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Anesthesiology and Pain Medicine

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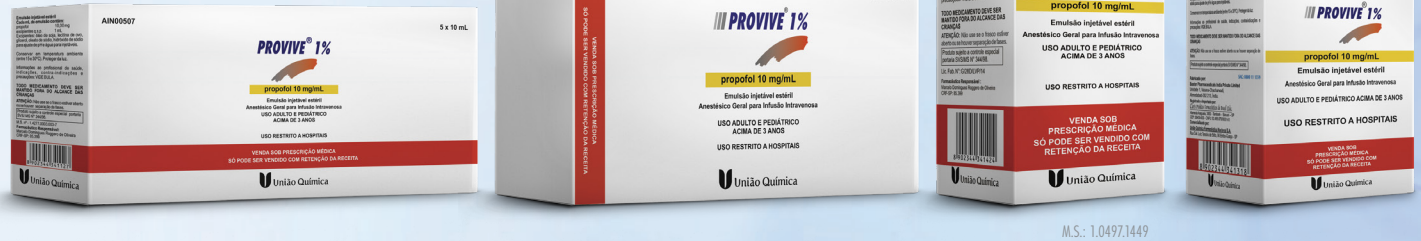

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Anesthesiology and pain medicine



Pain medicine was born in the cradle of Anesthesiology, given pain management has been one of the priorities since the beginning of the specialty. It is not by accident that the International Association for the Study of Pain IASP was created thanks to the determination of John Bonica, an American anesthesiologist.[1] In the United States, the idea of establishing pain management as a specialty emerged as early as 1989, and in 1990 the American Board of Anesthesiologists suggested the creation of the certification in pain to the American Board of Medical Specialties. The request was approved the following year. The first residency program in Pain Management was approved only in 1992. Later, in 2002, it was renamed Pain Medicine.[2]

In Brazil, the creation of residency programs preceded the acknowledgement of Pain Management as area of practice by the Federal Council of Medicine (CFM). One of the first Residency Programs in the area was organized at the Department of Anesthesiology of Faculdade de Medicina de Botucatu, Unesp and its first specialist graduated in 1994. Since its implementation, the Brazilian Society of Anesthesiology (SBA) has participated in the certification process of pain specialists. As of Resolution CFM n° 1.973/2011, another eight specialties can also apply for certification in Pain Management.[3]

Anesthesiologists have currently expanded their practice, formerly restricted to the operating room, to include perioperative medicine. The latter encompasses treatment of acute pain, postoperative and intensive care, in addition to chronic pain medicine, sleep medicine, and palliative care. Anesthesiology began to manage pain as a *continuum*, not limited to the intraoperative period.[4]

Acute pain response means identifying injury to avoid its recurrence as a survival mechanism. Onset and end of acute pain are related to the wound healing process. The more intense the trauma, the stronger is the register that something went wrong.[5] Thus, based on the idea that every stimulus from trauma causes memory, our early traumatic experiences related to loss, separation, frustration and physical injury may be the basis for a complex neuronal network able to express cause-effect inter-relations.[6] Therefore, for every acute trauma-related pain, such as perioperative pain, there is a physiological and emotional component of neuronal stimulation or a mental overload related to an individual's past history.

In this scenario, anxious and depressive patients have a lower threshold for response to tissue injury. Conversely, the way of dealing with disease may be more a factor related to the higher intensity of acute pain, than to mental disorder itself.[7]

Based on this assumption and on the higher occurrence of perioperative depression in the obese, the study of Tapar et al published in the current issue analyzed how the tendency toward catastrophizing can influence pain intensity and analgesic consumption during the postoperative period of laparoscopic surgery for obesity. The study included 72 participants without anxiety, depression, chronic pain or contraindication for morphine. The authors concluded that morphine consumption in the first 24 hours postoperatively had a strong negative correlation with pain tolerance scores; strong and positive correlation with high scores in a pain catastrophizing scale; moderate and positive correlation with anxiety and depression scores; and strong and positive correlation with pain intensity in the period observed. The article underlines what has already been reported in the literature and indicates obesity as a risk factor for depression, failure in dealing with suffering, catastrophizing propensity, and high scores for anxiety.[7]

Coincidentally, there is a high prevalence of mental disorders, such as anxiety or depression, in chronic pain.[8] Epidemiological studies have emphasized that there is a high prevalence of chronic pain in joints, and in lumbar and cervical regions.[9] Other factors can be associated with musculoskeletal pain in workers, mainly sedentarism, physical inactivity, obesity, and female sex. Higher occurrence of musculoskeletal pain in women may be due to lower muscle mass, greater hormone variation, double duty, lower maximum tolerance to mechanical stimulus, and lower response to pain pressure threshold (PPT). A study by Cordeiro et al, available in the current issue, showed that unlike in men, physical activity in women does not interfere as much in the

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maximum tolerance to mechanical stress as it does in PPT. This was demonstrated in an elegant study that showed that individuals who exercise a lot, mainly men, have higher PPT.[10]

In addition to constitutional factors inherent to each individual, early records of pain from birth may not be accessible to conscious recollection, although, they are codified in one's memory and promote abnormal behavioral patterns and modified sensorial processing in the future, possibly throughout an individual's lifetime. Some authors verified that animals exposed to repeated pain stimuli during the neonatal period, when adults, showed more anxiety and defensive behavior, associated with increased pain transmission.[11] An ill-adapted response to pain is observed in catastrophizing patients. Often, catastrophizing is regarded as a response within the anxiety and depression scenario, and it is characterized by irrational negative anticipation of future health events.[12]

The pediatric version of the pain catastrophizing scale (PCS-C) was validated in Brazil by Schneider et al and is published in the current issue. The validation showed effective linguistic translation and cultural adaptation. The tool emphasizes that we should study the impact of tissue trauma since early age, since chronic pain in children and adolescents has a prevalence of 20 to 30%, and leads to school absenteeism, anxiety, depression, and catastrophizing thoughts throughout life. High catastrophizing scores are associated with emotional suffering, physical inability, and high pain scores, and should be diagnosed throughout chronic pain management.[13]

