ) levels on comparison with preoperative values; percent increase in SCr levels of $>50 \%$ on comparison with preoperative values; and urine output < $0.5 \mathrm{~mL} . \mathrm{kg}^{-1} . \mathrm{h}^{-1}$ for more than 6 hours. Preoperative SCr values were defined as the most recent SCr values measured within seven days before surgery. Peak postoperative SCr values were defined as the highest creatinine levels within 48 hours after surgery.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 12 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as median or mean $\pm$ standard deviation. Categorical variables are presented as percentages. Continuous variables were compared using the Mann-Whitney $U$ test or Student's $t$-test, and Bonferroni corrections were applied when appropriate. Categorical variables were compared using the chi-squared and Fisher's tests.

Univariate analysis was performed to evaluate the risk factors and protective factors related to cardiac surgeryassociated AKI. Variables with a $p$-value $<0.1$ were selected for further multivariate analysis. Multivariate analysis was performed using logistic regression to identify the variables that were independently predictive of cardiac surgeryassociated AKI.

## Results

A total of 293 patients who underwent valve surgery or CABG at our center between March 2008 and December 2019 were selected for this study. We excluded three patients who underwent off-pump CABG surgery and 12 patients who were undergoing regular dialysis due to ESRD. The data were incomplete for 72 patients. Therefore, data from 206 patients were included in the final analysis (Fig. 1). In this study, the incidence of cardiac surgery-associated AKI was $37 \%$. The demographic data and clinical characteristics of the study population are presented in Table 1.

Patients who developed cardiac surgery-associated AKI were older ( $p=0.003$ ) and were more likely to have a history of hypertension ( $p=0.004$ ) (Table 1). There was a significant increase in the incidence of cardiac surgery-associated AKI among patients undergoing valve surgery and concomitant CABG ( $p=0.028$ ) (Table 1). Patients who experienced cardiac surgery-associated AKI had lower preoperative hemoglobin levels $(p=0.002)$ and higher preoperative myoglobin levels ( $p=0.001$ ) (Table 2).

Patients with cardiac surgery-associated AKI did not differ significantly from those without cardiac surgery-


Figure 1 CONSORT flow chart.
associated AKI in terms of the anesthesia time ( $p=0.049$ ), total input fluid ( $p=0.103$ ), or estimated blood loss ( $p=0.029$ ). However, the extracorporeal circulation (ECC) time was higher among patients with cardiac surgery-associated AKI than among those without cardiac surgery-associated AKI ( $p<0.0001$ ) (Table 3).

Postoperative creatinine levels were significantly higher among patients with cardiac surgery-associated AKI than among those without cardiac surgery-associated AKI ( $p<0.0001$ ) (Table 4). Patients with cardiac surgeryassociated AKI had a longer ICU stay than those without cardiac surgery-associated AKI ( $p=0.004$ ). (Table 4).

Patients with cardiac surgery-associated AKI had a higher incidence of pulmonary complications and continuous renal replacement therapy (CRRT; $p=0.007$ and $p=0.002$, respectively).

The results of univariate analysis to identify the risk and protective factors for AKI are presented in Table 5. The following variables were associated with the development of cardiac surgery-associated AKI: age, anesthesia time, ECC time, aortic cross-clamping time, and transfusion of red blood cells. Preoperative hemoglobin and albumin levels were inversely associated with the development of cardiac surgery-associated AKI (Table 5).

Covariates with $p<0.1$ in univariate analysis were entered in a multivariate logistic analysis. The independent risk factors for cardiac surgery-associated AKI included preoperative myoglobin levels and ECC time ( $O R=1.001$, 95\% CI, 1.000-1.002; $p=0.034$; and $\mathrm{OR}=1.009$, $95 \%$ $\mathrm{Cl}=1.000-1.019, p=0.048$, respectively) (Table 5).

## Discussion

We identified the potential of higher preoperative myoglobin levels as a predictive factor for cardiac surgery-associated AKI. Our main finding was that high preoperative myoglobin level was an independent risk factor for the development of cardiac surgery-associated AKI. Myoglobin is a low molecular weight heme protein that is abundantly found in skeletal muscles and cardiac muscle, and it is released from necrotic muscle. ${ }^{15}$ Valvular heart disease and coronary artery disease are associated with myocardial infarction. A group with mitral insufficiency in an animal study had an increased amount of myoglobin. ${ }^{16}$ It has also been reported that coronary artery disease, valve insufficiency (such as ischemic mitral regurgitation), and papillary muscle dysfunction are associated with myocardial infarction. ${ }^{17-19}$ The large quan-

Table 1 Demographic data.

| Variable | Non-AKI group ( $\mathrm{n}=129$ ) | AKI group ( $\mathrm{n}=77$ ) | $p$-value |
| :---: | :---: | :---: | :---: |
| Age (years) | $58.02 \pm 13.22$ | $62.94 \pm 13.03$ | $0.003{ }^{\text {a }}$ |
| Height (cm) | $163.83 \pm 9.44$ | $161.76 \pm 8.38$ | $0.115^{\text {b }}$ |
| Weight (kg) | $65.61 \pm 12.89$ | $62.70 \pm 12.04$ | $0.110^{\text {b }}$ |
| BMI (kg.m ${ }^{-2}$ ) | $24.35 \pm 3.81$ | $23.86 \pm 3.73$ | $0.365^{\text {b }}$ |
| Sex |  |  | $0.690^{\text {c }}$ |
| Male, n (\%) | 82 (63.6) | 46 (59.7) |  |
| Female, n (\%) | 47 (36.4) | 31 (40.3) |  |
| Underlying disease |  |  |  |
| Hypertension, n (\%) | 61 (47.3) | 53 (68.8) | $0.004{ }^{\text {c }}$ |
| Diabetes mellitus, n (\%) | 47 (36.4) | 28 (36.4) | $1.000^{\text {c }}$ |
| COPD, n (\%) | 4 (3.1) | 3 (3.9) | $1.000^{\text {c }}$ |
| CVA, n (\%) | 29 (22.5) | 24 (31.2) | $0.224^{\text {c }}$ |
| OHS Hx, n (\%) | 8 (6.2) | 5 (6.5) | $1.000^{\text {c }}$ |
| CAD, n (\%) | 69 (53.5) | 43 (55.8) | $0.854^{\text {c }}$ |
| IHD, n (\%) | 34 (26.4) | 25 (32.5) | $0.436{ }^{\text {c }}$ |
| CHF, n (\%) | 35 (27.1) | 19 (24.7) | $0.823^{\text {c }}$ |
| Type of surgery |  |  |  |
| Valve | 73 (56.6) | 40 (51.9) | $0.615^{\text {c }}$ |
| CABG | 55 (42.6) | 32 (41.6) | $0.995^{\text {c }}$ |
| Valve + CABG | 1 (0.8) | 5 (6.5) | $0.028^{\text {c }}$ |

AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; OHS Hx , open heart surgery history; CAD, coronary artery disease; IHD, ischemic heart disease; CHF, chronic heart failure; CABG, coronary artery bypass graft.
Data are displayed as mean $\pm$ standard deviation or number of patients (\%).
a $p$-value indicates comparisons between two groups using the Mann-Whitney $U$ test. Values < 0.0125 were considered significant following post-hoc Bonferroni correction.
${ }^{\text {b }} p$-value indicates comparisons between two groups using the $t$-test. Values $<0.0125$. were considered significant following post-hoc Bonferroni corrections.
${ }^{\text {c }} p$-value indicates comparisons between two groups using the chi-square test.

Table 2 Laboratory findings during the preoperative period.

| Variable | Non-AKI group $(\mathrm{n}=129)$ | AKI group $(\mathrm{n}=77)$ | $p$-value |
| :--- | :--- | :--- | :--- |
| Hemoglobin $\left(\mathrm{g} . \mathrm{dL}^{-1}\right)$ | $13.10(12.84 \pm 2.00)$ | $12.00(11.98 \pm 2.06)$ | $0.002^{\mathrm{a}}$ |
| Platelets $\left(\times 10^{3} / \mu \mathrm{L}\right)$ | $209.00(229.45 \pm 95.95)$ | $227.00(228.81 \pm 66.11)$ | 0.378 |
| PT $($ INR $)$ | $1.03(1.08 \pm 0.25)$ | $1.03(1.10 \pm 0.24)$ | 0.463 |
| Albumin $\left(\mathrm{g} . \mathrm{dL}^{-1}\right)$ | $4.00(4.04 \pm 0.49)$ | $3.80(3.87 \pm 0.47)$ | 0.021 |
| Sodium $\left(\mathrm{mmol} . \mathrm{L}^{-1}\right)$ | $141.00(140.46 \pm 2.85)$ | $141.00(140.23 \pm 3.08)$ | 0.742 |
| Potassium $\left(\mathrm{mmol}^{-1}\right)$ | $4.20(4.17 \pm 0.44)$ | $4.20(4.18 \pm 0.50)$ | 0.793 |
| Myoglobin $\left(\mathrm{ng} . \mathrm{mL}^{-1}\right)$ | $31.23(81.58 \pm 171.69)$ | $45.14(210.65 \pm 575.92)$ | $0.001^{\mathrm{a}}$ |
| Creatinine | $0.93(0.94 \pm 0.25)$ | $1.04(1.03 \pm 0.31)$ | 0.019 |
| Ejection fraction | $57.50(52.83 \pm 11.84)$ | $57.50(52.30 \pm 13.55)$ | 0.996 |
| eGFR | $79.93(80.38 \pm 22.33)$ | $68.73(73.90 \pm 31.27)$ | 0.0052 |

AKI, acute kidney injury; PT, prothrombin time; INR, international normalized ratio; eGFR, estimated glomerular filtration rate.
Data are displayed as median (mean $\pm$ standard deviation).
${ }^{\text {a }} p$-value indicates comparisons between two groups using the Mann-Whitney U test. Values < 0.005 were considered significant following post-hoc Bonferroni correction.
tities of myoglobin released into the circulation precipitate in the renal glomerulus, causing kidney injury. ${ }^{15}$

The basic mechanisms underlying the development of cardiac surgery-associated AKI are as follows: First, renal vasoconstriction, a consequence of intravascular volume depletion and altered expression of vasoactive compounds, markedly reduces renal blood flow. ${ }^{20}$ Nitric oxide is involved in maintaining renal blood flow, and myoglobin acts as a potent nitric oxide scavenger, thereby contributing to
vasoconstriction. ${ }^{21,22}$ Myoglobin induces the formation of F2-isoprostanes, which are potent renal vasoconstrictors formed during lipid peroxidation. ${ }^{23}$ Moreover, the released myoglobin leads to selective reduction in outer medullary blood flow and oxygenation. ${ }^{24}$ Myoglobin may adversely affect medullary oxygen balance, both by reducing oxygen supply and increasing oxygen demand and workload for distal tubular reabsorption, and it may cause ischemic tubular damage. ${ }^{20,25,26}$ Second, the precipitation of myo-

Table 3 Clinical variables during the intraoperative period.

| Variables | Non-AKI group $(\mathrm{n}=129)$ | AKI group $(\mathrm{n}=77)$ | $p$-value |
| :--- | :--- | :--- | :--- |
| Anesthetic time $(\mathrm{min})$ | $515.00(530.98 \pm 123.08)$ | $550.00(572.92 \pm 145.72)$ | 0.049 |
| Operative time $(\mathrm{min})$ | $420.00(434.51 \pm 117.19)$ | $450.00(478.03 \pm 143.74)$ | 0.037 |
| ECC time $(\mathrm{min})$ | $170.50(181.95 \pm 60.78)$ | $200.00(223.30 \pm 99.53)$ | $<0.0001^{\text {a }}$ |
| ACC time $(\mathrm{min})$ | $121.00(127.93 \pm 41.42)$ | $135.00(152.81 \pm 80.09)$ | 0.032 |
| MAP | $80.42(78.87 \pm 7.32)$ | $79.43(77.55 \pm 6.08)$ | 0.184 |
| MAP $($ pump $)$ | $65.31(65.00 \pm 5.43)$ | $64.26(63.95 \pm 5.68)$ | 0.188 |
| Input |  |  |  |
| $\quad$ Total $(\mathrm{mL})$ | $3873.50(4208.78 \pm 2831.02)$ | $4090.00(4689.83 \pm 2317.56)$ | 0.103 |
| $\quad$ Fluid $(\mathrm{mL})$ | $2400.00(2585.00 \pm 1964.47)$ | $2300.00(2704.81 \pm 1640.61)$ | 0.903 |
| Albumin $(\mathrm{mL})$ | $0.00(27.34 \pm 123.76)$ | $0.00(38.18 \pm 136.71)$ | 0.610 |
| $\quad$ Colloid $(\mathrm{mL})$ | $400.00(333.44 \pm 311.56)$ | $400.00(335.06 \pm 378.37)$ | 0.928 |
| $\quad$ RBC $(\mathrm{mL})$ | $600.00(732.41 \pm 644.01)$ | $800.00(938.57 \pm 650.65)$ | 0.007 |
| Output |  |  | 0.029 |
| $\quad$ EBL $(\mathrm{mL})$ | $1200(1492.97 \pm 2166.67)$ | $1020.00(1264.48 \pm 819.32)$ | 0.028 |
| $\quad$ Urine output $(\mathrm{mL})$ | $1272.50(1441.04 \pm 750.05)$ |  |  |

ACC, aortic cross clamping; AKI, acute kidney injury; EBL, estimated blood loss; ECC, extracorporeal circulation; MAP, mean arterial pressure; RBC, red blood cell.
Data are displayed as median (mean $\pm$ standard deviation).
${ }^{\text {a }} p$-value indicates comparisons between two groups using the Mann-Whitney U test. Values < 0.0045 were considered significant following post-hoc Bonferroni correction.

Table 4 Laboratory findings and clinical variables during the postoperative period.

| Variables | Non-AKI group $(\mathrm{n}=129)$ | AKI group $(\mathrm{n}=77)$ | $p$-value |
| :--- | :--- | :--- | :--- |
| $\mathrm{Hb}\left(\mathrm{g} . \mathrm{dL}^{-1}\right)$ | $10.30(10.57 \pm 1.47)$ | $10.10(10.32 \pm 1.64)$ | ${ }^{\mathrm{a}} 0.311$ |
| Platelet count $\left(\times 10^{3} / \mu \mathrm{L}\right)$ | $129.00(139.37 \pm 46.54)$ | $121.00(125.84 \pm 40.12)$ | ${ }^{\mathrm{a}} 0.090$ |
| Albumin $\left(\mathrm{g} . \mathrm{dL}^{-1}\right)$ | $3.60(3.59 \pm 0.44)$ | $3.50(3.42 \pm 0.48)$ | ${ }^{\mathrm{b}} 0.009$ |
| Sodium $\left(\mathrm{mmol} . \mathrm{L}^{-1}\right)$ | $144.00(143.61 \pm 3.00)$ | $144.00(144.30 \pm 3.76)$ | ${ }^{\mathrm{a}} 0.136$ |
| Potassium $\left(\mathrm{mmol} . \mathrm{L}^{-1}\right)$ | $3.90(3.94 \pm 0.43)$ | $4.10(4.10 \pm 0.51)$ | 0.017 |
| Creatinine | $0.96(0.98 \pm 0.24)$ | $1.40(1.58 \pm 0.68)$ | $\mathrm{a}^{\mathrm{a}} 0.0001$ |
| ICU stay (days) | $2.00(3.62 \pm 5.67)$ | $3.00(6.25 \pm 9.09)$ | 0.004 |
| POD (days) | $16.00(22.08 \pm 22.72)$ | $18.00(26.66 \pm 23.28)$ | ${ }^{\mathrm{a}} 0.016$ |

[^18]globin within the distal tubules results in cast formation and possibly, intratubular obstruction. ${ }^{27}$ In the tubular lumen, myoglobin may precipitate in combination with the TammHorsfall protein, forming tubular casts. ${ }^{22}$ Heyman et al. showed that myoglobin cast formation with marked dilation of the collecting ducts and focal tubular necrosis as well as rupture at the outer medullary region likely play a major role in the deterioration of kidney function. ${ }^{24}$ Third, myoglobin has the potential to be directly cytotoxic. ${ }^{28}$ Many studies suggest that the cytotoxic effects of myoglobin stem from iron-driven hydroxyl radical generation via the Haber Weiss reaction. ${ }^{29,30}$ If tubular cell death occurs, the necrotic debris provides additional substrates for cast formation, worsening tubular obstruction and leading to filtration failure. ${ }^{31}$ By this mechanism, the function of a vulnerable kidney exposed to myoglobin before cardiac surgery could deteriorate due to hypoperfusion, hypovolemia, and metabolic acidosis caused by cardiac surgery with cardiopulmonary bypass. Accord-
ing to Umberto et al., coexisting hypovolemia and acidic urine pH due to metabolic acidosis are regulating factors that intensify the nephrotoxic action of myoglobin. ${ }^{32}$

Patients who developed cardiac surgery-associated AKI were generally older, had a history of hypertension, had undergone valve surgery with concomitant CABG, had lower levels of hemoglobin, had prolonged ECC time, and had severe left ventricular dysfunction. ${ }^{33-35}$ Our findings align with the current data which show correlations between cardiac surgery-associated AKI and advanced age, history of hypertension, valve surgery with concomitant CABG, as well as lower hemoglobin levels. However, in this study, the ejection fraction was not significantly associated with the development of cardiac surgery-associated AKI. Christian et al. demonstrated that patients who developed AKI demonstrated a lower ejection fraction (<30\%) than those who did not. ${ }^{33}$ A possible explanation for the discrepancy in this finding is that in the present study, we did not classify

Table 5 Univariate and multivariate logistic regression analyses for AKI.

| Variables | Univariate |  | Multivariate |  |
| :---: | :---: | :---: | :---: | :---: |
|  | OR (95\% CI) | $p$-value | OR (95\% CI) | $p$-value |
| Age | 1.030 (1.007 to 1.054) | 0.012 | 1.022 (0.997 to 1.048) | 0.087 |
| BMI | 0.966 (0.895 to 1.041) | 0.363 |  |  |
| Pre Hb | 0.811 (0.703 to 0.936) | 0.004 | 0.848 (0.698 to 1.029) | 0.095 |
| Pre PT | 1.532 (0.497 to 4.717) | 0.458 |  |  |
| Pre albumin | 0.470 (0.254 to 0.870) | 0.016 | 0.832 (0.378 to 1.832) | 0.648 |
| Anes. time | 1.002 (1.000 to 1.005) | 0.034 | 1.001 (0.997 to 1.005) | 0.595 |
| ECC time | 1.008 (1.003 to 1.012) | 0.001 | 1.009 (1.000 to 1.019) | 0.048 |
| ACC time | 1.007 (1.002 to 1.013) | 0.007 | 0.995 (0.983 to 1.007) | 0.381 |
| Input |  |  |  |  |
| Total | 1.000 (1.000 to 1.000) | 0.274 |  |  |
| Fluid | 1.000 (1.000 to 1.000) | 0.688 |  |  |
| RBC | 1.001 (1.000 to 1.000) | 0.039 | 1.000 (1.000 to 1.001) | 0.740 |
| Output |  |  |  |  |
| EBL | 1.000 (1.000 to 1.000) | 0.478 |  |  |
| Urine output | 1.000 (0.999 to 1.000) | 0.096 | 1.000 (0.999 to 1.000) | 0.139 |
| Pre EF | 0.997 (0.974 to 1.019) | 0.767 |  |  |
| Pre eGFR | 0.990 (0.978 to 1.002) | 0.089 |  |  |
| OHS Hx | 1.050 (0.331 to 3.333) | 0.934 |  |  |
| Pre myoglobin | 1.001 (1.000 to 1.002) | 0.058 | 1.001 (1.000 to 1.002) | 0.037 |

AKI, acute kidney injury; BMI, body mass index; Pre, preoperative; Hb, hemoglobin; PT, prothrombin time; Anes., anesthesia; ECC, extracorporeal circulation; ACC, aortic cross clamping; RBC, red blood cell; EBL, estimated blood loss; EF, ejection fraction; eGFR, estimated glomerular filtration rate; OHS Hx, open heart surgery history.
Data presented with $p$ values and odds ratio's (OR) with $95 \% \mathrm{Cl}$.
Statistically significant $p$ value for univariate analysis: $p<0.1$ and for myltivariate analysis: $p<0.05$.
ejection fraction based on severity but rather analyzed it as a continuous variable.

This study had some limitations. It has been reported that perioperative myocardial infarction occurs infrequently in patients with valvular heart disease. ${ }^{36}$ However, this issue is controversial because the patients in the study were not limited to those with advanced valvular heart disease that required cardiac surgery. Another limitation of this study is that it was a retrospective single-center study. Nevertheless, our study provides the possibility that preoperative myoglobin level is a predictive factor for cardiac surgery-associated AKI. Controlled studies are needed to establish a clear association between preoperative myoglobin level and cardiac surgery-associated AKI.

Although it is difficult to verify an early diagnosis of cardiac surgery-associated AKI due to its complex and multifactorial pathogenesis, ${ }^{37}$ early identification is critical for optimizing perioperative management and improving outcomes. First, it may help in identifying the patients eligible for referral to nephrology; second, it could allow for timely interventions, such as CRRT, that could prevent complications and improve outcomes. ${ }^{38}$ Therefore, it is important to identify the patients who are at risk of developing AKI following cardiac surgery.

In summary, we found that preoperative myoglobin levels may be a predictor of cardiac surgery-associated AKI. Based on our findings, patients scheduled to undergo valve surgery or CABG who have high myoglobin levels should be managed appropriately to prevent the development of cardiac surgery-associated AKI.

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## Conflicts of interest

The authors declare no conflicts of interest.