It is important to remember that chronic pain management, mainly for adolescents, should follow a biopsychosocial model, with adequate assessment, mensuration, and diagnosis of symptoms, avoiding disastrous consequences in adulthood. Adequate multidisciplinary pain treatment for children and adolescents, with well-established pharmacological and non-pharmacological approaches have an effective positive impact on consumption of health services and reduction in operational costs, as it is shown in the review conducted by Silva et al published in the current issue.[14]

Regional blocks have become increasingly important in acute pain clinical practice. They bring on many benefits such as effective control of postoperative pain reducing systemic opioid consumption, and consequently promoting fewer adverse effects. However, there are risks that should be considered. In the current issue, Campos et al analyze the complications related to regional blocks in a sample of over 10,000 patients followed up by a tertiary hospital acute pain service. Roughly, 10% of the sample had some form of block-associated adverse effect, more frequent when neuraxis blocks were employed.[15]

As a multimodal analgesia component, regional techniques optimize postoperative acute pain control, and provide major advantages, such as shorter hospital length of stay, fewer pain-related readmissions, faster progression to post-anesthesia recovery phase II, higher compliance to physical therapy rehabilitation, and higher satisfaction scores.[16] Regional anesthesia techniques contribute to fewer opioid-associated adverse effects, and possibly reduce the risk of late postoperative opioid abuse, a contributing factor to the so-called "opioid crisis".[17]

Also in the current issue, Jowkar et al studied patients submitted to lumbar spine surgery and recorded an over 50% reduction in postoperative morphine consumption associated with continuous wound infiltration with local anesthetic via a catheter inserted into the surgical wound. In addition to classical neuraxis analgesia techniques, interfascial blocks have recently gained acceptance, and the increased availability and use of ultrasonography intraoperatively have enabled the identification of several anatomical sites for single shot or continuous local anesthetic injections.[18]

Suboptimal management of post-arthroplasty lower limb pain may result in reduced range of joint movement postoperatively, longer hospital length of stay, higher risk of thromboembolism, and may affect long-term joint function. Regional anesthesia can improve passive knee flexion, even months after surgery.[19] The continuous adductor canal block was superior to continuous femoral block, in a prospective randomized, controlled study with 60 participants submitted to knee arthroplasty, published by Sinha et al in the current issue.[20] Indeed, continuous or bolus adductor canal block has been recently considered as level of evidence 1a in this type of surgery.[21]

Reduction in opioid consumption and satisfactory analgesia in thoracic and abdominal surgeries, mastectomies, rib and vertebral body fractures have also been reported with the use of erector spinae plane block (ESPB) and serratus plane block (SPB).[22] They are also used as the regional anesthesia approach to treat chronic neuropathic thorax pain.[23] Two studies discuss these blocks in the current issue.

The first, by Arora et al, included 40 participants submitted to breast surgery and compared the traditional thoracic paravertebral block approach to SPB. The findings revealed that SPB resulted in longer time between surgery completion and the first rescue analgesia dose administered, lower pain scores, and lower nausea and vomiting incidence.[24] In the second study with 54 participants submitted to cardiac surgery, Silva et al assessed the efficacy of ESPB using bilateral single-shots of 0.5% ropivacaine (20 mL on each side). All individuals received multimodal anesthesia. Patients receiving ESPB showed lower morphine consumption, and lower pain scores only in the first 6 postoperative hours.[25]

In the past decade, multiple interfascial blocks techniques were introduced for acute pain management and their role has reached scientific soundness. Küpeli et al reported, in the current issue, two cases of shoulder surgery in which the pericapsular nerve group block (PENG block) was used. The PENG block was safe anesthesia and analgesia-wise, but alone may not be a sufficient anesthetic technique. There are still many questions and limitations related to PENG block regarding its mechanism of action, analgesic efficacy, pharmacokinetics, pharmacodynamics, and adverse effects.[26]

Despite increasing acceptance of regional analgesia techniques, opioids still play an essential role in acute postoperative pain management. However, judicious use is warranted by prescribing lower doses and for the shortest time possible.[27] The current issue brings three interesting studies assessing multimodal techniques of systemic analgesia.

Muniz da Silva et al compared three analgesia strategies for laparoscopic bariatric surgeries. Two techniques

employed sufentanil at anesthesia induction, followed by continuous infusion of remifentanil (P1) or dexmedetomidine (P2). Morphine was used for postoperative analgesia in the P1 and P2 techniques. The third technique (P3) used remifentanil during induction and maintenance, plus single doses of methadone, lidocaine, dexmedetomidine and magnesium — without administering any other opioid intraoperatively. The authors concluded that higher doses of sufentanil (P1) intraoperatively result in higher requirement of rescue analgesics and more intense pain when compared to multimodal technique that includes methadone. The postoperative incidence of nausea and vomiting was lower for P3.[28]

Savaji et al employed a standardized anesthetic technique with fentanyl/ nitrous oxide/isoflurane for robotic abdominal hysterectomy, and compared lidocaine, dexmedetomidine, lidocaine/dexmedetomidine to placebo. All interventions used loading and maintenance doses. Postoperative (PO) analgesia was performed using patient-controlled analgesia with fentanyl for all participants of the study. The lidocaine/dexmedetomidine combination resulted in lower PO pain scores and fentanyl consumption, in addition to enhanced quality recovery.[29]

In a narrative review including six studies, of which only two were high-quality, Chinchilla and Moyano analyzed the efficacy of opioids, gabapentinoids, ketamine, and lidocaine to control post-procedure acute pain for burned patients. The evidence of efficacy found was limited due to the low number of studies included, albeit favorable to fentanyl, nalbuphine and ketamine, and unfavorable to lidocaine and gabapentinoids.[30]

Even old and simple techniques, such as intercostal nerve blocks (INB), may be clinically valuable when appropriately assessed and promoted. Thus, Xiao et al, in a study also available in the current issue, revealed that INB provided better analgesia for video thoracoscopes when performed preemptively.[31] Better understanding of the mechanism of action, distribution, systemic absorption, interaction with multimodal analgesia, and benefits in comparison to other techniques should be continuously encouraged.

By providing readers with quality scientific information, the current issue aims to offer important data regarding pain management in several scenarios, and by using different tools and techniques.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Analgesic effect of continuous adductor canal block versus continuous femoral nerve block for knee arthroscopic surgery: a randomized trial

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KEYWORDS
Nerve block;
Femoral nerve;
Analgesia;
Arthroscopy;
Anterior cruciate ligament reconstruction

Abstract
Background and objectives: Anterior cruciate ligament reconstruction (ACLR) is one of the most frequently performed orthopedic procedures. The ability to perform ACLR on an outpatient basis is largely dependent on an effective analgesic regimen. The aim of the study was to compare the analgesic effect between continuous adductor canal block (cACB) and femoral nerve block (cFNB) during arthroscopy guided ACLR.
Method: In this prospective, randomized, controlled clinical trial, 60 ASA I/II patients for arthroscopic ACLR were recruited. Patients in Group I received cACB and those in Group II cFNB. A bolus dose of 20 cc 0.5% levobupivacaine followed by 0.125% 5 $mL.h^{-1}$ was started for 24 hours. Rescue analgesia in the form of paracetamol 1 g intravenous (IV) was given. Parameters assessed were time of first rescue analgesia, total analgesic requirement in 24 hours, and painless range of motion of the knee (15 degrees of flexion to further painless flexion).
Results: The time-to-first postoperative analgesic request (hours) was earlier in Group II (14.40 ± 4.32) than Group I (16.90 ± 3.37) and this difference was statistically significant ($p < 0.05$). The cumulative 24-h analgesic consumption (paracetamol in g) was 0.70 ± 0.47 in Group I and 1.70 ± 0.65 in Group II ($p < 0.001$). The painless range of motion (degree) was 55.67 ± 10.40 in Group I and 40.00 ± 11.37 in Group II ($p < 0.001$).
Conclusion: The findings of this study suggest that continuous adductor canal block provides superior analgesia in patients undergoing arthroscopic ACLR when compared to continuous femoral nerve block.
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Introduction

Anterior cruciate ligament reconstruction (ACLR) is a common orthopedic procedure.[1] ACLR reconstruction done on outpatient basis requires effective analgesic regimen with minimal adverse effects and effective mobilization.[2] Immediate weight-bearing postoperatively has shown to decrease pain.[3] Although the use of peripheral nerve blocks for ACLR has increased in recent years, consensus around the optimal pain management strategy after ACLR is lacking.[4] The advantage of continuous motor-sparing peripheral nerve blocks include decrease in ''rebound pain'' and early discomfort.[5,6] Continuous femoral nerve block (cFNB) is commonly used for postoperative analgesia. It may result in early and potentially prolonged quadriceps muscle weakness,[7,8] leading to concerns about early mobilization and risk of postoperative falls.[9,10] Continuous adductor canal block (cACB) has emerged as an alternative to cFNB, because it produces a sensory nerve block of the saphenous nerve. It provides comparable analgesia to cFNB without loss of quadriceps muscle strength.[11] This might be particularly useful in outpatient ACLR reconstruction which requires short stay and immediate mobilization.[10,12]

Our hypothesis was that cACB would result in improved analgesia for knee arthroscopic surgeries, without any increase in adverse effects. The primary outcome was time of first analgesic requirement. Secondary outcomes included 24-hour analgesic consumption and painless range of motion of the knee joint (15 degrees of flexion to further painless flexion).

Methods

This prospective, randomized, double-blind, controlled clinical trial was conducted from September 2017 to January 2020. This was done after clearance from the institutional ethical committee and registration in Clinical Trials Registry-India (CTRI/2017/08/009552).

Inclusion criteria

Sixty (60) American Society of Anesthesiologists (ASA) physical status I/II patients, between the age group of 15 to 60 years scheduled for knee arthroscopic procedures (anterior cruciate ligament repair) were recruited.

Exclusion criteria

Exclusion criteria included patients having coagulopathy, infection at puncture site, patients on chronic analgesic therapy, polytrauma patients, and those with fixed deformities of the knee joint hampering evaluation. Patients who refused to undergo surgery under general anesthesia were also excluded from the study.

Assessment and execution

Written informed consent was obtained from all subjects. Patients of Group I were administered continuous adductor canal block (cACB) while those in Group II were administered continuous femoral nerve block (cFNB). The patients were examined on the day before surgery and were familiarized with a standard visual analogue scale (VAS) for pain (0 = no pain, 10 = worst pain imaginable). Premedication in the form of oral alprazolam 0.5 mg was given at bedtime on the day before surgery. On arrival in the operating room, standard monitors like electrocardiography, pulse oximeter, and noninvasive blood pressure were connected. An IV line was secured and infusion of lactated Ringer's solution started as maintenance. General anesthesia was administered in a standardized manner (propofol 2 $mg.kg^{-1}$, fentanyl 2 $\mu g.kg^{-1}$, vecuronium 0.08 $mg.kg^{-1}$) intravenously and endotracheal intubation done. Anaesthesia was maintained with air in oxygen and isoflurane (MAC = 1). At the end of the surgery, the patients received ultrasound (US) guided adductor canal block or femoral nerve block with catheter insertion.

Intervention

(1) **Continuous Adductor Canal Block:** After sterile preparation and draping, at the midthigh level, adductor canal was visualized using a high-frequency linear array transducer (6 to 13 MHz; SonoSite M-Turbo). The transducer was placed transverse to the longitudinal axis of the extremity to identify the adductor canal underneath the sartorius muscle. The femoral artery was first identified as visible pulsations, with the vein just inferior and the saphenous nerve just lateral to the artery (Fig. 1). From the lateral side of the transducer a 10-cm, 18G Tuohy needle (Braun Medical, Melsungen, Germany) was inserted in plane, through the Sartorius muscle. With the tip of the Tuohy needle placed just lateral to the artery and the saphenous nerve, a bolus dose of 20 cc 0.5% levobupivacaine was injected to expand the adductor canal. A 20G catheter was inserted 4 cm through the cannula. To obtain the correct position of the catheter tip, the catheter was slowly retracted during injection of bolus dose under US guidance, until an expansion between the fascia and the vessels could be visualized followed by 0.125% levobupivacaine 5 $mL.h^{-1}$ was started.