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# Trans-nasal sphenopalatine ganglion block for post-dural puncture headache management: a meta-analysis of randomized trials 

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## KEYWORDS

Post-dural puncture headache;
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Pain management;
Conservative
treatment


#### Abstract

Objective: To evaluate the efficacy and safety of trans-nasal Sphenopalatine Ganglion (SPG) block over other treatments for Post-Dural Puncture Headache (PDPH) management. Methods: A systematic literature search was conducted on databases for Randomized Controlled Trials (RCTs) comparing trans-nasal SPG blockade for the management of PDPH over other treatment modalities. All outcomes were pooled using the Mantel-Haenszel method and random effect model. Analyses of all outcomes were performed as a subgroup based on the type of control interventions (conservative, intranasal lignocaine puffs, sham, and Greater Occipital Nerve [GON] block). The quality of evidence was assessed using the GRADE approach. Results: After screening 1748 relevant articles, 9 RCTs comparing SPG block with other interventions ( 6 conservative treatments, 1 sham, 1 GON and 1 intranasal lidocaine puff) were included in this meta-analysis. SPG block demonstrated superiority over conservative treatment in pain reduction at $30 \mathrm{~min}, 1 \mathrm{~h}, 2 \mathrm{~h}, 4 \mathrm{~h}$ after interventions and treatment failures with "very low" to "moderate" quality of evidence. The SPG block failed to demonstrate superiority over conservative treatment in pain reduction beyond 6 h , need for rescue treatment, and adverse events. SPG block demonstrated superiority over intranasal lignocaine puff in pain reduction at 30 min , $1 \mathrm{~h}, 6 \mathrm{~h}$, and 24 h after interventions. SPG block did not show superiority or equivalence in all efficacy and safety outcomes as compared to sham and GON block.


[^19]
#### Abstract

Conclusion: Very Low to moderate quality evidence suggests the superiority of SPG block over conservative treatment and lignocaine puff for short-term pain relief from PDPH. PROSPERO Registration: CRD42021291707. © 2023 Sociedade Brasileira de Anestesiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


## Introduction

Post-Dural Puncture Headache (PDPH) is an associated complication of spinal anesthesia. ${ }^{1}$ The mechanism of PDPH involves leakage of cerebrospinal fluid (CSF) through the puncture site and subsequently, a decrease in CSF pressure, leading to traction on the pain-sensitive structures of the brain and reflex vasodilation of the vessels of meninges caused by the parasympathetic nervous system. The reported incidence of PDPH varies from $10 \%$ to $40 \%$ depending on age, gender, and needle size. ${ }^{2-4}$ PDPH is managed with conventional treatments, including bed rest, intravenous hydration, abdominal binders, methylxanthines, analgesics, gabapentinoids, and sumatriptan. ${ }^{5}$ Epidural Blood Patch (EBP) is considered the gold standard over other treatments. Those patients who do not respond to conservative treatment within 48 h may require an EBP, which is considered the treatment of choice for moderate and severe PDPH, with success rates of $61-98 \% .{ }^{6-8}$ However, EBP is contraindicated in coagulopathies and local site infection and can lead to neurological infection and sequelae such as meningitis, arachnoiditis, seizures, loss of hearing or vision, radicular pain, and neural deficits. ${ }^{4,9}$ Therefore, several other interventions have also been practiced for the treatment of PDPH like Sphenopalatine Ganglion (SPG) block and Greater Occipital Nerve (GON) block. ${ }^{10-13}$

SPG is predominantly a parasympathetic ganglion positioned in the pterygopalatine fossa. In addition to parasympathetic fibers, the ganglion also receives sympathetic and sensory projections and en route to innervate the cerebral and meningeal vessels. Increased parasympathetic activity leading to vasodilation of these vessels has been postulated to be a cause of various headache disorders including PDPH. SPG is considered a target in the management of various headache disorders. ${ }^{14,15}$ SPG block for managing PDPH was first published by Cohen et al. in $2001^{16}$ and subsequently, various case reports, case series, retrospective and observational studies reported the efficacy of this superficial, noninvasive, and technically simple block for successful pain relief in PDPH ${ }^{17-19}$ although the results were inconclusive due to the paucity of reviews and lack of evidence. ${ }^{20}$ An earlier pilot meta-analysis of observational studies found no significant therapeutic advantage over conventional treatments. ${ }^{21}$ The literature on the use of SPG block for the management of PDPH is now available in Randomized Controlled studies (RCTs). So, we planned a meta-analysis of randomized trials to compare the efficacy of trans-nasal SPG block using a cotton-tipped applicator with other modalities for the treatment of PDPH.

## Methods

The current systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) checklist. ${ }^{22}$ The study protocol was prospectively registered to PROSPERO: CRD42021262516.

## Study identification

Two investigators independently and systematically searched the databases (PubMed, PubMed Central, Scopus, LILACS, Google Scholar, trial registry clinicaltrial.gov, and Cochrane Database of Systematic Reviews). Bibliographies of relevant narrative review articles, systematic reviews, and meta-analyses were also hand-searched to retrieve additional eligible studies. A literature search was conducted using the Boolean operator "AND" to combine the search terms: (post-dural puncture headache OR dural puncture headache OR PDPH) AND (sphenopalatine ganglion block OR pterygopalatine ganglion block OR SPGB). The last search was conducted on October 20, 2022. No language or time restrictions were applied to include the studies. Initially, two investigators independently assessed titles and abstracts as per the selection criteria. Subsequently, the full texts of relevant studies were assessed to decide the eligibility of retrieved articles. Any disagreements or discrepancies were resolved by discussion and consensus among the authors.

## Selection criteria of studies

Inclusion criteria: RCTs comparing the analgesic efficacy of SPG block with local anesthetic via trans-nasal approach using cotton-tipped applicator versus placebo or other interventions used to treat post-dural puncture headache.

Exclusion criteria: Studies performing SPG block by other routes or methods, retrospective studies, case reports, case series, abstract-only papers, or conference presentations, review articles, single-arm studies, duplicate studies (in such cases, studies with the most up-to-date and largest data were included).

## Types of interventions

SPG block with local anesthetic performed via nasal cavity using a cotton-tipped applicator in patients with PDPH and compared with other interventions used for the management of PDPH.

## Outcomes

The primary efficacy outcome was the pooled assessment of the effect of interventions in improving headache i.e., reduction in pain score at different time intervals (e.g., $30 \mathrm{~min}, 1 \mathrm{~h}, 2 \mathrm{~h}, 4 \mathrm{~h}, 6 \mathrm{~h}, 8 \mathrm{~h}, 12 \mathrm{~h}, 24$ hours, and 7 days) used by the authors of the primary studies. The secondary efficacy outcomes were need for rescue treatment and
treatment failures. The overall adverse events associated with the intervention were presented as safety outcomes. The subgroup analysis of each outcome was conducted based on the control arm. The studies that compared SPG block with noninvasive pharmacological treatment modalities were considered the Conservative Group. Other comparators in control arms were intranasal lignocaine puff, sham block and GON block.

## Data extraction

Two reviewers independently searched for all the clinical trials using retrieved titles and abstracts from the databases. The following data were extracted from the included studies: first author, publication year, study design, demographics, type of neuraxial block, type and size of the spinal needle used, type of surgery, technique of SPG block, contact time of cotton-tipped applicator, local anesthetic used (type, dose, and volume), pain rating scale, comparator technique, number of participants in each treatment arm, follow up duration, analgesic efficacy, and safety outcomes. For the extraction, data of pain scores provided in the median (range and/or interquartile range) were converted into mean (standard deviation) using an online tool ${ }^{23}$ based on Luo et al..$^{24}$ and Wan et al. ${ }^{25}$ The corresponding authors of included studies were contacted in case of missing data on efficacy and safety outcomes. The data were collected on an Excel sheet and cross-checked by another investigator to ensure quality. Trials being excluded were reviewed by both authors before the final agreement. Any disagreements regarding study selection and exclusion were resolved by discussion and consensus among the investigators or by a third investigator in the meta-analysis.

## Data synthesis

The effect sizes were summarized as a Standardized Mean Difference (SMD) with $95 \% \mathrm{Cl}$ (Confidence Interval) in case of continuous data (pain score at different time intervals) and as a Risk Ratio (RR) with $95 \% \mathrm{Cl}$ in case of dichotomous data (need for rescue treatment, treatment failure, and adverse events). The pooled meta-analytic summaries were estimated through the Mantel-Haenszel method using a randomeffect model with the DerSimonian-Laird approach. Heterogeneity was assessed using the $\mathrm{I}^{2}$ test. A forest plot was used for the graphical display of the results of individual studies and meta-analytic summaries of each outcome.

SPG block and control interventions were considered "equivalent" when the RR ( $95 \% \mathrm{CI}$ ) of the meta-analytic summary was within the range of a clinically significant difference of $20 \%(0.80-1.20)$ in the case of dichotomous outcomes. More than $20 \%$ difference was considered as 'superiority' of SPG block over control interventions. ${ }^{26}$ In the case of continuous outcomes, a meta-analytic summary (SMD [95\% CI]) should be within the range of a clinically significant difference of 20 units ( -0.20 to 0.20 ) to demonstrate the "equivalence" of interventions. More than a 20 -unit difference was considered as "superiority" of SPG block over control interventions. ${ }^{26}$

## Risk of bias assessment of included studies

The risk of bias was assessed in the included RCTs by using the ROB-II scale. Two investigators used the ROB-II tool to assess the methodological quality of the included RCTs. ${ }^{27}$ Each study was assessed for the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective outcome reporting. The studies were categorized into "low risk", "high risk" or having "some concerns" in the risk of bias assessment. ${ }^{27}$ The disagreements in the assessment were resolved through discussion and consensus among the authors. The sensitivity analysis of outcomes was performed based on the risk of bias assessment.

## Publication bias

Publication bias was assessed through a visual inspection of the "funnel plot" for asymmetry. It was plotted using (log [OR]) of effect size and standard error of each outcome.

## Certainty of the evidence

The GRADE approach was used to rate the certainty of the evidence for each efficacy and safety outcome. They were rated based on the risk of bias, imprecision, inconsistency, indirectness, and other factors (publication bias, magnitude of effect size, plausible confounding, and dose-response gradient). Each outcome was categorized into "high", "moderate", "low", or "very low" quality of evidence. The summary of findings table was created using GRADEpro software. ${ }^{28,29}$

The meta-analysis was conducted through the Review manager software version 5.4.1.

## Results

## Study characteristics

From the literature search, we retrieved 1748 references and assessed 29 full-text articles. A total of 9 RCTs with 381 patients fulfilling the selection criteria were included in the analysis (Fig. 1). ${ }^{30-38}$ Among the included studies, eight studies performed bilateral SPG block and one study. ${ }^{37}$ assessed unilateral SPG block. The block was performed using lidocaine $2 \%,{ }^{34-36,38} 4 \%^{30-33}$ and $10 \%^{37}$ along with ropivacaine $0.5 \%^{32}$ or dexamethasone $4 \mathrm{mg}^{34,38}$ or adrenaline $1 /$ 2000000. ${ }^{30}$ Among 9 included studies, there were 4 different modalities of interventions in the control group: sham SPG block using saline, ${ }^{32}$ SPG block with 2 puffs of intranasal lidocaine $10 \%,{ }^{35}$ bilateral GON block, ${ }^{38}$ and conservative measures which included noninvasive pharmacological methods (acetaminophen, diclofenac, tramadol, magnesium sulfate, theophylline, codeine and caffeine in various combinations along with intravenous fluids, abdominal binders and bedrest in 6 studies). ${ }^{30,31,33,34,36,37}$ Regarding the dural puncture proceeding the PDPH, all studies included patients developing PDPH after spinal anesthesia except ${ }^{31}$ Bohara et al. and Jespersen et al. ${ }^{32}$ who included patients developing a headache after lumbar puncture and epidural anesthesia. The surgical procedure in 6 studies ${ }^{31,34-38}$ was Lower


Figure 1 PRISMA flow diagram showing the study selection process.

Segment Cesarean Section (LSCS), while 3 studies included patients with various surgeries and procedures conducted under spinal anesthesia. ${ }^{30,32,33}$ Two studies reported pain score data in median (interquartile range). ${ }^{30,34}$ One study used median (range) to report pain score data. ${ }^{32}$ These outcome data were calculated to mean (standard deviation) using the online tool. ${ }^{23}$ The general characteristics of the included studies are summarized in Table 1.

## Risk of bias in included studies

The risk of bias assessment in individual randomized controlled trials is presented in the Supplementary Data File: Figure 1. In the overall risk of bias assessment, six studies were considered to have "some concern" as per the ROB-II tool ${ }^{27}$ and three randomized controlled studies were considered to have a "low" risk of bias.

## Efficacy outcomes

## Pain score at $30-\mathrm{min}$ after intervention

A total of six studies ( $\mathrm{n}=271$ patients) reported a "pain score at 30 min after intervention". As shown in Figure 2, SPG block significantly decreased pain score when compared to control interventions (SMD $=-1.99$ [95\% CI-3.88, -0.10]; $I^{2}=97 \%$ ) in the pooled analysis. Subgroup analysis showed the superiority of SPG block over conservative treatment (SMD $=-3.85[95 \% \mathrm{Cl}-4.42,-3.17] ; \mathrm{I}^{2}=0 \%$ ) and intranasal lignocaine puff (SMD $=-1.70$ [95\% CI $-2.76,-0.64]$ ). The GRADE approach suggested "low" quality of evidence for the comparison of SPG block and control interventions (Table 2).

The SPG block arm did not show a significant difference as compared to sham and GON block. Their comparisons did not fulfill the criteria of equivalence.

Pain score at 1 hour after intervention
A total of six studies ( $\mathrm{n}=271$ patients) reported a "pain score at 1 hour after intervention". SPG block significantly decreased the pain score as compared to control interventions (SMD $=-1.56$ [ $95 \% \mathrm{Cl}-2.65,-0.48] ; \mathrm{I}^{2}=93 \%$ ) in the pooled analysis. Subgroup analysis also revealed the superiority of SPG block over conservative treatment (SMD = -2.71 [ $95 \% \mathrm{Cl}-4.24,-1.18$ ]; $\mathrm{I}^{2}=86 \%$ ) and intranasal lignocaine puff (SMD $=-1.52$ [95\% CI -2.54, -0.50]) (Supplementary Data File: Fig. 2). The GRADE approach suggested "moderate" quality of evidence for the comparison of SPG block and control interventions (Table 2).

No difference between the SPG block and other control interventions was observed. They did not fulfill the criteria of equivalence.

## Pain score at 2 hours after intervention

A total of four studies ( $\mathrm{n}=211$ patients) reported a "pain score at 2 hours after intervention". As shown in Figure 3, no significant difference was observed in the overall pooled effect (SMD $=-1.23$ [ $95 \% \mathrm{CI}-3.06,0.59] ; I^{2}=97 \%$ ), however in subgroup analysis, SPG block significantly decreased pain score as compared to conservative treatment (SMD $=-2.01$ [ $95 \% \mathrm{Cl}-2.65,-1.36] ; \mathrm{I}^{2}=46 \%$ ). The superiority of the SPG block was demonstrated over conservative treatment. The GRADE approach suggested "very low" quality of evidence (Table 2).

There was no significant difference between the SPG block and the GON block. They did not fulfill the criteria of equivalence.

## Pain score at 4 hours after intervention

Four studies ( $\mathrm{n}=271$ patients) comparing SPG block and conservative treatment reported a "pain score at 4 hours after intervention". As shown in Figure 4, SPG block significantly decreased pain score as compared to conservative treatment (SMD $=-1.16[95 \% \mathrm{Cl}-1.91,-0.40] ; \mathrm{I}^{2}=70 \%$ ). The superiority of the SPG block was demonstrated over conservative treatment. The GRADE approach suggested "moderate" quality of evidence (Table 2).

## Pain score at 6 hours after intervention

A total of five studies ( $\mathrm{n}=231$ patients) reported a "pain score at 6 hours after intervention". No significant difference was observed between SPG block and control interventions (SMD $=-0.29[95 \% \mathrm{CI}-0.99,0.41] ; \mathrm{I}^{2}=83 \%$ ) in the pooled analysis. In subgroup analysis, SPG block significantly decreased pain score as compared to intranasal lignocaine puff (SMD = -1.58 [95\% CI -2.62, -0.55) (Supplementary Data File: Fig. 3). The comparison demonstrated superiority. However, the SPG block arm did not show a significant difference as compared to other control interventions. Both comparisons did not fulfill the criteria of equivalence.

## Pain score at 8 hours after intervention

The three studies ( $\mathrm{n}=98$ patients) comparing SPG block and conservative treatment reported a "pain score at 8 hours after intervention". No significant difference in pain score was observed between the study arms (Supplementary Data File: Fig. 4). GRADE approach suggested a "very low" quality of evidence (Table 2).

Table 1 General characteristics of included studies.

| Study | Study design | Total number of patients | Age in Mean <br> (SD) <br> SPGB/ <br> Comparator | Gender (\% <br> female) <br> SPGB/ <br> Comparator | Trans-nasal SPG <br> Block group: (n), drug, quantity, contact time | Comparator <br> group: ( $n$ ) <br> treatment | Type of neuraxial anesthesia/ surgery | Type/ size of needle for neuraxial block | Rescue treatment | Treatment failure | Outcomes |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Abotaleb et al. $2022^{30}$ | RCT (Open labelled) | 60 | $\begin{aligned} & 38.53(13.55) / \\ & 41.67(12.53) \end{aligned}$ | 43.3\%/36.7\% | (30) B/L SPGB with applicator saturated with Lignocaine $4 \%$ + adrenaline ( 1 / 2000000) in each nostril, NA, $5-\mathrm{min}$ | (30) (Conservative) PCM 1 gm IV QID $\times$ 3day | SA/ Lower limb surgeries | NS/NS | IV PCM 1 gm followed by IV Diclofenac $75 \mathrm{mg} / 12 \mathrm{~h}$ if NRS > 4 after 2h | Inadequate pain relief after 72h | VAS ( $0-10 \mathrm{~cm}$ ) after 30 min , 1h, 2h, 6h, $12 \mathrm{~h}, 24 \mathrm{~h}$, rescue treatment, treatment failure, adverse effects |
| Bohara et al.$2022^{31}$ | RCT (Open labelled) | 40 | $\begin{aligned} & 24.1(3.09) / \\ & 24.25(2.59) \end{aligned}$ | NS/NS | (20) B/L SPGB with applicator saturated with Lignocaine 4\%, NA, 5 -min | (20) (Conservative) oral codeine+ paracetamol X TDS + caffeine + oral fluid + bed |  |  |  |  |  |
|  |  |  |  |  | rest + abdominal binder | SA and epidural/ LSCS | NS/NS | IV tramadol if NRS $>7$ | NS |  | NRS (0-100) after 10 min , 4h, 8 h |
| $\begin{aligned} & \text { Jespersen } \\ & \text { et al. } \\ & 2020^{32} \end{aligned}$ | RCT (Triple blind) | 40 | $\begin{aligned} & 35.24(26.32) / \\ & 36.42(23.94) \end{aligned}$ | 70\%/70\% | (20) B/L SPGB with Lignocaine $4 \%$ + Ropivacaine $0.5 \%(1: 1), 1 \mathrm{~mL}, 10-$ min | (20) B/L SPGB with Saline | LP/ SA/ epidural/ Surgical or non-surgical procedure | Traumatic/ atraumatic or both/ 1827G | Repeat SPG <br> block if VAS $\geq$ <br> 30 mm | Not relieved after rescue block | VAS $(0-100 \mathrm{~cm})$ after 30 min and NRS ( 0 100) at 1 h and 7 days, rescue treatment, treatment failure, adverse effects |
| Kumar et al. $2021^{33}$ | RCT (Open labelled) | 40 | $\begin{aligned} & 35.50(12.16) / \\ & 36.58 \text { (12.91) } \end{aligned}$ | NS/NS | (20) B/L SPGB with Lignocaine $4 \%$, $1.5 \mathrm{~mL}, 10-\mathrm{min}$ | (20) Conservative (PCM + tramadol+ caffeine + oral fluid+ bedrest) | SA/ Various surgeries | Quincke needle/ 26G | Respective treatment repeated if pain not relieved after 1h of SPG Block | Not relieved after repeat treatment | VAS ( $0-10 \mathrm{~cm}$ ), treatment failure |
| Mowafi et al. $2022^{34}$ | RCT (Open labelled) | 40 | $\begin{aligned} & 28.7(3.7) / \\ & 27.5(3.0) \end{aligned}$ | 100\%/ 100\% | (20) B/L SPGB with Lignocaine $2 \%$ + dexamethasone 4 mg , ( $2 \mathrm{~mL}+1 \mathrm{~mL}$ ), 5-min | (20) (Conservative) PCM 1 gm IV TDS $\times$ 1day | SA/LSCS | NS/26G | IV Ketorolac 30 mg with a maximum dose of 120 mg . day $^{-1}$ if NRS $>$ 4 after 2h | Inadequate pain relief after 24h | NRS (0-100) after 30 min , 1h, 2h, 4h, 6h, $8 \mathrm{~h}, 12 \mathrm{~h}, 24 \mathrm{~h}$, treatment failure, adverse effects |
| Nazir et al. $2021^{35}$ | RCT (Single blind) | 20 | $\begin{aligned} & 28 \text { (NS)/ } 27.5 \\ & \text { (NS) } \end{aligned}$ | 100\%/100\% | (10) Applicator saturated with Lignocaine $2 \%$ in posterior nasopharynx followed by B/L SPGB with Lignocaine $2 \%$, $1 \mathrm{~mL}, 10-\mathrm{min}$ | (10) Two puffs of Lignocaine 10\% in each nostril | SA/LSCS | NS/NS | Injection Diclofenac IV 75 mg if VAS $\geq 5$ | Not relieved after treatment (VAS $\geq 8$ ) | VAS ( $0-10 \mathrm{~cm}$ ) after 30 min , 1h, 6h, 12h, $24 h$, rescue treatment, treatment failure, adverse effects |


|  | Table 1 (Continued) |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Study | Study design | Total number of patients | Age in Mean <br> (SD) | Gender (\% female) | Trans-nasal SPG Block group: ( n ), drug, quantity, contact time | Comparator group: ( n ) treatment | Type of neuraxial anesthesia/ surgery | Type/ size of needle for neuraxial block | Rescue treatment | Treatment failure | Outcomes |
|  |  |  |  | SPGB/ <br> Comparator | SPGB/ <br> Comparator |  |  |  |  |  |  |  |
|  | Puthenveettil et al. $2018^{36}$ | RCT (Open labelled) | 20 | NS/NS | 100\%/ 100\% | (10) B/L SPGB with Lignocaine 2\%, NA, 5-min | (10) (Conservative) PCM 1 gm TDS for 1day followed by addition of inj. Diclofenac 75 mg BD | SA/LSCS | NS/ NS | Conservative treatment (PCM 1 gm and Diclofenac 75 mg ) if NRS $>4$ | Inadequate pain relief after conservative treatment for 3 days. | NRS (0--10) after 30 min , 1h, 2h, 4h, 6h, 8h, 12h, 24h |
|  | Yilmaz et al. $2020^{37}$ | RCT (Open labelled) | 21 | $\begin{aligned} & 26.9(5.2) / \\ & 28.4(5.8) \end{aligned}$ | 100\% / 100\% | (10) U/L SPGB with 10\% Lignocaine, $2 \mathrm{~mL}, 15-\mathrm{min}$ | (10) (Conservative) normal saline 1000 ml over $4 \mathrm{~h}, \mathrm{MgSO}_{4}$ 1500 mg , Theophylline $200 \mathrm{mg}, \mathrm{PCM}$ 1000 mg ) | SA/LSCS | NS/NS | NS | NS | VAS ( $0-10 \mathrm{~cm}$ ) after 12 h , 24 h , adverse effects |
| স্ত | Youssef et al. $2021^{38}$ | RCT (Single blind) | 100 | $\begin{aligned} & 31.5(5.8) / \\ & 30.9(5.8) \end{aligned}$ | 100\%/100\% | (46) Applicator with Lidocaine 2\% in posterior nasopharynx followed by B/L SPGB with Lignocaine $2 \%$ + dexamethasone $4 \mathrm{mg}(2 \mathrm{~mL}+1 \mathrm{~mL})$, 10-min | (47) B/L GON block with same drug composition | SA/LSCS | Quincke needle/ 26G | PCM 1g IV Followed by $2^{\text {nd }}$ rescue block after 24 hours | Inadequate pain relief after $2^{\text {nd }}$ block (NRS $\geq 4$ ) | NRS (0-100) after 30 min , 1h, 2h, 6h, $12 h, 24 h$, rescue treatment, treatment failure, adverse effects |
|  | n, Number of patients; SPGB, Sphenopalatine Ganglion Block; LP, Lumbar Puncture; SA, Spinal Anesthesia; VAS, Visual Analog Scale; NS, Not Specified; PCM, Paracetamol; LSCS, Lower Segment Caesarean Section; NRS, Numerical Rating Scale; GON, Greater Occipital Nerve. |  |  |  |  |  |  |  |  |  |  |  |



Figure 2 Forest plot of the outcome pain score at $30-\mathrm{min}$ after intervention.

## Pain score at 12 hours after intervention

Six studies ( $\mathrm{n}=231$ patients) reported a "pain score at 12 hours after intervention". SPG block did not show an overall significant difference as compared to control interventions (SMD $=-0.30[95 \% \mathrm{CI}-0.67,0.06] ; \mathrm{I}^{2}=45 \%$ ] in the pooled analysis. In subgroup analysis, SPG block significantly decreased pain score as compared to intranasal lignocaine puff (SMD = -1.07 [95\% CI -2.03, -0.12). However, the comparison did not the fulfill criteria of superiority. SPG block did not show any significant difference in pain score as compared to conservative treatment and GON block (Supplementary Data File: Fig. 5). Both comparisons did not fulfill the criteria of equivalence.

## Pain score at 24 hours after intervention

A total of six studies ( $\mathrm{n}=251$ patients) reported a "pain score at 24 hours after intervention". Overall effect was observed as insignificant between SPG block and control interventions (SMD $=-0.40[95 \% \mathrm{Cl}-0.85,0.06] ; I^{2}=63 \%$ ) in the pooled analysis although SBG block significantly decreased pain score as compared to intranasal lignocaine puff (SMD = -1.79 [95\% CI -2.86, -0.72) (Supplementary Data File: Fig. 6). The criteria of equivalence could not be demonstrated due to the wide confidence interval.

## Pain score at 7 days after intervention

Only two studies ( $\mathrm{n}=133$ patients) comparing SPG block with a procedure group (sham block and GON block) reported "pain score at 7 days after the intervention". No significant difference was observed between the two groups (Supplementary Data File: Fig. 7). This comparison did not fulfill the criteria of equivalence.

## Rescue treatment

Three studies ( $\mathrm{n}=153$ patients) reported the need for "rescue treatment" among patients with inadequate pain relief after an intervention. Rescue treatment was given as diclofenac IV 75 mg (if VAS $\geq 5$ ), ${ }^{27}$ acetaminophen 1 g IV followed by a second rescue block (after 24 h ), ${ }^{29}$ repeat SPG block (if VAS $\geq 30 \mathrm{~mm}$ ). ${ }^{30}$ No data were available for comparison between the SPG block and the conservative treatment group. SPG block did not show an overall significant difference ( $R R=0.72[95 \% \mathrm{Cl} 0.36,1.44] ;\left.\right|^{2}=52 \%$ ) as compared to sham block ( $R$ R $=1.00$ [95\% CI 0.63, 1.58]), GON block $(R R=0.71[95 \% \mathrm{Cl} 0.34,1.49])$ and intranasal lignocaine puffs ( $\mathrm{RR}=0.17$ [95\% CI 0.02, 1.14) (Supplementary Data File: Fig. 8). The comparisons did not fulfill the criteria of equivalence. The GRADE approach suggested "low" quality of evidence.

## Treatment failure

Six studies ( $\mathrm{n}=293$ ) reported "treatment failure" which was defined as "no relief (NRS $\geq 4$ ) after rescue block ${ }^{28,29,34}$ or VAS $\geq 8$ after treatment ${ }^{31}$ inadequate pain relief after $24 \mathrm{~h}^{30}$ and after $72 \mathrm{~h} .{ }^{26,32}$ Overall effect showed significantly less patients with treatment failure in the SPG block group as compared to other interventions $(R R=0.40[95 \% \mathrm{Cl} 0.18$, $0.91] ; I^{2}=66 \%$ ). Subgroup analysis also showed a significantly lower number of patients with treatment failure after SPG block as compared to conservative treatment $[R R=0.22$ [95\% CI 0.10, 0.49]; $I^{2}=18 \%$ ). The superiority of the SPG block was demonstrated over conservative treatment. The GRADE approach suggested "low" quality of evidence (Table 2).

Table 2 GRADE approach for comparison of SPG block with control interventions for PDPH.

| Certainty assessment |  |  |  |  |  |  | $\mathrm{N}^{\circ}$ of patients |  | Effect |  | Certainty |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{N}^{\circ}$ of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPG block | control | Relative (95\% CI) | Absolute (95\% CI) |  |
| Pain score at $30-\mathrm{min}$ after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 6 | Randomized trials | Serious ${ }^{\text {a }}$ | Not serious | Not serious | Not serious | Publication bias strongly suspected ${ }^{\text {b }}$ | 135 | 136 | - | SMD 1.99 SD lower ( 3.88 lower to 0.1 lower) | $\oplus \oplus \emptyset$ <br> Low |
| Pain scor 6 | 1 hour after in randomized trials | on serious ${ }^{a}$ | Not serious | Not serious | Not serious | publication bias strongly suspected strong association ${ }^{\text {b }}$ | 135 | 136 | - | SMD 1.56 SD lower (2.65 lower to 0.48 lower) | $\oplus \oplus \oplus \mathrm{O}$ Moderate |
| Pain score at 2 hours after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 4 | randomized <br> trials | Serious ${ }^{\text {c }}$ | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 105 | 106 | - | SMD 1.23 SD lower (3.06 lower to 0.59 higher) | $\oplus \mathrm{O}$ Very low |
| Pain scor 4 | 4 hours after in randomized trials | ion Serious ${ }^{\text {c }}$ | Not serious | Not serious | Not serious | Publication bias strongly suspected strong association ${ }^{\text {b }}$ | 59 | 59 | - | SMD 1.16 SD lower (1.91 lower to 0.40 lower) | $\oplus \oplus \oplus \bigcirc$ <br> Moderate |
| Pain score at 6 hours after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 5 | Randomized trials | Serious ${ }^{\text {e }}$ | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 115 | 116 | - | SMD 0.29 SD lower (0.99 lower to 0.41 higher) | $\begin{aligned} & \oplus \infty \\ & \text { Very low } \end{aligned}$ |
| Pain score at 8 hours after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 3 | Randomized trials | Serious ${ }^{\text {f }}$ | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 49 | 49 | - | SMD 0.65 SD lower (2.38 lower to 1.08 higher) | $\begin{aligned} & \oplus \infty \\ & \text { Very low } \end{aligned}$ |
| Pain score at 12 hours after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 6 | Randomized trials | Serious ${ }^{\text {s }}$ | Not serious | Not serious | Not serious | Publication bias strongly suspected ${ }^{\text {b }}$ | 125 | 126 | - | SMD 0.3 SD lower ( 0.67 lower to 0.06 higher) | $\oplus \oplus \emptyset$ <br> Low |
| Pain score at 24 hours after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 6 | Randomized trials | Serious ${ }^{\text {s }}$ | Not serious | Not serious | Not serious | Publication bias strongly suspected ${ }^{\text {b }}$ | 125 | 126 | - | SMD 0.4 SD lower ( 0.85 lower to 0.06 higher) | $\oplus \oplus \emptyset$ <br> Low |
| Pain score at 7 days after intervention |  |  |  |  |  |  |  |  |  |  |  |
| 2 | Randomized trials | Not serious | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 66 | 67 | - | 0 (0 to 0) | $\oplus \oplus \emptyset$ <br> Low |
| Rescue treatment |  |  |  |  |  |  |  |  |  |  |  |
| 3 | Randomized trials | Not serious | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 23/76 (30.3\%) | 32/77 (41.6\%) | RR 0.72 (0.36 to 1.44) | 116 fewer per 1,000 (from 266 fewer to 183 more) | $\oplus \oplus \emptyset$ <br> Low |
| Treatment failure |  |  |  |  |  |  |  |  |  |  |  |
| 6 | Randomized trials | Serious ${ }^{\text {a }}$ | Not serious | Not serious | Not serious | Publication bias strongly suspected ${ }^{\text {b }}$ | 24/146 (16.4\%) | 58/147 (39.5\%) | RR 0.40 (0.18 to 0.91) | 237 fewer per 1,000 (from 324 fewer to 36 fewer) | $\oplus \oplus \emptyset$ <br> Low |
| Adverse events |  |  |  |  |  |  |  |  |  |  |  |
| 6 | Randomized trials | Serious ${ }^{\text {a }}$ | Not serious | Not serious | Serious ${ }^{\text {d }}$ | Publication bias strongly suspected ${ }^{\text {b }}$ | 53/136 (39.0\%) | 42/137 (30.7\%) | RR 1.19 (0.60 to 2.38) | 58 more per 1,000 (from 123 fewer to 423 more) | $\oplus \varnothing$ Very low |

CI, Confidence Interval; RR, Risk Ratio; SMD, Standardized Mean Difference.
Explanations:
a out of 6 studies had some concern in risk of bias assessment;
b Less than 10 studies;
c 2 out of 4 studies had some concern in risk of bias assessment;
${ }^{d}$ Wide confidence interval;
${ }^{e} 3$ out of 5 studies had some concern in risk of bias assessment;
${ }^{f} 1$ out 3 studies had some concern in risk of bias assessment;
${ }^{\mathrm{g}} 4$ out of 6 studies had some concern in risk of bias assessment.


Figure 3 Forest plot of the outcome pain score at 2 hours after intervention.

No difference between SPG block and other control groups was observed. It did not fulfill the criteria of equivalence (Supplementary Data File: Fig. 9).

## Safety outcomes

Adverse events were reported in 6 studies ( $\mathrm{n}=273$ ) in the form of nasal discomfort, seizures, blood-stained applicator, throat numbness, photophobia, dizziness, tinnitus, etc. No significant difference was observed among the groups (Supplementary Data File: Fig. 10). The GRADE approach suggested "very low" quality of evidence for the comparison of SPG block and conservative treatment (Table 2). The comparisons did not fulfill the criteria of equivalence.

## Sensitivity analysis

Among 6 studies using conservative treatments as a comparator, only one study had a "low" risk of bias, while 2 studies of the sham group and GON block had a "low" risk of bias in the risk of bias assessment. The sensitivity analysis of the low risk of bias studies suggests a similar trend for conservative treatment, sham and GON block (Supplementary Data File: Table 1). However, it was not possible to perform sensitivity analysis of all outcomes for the lignocaine puff based on the risk of bias assessment.

## Discussion

In this meta-analysis, outcome data from 9 RCTs were pooled to assess the efficacy and safety of SPG block as compared to other treatments for PDPH. We analyzed the included studies in four subgroups: conservative, intranasal lignocaine puffs, sham block and GON block because three studies compared SPG block with intranasal lignocaine puffs, ${ }^{35}$ sham block ${ }^{32}$ and GON block ${ }^{38}$ while six studies compared SPG block with non-invasive conservative treatments. ${ }^{30,31,33,34,36,37}$ Efficacy was assessed in terms of changes in pain scores at various intervals after intervention ( $30 \mathrm{~min}, 1 \mathrm{~h}, 2 \mathrm{~h}, 4 \mathrm{~h}, 6 \mathrm{~h}, 8 \mathrm{~h}, 12 \mathrm{~h}, 24 \mathrm{~h}$, and 7 days), need for rescue treatment or rescue block and treatment failure. We also analyzed adverse events reported in the intervention groups.

We observed that SPG block is more effective in relieving PDPH than conservative treatments. The meta-analytic summary of the overall pooled effect showed lower pain scores in patients treated with SPG block as compared to other interventions for $30 \mathrm{~min}, 1 \mathrm{~h}$ and 4 h . The subgroup analysis of SPG block with the conservative group found that SPG block-treated patients had significantly decreased pain scores at $30 \mathrm{~min}, 1 \mathrm{~h}, 2 \mathrm{~h}$, and 4 h after the intervention. Also, there were significantly less patients with treatment failures with SPG block. The superiority was demonstrated as these outcomes fulfilled the criteria of more than a $20 \%$ difference in RR or 20 units of SMD. GRADE evidence was

|  | SPG BLock |  |  | Control |  |  |  | Std. Mean Difference | Std. Mean Difference IV, Random, 95\% CI |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95\% CI |  |  |  |
| 2.4.1 Conservative |  |  |  |  |  |  |  |  |  |  |  |
| Bohara 2022 | 2.65 | 1.08 | 20 | 5.05 | 1.63 | 20 | 27.2\% | -1.70 [-2.44, -0.97] |  | - |  |
| Mowafi 2022 | 1.36 | 0.79 | 20 | 1.78 | 1.43 | 20 | 29.3\% | -0.36 [-0.98, 0.27] |  |  |  |
| Puthenveettil 2018 | 1.7 | 1.7 | 9 | 2.9 | 0.6 | 9 | 22.6\% | -0.90 [-1.88, 0.09] |  |  |  |
| Yilmaz 2020 | 2.2 | 1.14 | 10 | 4 | 0.67 | 10 | 20.9\% | -1.84 [-2.93, -0.76] |  |  |  |
| Subtotal (95\% CI) |  |  | 59 |  |  | 59 | 100.0\% | -1.16 [-1.91, -0.40] |  |  |  |
| Heterogeneity: $\mathrm{Tau}^{2}=0.41 ; \mathrm{Chi}^{2}=9.91, \mathrm{df}=3(\mathrm{P}=0.02) ; \mathrm{I}^{2}=70 \%$ |  |  |  |  |  |  |  |  |  |  |  |
| Test for overall effect: $Z=3.00(P=0.003)$ |  |  |  |  |  |  |  |  |  |  |  |
| Total (95\% Cl) |  |  | 59 |  |  | 59 | 100.0\% | -1.16[-1.91, -0.40] |  |  |  |
| Heterogeneity: $\mathrm{Tau}^{2}=$ Test for overall effect: Test for subaroup diffe | $0.41 ; \mathrm{Ch}$ = 3.00 rences: | $\mathrm{i}^{2}=9$ $(P=0$ Not ap | 91, df de dicabl | $3(\mathrm{P}=$ | 0.02); | $\mathrm{l}^{2}=70$ |  |  | $\stackrel{1}{-4}$ | -2 | $\begin{array}{llr} 1 & 1 & 1 \\ 0 & 2 & 4 \\ 3 & \text { Other inter } \end{array}$ |

Figure 4 Forest plot of the outcome pain score at 4 hours after intervention.
"very low" to "moderate" for these parameters as the outcomes were based on open labels and a small number of studies. We found that the effect of SPG block was immediate and short-lasting in the treatment of PDPH. This is because SPG block failed to demonstrate superiority in pain score assessment at 6 hours and beyond in this meta-analysis. GRADE evidence was "very low" for these outcomes. These findings highlight trends for faster relief from headache after block. ${ }^{39}$ Similar findings were reported in previous retrospective studies comparing SPG block with EBP ${ }^{18,19,40}$ where effective pain relief was noted within 30 min of a block. In our analysis, no significant difference was observed for later time intervals ( $6 \mathrm{~h}, 8 \mathrm{~h}, 12 \mathrm{~h}, 24 \mathrm{~h}$, and 7 days), which is in line with previous studies. ${ }^{41-43}$ Patients treated with SPG block may require repeat blocks for the recurrence of pain.

The mechanism of pain relief after SPG block is still not exactly known, although as described in the literature, either mechanical stimulation of sphenopalatine ganglion ${ }^{31,44,45}$ or absorption of local anesthetic through the mucous membrane overlying the ganglia, finally block the parasympathetic mediated vasodilation and relieve headache. ${ }^{46}$ The short-term effectiveness of the block can be attributed to the short-lasting mechanical stimulation or pharmacological profile of the local anesthetic used for the SPG block. All included studies used lidocaine, and only one study used lidocaine with ropivacaine. ${ }^{32}$ Adjuvants like adrenaline and dexamethasone were also included in one and two studies, respectively, which may affect the duration of the block. ${ }^{30,34,38}$

SPG block through the application of local anesthetic using a cotton tip applicator could be more effective than trans-nasal local anesthetic spray or puffs. Various approaches are practiced for SPG block like trans-nasal, trans-oral, sub-zygomatic, and lateral infratemporal approaches. The trans-nasal SPG block is a simple, noninvasive technique, ${ }^{47}$ which can be achieved by local anesthetic administration through a hollow cotton tip applicator, transnasal local anesthetic spray or puffs, ${ }^{48}$ trans-nasally inserted cotton gauze soaked in local anesthetic ${ }^{49}$ and nasal drops of local anaesthetic, ${ }^{50}$ although, the last three methods cannot ensure adequate concentration of local anesthetic reaching the effective site to be blocked. In this meta-analysis, one study compared SPG block with local anesthetic spray (lignocaine puffs) and subgroup analysis of the same observed superiority of SPG block over lignocaine puff for pain relief at $30 \mathrm{~min}, 1 \mathrm{~h}, 6 \mathrm{~h}, 12 \mathrm{~h}$, and 24 h . However, this data was from only one study with a small sample size of 20 patients, therefore more studies with large sample sizes are needed for evaluating potential advantage of using local anesthetic spray or puff over trans nasal block with cotton tip applicator. Like the intranasal lignocaine puff, SPG block was compared with sham block and GON block in only one study each and there is insufficient evidence to interpret the superiority, inferiority, or equivalence between the efficacy of SPG block and sham or GON block in the treatment of PDPH.

There is insufficient evidence regarding the safety of SPG block in the treatment of PDPH. This is also based on "low" to "very low" quality evidence. Common adverse effects associated with SPG block are local, mostly procedurerelated or because of local anesthetic. The trans-nasal approach may cause mild discomfort during the technique,
bleeding, infection, and numbness of the throat which are usually short-lasting. Changes in face temperature and lacrimation due to sympathetic blockade can also occur and are considered reliable signs of block success, ${ }^{51,52}$ although these are not frequent findings. We did not observe any lifethreatening adverse events among the included studies and all groups were comparable regarding the safety of transnasal SPG block.

Several limitations exist in this meta-analysis. It included only 9 RCTs with a small sample size. Six out of nine included studies had "some concerns" in risk of bias assessment due to open labelled design. There was significant heterogeneity because of sample composition (e.g., demography, type of surgery, and anesthesia) and different interventions in the control group (conservative, sham, GON block, intranasal lidocaine puff). Each study used different cut-off points for pain relief and the rescue treatment regimen was also nonsimilar among the groups. Similarly, the definition of treatment failure was also different among the studies. Different pain measuring tools were used among studies (VAS 0 -10 cm , VAS $0-100 \mathrm{~cm}$, NRS $0-10$, NRS $0-100$ ), therefore we used Standardized Mean Difference (SMD) to present the meta-analytic summary The block technique was also not uniform in studies, as different drugs with a wide range of strength and doses were chosen for performing the block. Therefore, interpreting study data included in this metaanalysis requires caution concerning heterogeneity across the trials due to small sample size of studies ( $<30$ patients/ group) and small number of studies ( $\leq 5$ studies). Considering this, we preferred random-effect models for our metaanalysis. Publication bias was observed in all outcomes, and it may have affected precision. Also, we could not extract and analyze data regarding the duration of block effect, overall analgesic consumption, patient satisfaction. and its impact on the long-term recovery of patients as limited data were available in the included studies.