(2) **Continuous Femoral Nerve Block:** After sterile preparation and draping, a high-frequency linear array transducer (6 to 13 MHz; SonoSite M-Turbo) probe was placed parallel and slightly caudal to the inguinal crease and adjusted as necessary to visualize the femoral nerve in short axis. The femoral artery, vein, and iliopsoas muscle were identified (Fig. 1). The femoral nerve was sought within a triangular hyperechoic region, deep to the fascia iliaca, lateral to the femoral artery, and superficial to the iliopsoas muscle. The FNB was performed using a 10-cm, 18G Tuohy needle (Braun Medical, Melsungen, Germany) which was inserted in plane with the ultrasound probe and advanced a lateral-to-medial approach until the needle tip was adjacent to the femoral nerve. A bolus dose of 20 cc 0.5% levobupivacaine was injected to expand the triangular hyperechoic region deep to the fascia iliaca. A 20G catheter was then inserted 4 cm through the cannula. To obtain the correct position of the catheter tip, the catheter was slowly

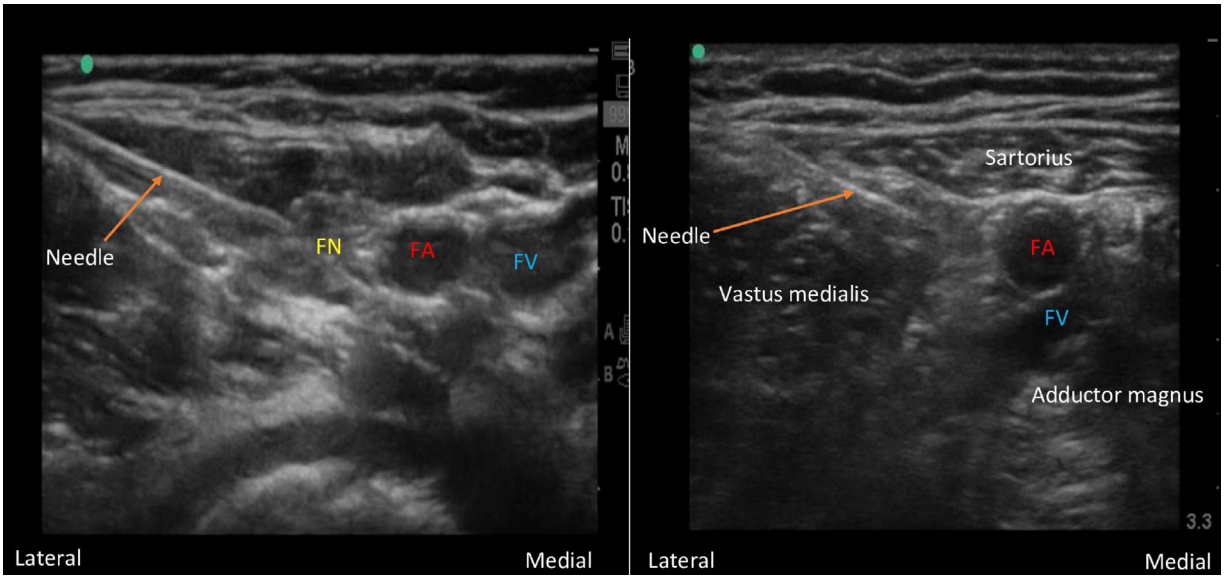

Figure 1 In-plane approach of femoral nerve block and Adductor canal block. FN, femoral nerve; FA, femoral artery; FV, femoral vein.

retracted during injection of bolus dose under US guidance, until an expansion between the fascia and the vessels could be visualized followed by 0.125% levobupivacaine 5 mL.h^{-1} was started. The femoral catheter was tunneled subcutaneously just below and parallel to the inguinal crease. A clear sterile dressing was placed over the catheter insertion site and femoral catheter.

In both groups patients were given a loading dose of 20 cc injection levobupivacaine 0.5% followed by 0.125% levobupivacaine 5 mL.h^{-1} was started for 24 hours. Pain was assessed hourly (VAS score) till 24 hours. Rescue analgesia in the form of paracetamol 1 g IV was administered as per requirement. Parameters like time of first analgesic requirement, total analgesic requirement in the first 24 hours, painless range of motion of the knee (15 degrees of flexion to further painless flexion) were assessed in both groups. Any adverse effects like inadvertent vascular puncture, hematoma, or adverse effect of systemic local anesthetic toxicity like seizure, arrhythmia and persistent paresthesia were also noted.

Randomization, blinding method, and sample size

Randomization: Computer-generated random numbers allocated the patients into two groups of 30 patients. The random allocation sequence was concealed in opaque, sealed envelopes until a group was assigned. **Blinding:** Anesthesiologists experienced in ultrasound-guided nerve blocks performed all the interventions. They subsequently refrained from any further contact with the patient or the assessor. All the postoperative assessments were made by on floor pain nurses who were unaware of the group assigned.

The sample size was calculated on the basis of our preliminary results on 6 patients, the timing of first rescue analgesia in femoral catheter patients was 8.64 ± 1.78 hours. Anticipating a 20% increase in timing of first requirement of rescue analgesia with adductor canal block, alpha error of 5% and power of 90, we calculated a sample size of 22 in each group. To overcome the dropout rate, we increased the sample size further to 30 in each group.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM, Armonk, New York, USA). Data distributions were initially evaluated for normality using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. For normally distributed data, Student's *t*-test was used to compare the differences between two independent groups. Otherwise, Mann-Whitney U test was used. *P*-values below 0.05 were taken to signify statistical significance.

Results

We assessed 64 patients for eligibility, of which 4 did not meet the inclusion criteria (two patients refused general anesthesia while the other two peripheral nerve catheter insertion). Fig. 2 depicts the CONSORT flow diagram of patient progress through the study. All the patients enrolled for the study (cACB group: n = 30; cFNB group: n = 30) completed the study. Data was complete for the primary outcomes assessed; only minimal secondary outcome data was missing.

Patient demographics: Enrolled patients had similar demographic characteristics, and no clinically important differences existed between the study groups (Table 1). Block success was confirmed in all study participants.