In conclusion, very low to moderate quality evidence suggests that SPG block provides pain relief in PDPH, but it does not last till 6 hours or afterwards. The superiority of SPG block over conservative treatment and lignocaine puff was demonstrated. This meta-analysis failed to provide directions regarding comparisons of SPG blocks with sham and GON blocks. Further large-scale RCTs are required to assess the definite role of SPG block with its effect on overall patient recovery, analgesic consumption, and satisfaction.

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## 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.2023. 06.002.

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# Pericapsular Nerve Group (PENG) block versus fascia iliaca compartment (FI) block for hip surgery: a systematic review and meta-analysis of randomized controlled trials 

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## KEYWORDS

PENG block;
Pericapsular nerve group block; Fascia iliaca block;
Hip surgery;
Hip replacement;
Meta-analysis


#### Abstract

Background: This study compares Fascia lliaca compartment (FI) block and Pericapsular Nerve Group (PENG) block for hip surgery. Methods: Pubmed, Embase and Cochrane were systematically searched in April 2022. Inclusion criteria were: Randomized Controlled Trials (RCTs); comparing PENG block versus FI block for hip surgery; patients over 18 years of age; and reporting outcomes immediately postoperative. We excluded studies with overlapped populations and without a head-to-head comparison of the PENG block vs. FI block. Mean-Difference (MD) with $95 \%$ Confidence Intervals (CI) were pooled. Trial Sequential Analyses (TSA) were performed to assess inconsistency. Quality assessment and risk of bias were performed according to Cochrane recommendations. Results: Eight RCTs comprising 384 patients were included, of whom 196 (51\%) underwent PENG block. After hip surgery, PENG block reduced static pain score at 12 h post-surgery ( $\mathrm{MD}=0.61 \mathrm{~mm} ; 95 \% \mathrm{Cl} 1.12$ to $-0.09 ; p=0.02$ ) and cumulative postoperative oral morphine consumption in the first 24 h ( $\mathrm{MD}=-6.93 \mathrm{mg} ; 95 \% \mathrm{CI}-13.60$ to $-0.25 ; p=0.04$ ) compared with the FI group. However, no differences were found between the two techniques regarding dynamic and static pain scores at 6 h or 24 h post-surgery, or in the time to the first analgesic rescue after surgery. Conclusion: The findings suggest that PENG block reduced opioid consumption in the first 24 h after surgery and reduced pain scores at rest at 12 h post-surgery. Further research is needed to fully understand the effects of the PENG block and its potential benefits compared to FI block.


[^20]
## PROSPERO registration: CRD42022339628

PROSPERO registration: https://www.crd.york.ac.uk/prospero/display_record.php? RecordID=339628
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## Introduction

It is well-established that regional anesthesia techniques reduce postoperative opioid consumption and pain scores, leading to higher patient satisfaction and better outcomes. ${ }^{1}$ Considering the increase in the life expectancy of the population and the development of new techniques and implants, the incidence of hip surgery due to trauma or elective causes is expected to grow.

The Fascia Iliaca compartment (FI) block is a popular analgesic strategy for this surgery, but analgesia from this block is only moderate. ${ }^{2}$ This drawback results from the innervation of the anterior hip capsule by the obturator, the accessory obturator, and the femoral nerves, as reported by previous anatomic studies. In contrast, the literature suggests that the articular branches of these nerves are inconsistently blocked by this technique. ${ }^{3-6}$ Trying to improve those drawbacks, in 2018, Girón-Arango et al developed a new ultrasound-guided technique for the blockade of those articular branches to the hip, the Pericapsular Nerve Group (PENG) block. ${ }^{7}$

We conducted a systematic review of the literature and meta-analysis of Randomized Controlled Trials (RCTs) that compared FI and PENG blocks for hip surgery. Our primary outcomes were static and dynamic pain scores at different timeframes. Secondary outcomes were cumulative opioid consumption in the first 24 hours and the time to first opioid rescue.

## Methods

The International Prospective Register of Systematic Reviews (PROSPERO) was used to prospectively register the protocol for this study (CRD42022339628), which is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. ${ }^{8}$

## Eligibility criteria

Studies meeting the following criteria were included: RCTs; comparison of PENG block versus Fl block; patients over 18 years of age undergoing hip surgery; report of any of the clinical outcomes of interest; and outcome assessment conducted in the immediate postoperative period. We excluded studies with overlapping patient populations or without a control group.

## Search strategy and data extraction

The search was conducted via PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for studies that met the eligibility criteria published until April 2022.

The precise search strategy consisted of: ("hip arthroplasty" OR "hip replacement" OR "hip fracture" OR "hip-fracture" OR "THA" OR "hip surgery" OR "femur fracture") AND ("PENG block" OR "Pericapsular nerve group block") AND ("fascia iliaca block" OR "fascia iliaca blockade" OR "fascia iliaca compartment block" OR "fascia-iliaca compartment block" OR "iliac fascia block"). The search strategy was conducted by two authors (P.A. and R.L.); besides searching databases, references from the included studies were manually reviewed. No language restrictions were applied to the search. Two authors (R.L. and B.I.) independently extracted baseline characteristics and recorded them on an Excel template for the elaboration of Table 1 and the outcome data based on predefined search criteria. Disagreements among the authors were resolved by consensus. PROSPERO registered the prospective meta-analysis protocol on June 24, 2022 (PROSPERO ID: CRD42022339628).

## Endpoints

The outcomes of interest were static (at rest) pain score at 6 h post-surgery; dynamic (with hip movement) pain score at 6 h post-surgery; static pain score at 12 h post-surgery; dynamic pain score at 12 h post-surgery; static pain score at 24 h post-surgery; dynamic pain score at 24 h post-surgery; cumulative postoperative oral morphine consumption in the first 24 h ; time to first analgesic rescue after surgery; and Postoperative Nausea and Vomiting (PONV). A metaanalysis with pooled results was performed whenever at least three RCTs had results for an endpoint. Considering that pain assessment could vary among studies, it was established that eligible studies should use either the Numeric Rating Scale (NRS) or the Visual Analog Scale (VAS) to evaluate a patient's pain level. In both scores, zero corresponds to "no pain", 5 corresponds to "moderate pain", and 10 corresponds to "worst imaginable pain".

## Synthesis methods

The pain assessment and the opioid selection and dosage were expected to differ among studies; therefore, it is crucial to clarify the data gathered from each study included in this meta-analysis. For the pain rating, it was determined that the NRS and VAS scores were acceptably similar to be combined in the same pooled analysis; thus, no conversions were necessary. ${ }^{9}$ Nevertheless, concerning cumulative postoperative opioid consumption, data from each trial were converted to an equivalent dose of morphine using an equianalgesic dosage conversion calculator; ${ }^{10}$ hence, the analysis is given in terms of oral morphine consumption. Studies reporting results as median and Interquartile Range (IQR) were converted to estimate mean and Standard Deviation (SD). ${ }^{11}$

Table 1 Baseline characteristics of included studies.

| Study | Design | Patients <br> FI/ PENG | ASA | BMI <br> FI/ PENG | Male (\%) <br> FI/ PENG | Age, y <br> FI/ PENG | Surgical time <br> FI/ PENG | IV PCA | Fl Anesthetics | PENG <br> Anesthetics |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Aliste $2021{ }^{26}$ | RCT | 20/20 | I, II, III | 28.4/27.6 | 35/35 | 59.6/56.8 | 73.5/ 74.9 | Morphine <br> (mg) IV PCA | 40 ml adrenalized levobupivacaine 0.25\% | 20 ml adrenalized levobupivacaine 0.50\% |
| Choi $2022{ }^{28}$ | RCT | 27/27 | I, II, III | 25/25.8 | 59.3/51.9 | 61.51/ 60.27 | 69.90/67.43 | Fentanyl (mcg) IV PCA | 30 ml of adrenalized ropivacaine 0.2\% | 20 ml of adrenalized ropivacaine $0.2 \%$ |
| Hua $2022^{12}$ | RCT | 24/24 | II, III | 23/24 | 54.2/58.3 | 74/74 | 129/133 | Sufentanil (mcg) IV PCA | 30 ml ropivacaine hydrochloride 0.4\% | 20 ml ropiva- <br> caine 0.4\% |
| Jadon $2021{ }^{13}$ | RCT | 33/33 | I, II, III | 29.5/30/15 | 42.4/39.4 | 67.87/70.39 | NA/NA | Number of doses of Tramadol 50 mg | NA | NA |
| Mosaffa $2021{ }^{18}$ | RCT | 22/30 | I, II | NA/NA | 72.7/73.3 | 50/53 | NA/NA | Morphine (mg) IV PCA | $3 \mathrm{ml} . \mathrm{kg}^{-1}$ (a maximum of 40 ml ) of ropivacaine 0.5\% | $3 \mathrm{ml} . \mathrm{kg}^{-1}$ (a maximum of 40 ml ) of ropivacaine $0.5 \%$ |
| Natrajan $2021{ }^{19}$ | RCT | 12-Dec | I, II | NA/NA | NA/NA | NA/NA | NA/NA | N/A | 20 ml of $0.5 \%$ ropivacaine | 20 ml of $0.5 \%$ ropivacaine |
| Senthil $2021{ }^{29}$ | RCT | 20/20 | I, II | NA/NA | 50/60 | 52.5/53.9 | NA/NA | Fentanyl (mcg) IV PCA | 30 ml levobupivacaine $0.25 \%$ \& 4 mg dexamethasone | 30 ml levobupi- <br>  <br> 4 mg <br> dexamethasone |
| Shankar 2020 ${ }^{20}$ | RCT | 30/30 | I, II, III | NA/NA | 30/66.6 | 49.54/53.58 | NA/NA | N/A | 25 ml ropivacaine $0.25 \%$ | 25 ml ropivacaine 0.25\% |

Surgical time, minutes; NA, Not Available; Age and BMI, mean.

## Quality assessment and sensitivity analysis

To assess the risk of bias in each RCT, the risk of bias tool for randomized trials (RoB-2) was the chosen tool. ${ }^{12}$ The risk of bias was conducted independently by two authors (P.A. and I.M.); a consensus was reached after discussing the reasons for divergences (Table 2).

To explore the robustness of the results and identify possible outliers, sensitivity analyses were conducted by systematically removing each study from the research and recalculating the results. Additionally, to verify the consistency of this review's findings, results were also calculated after removing studies with an increased risk of bias. Publication bias was assessed with funnel-plot analysis and Egger's test of all endpoints to evaluate the symmetric distribution of trials with similar weights; $p$-values $<0.05$ were considered statistically significant.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to assess the certainty of the evidence in this review as high, moderate, low, or very low. ${ }^{13}$ The grading of the strength of recommendations was carried out by two independent authors (I.M. and P.A.) using the GRADEpro Guideline Development Tool (McMaster University and Evidence Prime, 2022); disagreements were settled by a third author (R.L.).

## Statistical analysis

The Minimally Clinically Important Difference (MCID) in the pain score was set at -18.6 mm for improvement and 23.6 mm for worsening pain, as per findings by Danoff et al ${ }^{14}$ The MCID for opioid consumption was set at 10 mg of Morphine Equivalents, as per findings by Laigaard et al ${ }^{15}$ Treatment effects on continuous outcomes were compared using Mean Differences (MD) with $95 \%$ Confidence Intervals ( $95 \% \mathrm{Cl}$ ). Cochran Q test, $I^{2}$ statistics, and visual inspection of the forest plots were used to assess heterogeneity; when the visual inspection of the forest plot was suggestive of heterogeneity in effect size, the $p$-value was $<0.10$ or $I^{2}$ statistics was $\geq 25 \%$, heterogeneity was considered significant,
and a random-effects model was used. The statistical analysis was conducted using Review Manager 5.4 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Trial sequential analysis (TSA) was performed with the TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen). ${ }^{16}$

## Results

## Study selection and characteristics

As detailed in Figure 1, our complete search generated 78 results and 15 duplicates; 54 studies were excluded based on their titles or abstracts. The remaining 9 articles were thoroughly screened and, after consideration of the inclusion and exclusion criteria, eight RCTs were included in this systematic review and meta-analysis. The exclusion of the $9^{\text {th }}$ study was based on the lack of report for outcomes of interest.

## Pooled analysis of outcomes

In the 24 hours of follow-up post-surgery, no significant difference was found between PENG and FI blocks in terms of dynamic pain score at 6 h post-surgery ( $\mathrm{MD}=-0.22$; $95 \% \mathrm{Cl}$ 0.81 to $0.81 ; p=0.46 ; I^{2}=27 \%$; Fig. 2 A ; 4 RCTs, 200 patients) nor regarding the static pain score at 6 h post-surgery (MD = $-0.32 ; 95 \% \mathrm{Cl}-0.96$ to $0.32 ; p=0.33 ; \mathrm{I}^{2}=63 \%$; Fig. 2 B ; 4 RCTs, 212 patients). Additionally, the analysis referred to the dynamic pain score at 24 h post-surgery ( $M D=0.57$; $95 \% \mathrm{Cl}-0.01$ to 1.14; $p=0.05$; $\mathrm{I}^{2}=74 \%$; Fig. 2 C ; 4 RCTs, 200 patients) and the static pain score at 24 h post-surgery (MD = -0.14; $95 \% \mathrm{Cl}-0.49$ to $0.22 ; p=0.45 ; I^{2}=43 \%$; Fig. 2D; 4 RCTs, 220 patients) yielded similar results. The time to first analgesic rescue after surgery was not significantly longer for patients with a PENG block (MD = 1.07; 95\% CI 0.07 to $2.21 ; p=0.06 ;\left.\right|^{2}=92 \%$; Fig. 2E; 4 RCTs, 196 patients). Furthermore, incidence of PONV was not significantly

Table 2 Critical appraisal according to the RoB-2 tool for assessing the risk of bias in randomized trials.

|  | Risk of bias domains |  |  |  |  |  |  |  |
| ---: | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
|  | D1 | D2 | D3 | D4 | D5 | Overall |  | Judgment |
| Aliste 2021 | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ |  |  |
| Choi 2022 | $(+)$ | $(-)$ | $(+)$ | $(+)$ | $(+)$ | $(-)$ | $(x)$ | High |
| Hua 2022 | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(x)$ | $(x)$ |  |  |
| Jadon 2021 | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(-)$ | Some Concerns |
| Mosaffa 2022 | $(-)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(-)$ |  |  |
| Matrajan 2021 | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | Low |
| Senthil 2021 | $(+)$ | $(-)$ | $(+)$ | $(+)$ | $(+)$ | $(-)$ |  |  |
| Shankar 2022 | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ | $(+)$ |  |  |
|  |  |  |  |  |  |  |  |  |

## Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

## Identification of studies via databases and registers



Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study screening and selection.
different in the groups ( $\mathrm{RR}=2.00$; $95 \% \mathrm{Cl} 0.82$ to 4.9; $p=0.13 ; I^{2}=0 \%$; Fig. $2 \mathrm{~F} ; 3$ RCTs, 118 patients).

In contrast, the static pain score at 12 h post-surgery was significantly lower among patients who underwent PENG block than for the FI group ( 4 RCTs, 218 patients) (MD = 0.61 ; $95 \% \mathrm{Cl}-1.12$ to $-0.09 ; p=0.02 ; \mathrm{I}^{2}=73 \%$; Fig. 3 A ). Moreover, there was a lower rate of cumulative postoperative oral morphine consumption in the PENG group with statistical significance ( 6 RCTs, 300 patients) ( $\mathrm{MD}=-6.93$; $95 \% \mathrm{Cl}-$ 13.60 to $-0.25 ; p=0.04 ; I^{2}=92 \%$; Fig. 3B). This decreased opioid consumption in the PENG group did not remain in a subgroup analysis performed pooling the results of patients undergoing surgery for hip fractures (4 RCT, 206 patients) (MD $=-6.29 ; 95 \% \mathrm{Cl}-13.85$ to $1.27 ; p=0.1 ; I^{2}=92 \%$; Fig. 3 C ).

Only one RCT reported a dynamic pain score at 12 h post-surgery, ${ }^{17}$ hence it was impossible to perform a meta-analysis on that outcome.

## Trial sequential analysis

In the TSA, neither pooled results for pain score at rest at 12 $h$ postoperatively nor cumulative opioid consumption in 24 $h$ reached the required information sample size. Both crossed the conventional boundary, confirming the significant statistical difference benefiting PENG over FI, but not crossing the monitoring boundaries. For the outcomes of static and dynamics pain scores at 6 h and 24 h post-surgery and time to first analgesic rescue, the $z$-curve did not cross

## 2A



## 2B



## 2 C



## 2D



## 2 F



Figure 2 (A) Dynamic pain score at 6h post-surgery was not significantly different between PENG and FI block groups. (B) Static pain score at 6h post-surgery was not significantly different between PENG and FI block groups. (C) Dynamic pain score at 24h postsurgery was not significantly different between PENG and FI block groups. (D) Static pain score at 24 h post-surgery was not significantly different between PENG and FI block groups. (E) The time to the first analgesic rescue after surgery was not significantly different between PENG and FI block groups. (F) Postoperative nausea and vomiting were not significantly different between PENG and FI block groups.


## 3B

| Study or Subgroup | PENG Block |  |  | Fi block |  |  |  | Mean Difference <br> IV, Random, 95\% CI | Mean Difference IV, Random, 95\% CI |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Mean | SD | Total | Mean | SD | Total | Weight |  |  |  |
| Aliste 2021 | 12 | 30 | 20 | 11.25 | 11.75 | 20 | 11.2\% | 0.75 [-13.37, 14.87] |  |  |
| Chol 2022 | 59.5 | 5 | 27 | 71.8 | 9.5 | 27 | 20.8\% | -12.30 [-16.35, -8.25] | $=$ |  |
| Hua 2022 | 40.5 | 7.25 | 24 | 43.38 | 5.12 | 24 | 21.2\% | -2.88 [-6.43, 0.67] | $=$ |  |
| Jadon 2021 | 8 | 4.2 | 33 | 6.5 | 4 | 33 | 22.1\% | 1.50 [-0.48, 3.48] |  |  |
| Mosaffa 2022 | 135 | 64.18 | 30 | 185 | 47.18 | 22 | 4.0\% | -50.00 [-80.27, -19.73] |  |  |
| Senthil 2021 | 53.25 | 5.05 | 20 | 63.75 | 8.07 | 20 | 20.7\% | $-10.50[-14.67,-6.33]$ | - |  |
| Total (95\% CI) |  |  | 154 |  |  | 146 | 100.0\% | -6.93 [-13.60, -0.25] |  |  |
| Heterogeneity: $\mathrm{Tau}^{2}$ <br> Test for overall effec | $\begin{aligned} & 51.44 ; \\ & z=2.0 \end{aligned}$ |  | $\begin{aligned} & \text { 61.94, } \\ & 0.04) \end{aligned}$ | $\mathrm{df}=5$ | $P<0.0$ | $0001 \text { ); }$ | $1^{2}=92 \%$ |  | $-50-\frac{1}{-25}$ Favours PENG | $\begin{array}{ccc} 1 \\ 0 & 25 & 50 \\ \text { Favours } \mathrm{FI} \end{array}$ |

3C


Figure 3 (A) Static pain score at 12 h post-surgery was significantly lower in the PENG block group. (B) The cumulative postoperative oral morphine consumption in 24h was significantly lower in the PENG block group. (C) Opioid consumption in subgroup hip fracture was not significantly different between PENG and FI block groups.
the trial sequential monitoring boundaries and did not reach the required information sample size. These results are reported in Figure 5 in the Supplementary Material.

## Quality assessment

In a pooled sensitivity analysis removing the only RCT with a high risk of bias, ${ }^{18}$ the rate of cumulative postoperative oral morphine consumption, which at first favored the PENG group (MD = -6.93; 95\% CI-13.60 to -0.25; $p=0.04 ; I^{2}=92 \%$; Fig. 3B), lost its statistical significance (MD $=-8.61$; $95 \% \mathrm{Cl}$ 17.65 to $0.43, p=0.06 ;\left.\right|^{2}=94 \%$; Fig. 4A). Nevertheless, considering the heterogeneity measured by $\mathrm{I}^{2}$ statistics seemed to increase with the withdrawal of Hua et al, ${ }^{18}$ a further analysis was conducted to assess the origin of the severe heterogeneity for this particular outcome. After the removal of each study, and even though heterogeneity was still high, the most robust reduction in heterogeneity was found with the exclusion of Jadon et al, ${ }^{19}$ and once again it showed a significantly lower rate of cumulative postoperative oral morphine consumption among the PENG group (MD = -9.00; $95 \% \mathrm{Cl}-15.45$ to $-2.54 ; p=0.006 ; \mathrm{I}^{2}=82 \%$; Fig. 4B). Finally, $a$
combined analysis removing both Hua et al ${ }^{18}$ and Jadon et al ${ }^{19}$ confirmed a statistically significant mean difference in favor of the PENG block with only moderate heterogeneity (MD = -11.26; $95 \% \mathrm{Cl}-17.97$ to $-4.56 ; p=0.001 ; \mathrm{I}^{2}=68 \%$; Fig. 4C). On funnel plot analyses, there was no evidence of publication bias, as a symmetrical distribution was observed around the meta-analysis point estimate based on the weight. Egger's test also indicates no evidence of publication bias (Figure S2 in the Supplementary Material). ${ }^{20}$

On the other hand, a sensitivity analysis could not be performed for the time to the first analgesic rescue after surgery, even though results evidenced a high heterogeneity among studies, because of the limited number of RCTs reporting this particular outcome.

According to the GRADE tool, the overall certainty of the evidence for the outcomes assessed was high at first and downgraded to moderate or low certainty due to a serious risk of bias, imprecision, or inconsistency. There was a large magnitude of the effect, upgrading by one level the corresponding outcome. Table 3 reports the evidence profile from this review, while Table 4 summarizes our findings. Both can be found in the Supplementary Material.