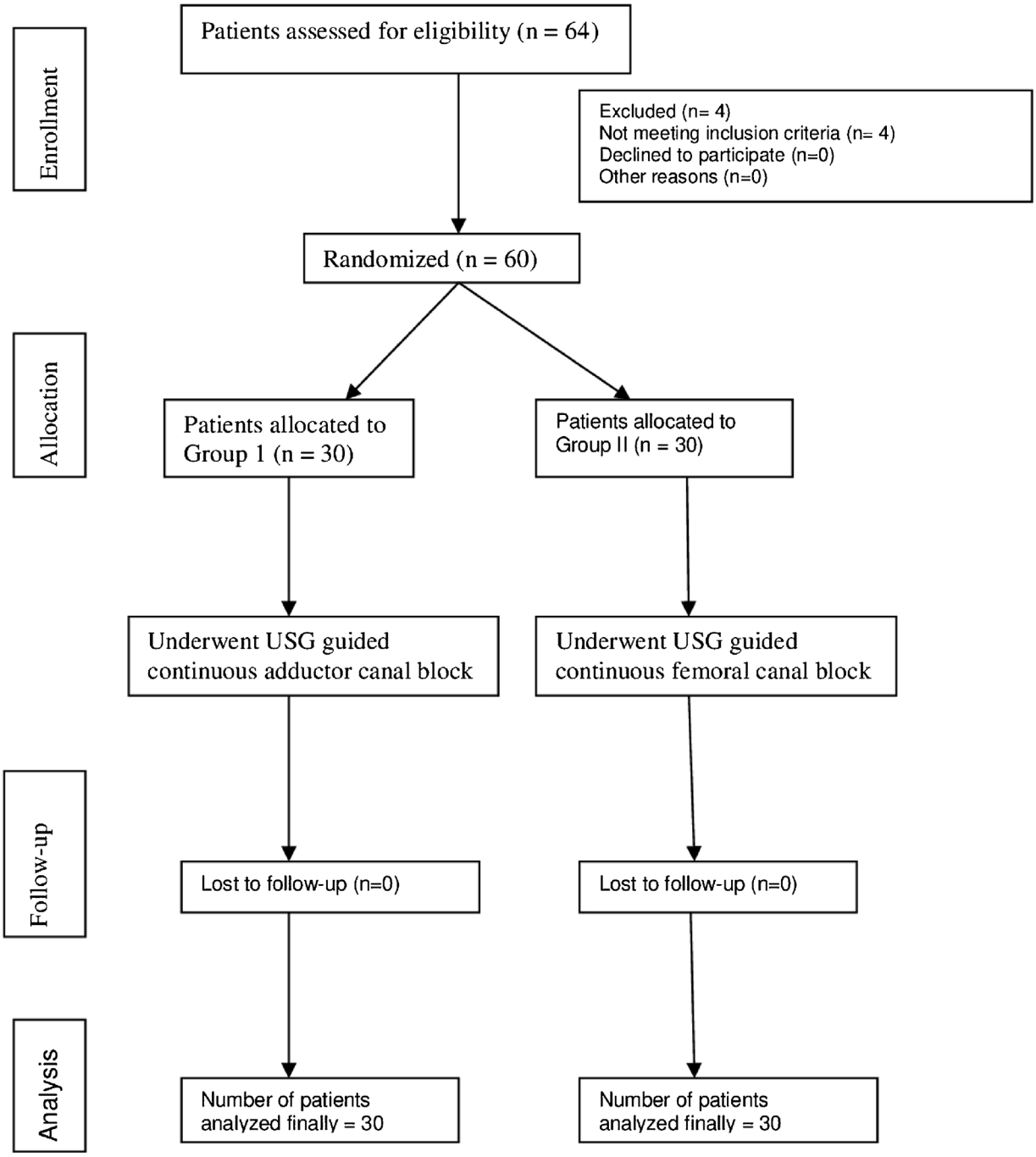

Figure 2 Consort flow chart.

Table 1 Demographic parameters.

Variables	Group I		Group II		*p*-value
	Mean	SD	Mean	SD	
Age (years)[a]	29.43	4.30	28.93	4.19	0.65
Weight (kg)[a]	60.07	7.80	59.63	6.44	0.81
Duration of surgery (min)[a]	72.13	6.69	72.30	7.54	0.92

SD, standard deviation.
[a] Student's t-test.

Table 2 Analgesic requirement, total analgesic consumption, and range of motion.

Variables	Group I		Group II		*p*-value
	Mean	SD	Mean	SD	
Total analgesic (paracetamol) consumption (g)[a]	0.70	0.47	1.70	0.65	0.0001[b]
Time of first analgesic required (h)[a]	16.90	3.37	14.40	4.32	0.0153
Painless range of motion (>15º flextion)[a]	55.67	10.40	40.00	11.37	0.0001[b]

SD, standard deviation.
[a] Unpaired t-test.
[b] *p*-value highly significant.

Primary outcomes

The time-to-first postoperative analgesic request (hours) was earlier in Group II (14.40 ± 4.32) than Group I (16.90 ± 3.37) and this difference was statistically significant ($p < 0.05$) (Table 2).

Secondary outcomes

The cumulative 24-hour analgesic (paracetamol) consumption (g) in the study groups was 0.70 ± 0.47 in Group I and 1.70 ± 0.65 in Group II (Table 2). The difference between two groups was highly significant ($p < 0.001$). Consequently, cACB was found superior to cFNB in cumulative 24-hour postoperative analgesic consumption after ACLR.

Pain (rest) severity VAS scores for the two groups during the first 24 hours postoperatively were plotted over time (Fig. 3). The difference in VAS between both groups was insignificant for the most of the time periods ($p > 0.05$). Consequently, cACB was found to be similar to cFNB in postoperative rest pain severity scores during the first 24 hours after ACLR. The painless range of motion (degree) was 55.67 ± 10.40 in Group I and 40.00 ± 11.37 in Group II (Table 2). The difference between the two groups was highly significant ($p < 0.001$). These findings suggest that cACB provides superior analgesia up to 24 hours postoperatively and preserves quadriceps muscle strength when compared with cFNB in patients undergoing ACLR. There was no inadvertent vascular puncture or adverse effect of systemic local anesthetic toxicity in either group.

Discussion

This study demonstrates that cACB is a better alternative to cFNB in patients undergoing ACLR, as it provides better postoperative analgesia cFNB that is as effective as that of cFNB.