## 4A



## 4B



Figure 4 (A) Sensitivity analysis by removal of studies with a high risk of bias: the rate of cumulative postoperative oral morphine consumption was not significantly different between PENG and FI block groups. (B) Sensitivity analysis by removal of outliers: lower rate of cumulative postoperative oral morphine consumption among the PENG group with statistical significance. (C) Sensitivity analysis by removal of studies with a high risk of bias and outliers: lower rate of cumulative postoperative oral morphine consumption among the PENG group with statistical significance.

## Discussion

This systematic review and meta-analysis of 8 studies and 384 patients compared the PENG Block to the FI Compartment Block. The main findings with PENG block include: 1 - Lower opioid consumption in the first 24 hours after surgery; 2 - Decreased pain score at rest 12 hours after surgery; 3 - No difference in the pain score at rest or with movement 6 hours after surgery; 4 - No difference in the pain scores at rest or with movement 24 hours after surgery; 5 - No difference in the time to first analgesia rescue after surgery; and 6 - No difference in the incidence of PONV.

Hip fracture is a typical orthopedic emergency in the elderly associated with significant morbidity and mortality. Adequate postoperative analgesia minimizing the need for opioids and their related adverse effects is fundamental for that population. ${ }^{7}$ Considerable pain, if inadequately controlled, can impair early rehabilitation and functional recovery and reduce patient satisfaction after surgery. ${ }^{21}$ Several
blocks have been proven effective for hip surgery, like the fascia iliaca block and the femoral nerve block. ${ }^{22,23}$ Despite their steadily increasing use, there is limited evidence of their effectiveness. ${ }^{24}$

This study compares postoperative pain scores and opioid consumption between PENG block and FI block after Total Hip Arthroplasty (THA) with a subgroup analysis of hip fracture surgeries. The most outstanding finding of this study was that despite limited evidence of its effectiveness, the PENG block showed a statistically significant lower opioid consumption than the FI block. This limited evidence can be explained by the fact that the PENG block is a relatively new regional anesthesia technique, with few studies published about it. ${ }^{7}$

The PENG block has been studied recently and its efficacy was reported in some clinical trials. It has shown decreased opioid consumption in the first 24 h postoperatively and decreased pain scores in the short-term postoperative period and post-anesthesia care unit after open hip surgeries

Table 3 Evidence profile: PENG block compared to FI block for hip surgery.

| Outcomes | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Mean difference (95\% CI) | Number of participants (studies) | Quality or certainty of the evidence (GRADE) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Cumulative postoperative oral morphine consumption | Serious ${ }^{\text {a }}$ | Not serious | Not serious | Not serious | Not detected | $\begin{aligned} & \text { MD }-6.93 \\ & (-13.60 \text { to }-0.25) \end{aligned}$ | 300 (6 RCTs) | $\oplus \oplus \oplus \oplus \mathrm{High}^{\text {b }}$ |
| Dynamic pain score at 6 hours postsurgery | Not serious | Not serious | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & \text { MD }-0.22 \\ & (-0.81 \text { to } 0.37) \end{aligned}$ | 200 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate |
| Static pain score at 6 hours postsurgery | Not serious | Not serious | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & M D-0.32 \\ & (-0.96 \text { to } 0.32) \end{aligned}$ | 212 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate |
| Static pain score at 12 hours postsurgery | Not serious | Not serious | Not serious | Not serious | Not detected | $\begin{aligned} & \text { MD }-0.61 \\ & (-1.12 \text { to }-0.09) \end{aligned}$ | 218 (4 RCTs) | $\oplus \oplus \oplus \oplus$ High |
| Dynamic pain score at 24 hours post-surgery | Not serious | Not serious | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & \text { MD } 0.57 \\ & (-0.01 \text { to 1.14) } \end{aligned}$ | 200 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate |
| Static pain score at 24 hours postsurgery | Not serious | Not serious | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & \text { MD }-0.14 \\ & (-0.49 \text { to } 0.22) \end{aligned}$ | 220 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate |
| Time to first analgesic rescue after surgery | Not serious | Serious ${ }^{\text {d }}$ | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & \text { MD }-1.07 \\ & (-2.21 \text { to } 0.02) \end{aligned}$ | 202 (4 RCTs) | $\oplus \oplus \bigcirc$ Low |
| Subgroup for hip fracture opioid consumption | Serious ${ }^{\text {a }}$ | Serious ${ }^{\text {d }}$ | Not serious | Serious ${ }^{\text {c }}$ | Not detected | $\begin{aligned} & \text { MD -6.29 } \\ & (-13.85 \text { to 1.27) } \end{aligned}$ | 206 (4 RCTs) | $\oplus め$ Very low |
| Postoperative nausea and vomiting (PONV) | Not serious | Not serious | Not serious | Not serious | Not detected | $\begin{aligned} & M D-2.00 \\ & (0.82 \text { to } 4.90) \end{aligned}$ | 59 (3 RCTs) | $\oplus \oplus \oplus \oplus$ High |

[^21]Table 4 Summary of findings: PENG block compared to FI block for hip surgery.

| Outcomes | Anticipated absolute effects ${ }^{\text {a }}$ (95\% CI) |  | Relative effect <br> (95\% CI) | $\mathrm{N}^{\circ}$ of participants (studies) | Certainty of the evidence (GRADE) |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | Risk with FIC | Risk with PENG |  |  |  |
| Cumulative postoperative oral morphine conumption | The mean cumulative postoperative oral | MD 6.93 lower | - | 300 (6 RCTs) | $\oplus \oplus \oplus \oplus \mathrm{High}^{\text {a }}$ |
| Follow-up: mean 1 day | morphine conumption was 0 | (13.6 lower to 0.25 lower) |  |  |  |
| Dynamic pain score at 6 hours post-surgery | The mean dynamic pain | MD 0.22 lower | - | 200 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate $\ddagger$ |
| Follow-up: mean 1 day | score at 6 hours post-surgery was 0 | ( 0.81 lower to <br> 0.37 higher) |  |  |  |
| Static pain score at 6 hours post-surgery | The mean static pain score at | MD 0.32 lower | - | 212 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate $\ddagger$ |
| Follow-up: mean 1 day | 6 hours post-surgery was 0 | (0.96 lower to <br> 0.32 higher) |  |  |  |
| Static pain score at 12 hours postsurgery | The mean static pain score at 12 hours post- | MD 0.61 lower | - | 218 (4 RCTs) | $\oplus \oplus \oplus \oplus$ High |
| Follow-up: mean 1 day | surgery was 0 | (1.12 lower to 0.09 lower) |  |  |  |
| Dynamic pain score at 24 hours postsurgery | The mean dynamic pain score at 24 hours | MD 0.57 higher | - | 200 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate $\Psi$ |
| Follow-up: mean 1 day | post-surgery was 0 | (0.01 lower to <br> 1.14 higher) |  |  |  |
| Static pain score at 24 hours postsurgery | The mean static pain score at 24 hours post- | MD 0.14 lower | - | 220 (4 RCTs) | $\oplus \oplus \oplus \bigcirc$ Moderate $\ddagger$ |
| Follow-up: mean 1 day | surgery was 0 | (0.49 lower to <br> 0.22 higher) |  |  |  |
| Time to first analgesic rescue after surgery | The mean time to first analgesic | MD 1.07 lower | - | 202 (4 RCTs) | $\oplus \oplus \bigcirc$ Low ** $^{*}$ |
| Follow-up: mean 1 day | rescue after surgery was 0 | (2.21 lower to 0.07 higher) |  |  |  |
| Subgroup for hip fracture opioid consumption | The mean subgroup for hip fracture opioid | MD 6.29 lower | - | 206 (4 RCTs) | $\oplus$ ¢ Very low * ${ }^{* *}$ |
| Follow-up: mean 1 day | consumption was 0 | (13.85 lower to 1.27 higher) |  |  |  |
| Postoperative nausea and vomiting (PONV) | 85 per 1.000 | $\begin{aligned} & 169 \text { per } 1.000 \\ & (69 \text { to } 415) \end{aligned}$ | $\begin{aligned} & \text { RR } 2.00 \\ & \text { (0.82 to } 4.90 \text { ) } \end{aligned}$ | 118 (3 RCTs) | $\oplus \oplus \oplus \oplus$ High |

[^22]compared to sham block and compared to conventional postoperative analgesia. ${ }^{21,25,26}$

Four trials reported time to first rescue with high heterogeneity in the pooled results $\left(I^{2}=92 \%\right) .{ }^{19,27-29}$ This
heterogeneity can be explained by the differences in their local anesthetic choice and doses as showed in Table 1. While Mosaffa et al ${ }^{27}$ and Natrajan et $a^{28}$ had conflicting results, with the first showing a significant shorter time for

### 5.1 A


5.1 B

5.1 C


Figure 5 (1A) Cumulative opioid consumption 24 h . (1B) Dynamic pain score at 6 h . (1C) Static pain score at 6 h . (2A) Static pain score at 12 h . (2B) Dynamic pain score at 24 h . (2C) Static pain score at 24 h . (3A) Time to first rescue. (3B) Cumulative opioid consumption 24 h for hip fracture subgroup. (3C) PONV.

5.2 B

5.2 C


Figure 5 Continued.

5.3 B

5.3 C


Figure 5 Continued.
the PENG group and the second a shorter time for FI group, no difference was found by Jadon et al ${ }^{19}$ and Shankar et al ${ }^{29}$ This meta-analysis did not find a significant difference between the time to first rescue after the surgery between FI and PENG blocks. The TSA performed for this outcome did not reach the required information sample size and the Zcurve stayed inside the non-statistically significant zone and not reaching the futility boundary (Fig. 5.3B), thus more studies are required for a definitive answer.

We could plot the results for pain scores at rest at $6 \mathrm{~h}, 12$ h , and 24 h and pain scores at movement at 6 h and 24 h . The only statistically significant outcome was pain at rest at 12 h , which showed an MD of -0.61 ( $95 \% \mathrm{Cl}-1.12$ to -0.09 ), favoring PENG block with moderate heterogeneity $\left(1^{2}=72 \%\right)$. Jadon et $\mathrm{al}^{19}$ and Mosaffa et $\mathrm{al}^{27}$ had a similar result with significantly decreased pain score at rest at 12 h . This statistically significant decrease in the postoperative pain scores does not reflect a minimal clinically significant difference in the hip replacement pain score. ${ }^{14}$ TSA performed for this outcome did not reach the required information sample size and showed a Z-curve not reaching the monitoring boundaries, not matching the statistically significant difference found in the meta-analysis (Fig. 5.2A), raising concerns of possible type 1 error, thus further studies are needed for this outcome. Important to note that all outcomes reporting pain scores had low to moderate heterogeneity.

Our meta-analysis showed a statistically significant reduction in opioid consumption in the first postoperative 24 h using the PENG block (Fig. 3B). PENG block had an MD of 6.93 mg of morphine in $24 \mathrm{~h}(95 \% \mathrm{Cl}-13.60$ to -0.25$)$ with high heterogeneity amidst all studies ( $1^{2}=92 \%$ ). This significant difference was not sustained in the subgroup analysis with RCTs with hip fracture population (MD $=-6.29,95 \% \mathrm{CI}-$ 13.85 to 1.27 ) (Fig. 2F) Although statistically significant, this decrease in opioid consumption cannot be considered clinically significant, since MCID for opioid consumption was not reache. ${ }^{15}$ The inconclusive data available in this study have impeded our ability to provide any significant recommendations or propose meaningful changes in the management of this patient population. TSA for cumulative opioid consumption in the first 24 hours once more did not reach the required information sample size and showed a Z-curve not reaching the monitoring boundaries, not matching the statistically significant difference found in the meta-analysis and again raising concerns for type 1 error (Fig. 5.1A). As for cumulative opioid consumption in the hip fracture subgroup, TSA had its Z-curve in the not-statistically significant zone, calling for more studies for additional conclusions (Fig. 5.3B). Results were converted to oral equivalents of morphine for better comparison and plotting. ${ }^{10}$ Sensitivity analysis after removing the studies with a high risk of bias, ${ }^{18}$ and the outlier, ${ }^{19}$ decreased the heterogeneity $\left(I^{2}=68 \%\right.$, previously $92 \%$ ) with a further decrease in opioid consumption by PENG block patients (MD = -11.26 mg of morphine, $95 \% \mathrm{Cl}-17.97$ to -4.56 ). Jadon et al ${ }^{19}$ probably led to an increased heterogeneity for being the only study not using PCA for postoperative pain control.

A meta-analysis conducted by Farag et al ${ }^{30}$ was recently published, which demonstrated a reduction in opioid consumption within the first 24 hours following the Pericapsular Nerve Group (PENG) block when compared to other
interventions. However, there were notable disparities between Farag et al's meta-analysis and ours. Firstly, our meta-analysis only incorporated studies that compared PENG block to Femoral Nerve (FI) block, while Farag et al included studies that compared PENG block to various interventions and non-surgical populations, combining them in the same forest plot for multiple outcomes. Secondly, their search strategy failed to identify all studies that compared PENG block to FI block. Thirdly, Farag et al used the Standard Mean Deviation (SMD) as the effect measure, even for results reported in the same unit, whereas our study reported outcomes in mean deviation. These were methodological inadequacies in the planning, execution, and writing of the study, which do not comply with the Cochrane Guidelines and raise doubts about the validity of its results. ${ }^{31}$

This study has limitations. There was high heterogeneity for most outcomes, due to multiple reasons: (a) Clinical diversity with a different interpretation of pain by the different populations in the studies and cultural differences among patients; ${ }^{32-34}$ (b) Differences among the RCT populations since we included studies with a wide range of hip surgeries, from elective primary THA to hip fracture surgeries. Even after performing a subgroup analysis only with the hip fracture population, heterogeneity was still high, which may be caused by variations in the surgical techniques from different countries and medical centers, differences in the local anesthetic drugs and dosage, different opioids, and delivery methods used in each RCT (Table 1). Although all data were converted to oral morphine equivalents, ${ }^{10}$ opioids may have similar pharmacodynamics but variable pharmacokinetics, leading to different outcomes; (c) Methodological diversity: although similar enough to be compared, ${ }^{9,35,36}$ pain assessment was not uniform among the studies, with different pain scores used, and a different patient approach using VAS or NRS can significantly change the pain assessment. Different pain scores have been elicited by simply showing VAS in a vertical or horizontal way; ${ }^{37}$ and (d) Finally, some studies reported pain outcomes with median and IQR, ${ }^{17,19}$ while others reported in mean and standard error. The conversion of medians and IQR to mean and SD, albeit validated, ${ }^{11}$ may introduce inaccuracies. Also, there was a relatively low number of studies and low number of patients. A TSA showed that none of the outcomes reached the required information sample size, but on the other hand no Z-line crossed the futility boundary, calling for new studies comparing those blocks, with larger number of patients and better standardization of drugs and protocols.

## Conclusion

The present meta-analysis suggests that PENG block reduces opioid consumption during the initial 24 hours post-procedure and decreases pain score at rest at 12 hours postoperatively, although those decreases may not be clinically significant. However, there was elevated heterogeneity in study outcomes. In addition, TSA findings suggest limited power to assess the difference between the two techniques. Hence, further studies with larger sample sizes, employing standardized methodologies, are warranted to establish more definitive conclusions.

## Data sharing

Because this meta-analysis was based on data extracted from previously published research, all the data and study materials are available in the public domain. The authors of this meta-analysis do not have access to patient-level data of the individual studies. Researchers interested in individ-ual-level data from the studies included in this meta-analysis are encouraged to contact the corresponding author from each study for such requests.

## Implication statement

This study compares the efficacy of Pericapsular Nerve Group (PENG) block and fascia iliaca compartment block for hip surgeries by pooling the available data published to date. Our analysis aims to improve the evidence-based knowledge of PENG block regarding outcomes such as opioid consumption and pain scores of the patient.

## 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.2023.07.007.

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Sociedade Brasileira de Anestesiologia

# Prevention of drug diversion and substance use disorders among anesthesiologists: a narrative review 

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#### Abstract

Diversion of substances from the care of the intended patient is a significant problem in healthcare. Patients are harmed by the undertreatment of pain and suffering, transmission of disease, as well as the risk associated with impaired vigilance. Healthcare providers may be harmed by the physical and mental impact of their addictions. Healthcare systems are placed in jeopardy by the legal impact associated with illegal routes of drug release including sanction and financial liability and loss of public trust. Healthcare institutions have implemented many measures to reduce diversion from the perioperative area. These efforts include education, medical record surveillance, automated medication dispensing systems, urine drug testing, substance waste management systems, and drug diversion prevention teams. This narrative review evaluates strengths, weaknesses, and effectiveness of these systems and provides recommendations for leaders and care providers.


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## Introduction

Drug diversion is the illegal distribution or abuse of prescription drugs or their use for purposes not intended by the

[^23]prescriber. ${ }^{1}$ Areas considered among the highest risk include the central hospital pharmacy, procedural areas, emergency departments, surgical centers, and remote care locations. ${ }^{2}$ The perioperative environment is a significant source of diversion of highly potent substances. Such action by anesthesia team members and other healthcare workers may result in substance use disorders by the individual diverting substances, inadequate pain management for the patient
from whom substances were diverted, or even a direct threat to the health and life of the patient under the care of individuals who are impaired by substances via the impact on performance or through transmission of communicable diseases. ${ }^{3}$ Diversion also impacts the healthcare systems through fines imposed by regulatory bodies and erosion of the trust that society places in those institutions that hold the safety of the public in their hands.

This narrative review introduces points of vulnerability for drug diversion in healthcare and the impact that diversion has on patients, providers, and systems. We explore methods to deter anesthesiologists from initiating the use of substances, prevent healthcare workers from diverting those substances from the perioperative area, and detect individuals that may be diverting substances for their personal use. The efforts to be reviewed include education, medical record surveillance, substance control methods, drug testing, substance waste management, drug diversion prevention teams, and the role of the pharmacy system.

We searched the PubMed database for English papers with no data limit. Our search strategy included terms such as "substance use disorder", "drug abuse, "drug diversion", "perioperative", "anesthesia", "anesthesiology", "anaesthesia", "anaesthesiology", "anesth"", "anaesth*", "drug testing", "drug screening", and "substance abuse detection". Boolean operators AND and OR were used. The reference list of selected articles was also screened for other relevant papers. Google News was also assessed using similar terms for news and relevant material not published in scientific journals, such as Center for Disease Control (CDC) recommendations.

## Points of vulnerability for drug diversion within health-systems

Drug diversion within health-systems may occur at multiple phases through which controlled pharmaceuticals travel. Purchasing by the facility or system through the final physical destruction of unused substances creates multiple "points of vulnerability" (Table 1). Points of vulnerability include those associated with the central pharmacy system including initial ordering, receiving and logging, procurement, storage, preparation, and dispensing to patients in the case of prescription medications or satellite pharmacies, unit medication cabinets, or automated medication dispensing systems. Points of vulnerability associated with the perioperative environment include obtaining substances from the pharmacy or drug dispensing system, preparation within the operating room, administration to the patient, and wastage of residual medications.

Risk of diversion within the inpatient pharmacy system occurs at four common process points according to a study of vulnerabilities for drug diversion by de Vries et al. ${ }^{4}$ The process points where vulnerabilities were identified include procuring controlled substances for the inpatient system, receiving from vendors, packaging controlled substances into unit doses, and delivery of controlled substances to automated dispensing cabinets on different wards within the hospital. Three categories of Critical Failure Modes (CFM) are identified: handling, data entry, and verification.

Table 1 Points of vulnerabilities to drug diversion.

| Pharmacy |  |
| :--- | :--- |
| Procurement <br> (ordering, <br> purchasing, <br> receiving) | Unauthorized orders <br> Ptorage |
| Packaging slips removed from records |  |
| Preparation | Replacement of substances with similar <br> appearing medications, liquids <br> Product switch (saline for medication) <br> Substance dilution |
|  | Removing small volumes of substance <br> "Accidental" product damage or discard |
| Prescribing | Verbal orders <br> Expired substances diverted |
| Wastage | Returned substances retained for per- <br> sonal use <br> False documentation of wastage |
|  | Fals |


| Operating room |  |
| :--- | :--- |
| Preparation | Theft <br> Dilution <br> Saline substitution <br> Obtaining substances under another <br> providers credentialing or name <br> Unsecured substances switched by <br> another individual |
| AdministrationLack of administration to patient <br> Documentation <br> False documentation of usage or <br> amount administered |  |
| WastageSubstance switch or dilution prior to <br> disposal <br> Substance removed from waste <br> containers |  |
| Theft of biohazard boxes <br> Collaboration between providers to <br> divert drugs |  |

Substance handling refers to preparation, movement of substances from place to place, wastage, and general substance security. Data entry is entering information into electronic databases, maintaining records, and assuring inventory counts. Verification is the use of a second provider or technology (scanners) to check the work or accountability of another individual. Anonymous discussions with pharmacists monitored due to substance-related impairment noted six primary means that substances are diverted. ${ }^{5}$ Diversion tactics included direct diversion of expired substances, changing inventory records to hide missing medications, forging prescriptions, practicing "sleight of hand" to acquire substances during work, stealing substances (despite surveillance), and taking unused substances that patients return for disposal. ${ }^{5}$

The same CFMs can apply to substance control in the perioperative period. Substance handling weaknesses include product loss or theft before patient use or during wastage, drug dilution, or solution substitution. Data entry failure modes include falsifying anesthetic records during patient
care, during provider transition, or as a part of the wastage process to fabricate dishonest drug usage. Verification failure modes include obtaining substances under another provider's identification, collaboration with another provider to misrepresent use or wastage, or altering anesthesia records after care.