Knee arthroscopy is a diagnostic and therapeutic approach for various knee pathologies.[13] The knee joint is supplied by the femoral, sciatic, and obturator nerves.[14] Different block combinations of these nerves have been used for knee arthroscopy.[15] Peripheral nerve block improves the recovery profile and allows early discharge.[15] The femoral nerve innervates the majority of the joint and the skin at the medial portal site.[14] Hence, its successful block is important for painless knee surgery. The sciatic nerve supplies both the knee joint (via six articular branches) and the skin at the lateral portal site (via the lateral sural cutaneous nerve).[14] Though blockade of all the three nerves is required for adequate analgesia, it might not be feasible.

In our study, the analgesic consumption with cACB was less than cFNB (0.70 ± 0.47 vs. 1.70 ± 0.65) 24 hours postoperatively. The range of motion produced in cACB group was more compared with FNB, and this difference was statistically significant. This might be due to the spread of a large amount of local anesthetics into the popliteal fossa, blocking the popliteal nerve plexus which contributes to afferent knee-pain conduction in cACB. Genicular branches from the posterior obturator and the tibial nerves, innervating the intra-articular and posterior knee region, mainly form popliteal nerve plexus.

In contrast to earlier work,[16–19] our findings favor the cACB in the setting of ACLR. In the first study, Espelund et al.[16] found no analgesic benefit when ACB was compared to placebo. The study was designed to detect change in pain score (50%) at a single time point: 2 hours, with the patient in a standing posture. The study was not powered enough to detect difference in opioids consumption and resting pain scores. In another study, El Ahl[17] compared single shot ACB to FNB and observed pain scores up to 12 hours postoperatively. He concluded that ACB provides inferior analgesia based on differences in pain scores and analgesic consumption. The time interval studied by them was 12 to 24 hours and possibly the block would have worn out by that time. In another study ACB was found to be similar to placebo for rest pain during the first 90 minutes after ACL reconstruction.[18]

Abdallah et al.[19] compared ACB with FNB and suggested that ACB preserves quadriceps strength and provides noninferior postoperative analgesia for outpatients undergoing anterior cruciate ligament reconstruction. In our study, there was no difference between the groups in mobilization ability 24 hours after surgery.

Gao et al.[20] performed a meta-analysis of 7 randomized controlled trials comparing cACB to cFNB after total knee arthroplasty and found no difference in early postoperative pain scores or opioid use. The possible reason for similar analgesic effect between the groups is that most of the nerves in adductor canal are sensory (medial femoral cutaneous nerve, articular branches from the obturator nerve, as well as the medial retinacular nerve) dominating knee joints in addition to saphenous nerve. These nerves innervate the medial, lateral, and anterior aspects of the knee.[21]

Patel et al.[22] compared FNB vs ACB in patients undergoing ACLR and found no differences in postoperative narcotic requirements on days 1 to 4. Holland et al.[23] found no difference in analgesic effect between two groups with similar

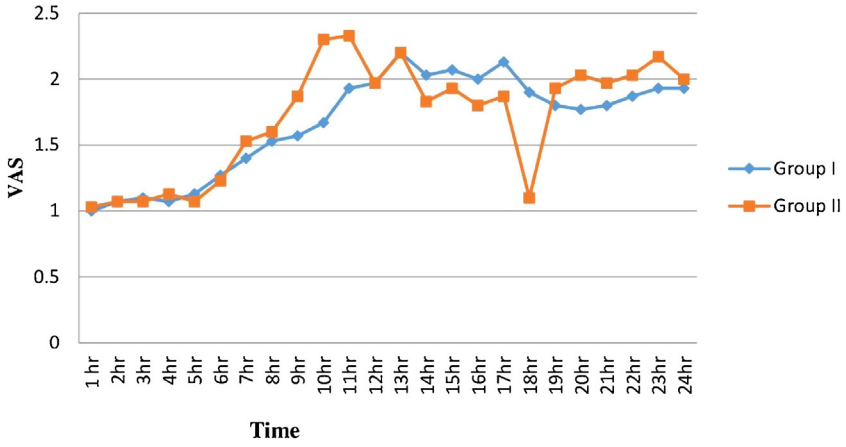

Figure 3 Trend of VAS scores over time.

opioid consumption and satisfaction scores. They speculated that the possible mechanism would be blockade of sensory nerve supply to knee joint in the adductor canal. Thus, cACB seemed to provide similar pain relief, along with early rehabilitation exercise when compared with femoral nerve block. But in our study, the postoperative analgesia was superior with cACB. This could be due to spread of the local anesthetic into popliteal fossa.

Limitations

The limitations of this study could be limited sample size, the anesthesiologist performing the blocks were not blinded to treatment, although they refrained from further contact with the patient. We did not assess drug spread to popliteal fossa in cACB group (Group I).

Conclusion

Study findings suggest that continuous adductor canal block (cACB) provide superior analgesic modality to continuous femoral nerve block (cFNB) in patients undergoing anterior cruciate ligament reconstruction.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparison of three intraoperative analgesic strategies in laparoscopic bariatric surgery: a retrospective study of immediate postoperative outcomes

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Abstract
Introduction and objectives: Multimodal Analgesia (MMA) has shown promising results in postoperative outcomes across a broad spectrum of surgeries, including bariatric surgery. We compared the analgesic effect immediately after Laparoscopic Bariatric Surgery (LBS) of the combined effect of MMA and methadone against two techniques that were based mainly on the use of high-potency medium-acting opioids.
Methods: Two hundred seventy-one patients were retrospectively reviewed. The primary outcome was postoperative pain score > 3/10 measured by the Verbal Numeric Scale (VNS) during the Postanesthetic Care Unit (PACU) stay. The three protocols of intraoperative analgesia were: (P1) sufentanil at anesthetic induction followed by remifentanil infusion; (P2) sufentanil at induction followed by dexmedetomidine infusion; and (P3) remifentanil at induction followed by MMA including dexmedetomidine, magnesium, lidocaine, and methadone. Only P1 and P2 patients received morphine toward the end of surgery. Poisson regression was used to adjust confounding factors and calculate Prevalence Ratio (PR).
Results: Postoperative VNS > 3 was recorded in 135 (49.81%) patients, of which 93 (68.89%) were subjected to P1, 25 (18.56%) to P2, and 17 (12.59%) to P3. In the final adjusted model, both anesthetic techniques (P3) (PR = 0.10; 95% CI [0.03–0.28]), and (P2) (PR = 0.42%; 95% CI [0.20–0.90]) were associated with lower occurrence of VNS > 3, whereas age range 20–29 was associated to higher occurrence of VNS > 3 (PR = 3.21; 95% CI [1.22–8.44]) in PACU. Postoperative Nausea and Vomiting (PONV) was distributed as follows: (P1) 20.3%, (P2) 31.25% and (P3) 6.77%; (P3 < P1, P2; $p < 0.05$). Intraoperative hypotension occurred more often in P3 (39%) compared to P2 (20.31%) and P1 (17.46%) ($p < 0.05$).

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Conclusion: MMA + methadone was associated with higher incidence of intraoperative hypotension and lower incidence of moderate/severe pain in PACU after LBS.
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Introduction

One of the challenges of general anesthesia is to allow smooth emergence at the end of surgery with relative comfort. Inadequate analgesia in the Postanesthetic Care Unit (PACU) is common[1] and negatively affects hemodynamics, respiration, metabolism, delayed discharges from PACU, and creates dissatisfaction. Poor pain control after emergence from anesthesia negatively impact postoperative outcomes.[2] Obesity may be associated with increased pain perception after surgery and increased risk of developing chronic pain.[3] The additional presence of obstructive sleep apnea, restrictive lung disease, coronary artery disease, metabolic syndrome, etc. make postoperative analgesia particularly crucial and challenging in obese patients.[4] Medium-acting opioids such as morphine and hydromorphone are commonly used during and after surgery to mitigate moderate-to-severe postoperative pain while striving to avoid obstructive sleep apnea and excessive respiratory depression.[4] Perioperative Multimodal Analgesia (MMA) combines medications that act synergistically at different sites and pathways with the ultimate goal of achieving pain relief while minimizing side effects. Under the umbrella term of MMA, practices vary widely.[5] Most strive to maintain consistent superior analgesia without large breakthroughs and reduce dependency on the use of medium-acting opioids such as morphine for analgesia.[5]

Methadone is a strong opioid μ-receptor agonist, N-Methyl-Aspartate (NMDA) receptor antagonist, and serotonin and noradrenaline reuptake inhibitor in the central nervous system. It has a long elimination half-life of 24–36 hours.[6] A recent meta-analysis of Randomized Controlled Trials (RCTs) showed that intraoperative methadone results in reduced pain and reduced morphine (equivalent) requirements in PACU and for 2–3 days postoperative across a spectrum of surgeries.[7] Machado et al. compared intraoperative methadone vs. fentanyl in a RCT involving patients undergoing open bariatric surgery and found that the methadone group had less postoperative pain and less morphine requirements.[8]

The recognition of the advantages of MMA and methadone prompted our group to incorporate them in January 2019 into our enhanced recovery protocol for laparoscopic bariatric surgery. Hence, the objective of the present investigation was to retrospectively review immediate postoperative outcomes (namely pain scores, nausea/vomiting, and occurrence of hypoxemia) as well as incidence of intraoperative hypo/hypertension in patients undergoing laparoscopic bariatric surgery before (up to December 2018) and after (January–December 2019) such protocol had been observed.

Methods

Institutional ethics approval (nº 3.664.935) was obtained to conduct this review at a tertiary hospital in Sao Paulo, Brazil. Patients undergoing laparoscopic bariatric surgery (Roux-en-Y or sleeve gastroplasty) from January 2014 to December 2019 were reviewed. Primary outcome was pain > 3/10 assessed by the Verbal Numeric Scale (VNS) at any time in PACU.

Patients included in the study were registered in a hospital database. Exclusion criteria were open bariatric surgery, chronic opioid use, ASA (American Society of Anesthesiologists) physical status ≥ IV, reoperation, allergy to any medication used in the study, drug addiction, combined surgical procedures, general anesthesia combined with neuraxial blockade, administration of other analgesic adjuvants not included in the protocol in force at the time, and other protocol violations.

During the study period, 1447 bariatric surgeries were performed, of which 271 were eligible (Fig. 1). During the study period, three standardized intraoperative protocols related to opioids and opioid-adjuncts/coanalgesics were observed:

P1: Protocol (sufentanil-remifentanil-morphine for analgesia) in force for period Jan 2014–Aug 2017. Sufentanil 1.0 $\mu g.kg^{-1}$ of Corrected Body Weight (CBW) at anesthetic induction followed by continuous infusion of remifentanil (0.1–0.3 $\mu g.kg^{-1}.min^{-1}$). Twenty minutes prior to surgical completion, patients received ondansetron 0.1 $mg.kg^{-1}$ (max. 8 mg) and morphine 100 $\mu g.kg^{-1}$.

P2: Protocol (sufentanil-dexmedetomidine-morphine for analgesia) in force for the period Sept 2017–Dec 2018. Sufentanil 0.5–07 $\mu g.kg^{-1}$ CBW at anesthetic induction followed by dexmedetomidine (initial bolus of 1 $\mu g.kg^{-1}$ over 10 minutes, followed by maintenance of 0.4–0.7 $\mu g.kg^{-1}.h^{-1}$). Twenty minutes prior to surgical completion, patients received morphine 100 $\mu g.kg^{-1}$. The antiemetic palonosetron 0.075 mg was administered upon anesthetic induction.

P3: Protocol (MMA incorporating methadone) in force for period Jan–Dec 2019. Target-controlled infusion of remifentanil (initial bolus of 4 $ng.mL^{-1}$ over 5 minutes at anesthetic induction, followed by maintenance with 2–5 $ng.mL^{-1}$), methadone 0.2 $mg.kg^{-1}$ (real body weight) up to 20 mg, lidocaine 2 $mg.kg^{-1}$, dexmedetomidine 0.5 $\mu g.kg^{-1}$ single dose over 1 minute, and magnesium sulphate 40 $mg.kg^{-1}$ after loss of consciousness. Twenty minutes prior to surgical completion, patients received ondansetron 0.1 $mg.kg^{-1}$ (max. 8 mg). No sufentanil or morphine was administered intraoperatively.