## Impact of diversion of substances in the perioperative period

Diversion of drugs in the perioperative period places providers, patients, and institutions at risk via the delivery of care while impaired, by failure to adequately treat pain and provide comfort, reduced clinical vigilance, and the potential exposure of patients to bloodborne pathogens. ${ }^{1,3}$ Most healthcare leaders and executives recognize that diversion is a problem in healthcare facilities, but few believe that the problem exists in their own facility. ${ }^{6}$

The incidence of Substance Use Disorders (SUD) among faculty and resident physicians in anesthesiology is between $1-2 \% .^{7-9}$ The incidence among resident physicians appears to be increasing according to a study by Warner et al. ${ }^{10}$ The retrospective study examined SUD among resident physicians between 1975 and 2009. Other than a small reduction in the incidence of SUD between 1996-2002, the highest incidence has been reported since 2003 ( 2.87 per 1000 resident-years). The cumulative incidence of relapse was $43 \%$. Death is the presenting indication of a problem in many of these cases. ${ }^{11}$ Individuals in anesthesia who survive the initial SUD episode have a $40 \%$ risk of relapse, and nearly $20 \%$ will die of the disease. ${ }^{12}$ A recent study of Brazil reported that most anesthesiologists (82.1\%) have known of an anesthesia provider with a substance use disorder, and $23 \%$ admitted to personal use at some point in their lives. ${ }^{13}$ These incidences appear to persist despite the increased implementation of measures such as education and substance control via automated dispensing machines. ${ }^{9}$ Fewer studies have been performed among nurse anesthetists. Bell et al noted that up to $10 \%$ of nurse anesthetists admitted misuse of anesthetic agents at some point during their career. ${ }^{14}$ Among student nurse anesthetists the reported incidence is $0.65 \% .{ }^{15}$ Pharmacists are not immune to the problem of diversion. Most cases of diversion in pharmacies are controlled substances by technicians for personal use. ${ }^{16}$

Opioids and alcohol have been the most common substances of misuse by anesthesiologists, but other substances of abuse are appearing. ${ }^{10,12}$ A retrospective study of SUD among anesthetists in Australia and New Zealand published in 2014 revealed that propofol exceeded opioids ( $41 \%$ of cases vs. $32 \%$ ). ${ }^{17}$ Wischmeyer et al. showed a fivefold increase in propofol abuse over two decades in academic anesthesiology training in the United States. ${ }^{18}$

SUDs among perioperative personnel can threaten the well-being and health of the patients who entrust their care to our hands. ${ }^{19}$ Grissinger reported the case of an impaired healthcare worker desperate for controlled substances who died after obtaining and injecting an unknown solution from a biohazard box, which was later determined to be a neuromuscular blocking agent. ${ }^{20}$ Berge et al reported the impact
of diversion of substances on the health of patients at the Mayo Clinic in Rochester, MN. ${ }^{3}$ Events included diversion of substances during a procedure resulting in excruciating pain and anxiety for the patient and Transmission of Hepatitis C (HCV) by impaired providers. ${ }^{3}$ The largest hospital-related HCV outbreak ever recorded in the US concluded that the 32 confirmed cases were linked to drug diversion by an impaired healthcare technician. ${ }^{21}$ Many cases of infectious disease transmission related to drug diversion by impaired providers have been reported. ${ }^{22-25}$ The United States Centers for Disease Control and Prevention reported on 13 outbreaks of communicable diseases between 19832018 directly associated with drug diversion by healthcare providers. ${ }^{26,27}$

Diversion can occur even when institutions establish practices directed towards prevention of diversion. ${ }^{28}$ The reputation of an institution is threatened when diversion of substances occurs. Berge et al noted that the diversion of drugs by healthcare workers induced risk by "failure to prevent, recognize, or address signs of drug diversion or of an impaired or addicted employee". ${ }^{3}$ Healthcare facilities have paid millions of dollars in fines due to failure to maintain inventory control, accurate records, and strict security over substances. ${ }^{29}$ The Massachusetts General Hospital paid $\$ 2.3$ million in fines related to diversion of substances by healthcare providers for personal use. ${ }^{30}$ Although the inciting event was unrelated to anesthesia practice, multiple errant practices were identified during the ensuing audit including a physician writing prescriptions for a patient without maintaining records and medical staff failing to secure medications, including keeping medications with them while at lunch.

## Education

Education on the risks of SUD among healthcare providers has long been the primary focus of institutional efforts to reduce SUD and diversion. ${ }^{9}$ These efforts have included data presentations, videos such as the Wearing Masks series, and presentations by healthcare providers who have entered recovery and discussed their journey. ${ }^{31}$

The amount of educational time devoted to SUD education varies among academic programs. Lutsky et al reported that in 1991 between $47 \%$ and $89 \%$ of anesthesia programs devoted at least one lecture to the topic of substance abuse. ${ }^{32}$ Only $33 \%$ of programs had an identifiable formal substance abuse program or committee at the time of the study. A second study revealed that 70\% of anesthesiologists considered their hospitals' drug control policies as fair or poor. ${ }^{33}$ The widely cited survey of SUD among anesthesiologists published in 2002 showed that despite an increase in the number of hours of education devoted to SUD, the incidence of cases of SUD did not decrease over the study period. ${ }^{9}$ There was also no difference in the incidence of SUD among programs that devoted more time to education than those that had less dedicated time. In 2013, Boulis et al surveyed academic programs in Canada and found that although mandatory education of residents was required by $75 \%$ of programs, less than $10 \%$ required training for fellows or faculty. ${ }^{8}$ A recent survey of professionals in infection control, public health, and pharmacy reported that only $25 \%$

Table 2 Critical components to education in healthcare provider SUD and diversion.

Awareness of SUD incidence and impact on providers, patients, and healthcare systems Indicators of colleague impairment by substances
Indicators of diversion
Formal substance handling protocols and expectations
Policies regarding practice and record surveillance
Routes of confidentially raising concerns about a potentially impaired colleague or diversion
Routes to seek care for personal SUD
of faculty and staff received training in diversion and nearly half did not know if their facility had an internal mechanism to report diversion. ${ }^{34}$ The Cleveland Clinic instituted a formal process focused on active prevention of SUD. ${ }^{35}$ The components included mandatory educational programs for all members of the department on a recurring basis and enhanced skill building for the detection of impairment. ${ }^{35}$ However, these efforts have never been shown to result in a direct correlation to a reduction in SUD. Still, nearly $50 \%$ of respondents in the survey by Boulis et al believed that additional education is effective in reducing SUD. ${ }^{8}$

Web-based instruction on substance abuse and diversion may hold promise. Web-based material may be distributed to a large number of individuals whose work schedules and availability are not suitable for in-person learning, allows workers to train at their convenience, facilitates easy tracking of compliance, is easy to update, simplifies assessment of effectiveness, and may include novel delivery of education. Web-based education does not allow learners to pose questions, is subject to technological problems or web access. The Department of Pharmacy and Pharmacy Administration at the University of Sciences in Philadelphia designed an online module focused on the effectiveness of web-based education on SUD and drug diversion. ${ }^{36}$ A significant gain in knowledge was noted by participants, but the study was not designed to assess long-term retention of knowledge. ${ }^{36}$

The benefit of education to reduce the incidence of SUD in healthcare providers is debatable. The finding that programs with more education do not necessarily have lower rates of SUD and the observation that despite increases in education over time has not resulted in a reduction in SUD, does not negate the potential benefits. Educational efforts should include several key components including the incidence of SUD, impact, signs, reporting mechanisms, as well as means to obtain personal help (Table 2). Educational programs should also clearly identify routes that individuals can use to anonymously report suspicions of drug diversion or colleague impairment.

## Medical record surveillance

Automated Operating Room Information Management Systems (ORIMS), Anesthesia Information Management Systems (AIMS), and automated medication dispensing systems are in widespread use in modern operating rooms, procedural areas, and patient care locations. Analysis of data from information management systems can reveal indicators of
practices or medication distribution patterns that are potential indicators of diversion of drugs. Epstein et al utilized a mining approach to evaluate data obtained from the operating room ORIMS, AIMS, and automated medication dispensing system (Pyxis ${ }^{\top M}$, Becton, Dickenson, and Company, Franklin Lakes, New Jersen, USA). ${ }^{37}$ Data was utilized to determine whether two index cases of known diversion could have been detected earlier with medication record surveillance. Drug transactions after completion of the anesthetic and drug transactions occurring in locations away from the actual point-of-care were findings that indicated diversion in the two index cases. High use of opioids, high wastage of controlled substances, and transactions on canceled cases were not associated with diversion. A follow-up study in 2011 reported the identification of two individuals that were diverting drugs from the workplace. ${ }^{38}$ Those individuals' frequency of abnormal transactions fell more than two standard deviations from normal and prompted further investigation.

Surveillance of drug transactions is challenged by a high percentage of discrepancies between dispensed controlled substances and what is documented as administered to the patient. Vigoda et al found that discrepancies were discovered in $15 \%$ of records. ${ }^{39}$ Discrepancies were found in the AIMS system ( $8 \%$ ) and the automated medication dispensing system (10\%). ${ }^{39}$ Most errors were related to incorrect documentation of medication wastage in the medication dispensing system (35\%) or documenting the medication in AIMS (40\%). Careful hand-offs between care providers as well as case duration have been identified as a significant source of controlled substances documentation errors. ${ }^{40}$

Shah et al demonstrated a significant reduction in the incidence of controlled substance discrepancies through development of an automated web-based software application and measured by the number of missing controlled substance medications and medication kit return errors. ${ }^{41} \mathrm{~A}$ similar approach was also described in a pediatric surgical center. ${ }^{42}$ The use of health-system data coupled with machine learning and advanced analytics has been shown to be highly accurate in detecting transactions involving a high risk of diversion. ${ }^{43}$ Machine learning detected diversion an average of 160 days (median 74 days) faster.

It is critical that implementation of a surveillance system include a process to resolve discrepancies and investigate patterns of suspicious transactions. The American Society of Health-Systems Pharmacists recommends that pharmacy discrepancies be resolved by the end of the work shift and that discrepancies which cannot be resolved be reported to pharmacy and patient care leadership, reviewed, and resolved
within 24-72 hours. These requirements can apply to perioperative discrepancies. ${ }^{2}$

## Drug testing

The number of healthcare providers with SUDs as well as the impact on the safety of patients has led to calls for drug testing to become a standard part of medical practice. ${ }^{44}$ Defense of drug testing among healthcare providers may serve several purposes including deterrence from initiating the use of substances via pre-placement (pre-employment) testing, surveillance for personal illicit use (random testing), and to detect whether a substance is present when a healthcare provider's performance may indicate a potential SUD (reasonable suspicion or "for cause"). Others have gone so far as to suggest that drug testing should occur after a critical event while others have argued against such a practice. ${ }^{45,46}$ Acceptance of drug testing is variable. Sousa et al. reported that over $80 \%$ of surveyed physicians believed that drug testing could improve provider and patient safety. ${ }^{13}$ Individuals with a personal history of SUD were less likely to believe in the benefit. This contrasts with Boulis et al., which indicated nearly $79 \%$ of respondents did not perceive a role for drug testing as an effective measure to reduce SUD. ${ }^{8}$

The Massachusetts General Hospital (MGH) first reported that a program which included random drug testing of anesthesiology residents was feasible in $2008 .{ }^{47}$ The program was initiated to reduce the incidence of SUD among trainees. Since the time of the initial publication, other institutions have followed with their own programs including the Cleveland Clinic, ${ }^{35}$ Vanderbilt University Medical Center, ${ }^{48}$ and the University of Colorado. More than half of pharmacy programs have implemented drug screening to reduce SUD. ${ }^{49}$

Drug testing in medicine has shown success. Lange et al reported the results of pre-employment drug testing at Johns Hopkins Hospital in 1989 and 1991. ${ }^{50}$ The positive rate was $10.8 \%$ in 1989 before the establishment of a formal preemployment testing program. Testing was performed without identifying information on the individual tested. After the establishment of a formal program, the incidence was reduced to $5.8 \%$. The study concluded that "pre-employment drug testing can serve as a deterrent for a drug-using person applying for employment". ${ }^{50}$ A follow-up report of the MGH program published in 2018 demonstrated a significant reduction in the incidence of SUD but cautioned that a larger multi-center clinical trial was necessary to determine the true effectiveness. ${ }^{51}$ Darbishire et al. reported testing in pharmacy students detected 2.2 events per 100 students annually. ${ }^{43}$

Arguments against drug testing include the possibility of false positive and false negative results. Errors can occur at any phase of the test process. Pre-analytic errors include incorrect labeling of a specimen, incorrect ordering of a test, use of a wrong container for collection, or adulteration of a specimen. ${ }^{52}$ Analytical errors include assay cross-reaction with a pharmacologically or structurally unrelated molecule or impaired binding of the antigen (drug or metabolite) to the detection antibody. Post-analytical errors are logistical errors such as incorrect interpretation of a test
result such as considering a result positive despite the quantitative level falling below the threshold required for a positive result. Tests may also fail to reveal the presence of a substance if the urine level falls below a positive threshold due to test timing. False positive results have been reported in drug testing physicians. ${ }^{47,53}$ A study of a single year of pre-employment drug testing in a healthcare system revealed an initial positive rate of $5 \%$ which was reduced to $2.2 \%$ after discussion with a Medical Review Officer (MRO). ${ }^{54}$ Most cases of "false" positive results were due to unreported prescription medications. The incidence of false positive results is far lower when appropriate protective measures are applied including notification of individuals regarding testing protocols, substances to be screened, consequences for positive tests, and adherence to established guidelines.

Two aspects of confirmation are critical to interpretation of urine screening results. Immunoassay testing alone is insufficient to determine whether a test is truly positive. Confirmation must occur via gas chromotography/mass spectroscopy which also determines quantitative level. It is also imperative that positive tests are then scrutinized by a certified MRO. The MRO evaluates the report and speaks to the individual to determine whether there is a legitimate reason for a positive test result such as a prescription or consumption of another substance. It is cautioned that even results confirmed as positive by a MRO do not determine the abuse, misuse, or diversion of a substance, only the presence of a substance. Results should then be presented to the individual in a coordinated intervention.

Urine drug testing is becoming more widespread in medicine and success has been demonstrated. Programs should inform applicants for employment that urine drug screening is a component of diversion prevention, which substances are included in testing, and the process for a failed test. Programs are encouraged to maintain quality standards including specimen collection by trained personnel, split sampling at the time of collection, strict chain of custody from collection to testing at an accredited laboratory, result review by a MRO, and professional intervention for an individual who tests positive for a substance or is subject to testing for reasonable cause. It is critical that institutions evaluate the validity of any positive results to avoid false accusations of SUD or diversion.

## Substance waste management

Residual substances after administration create another point of vulnerability for diversion. Additionally, remaining anesthetic and controlled substances contribute to the tremendous cost of healthcare. A recent study estimated an overall medication wastage rate of $38 \% .{ }^{55}$ Wastage rates for individual substances with a high risk of diversion include morphine (26.3-57.5\%), ${ }^{56,57}$ propofol (15.2-54.8\%), ${ }^{55-57}$ diazepam ( $10 \%$ ), ${ }^{57}$ midazolam (19-46\%). ${ }^{55,57}$

Rules for wastage of substances are regulated beyond mere local practices. The United States Drug Enforcement Agency (DEA) as well as the Environmental Protection Agency (EPA) have an interest in the proper disposal of substances. A study in 2013 evaluated wastewater

Table 3 Weak points in witnessed wasting.

| Diversion weak point | Potential fix |
| :---: | :---: |
| False documentation of complete use of a substance with diversion of full vial | Return of all full and empty vials. |
| False documentation of full use with partial diversion of remaining substance | Video recording of operating room practices. |
| Return of substituted fluid (saline) | Qualitative analysis of returned substances |
| Return of diluted substance | Quantitative analysis of returned substance |
| False documentation of waste observation | Formal sanction of individuals falsely documenting observation. Requirement for all waste observation to occur in pharmacy. Video recording of waste. |
| Collaboration by witnessing and wasting individual | Video recording of waste. |

from two hospitals in New York. ${ }^{58}$ Three drugs accounted for $87.5 \%$ of the total wasted (midazolam, acetaminophencodeine, and fentanyl). Stackelberg et al. evaluated the effectiveness of conventional waste treatment and determined that many contaminants survive treatment and end up in potable water sources. ${ }^{59}$

The practice of "witnessed wasting" is common in operating rooms. Witnessed wasting involves one individual attesting that a volume of residual controlled substance is expelled from a syringe into a container from which it cannot be retrieved for use. The American Society of Health-System Pharmacists guidelines suggest that in high-risk areas or when high-risk controlled substances (fentanyl) are wasted that an authorized healthcare worker witness and that the amount initially obtained match that documented as administered plus that wasted. ${ }^{2}$ Several weak points exist in this process (Table 3). ${ }^{60}$ The provider may simply document that a substance was used and take the substance for personal use. Providers may divert portions of a substance rather than administer it to a patient. Providers may also return diluted or substituted solutions rather than appropriate medication and concentration. Finally, collaboration between two providers that are diverting substances can occur.

Diversion of unused substances from biohazard ("sharps" boxes) has been reported. Individuals who are desperate for a substance have been known to search through collection containers for small amounts of controlled substances from discarded vials, primarily opioids. ${ }^{3,20}$ Controlled substances should be disposed in a system that makes the drug irretrievable and ineffective. There are commercially available products that chemically neutralize liquid pharmaceuticals without the need for water or incineration. ${ }^{60}$ These systems render discarded substance impossible to retrieve but do not impact substance that remain within a discarded vial.

## Drug diversion prevention teams

The significant role that diversion of drugs can play in the well-being of healthcare workers, patients, and colleagues has resulted in calls to establish formal processes to manage suspected and confirmed diversion. ${ }^{61}$ The Mayo Clinic has established the Medication Diversion Prevention Committee (MDPC) to lead efforts. ${ }^{61}$ The organization also created
smaller groups known as Drug Diversion Response Teams (DDiRT) which fall under the MDPC. The DDiRT teams include members of the MDPC, pharmacy, security and safety, and a physician chair of the MDPC. Any organization employee who suspects diversion can initiate an investigation. A suspected event prompts notification of the MDPC and the Director of Pharmacy. The director then performs a preliminary investigation. If no evidence of diversion is found, the case is closed. If suspicion remains, the DDiRT follows a formal course to investigate. Further action includes an employee interview, additional surveillance, and drug testing, as the DDiRT believes is appropriate. Senior institutional leadership is notified as necessary.

The action plan after the DEA investigation at the Massachusetts General Hospital included creation of the drug diversion prevention team as well as the establishment of a drug diversion compliance position. ${ }^{30}$

The American Society of Health-Systems Pharmacists established guidelines for prevention of diversion within healthcare facilities. The guidelines define the many responsibilities of the Controlled Substances Diversion Prevention Program Committee including leadership, policy development, routine auditing of data that could indicate diversion, investigation of suspected incidences of diversion, quality improvement, communication to patients potentially impacted by controlled substances, and others. ${ }^{62}$

## The importance of the health-system pharmacy

Health-system pharmacies maintain primary responsibility for substance procurement, prescribing, preparation and dispensing, and wastage. ${ }^{2}$ The importance of involvement of pharmacy leadership in prevention of diversion is critical for success. An all-inclusive Controlled Substances Diversion Prevention Program (CSDPP) focuses on the safety of patients and providers while assuring adherence to federal laws, state regulations, and accrediting agency guidelines. The American Society of Health-Systems Pharmacists have developed Guidelines on Preventing Diversion of Controlled Substances. ${ }^{2}$ These guidelines address core elements such as legal and regulatory requirements. System-level controls include human resources, technology and monitoring and surveillance, and investigations into suspected diversion. Individual level controls include chains of custody and wastage.

## Conclusion and recommendations

Diversion of drugs from health systems including the perioperative environment has significant negative effects on patients, healthcare personnel, organizations, as well as the general trust the public holds in systems designed for their care. The anesthesiologist's experience and input are critical to preventing diversion and its impact (Fig. 1). Healthcare organizations are encouraged to develop comprehensive controlled substance diversion prevention programs that harness the knowledge and skills of leadership, pharmacists, and anesthesiologists. Critical components of such programs include education, medical record surveillance, tamper-proof secure substance waste management systems, and drug diversion prevention teams trained to provide oversight of prevention efforts and investigation of events (Table 4).


Figure 1 The vulnerable chain of drug diversion.

Table 4 Recommendations for prevention of drug diversion and substance use disorders among anesthesiologists

| Focus | Recommendations |
| :---: | :---: |
| Education | Program should institute mandatory substance use disorders and drug diversion prevention education sessions. Such sessions should address indicators of diversion, impairment, and impact as well as protocols for management of substances abuse, record surveillance, and means to report concerns. |
| Medical record surveillance | Programs should establish ongoing surveillance of medication records and include controlled substance between drug transactions. The effectiveness of automated information management systems should be harnessed to estabish unbiased daily reports. Indicators of diversion including mismatch between drug transactions and location of care, transactions after hours, and frequent errant documentation should trigger local investigation. |
| Urine drug screening | Programs should consider development of urine drug screening programs which include pre-placement, random, and "reasonable suspicion" components. Drug screening should meet regulatory standards including strict chain-of-custody, testing through credentialed laboratories, and review of results through a certified review officer (MRO). Drug screening must be accompanied by a formal system to adress results with the healthcare provider in the form of a formal intervention. |
| Substance waste management | Programs should establish formal policies which address medication return, wastage, and disposal. <br> Waste practices should include verification and documentation. Controlled substance waste systems should include security that renders substances irretrevable and inactive. <br> Return and waste policies should define management of drug discrepancies, a clear time frame, and penalty for violation. |
| Drug diversion prevention team (DDPT) | Institutions should estabilish drug diversion prevention teams, which are responsible for investigation of any suspected drug diversion. Teams assess medical records, interview individuals, perform additional surveillance, and enforce event specific drug testing if indicated. |
| Controlled Substances Diversion Prevention Committee | Hospitals should establish a multidisciplinary controlled substance diversion prevention committee to establish policy, assure compliance with regulations, oversee DDPTs, and assess the impact of interventions focused on reduction for drug diversion. |

## Declaration of Competing Interest

## The authors declare no conflicts of interest.

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Sociedade Brasileira de Anestesiologia

## CASE REPORT

# Quadratus Lumborum block as primary anesthetic technique for colostomy procedure: a case report 

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## KEYWORDS

Regional anesthesia; Colostomy;
Patient safety


#### Abstract

An elderly patient was admitted to the hospital due to an enterovesical fistula and a terminal colostomy was proposed. The patient had a high anesthetic risk and thus a quadratus lumborum block was chosen as the sole anesthetic technique. This block has been described to provide both somatic and visceral analgesia to the abdomen. In fact, it yielded good anesthetic conditions to perform the procedure and allowed the patient to be hemodynamically stable and comfortable throughout the case. The postoperative period was uneventful. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


## Introduction

The quadratus lumborum (QL) muscle is located in the posterior abdominal wall, laterally to psoas major muscle. Quadratus lumborum block (QLB) was fist described in 2007 by Rafael Blanco as a modified approach to tranversus abdominis plane (TAP) block. Since then, QLB has been shown to provide effective analgesia for several types of surgery, including cesarean section, renal, abdominal and orthopedic surgeries. ${ }^{1}$

The authors present a case report of a terminal colostomy successfully performed using a type 1 QLB as the sole anes-

[^24]thetic technique in a patient to whom general anesthesia posed substantial risk.

The patient gave her consent for anesthesia and to publication of the case in an anonymous form. The CARE checklist was followed to write the present report.

## Case report

A 93-years-old female patient presented to the emergency department with symptoms suggestive of an enterovesical fistula. She was independent for daily activities but had several co-morbidities such as stage 3 chronic kidney disease, coronary artery disease with a previous myocardial infarction, chronic anemia, hypertension, and type 2 diabetes mellitus. Additionally, she had been recently admitted for aspiration pneumonitis, four months before this event. She had a chronic urinary catheter due to obstructive uropathy.

Surgical background included several urinary incontinence correction surgeries, a total hysterectomy due to uterine neoplasia, and an aorto-femoral bypass. She weighed 58 kilograms.

Computed tomography imaging evidenced two fistulous paths from the colon to the bladder and the patient was admitted for conservative treatment. On the $6^{\text {th }}$ day after admission, she developed acute pulmonary edema that resolved with diuretics and isosorbide dinitrate infusion. During the $8^{\text {th }}$ day, the patient underwent a sigmoidoscopy for identification of the fistulous path. After the procedure, a new onset of acute pulmonary edema with signs of malperfusion ensued, with an additional analogous episode repeated at the $11^{\text {th }}$ day. Comparably to the first event, these also resolved with medical therapy. Due to the small dimensions of the fistulous aperture, an endoscopic prosthesis could not be placed, and a terminal colostomy was proposed to the patient.

During the anesthetic preoperative visit, the patient and her family were informed about the procedure risks and informed consent was obtained.

In the operating room, the patient was monitored, and an epidural catheter was placed at L1-L2 level has a rescue option. Prophylactic anticoagulation was stopped 12 hours before the technique which was uneventful, and no drugs were administered through this route. The patient was then positioned in the right lateral decubitus to perform an ultrasound guided type 1 QLB, under sterile technique. An in-plane block was performed at the level of L 3 in the midaxillary line using $0,35 \mathrm{~mL} . \mathrm{kg}^{-1}$ of local anesthetic, namely 20 ml of $1,33 \%$ Mepivacaine. The anesthetic was seen to distribute through the anterior surface of QL muscle and posteriorly to the anterior layer of the thoracolumbar fascia. Loss of cold sensation was observed from T 8 to L1, after which the procedure was initiated.

Four milligrams of intravenous dexamethasone and fractionated boluses of intravenous fentanyl to a total of $75 \mu \mathrm{~g}$ were administered during the procedure. A circular skin area of approximately $2,5 \mathrm{~cm}$ of diameter was excised in the left lower quadrant of the abdomen, at the level of T10 and T11 dermatomes, and the terminal colostomy was performed. The patient remained conscious and hemodynamically stable throughout the procedure that lasted 50 minutes.

During her stay in the postanesthesia care unit, she did not require rescue analgesic or antiemetic medication and was discharged to the ward 1 hour after admission. No analgesic medication was needed in the postoperative period and the patient was discharged home in the $27^{\text {th }}$ day after admission, with no further complications registered.

She returned for scheduled appointments at 2 weeks and 3 months after hospital discharge and presented on both visits with a functioning colostomy, good general condition, clean urine and a high-level of satisfaction for the period she was admitted.

## Discussion

Enterovesical fistulas have a greater prevalence in men between the $5^{\text {th }}$ and $8^{\text {th }}$ decades and surgical intervention is typically the treatment of choice, given the high risk of infection and malnutrition. Nevertheless, conserva-
tive treatment can be an option for minimally symptomatic patients or in those for whom surgery is not possible or is hazardous. The type of surgery depends on the position of the fistulous path, although most of the times it consists in a colonic resection with primary anastomosis.

In the present case, a conservative approach was attempted but no resolution of symptoms was achieved. Also, due to the small fistulous aperture, an endoscopic prothesis could not be placed. The anesthetic technique chosen had to provide good surgical conditions for both the surgeon and the patient whilst not eliciting another episode of cardiac decompensation that seemed to ensue at the minimal stressful event. Thus, the authors decided to refrain from a general anesthesia and preferred a regional technique.

To perform a terminal colostomy, visceral analgesia of the descendent colon is required, as well as analgesia from T7 to L1 dermatomes of the skin. Innervation to the descendent colon derives from the inferior mesenteric plexus that arise from L1 to L3 lumbar roots. Therefore, the chosen technique should provide analgesia from T7 to L3 to be able to cover the intervention area.

There are several regional techniques that could be employed to achieve these levels, namely a neuraxial technique. However, to provide such a high level of analgesia, hypotension was possible and the fluid therapy and vasopressors that would be necessary to maintain arterial blood pressure were a concern that precluded it to be our first choice. Still, the authors decided to place an epidural catheter in case a rescue technique was needed, since its combination with the QLB would diminish the dose of anesthetic required and enhance its safety.

TAP block is commonly used for analgesia in abdominal surgeries as it can provide analgesia of the abdominal wall from T 7 to T12, depending on the chosen approach. However, it does not provide visceral analgesia.

Erector spinae plane (ESP) block could also be used to provide analgesia to the abdominal wall. ESP muscles anatomy provides a pathway for the local anesthetic to spread along the thoracolumbar fascia. Chin and collaborators ${ }^{2}$ found that it can provide visceral analgesia if performed at T7 level, through the spread of local anesthetic to the paravertebral space. However, these results are not consistent and are still poorly defined. In fact, ESP block has been found to reliably provide analgesia to the posterior chest wall, while abdominal and visceral analgesia fail to be regularly achieved. ${ }^{3}$

QLB mechanism of action is not yet clearly defined but studies in cadavers show that it probably relies on the diffusion through the thoracolumbar fascia. ${ }^{4}$ The local anesthetic is thought to spread through the fascia to the paravertebral space, causing parietal and visceral analgesia. ${ }^{5}$ There is reason to believe that different approaches have different mechanisms of action, and that the level of analgesia provided can go from T4 to L4, with subcostal, iliohipogastric and ilioinguinal nerves being consistently blocked, regardless of the chosen block type. ${ }^{4,5}$ However, there is still insufficient evidence to recommend one approach over the other. ${ }^{4}$ In fact, successful use of QLB has been described with all the three approaches.

In conclusion, this case illustrates the possibility to perform minor abdominal surgeries in high anesthetic risk
patients using regional anesthesia, with minimal sedation and complementary analgesia, thus minimizing iatrogenic injury and maintaining hemodynamic stability.

## Conflicts of interest

The authors declare no conflicts of interest.

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Sociedade Brasileira de Anestesiologia

## CASE REPORT

# Anatomic barriers to paraspinal blocks: a cadaver case series 

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Dissection;
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Paraspinal muscles;
Regional Anesthesia;
Ultrasound


#### Abstract

The paraspinal space is intriguing in nature. There are several needle tip placements described in compact anatomical spaces. This has led to an incertitude regarding the appropriate anatomic locations for needle tip positions. Through our cadaver models we try to resolve the issues surrounding needle tip positions clarifying anatomical spaces and barriers. Further we propose an anatomical classification based on our findings in cadaveric open dissections and cross and sagittal sections. © 2021 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).


## Introduction

In patients undergoing thoracic and upper abdominal surgeries, thoracic epidural and thoracic paravertebral blocks (PVB) are used for managing acute postoperative pain. ${ }^{1}$ Although ultrasound (US) has revolutionized needle placements and block accuracies, these are technically demanding and contraindicated in patients on anticoagulants. After thoracic erector spinae plane block (ESPB) was described, there were widespread applications in thoracotomies, and abdominal and dorsal spine surgeries. However, it also has created a furor in needle tip placements in the paraspinal space which has widened the perplexity and intricacies of the increasingly new blocks. ${ }^{2,3}$ Classified as "paravertebral blocks by proxy", they all aim at depositing local anesthetic (LA) into the paravertebral space (PVS). Though the

[^25]plausible mechanism of action of paraspinal blocks is by seepage of LA into the thoracic PVS, it is debatable if it occurs through the apertures and perforations in the bony-ligament-muscular mesh. ${ }^{4}$ To understand the numerous needle tip placements in the paraspinal areas and the anatomic barriers encountered, we explored the anatomic structures with open dissection and cross-sections. We inspected the paraspinal area in an attempt to establish the credible anatomic structures that would offer needle tip placements and the obstacles encountered which would limit LA diffusion. Based on our dissection we propose a simple anatomic nomenclature for paraspinal blocks.

## Case description

The study was approved by the Research Ethics Committee of the University of Barcelona and was performed in the dissection room of the Anatomy and Embryology Department of


Figure 1 Anatomic barriers and spaces. A, Cadaver in prone position; probe position in parasagittal scan from R1 and shifting (Grey arrows) caudal-Rose; bilateral parasagittal lines-Dark red; blue lines for sections at the level of thoracic spinous process' $1^{\text {st }}$, $3^{\text {rd }}$ and $5^{\text {th }}$ levels; Axial probe placements (light blue from the midline (black oval-spinous process) to the CTJ. B, Prone dissection of the back revealing the three erector spinae muscles spinalo thoracis (STM); Longissimus muscle (LoM); Iliocostalis (ILc); emergence of thoracodorsal nerves (TDNs) between Lo and ILco traversing lateral are visualized. C. ESM (LoM and Ilc) detached from its attachments demonstrating the lateral and medial erector spinae plane in relation to thoracic TP. Short oblique muscles are visualized lateral (LC-leavator costarum) and medial (RT-rotator thoraces) to thoracic TP forming the floor of the erector spinae plane. D, Outlay of axial section through the costotransverse junction; 1-lung; 2 hof rib; 3- spinal cord; 3a-parietal pleura; 4-paravertebral space;5intervertebral foramina;6-rib; 7-lamina;8-erector spinae muscle; 9-transverse process; 10-lateral erector spinae plane; 11-medial erector spinae plane (10 and 11 continuous blue line); dark yellow - ventral nerve root; light yellow - dorsal nerve root; thick light green - site of costotransverse ligament. E, Outlay of sagittal section through the costotransverse junction: 1 is the posterior thoracolumbar fascia; 2 is the posterior erector spinae sheath, 3 is the anterior erector spinae sheath, 4-ITL-inter-transverse ligament; 5CTL - costotransverse ligament; 6-R-Rib; 7-TP - transverse process. The space deep to the AES is the DESP (light blue), deep to ITL and superficial to the CTL is the ILS (blue) and deep to the CTL is the PVS (dark blue). F, Cadaveric parasagittal dorsal ultrasound at the T 4-5 CTJ level depicts the three spaces (ESP, ILS, and PVS) and barriers (ITL, ILS and CTL). G, Cadaveric parasagittal dorsal ultrasound at the T 4-5 CTJ level depicts the three needle positions; 1-ESPB; 2-ILSB; and 3-PVB. TzM, trapezius muscle; ESM, erector spinae muscle; CTJ, costotransverse junction; ESP, erector spinae plane; ITL, intertransverse ligament; ILS, inter-ligament space; PVS, paravertebral space; CTL, costotransverse ligament.
the Faculty of Medicine of the Universitat de Barcelona. Three adult non-embalmed (cryopreserved) cadavers without obvious pathology or previous thoracic procedures were studied. Cadaver 1(C1) underwent an open dissection, cadaver 2 (C2) was subjected to axial section, and cadaver 3 (C3) was put through a sagittal section. C2 and C3 were frozen at $-20^{\circ} \mathrm{C}$ for 48 hours before being processed. After defrosting the specimen of C2 and C3, an exploration of the different anatomic structures with a loupe magnification was performed. The specimens of three cadavers were photographed with SLR Canon D 1000 camera.

## Cadaver 1 (C1)

For open dissection, C1 was covered with a plastic sheet and kept at room temperature for 6 hours, after retrieving from the deep freeze chamber $\left(-20^{\circ} \mathrm{C}\right)$. A skin incision along the midline over the spinous processes from C7 to L4 vertebrae was made in the prone position for C 1 , exposing the posterior thoracic wall and scapula. The lumbar to thoracic erector spinae muscles (ESM) were examined in C1, and the arrangement and attachments of the fibers were evaluated
from medial to lateral and from caudal to cephalad. The ESM and aponeurosis were separated from bony and ligamentous attachments.

Deep to the dorsal layer of the thoracolumbar fascia and the superficial dorsal muscles (trapezius, latissimus dorsi, and rhomboids [Fig. 1A]) three vertical group of muscles were revealed: medially, was the spinalis thoracis muscle (STM) that travelled between the spinous process and thoracic transverse process (TP), the longissimus muscle (LoM) coursed cephalad in the middle, and the tendons of the iliocostalis muscle (ILCM) fanned out lateral with its attachments over the ribs (Fig. 1B). The thoracolumbar nerves emerged from LoM and could be traced laterally and superficially to the tendons of ILcM to innervate the cutaneous areas. On elevating the tendons of LoM and ILcM (Fig. 2C) from their bed, a potential space was revealed, lateral to the thoracic TP - the "lateral erector spinae plane" (L-ESP) (Fig. 1C). The bed of the L-ESPB was formed by the levator costarum brevis, longus muscles and tendons (short oblique muscle from TP to ribs) (Fig. 1C). Detaching the STM from the thoracic TP revealed the short oblique muscles of the spine, the rotatores thoracis between the spinous process,


Figure 2 Possible needle tip positions in DESP, ILS and PVS - In Sagittal section (top row) and Transverse section (bottom row). A, Sagittal section - needle in DESP; B, Sagittal section - needle in ILS; C, Sagittal section - needle in PVS; D, Sagittal section - needle in DESP; E, Sagittal section - needle in ILS; F, Sagittal section - needle in PVS. ITL, inter-transverse ligament; CTL, costotransverse ligament; R-Rib; TP, transverse process R-rib; TP, thoracic transverse process; Vnr-ventral nerve root; Dnr-dorsal nerve root.
and the medial part of the thoracic TP (Fig. 1C). There was a space between the STM and rotatores thoracis which we refer to as the medial ESP (Fig. 1C). Projections of thoracic TP were visualized at regular intervals which were connected through the inter-transverse ligament (ITL). We envisaged that thoracic TP divided the ESP medially and laterally, to form the medial and the lateral ESP respectively.

## Cadaver 2 (C2)

In the prone position, C2 was scanned from the level of R1 to R9 (R-rib). R1 was identified in the supraclavicular fossa and the probe was shifted dorsally keeping R1 in real-time view. R3, R5, and R7 were noted in particular, and subsequently with a medial shift of the probe bilateral to costo-transverse junction (CTJ) at the $3^{\text {rd }}, 5^{\text {th, }}$ and the $7^{\text {th }}$ levels, were identified and marked (Fig. 1). An explicit axial section was performed in C2 with a mechanical saw through the markings at the $3^{\text {rd }}, 5^{\text {th, }}$ and $7^{\text {th }}$ CTJs. With C2 placed in the prone position, bilateral CTJ from the $1^{\text {st }}$ to the $9^{\text {th }}$ were identified and marked on the dorsum of the skin (Fig. 1A). The specimens of C2 were examined for gross anatomic structures dorsal and ventral to the thoracic TP.

The axial section demonstrated the posterior thoracic lumbar fascia that ran continuously along the dorsal aspect of the ESM. Bilaterally, lateral, and dorsal to the spinous process and laminae was the ESM engulfed in its sheath. The CTJ could be distinctly visualized. Deep to the ESM lies the deep erector spinae plane (DESP), outlined with blue. The thoracic TP arbitrarily divides the DESP into medial and lateral ESP's M-ESP and L-ESP. The paravertebral space (PVS) was situated beyond the costotransverse ligament (CTL), bordered anterolaterally by the pleura and medially by the intervertebral foramina through which communicated to the
neuraxial space. The position of the thoracic ventral and dorsal nerve roots are depicted in (Fig. 1D).

## Cadaver 3 (C3)

With cadaver 3 in the prone position, an ultrasound scan identified the levels of R1 to R9 (R-rib), as mentioned earlier. Eventually, bilateral CTJ at the $3^{\text {rd }}, 5^{\text {th, }}$ and $7^{\text {th }}$ levels were identified and marked (Fig. 1). Exemplary sagittal sectioning at the CTJ level (from $1^{\text {st }}$ to $9^{\text {th }}$ ) was performed using a mechanical saw.

Superficial to the posterior ESM sheath (PES), the rhomboid muscle could be observed as a thin muscular slip. Deep to the anterior erector sheath (AES), a plane filled with connective tissue was observed and was considered the erector spinae plane. Thoracic TP could be visualized at definite intervals. Between the two thoracic TP engulfed in a strong sheath was a slip of muscle layer, the "intertransverse ligament" (ITL) [Fig. 1E], which was also a constant feature connected between the two thoracic TP.

Extending from the TP to the rib was the CTL (Fig. 1E), that was consistently present in all specimens and had a definite anatomic structure (oval), and unlike the ITL possessed a relatively weak sheath enclosing connective tissue. The space between the ITL and the CTL was consistent and was termed the "inter-ligament space" (ILS). Loupe magnification dissection of the space between the ITL and the CTL demonstrated a predominant fat tissue content with the dorsal branch of the spinal nerve. The ILS was bordered by dense ligaments, on its anterior and posterior areas, the TP and the ribs on its superior and inferior aspect (Fig. 1E).

In front of CTL and behind the pleura was the PVS consistent and continuous in its superior and inferior aspects. Fat tissue and the ventral branch of the spinal nerve

Table 1 Macroscopic and loupe magnification details.

|  | OD/C1 left | OD/C1right | AX/C2left | AX/C2right | SAG/C3left | SAG/C3right |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| PESS | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ |
| AESS | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ |
| DESS | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ |  |
| ITL | $Y$ | $Y$ | - | $Y$ | $Y$ |  |
| ILS | - | - | - | $Y$ | $Y$ |  |
| DNr | $Y$ | $Y$ | $Y$ | $Y$ | $Y$ |  |
| CTL | - | - | $Y$ | $Y$ | $Y$ |  |
| PVS | - | - | $Y$ | $Y$ | $Y$ |  |
| VNr | - | - | $Y$ | $Y$ | $Y$ |  |

OD/C1 left, Open Dissection Cadaver 1 left side specimen; OD/C1 right, Open Dissection Cadaver 2 right side specimen; SAG/C2 left, Sagittal Cadaver 2 left side specimen; SAG/C2 right, Sagittal Cadaver 2 right side specimen; AX/C3 left, Axial Cadaver 3 left side specimen; AX/ C3 right, Axial Cadaver 3 right side specimen.
PESS, posterior erector sheath; AESS, anterior erector sheath, DESS, deep erector spinae plane; ITL, intertransverse ligament; ILS, interligament? space; Dnr, dorsal nerve root; CTL, costotransverse ligament; PVS, paravertebral space; VnR, ventral nerve root.

Table 2 Anatomic classification of paraspinal blocks.

| Block type | Block space |
| :--- | :--- | :--- | :--- |
| Erector Spinae Plane |  |$\quad$ Inter Ligament? Space $\quad$ Paravertebral Space

predominated the PVS. Loupe magnified dissection revealed the ventral nerve exiting the IVF in all 4 specimens in the thoracic PVS, but the dorsal nerve was evident in 1 specimen behind thoracic TP (Fig. 1E).

## Needle tip positioning

In C2 (axial section), the needle tip could be positioned in two confirmed areas: deep to the AES and superficial to the ITL is the ESP (Fig. 2D), before the anterior sheath of the ESM in the ITS, and in front of the imaginative CTL is the PVS. In the sagittal sections, the needle tip is illustrated deep to the AES and superficial to the ITLwhichis the ESP
(Fig. 2A), before the ITL and before the CTLwhich isthe ILS (Fig. 2B), and before the CTLwhich isthe PVS (Fig. 2C).

Based on our results of cadaver models of open dissection, and axial and parasagittal sections at the thoracic level, we define these barriers and spaces as depicted in the US images (Figs. 1F and 1G).

## Discussion

Our findings precisely illustrated three anatomic spaces that exist in the paraspinal area, and the needle placements are in these three designated spaces (Table 1). These spaces are the ESP, the ILS, and the PVS. The numerous needle tip
placements with complex names would be unnecessary since this would lead to incertitude amongst regional anesthesiologists who would like to initiate paraspinal blocks in routine clinical practice. Unpretentiously, we wish there would be no new anatomic tip locations in the thoracic ESP.

The mechanisms explained in earlier studies are conflicting and debatable. ${ }^{4,5}$ In open dissection the tightly woven floor of deep ESP is almost anatomically impermeable, though the costotransverse foramen is implicated in translocation of solution. ${ }^{4}$ In the sagittal sections, the potential anatomic barriers for the spread of fluid are the ITL, the ILS, and the CTL. Of the three, the ITL seems to be the strongest barrier, while the fat-filled ILS would be soaked with LA and act as a reservoir. Apart from the above factors, needle tip placement immediately medial or lateral to the thoracic TP affects the spread of solution, medially into the M-ESP and laterally into the L-ESP.

Thus, all the described paraspinal blocks can be anatomically classified into a simple nomenclature (Table 2). Of the three models, the sagittal section offered an excellent panoramic view from dorsal to the ventral aspect of the anatomical barriers, following needle tip placements in the paraspinal spaces. Cadaver numbers were a major limitation of this study. A simultaneous injection into the three spaces in different cadavers could have correlated better with the anatomic description.

In summary, based on our anatomic models we describe three important paraspinal areas where needle tips can be positioned. A subsequent cadaver injection study would further strengthen our proposed anatomic nomenclature.

## Conflicts of interest

The authors declare no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j. bjane.2021.10.011.

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# Brazilian Journal of ANESTHESIOLOGY 



## LETTER TO THE EDITOR

## Medication adherence in treating non-oncologic chronic pain: a problem to solve?

## Dear Editor

The World Health Organization (WHO) understands adherence to be the behaviors of a patient regarding recommendations or treatment prescribed by healthcare professionals. Nonadherence to long-term treatment in the overall population is approximately $50 \%$. This high rate encourages the investigation of elements involving nonadherence because it interferes with treatment results and prognosis. ${ }^{1}$

In Brazil, Low Adherence to Pharmacological Treatment (LAPT) in non-communicable chronic diseases is $20.2 \%$. $^{2}$ Concerning non-oncological chronic pain, nonadherence varies from $8 \%$ to $53 \%$. ${ }^{1}$

LAPT has been associated with a lack of financial resources; social, cognitive, motivational, and adverse effect behavioral issues; and unique perceptions, beliefs, and expectations about therapeutic efficacy. Moreover, it is a process with intrinsic factors related to the local patient, health team, and health system. ${ }^{3}$

An integrative literature review assessed LAPT-related factors in non-oncological chronic pain based on these assumptions. Two independent researchers searched PubMed in June 2023. The descriptors used to search for articles in the database followed the Health Sciences Descriptors (DeCS) of the Virtual Health Library and the MESH database, established as follows: "chronic pain" [All Fields] AND "medication adherence" [All Fields].

Original articles published between January 2013 and June 2023 in English, Portuguese, or Spanish with titles and abstracts related to adherence to medical treatment of chronic pain were included. The researchers accessed the abstract of each retrieved article to determine whether it met the inclusion criteria. Disagreement between the reviewers were resolved by consensus.

The PubMed search retrieved 96 potentially eligible articles. Twenty-one articles were selected for a complete reading. After applying the inclusion criteria, eight articles were included in the review. These articles addressed medication adherence in the treatment of non-oncological chronic pain. From the selected articles analyzed, eight presented cross-sectional observational, cohort, and
longitudinal quantitative methodologies, and one article had a qualitative methodology.

There are many aspects of nonadherence to treatment by patients. Table 1 presents the principal issues found in the included studies. On the other hand, some elements presented in Table 1 could lead a patient to adhere to their treatment. The possibility of the patient having a choice in treatment could be a positive factor in treatment results and adherence. For example, patients undergoing treatment for migraines with flexible doses of subcutaneous injections of a drug had the option of choosing either monthly or quarterly treatment. Both options are patient friendly, reduce LAPT, and establish an easier-to-follow treatment routine. ${ }^{4}$ Moreover, the level of satisfaction with pain management and treatment adherence can also influence LAPT. For example, patients who reported having access to treatment information showed increased levels of medication acceptance, facilitated pain management, and better interactions with their physician. ${ }^{5}$

We can conclude that, to minimize the LAPT problem, the following measures are necessary: patient education, effective communication between patient and physician,

Table 1 Factors associated with Low Adherence to Pharmacological Treatment (LAPT) in patients with non-oncologic chronic pain.

The relationship between persistent pain and the sense that the disease is worsening ${ }^{8}$
The belief that taking medication will lead to addiction ${ }^{7,11}$
Fear of adverse reactions ${ }^{7-9}$
The reduction of pain intensity leads to adjusting the medication with no medical orientation $7,8,11$
Presence of other comorbidities associated with mental disorders ${ }^{6,7,10}$
Use of polypharmacy due to associated comorbidities ${ }^{10}$
High cost of recommended medical treatments ${ }^{8}$
Low satisfaction with the treatment and health service ${ }^{5,9}$
Routine ${ }^{4}$ and daily working schedule influence the assiduity of treatment with anesthetic blockade ${ }^{5}$
Lack of information about the side effects or planned duration of the treatment when prescribing opioids ${ }^{7}$
Influence of other medical professionals in decision-making regarding reducing or interrupting the prescribed treatment with opioids ${ }^{7}$
psychological intervention based on cognitive behavioral therapy, and minimization of socioeconomic aspects that interfere with treatment. ${ }^{6,7}$

## Conflicts of interest

The authors declare no conflicts of interest.

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# Brazilian Journal of ANESTHESIOLOGY 



LETTER TO THE EDITOR

## Genetic specification of malignant hyperthermia susceptibility is warranted for assessing fatigue, depression, and exercise intolerance

## Dear Editor,

We read with interest the article by de Andrade et al on the prevalence of fatigue, depression, and physical activity in a cohort of 22 patients with Malignant Hyperthermia Susceptibility (MHS) diagnosed by an In Vitro Contracture Test (IVCT), compared with 13 MHS-negative patients and 22 healthy controls. ${ }^{1}$ There were no significant differences between the three groups in terms of fatigue intensity, fatigue associated with specific situations, psychological consequences of fatigue, fatigue response to rest/sleep, depression, number of active/sedentary participants, and the mean time and habitual physical activity characteristics, but physically active MHS patients showed a greater fatigue response to rest/sleep than the sedentary MHS subgroup. ${ }^{1}$ The study is compelling but has limitations that should be discussed.

A limitation of the study is the design. ${ }^{1}$ Patients and controls were assessed using a clinical/demographic questionnaire and scales (fatigue severity scale, Baecke Habitual Physical Exercise Scale (BHPES), and the Beck Depression Inventory (BDI), and were thus based on self-assessment and not on objective findings. ${ }^{1}$ The methods also didn't mention whether patients filled out the forms online or in person, and it is unclear if all patients filled out the forms by themselves, or if caregivers or relatives were allowed to answer and respond to the questions.

Another limitation is the diagnosis of MHS. ${ }^{1}$ Patients were only diagnosed by IVCT, but no genetic testing was performed. ${ }^{1}$ Knowledge of the underlying mutation and the mutated gene is crucial, as different mutations may appear differentially on the scales used. Since MHS can lead to muscle weakness and wasting, cramps, myalgia, hypotonia, fatigue and exercise intolerance, and this is highly dependent on the underlying mutation, it is important to know the causative genetic defect.

Information is also lacking as to why the non-MHS patients underwent IVCT. Have these patients had a history of malignant hyperthermia or malignant hyperthermia-like reaction
during anaesthesia, or were these patients' relatives of MHS patients?

Fatigue depends not only on comorbidities and medications, but also on diet, intake of adrenergic substances (caffeine, theophylline, energy drinks, nicotine), subclinical hypothyroidism, pre-diabetes, renal function, and environmental conditions. Therefore, it is crucial to know the results of routine blood tests at the time of the study (how many had subclinical hypothyroidism, pre-diabetes, electrolyte disturbances, untreated arterial hypertension), and what diet the 22 included patients were on.

We disagree that fatigue is the same as effort (exercise) intolerance. ${ }^{1}$ There are patients with exercise intolerance but no fatigue and vice versa, and also patients with both, fatigue and exercise intolerance.

We also disagree with the statement in the introduction that MHS is an autosomal dominant disorder. ${ }^{1}$ For example, Central Core Disease (CCD) is not only inherited as an autosomal dominant trait but can also follow an autosomal recessive pattern of inheritance. ${ }^{2}$ MHS due to an autosomal recessive trait of inheritance has also been reported in patients with mutations in STAC3. ${ }^{3}$

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. The comparison of MHS patients with non-MHS patients and healthy controls requires homogenous groups with regard to the etiology of MHS, diet, and physical activity, and similar group sizes.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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# Brazilian Journal of ANESTHESIOLOGY 



## LETTER TO THE EDITOR

## Brazilian version of the Heidelberg Peri-Anaesthetic Questionnaire

## Dear Editor,

Quality and safety have historically been measured in anesthesia by analyzing perioperative morbidity and mortality. However, these measures are often associated with factors beyond the control of anesthesiologists. Patient satisfaction and their perception of outcomes have recently become essential to service quality in anesthesia. ${ }^{1}$ Gathering information on the patient's experience from their perspective can assist healthcare professionals in making decisions about various available pharmacological options considering patient preferences, not just the anesthesiologist's view. ${ }^{2}$

The Heidelberg Peri-Anaesthetic Questionnaire (HPAQ) ${ }^{3}$ was developed in Germany to evaluate patient satisfaction in the perianesthetic period. It consists of 38 questions, with responses ranging from 0 (unimportant to me) to 3 (very important to me) on a Likert scale. It assesses satisfaction in five main dimensions: "trust and atmosphere", "fear", "discomfort", "treatment by personnel", and "information and waiting". However, a validated Brazilian version of the HPAQ is still unavailable.

The aim of this letter is to inform that the HPAQ was cross-culturally adapted ${ }^{4}$ to ensure its suitability for the Brazilian Portuguese language and culture. Two translators were enlisted for the initial translation stage: one native German speaker and one bilingual Brazilian with no medical or academic affiliations. Following a synthesis stage, a back translation was carried out by a native German speaker with no medical or academic affiliations who translated the Brazilian Portuguese version back to German. An expert committee assessed the semantic, idiomatic, experimental, and conceptual equivalence of the Brazilian Portuguese version of the HPAQ. The committee comprised two PhD professors
with experience in epidemiological studies using questionnaires, one anesthesiologist, one surgeon, and three medical students. The committee conducted a comparative analysis between the questionnaire's backtranslated and original German versions to identify any discrepancies in the translation process. The committee members discussed the issues and potential solutions were proposed. As a result of this evaluation, a prefinal version of the HPAQ-Br was developed.

This version of the HPAQ-Br was then administered to 10 patients who had undergone general anesthesia in a private plastic surgery clinic in Florianópolis/SC, Brazil. This aimed to identify comprehension problems and other difficulties in understanding the meaning of each item. The participants were selected based on being native Brazilian Portuguese speakers, above 18 years old, and having undergone general anesthesia. The results showed that no further modifications were necessary, indicating the adequacy of the translation and adaptation process. Therefore, a final version of the HPAQ-Br was proposed (Table 1). The successful translation and cross-cultural adaptation of HPAQ to Brazilian Portuguese led to the development of HPAQ-Br.

While the HPAQ has already been translated and validated into Portuguese in the context of Portugal culture, ${ }^{5}$ discrepancies between the original and Brazilian Portuguese translations were identified and resolved by our research committee. Similar linguistic differences were also reported in the Portuguese (Portugal) version. Notably, the translation and transcultural adaptation conducted by Moura et al. ${ }^{5}$ differed from our process as they translated the questionnaire from an English-published version into Portuguese, which may have influenced the results.

Now, it is necessary to determine the psychometric properties of validity and reliability of the Brazilian version proposed. However, the availability of the HPAQ in a Brazilian Portuguese version offers a valuable tool for improving perianesthetic care assessment in Brazil.

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Table 1 Proposed version of The Heidelberg Peri-Anaesthetic Questionnaire in Brazilian Portuguese (HPQ-Br).

|  |  | Concordo totalmente | Concordo um pouco | Discordo um pouco | Discordo totalmente |
| :---: | :---: | :---: | :---: | :---: | :---: |
| As afirmações 1 a 6 a seguir referem-se à discussão de informações anestésicas: |  |  |  |  |  |
|  | O tempo de espera antes da consulta pré-anestésica foi longo. | 3 | 2 | 1 | 0 |
| 2 | O esclarecimento sobre anestesia ocorreu em ambiente agradável (sala). | 3 | 2 | 1 | 0 |
| 3 | O anestesista da consulta pré-anestésica deveria ser mais gentil. | 3 | 2 | 1 | 0 |
| 4 | O anestesista da consulta pré-anestésica pareceu estar com pressa durante a consulta. | 3 | 2 | 1 | 0 |
| 5 | O anestesista da consulta pré-anestésica não deu informações suficientes. | 3 | 2 | 1 | 0 |
| 6 | As informações do anestesista foram claras. | 3 | 2 | 1 | 0 |
| As afirmações 7 a 14 a seguir referem-se ao período desde a consulta pré-anestésica até pouco antes da anestesia: |  |  |  |  |  |
| 7 | 0 medo da anestesia foi significativo. | 3 | 2 | 1 | 0 |
| 8 | O medo da cirurgia foi significativo. | 3 | 2 | 1 | 0 |
| 9 | Eu me senti tranquilo(a) na noite anterior à cirurgia. | 3 | 2 | 1 | 0 |
| 10 | A cirurgia foi adiada para outro dia. | 3 | 2 | 1 | 0 |
| 11 | Antes da cirurgia, senti muito medo. | 3 | 2 | 1 | 0 |
| 12 | No dia, o tempo de espera até o início da cirurgia foi longo. | 3 | 2 | 1 | 0 |
| 13 | A sensação de ser deixado(a) sozinho(a) foi muito angustiante. | 3 | 2 | 1 | 0 |
| 14 | Em geral, a agitação e/ou medo no período antes da anestesia foi significativo. | 3 | 2 | 1 | 0 |
| As afirmações 15 a 20 a seguir referem-se à anestesia: |  |  |  |  |  |
| 15 | A sede foi um problema antes da anestesia. | 3 | 2 | 1 | 0 |
| 16 | Houve sensação de frio ou tremor na sala cirúrgica. | 3 | 2 | 1 | 0 |
| 17 | A dor antes da anestesia foi angustiante. | 3 | 2 | 1 | 0 |
| 18 | A anestesia ocorreu exatamente como explicada pelo anestesista. | 3 | 2 | 1 | 0 |
| 19 | Havia um ambiente agradável na sala cirúrgica. | 3 | 2 | 1 | 0 |
| 20 | A equipe foi cuidadosa e prestativa na anestesia. | 3 | 2 | 1 | 0 |
| As afirmações 21 a 36 a seguir referem-se ao período desde o despertar da anestesia até algumas horas após a anestesia: |  |  |  |  |  |
| 21 | O despertar da anestesia foi agradável. | 3 | 2 | 1 | 0 |
| 22 | Após o despertar da anestesia, houve dor na área da cirurgia. | 3 | 2 | 1 | 0 |
| 23 | Após o despertar da anestesia, houve poucas dores em outros locais (por exemplo, cabeça). | 3 | 2 | 1 | 0 |
| 24 | A dor foi levada a sério pela equipe. | 3 | 2 | 1 | 0 |
| 25 | A dor foi rapidamente aliviada pela equipe. | 3 | 2 | 1 | 0 |
| 26 | Após a anestesia, ocorreram náuseas e vômitos. | 3 | 2 | 1 | 0 |
| 27 | A rouquidão e/ou dor de garganta foi um problema após a anestesia. | 3 | 2 | 1 | 0 |
| 28 | Após a anestesia, houve fraqueza muscular. | 3 | 2 | 1 | 0 |
| 29 | Após a anestesia, houve sede. | 3 | 2 | 1 | 0 |
| 30 | A urgência de urinar foi um problema após a anestesia. | 3 | 2 | 1 | 0 |
| 31 | Após a anestesia, houve sensação de frio ou tremor. | 3 | 2 | 1 | 0 |
| 32 | Após a anestesia, houve dificuldade em respirar. | 3 | 2 | 1 | 0 |
| 33 | Sonolência e/ou dificuldade de concentração após a anestesia foi um problema. | 3 | 2 | 1 | 0 |
| 34 | Logo ao despertar, a equipe foi cuidadosa e prestativa. | 3 | 2 | 1 | 0 |
| 35 | A equipe de anestesia na sala de recuperação ou na unidade de terapia intensiva foi gentil. | 3 | 2 | 1 | 0 |
| 36 | A recuperação após a anestesia ocorreu bem. | 3 | 2 | 1 | 0 |
| Ainda em relação à anestesia: |  |  |  |  |  |
| 37 | Posso confiar na equipe de anestesia. | 3 | 2 | 1 | 0 |
| 38 | Tenho certeza de que o anestesista tomou as melhores decisões para o paciente. | 3 | 2 | 1 | 0 |

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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# Brazilian Journal of ANESTHESIOLOGY 



## CLINICAL IMAGES

# Tension pneumocephalus 

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Pneumocephalus, defined as presence of air or gas within the compartments of the cranial vault, can occur after neurosurgery and is typically benign. In contrast, tension pneumocephalus occurs when the pressure of the intracranial air collection exceeds atmospheric pressure, leading to brain compression. The resulting increase in intracranial pressure can precipitate nausea and vomiting, headaches, focal neurological deficits, seizures, altered mental status, and death. Consequently, tension pneumocephalus is a neurosurgical emergency. ${ }^{1,2}$ The accompanying images demonstrate this rare complication (Fig. 1: Panel A and B) and are from a patient who underwent craniotomy for meningioma resection. Delayed emergence and bilious vomiting prior to extubation prompted computed tomographic imaging revealing extensive pneumocephalus and the classic Mount Fuji sign in the axial section. ${ }^{3}$

Relief of the increased intracranial pressure can be achieved via needle aspiration, redo craniotomy, or drilling of burr holes. Hyperventilation, hypotension, and high airway pressures during mechanical ventilation in such patients can precipitate brain ischemia, infarction and/or herniation. High intrathoracic pressures decrease cerebral venous outflow, further raising intracranial pressure. Hyperventilation decreases cerebral blood flow while hypotension compromises cerebral perfusion pressure. When tension pneumocephalus is suspected, it is best to avoid nitrous oxide during anesthetic maintenance as it can lead to rapid

[^26]

Figure 1 Computed tomographic imaging of the brain in the axial and coronal sections (Panel A and B respectively) demonstrates presence of air (blue star) inside the cranial vault (pneumocephalus) after resection of a pineal meningioma. Possibility of tension pneumocephalus is suggested by the presence of the Mount Fuji radiographic sign in Panel A; the frontal lobes (red triangles) are compressed by the subdural air collection (blue star) with widening of the interhemispheric fissure (gold star), creating a resemblance to the silhouette of Mount Fuji.
expansion of the intracranial gas collection, worsening pneumocephalus severity.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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[^3]:    Abbreviations: BMI, Body Mass Index; CONSORT, Consolidated Standards of Reporting Trials; HR, Heart Rate; LA, Local Anesthesia; LL, Lower Limbs; MAP, Mean Arterial Pressure; NIMAP, Noninvasive Mean Arterial Pressure; PB, Perineal Blocks; PONV, Postoperative Nausea and Vomiting; POUR, Postoperative Urinary Retention; RCT, Randomized Controlled Trial; SA, Ultra-low-dose Spinal Anesthesia; SD, Standard Deviation; $\mathrm{SpO}_{2}$, Peripheral Oxygen Saturation; SPSS, Statistical Package For Social Sciences; VAS, Visual Analog Scale.

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[^4]:    ${ }^{a}$ (Pearson's qui-square).
    ${ }^{\mathrm{b}}$ ( $t$-test for independent samples).
    AS, Ultra-low-dose Spinal Anesthesia; PB, Perineal Blocks; ASA, American Society of Anesthesiologists; SD, Standard Deviation; BMI, Body Mass Index.

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[^6]:    1 - HB adjusted $\alpha$ level

[^7]:    FORT, First Opioid Request Time; TPOC, Total Postoperative Opioid Consumption; IQR, Interquartile range.
    ${ }^{\text {a }}$ Mann-Whitney U test.
    b Hodges-Lehman Estimator were used.

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[^10]:    ${ }^{\text {a }}$ Dose adjustment plus airway maneuvers.
    b Jaw thrust and/or facemask ventilation.
    ${ }^{\text {c }}$ Time required for the patient to reach a score of 1 on the OAA/S after the start of propofol administration.

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[^14]:    MV, minute respiratory volume; RR, minute respiratory rate.
    ${ }^{a}$ Difference between Groups $C$ and $P, p \leq 0.05$

[^15]:    ONSD, optic nerve sheath diameter.

[^16]:    Cdyn, Dynamic lung compliance.
    ${ }^{\text {a }}$ Difference between Groups $C$ and $P, p \leq 0.05$.

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[^18]:    AKI, acute kidney injury; Hb , hemoglobin; ICU, intensive care unit; POD, postoperative date to discharge.
    Data are displayed as median (mean $\pm$ standard deviation).
    ${ }^{a} p$ values indicate comparisons between two groups using Mann-Whitney $U$ test. Values < 0.00625 were considered significant following post-hoc Bonferroni correction.
    ${ }^{b} p$ values indicate comparisons between two groups using the t-test. Values $<0.00625$ were considered significant following post-hoc Bonferroni correction.

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[^21]:    CI, Confidence Interval; FI, Fascia lliaca compartment block; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, Mean Difference; PENG, Pericapsular Nerve Group block.
    ${ }^{\text {a }} 1$ trial was considered to carry a high risk of bias. Downgraded by one level for risk of bias.
    ${ }^{\mathrm{b}}$ The estimated effect is -6.93 . Upgraded by one level for large magnitude of the effect.
    ${ }^{\text {c }}$ Wide confidence interval including null. Downgraded by one level for imprecision.
    d There was high heterogeneity ( $1^{2}=90 \%$ ). Downgraded by one level for inconsistency.

[^22]:    ${ }^{\text {a }}$ The risk in the intervention group (and its $95 \%$ Confidence Interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its $95 \% \mathrm{CI}$ ).
    Cl , Confidence Interval; MD, Mean Difference; RR, Risk Ratio.
    GRADE Working Group grades of evidence.
    High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
    Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
    Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
    Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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