In all patients, anesthesia was induced with propofol and rocuronium and maintained with sevoflurane to keep a Bispectral Index (BIS) of 40–60. Prior to surgical incision, all

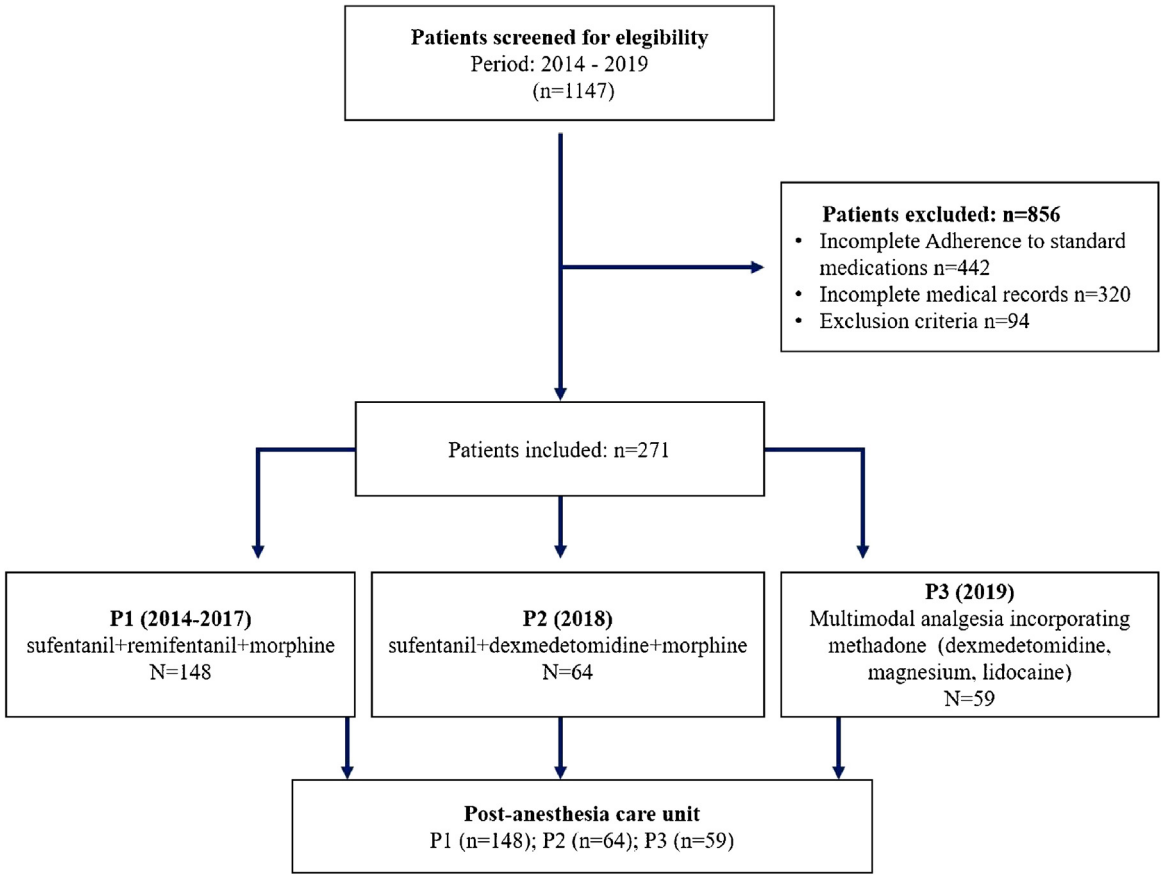

Figure 1 STROBE flow diagram.

patients received parecoxib 40 mg, pantoprazole 40 mg, and dexamethasone 0.1 mg.kg^{-1} (max. 10 mg). Twenty minutes prior to surgical completion, all patients received dipyrone (a non-steroidal anti-inflammatory drug) 2000 mg.

Intraoperative monitoring consisted of Noninvasive Blood Pressure (NIBP), ECG, oximetry (SpO_2), capnography, and BIS. Controlled ventilation was performed in a closed circuit with a flow up to 2 L.min^{-1}, tidal volume up to 8 mL.kg^{-1} based on CBW, with a positive end expiratory pressure of 6–8 mmHg, inspired oxygen fraction up to 50% and respiratory rate to maintain end-tidal CO_2 35–40 mmHg. Neuromuscular blockade was maintained at a post-tetanic count < 5 (i.e., deep block). Reversal of neuromuscular blockade was achieved with sugammadex in all patients. All patients received Ringer's lactated solution 10 mL.kg^{-1} before anesthetic induction. Intraoperatively, crystalloid was infused at 5 mL.kg^{-1}.h^{-1}. Nasogastric tubes and surgical drains were not used routinely. Normothermia was maintained by a convective air circulation heating system (Bair Hugger, 3M-Switzerland, Ruschlikon, Swtzerland).

The studied variables included age, gender, body weight, height, Body Mass Index (BMI), Heart Rate (HR), NIBP, SpO_2, and anesthetic technique according to the protocol in force. HR, NIBP and SpO_2 were recorded prior to anesthetic induction and every 10 minutes thereafter until the end of the procedure. Hypotension and hypertension were defined as > 20% decrease and > 20% increase in mean arterial pressure, respectively, from pre-induction blood pressure, and treated initially with changes in end-tidal sevoflurane and remifentanil and/or dexmedetomidine infusion rates, followed by ephedrine or hydralazine, respectively, when anesthetic dose adjustment was insufficient to reestablish the target blood pressure.

In PACU, the VNS score (0–10 scale) was assessed every 15 minutes. Postoperative Nausea and Vomiting (PONV) was assessed based on a 0–4 intensity scale (modified from Wengritzky et al.)[9] in which 0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea, and 4 = retching/vomiting. Upon arrival to PACU, hypoxemia was defined as a SpO_2 < 90%.[10]

Pain was treated with morphine 30–50 μg.kg^{-1} and PONV with dimenhydrinate 30 mg. Discharge from PACU was considered when Aldrete score ≥ 9 and pain score ≤ 3.

Statistical analysis

Histograms and the Shapiro-Wilk test were utilized for verification of data distribution symmetry. Pearson Chi-squared test was employed for categorical variables, and partitioning Chi-Square when $p < 0.05$. Variables with normal distribution were compared with ANOVA (3 groups), followed by the Tukey post-hoc test in case of $p < 0.05$ or two-sample independent *t*-test, when two groups were compared. The pain scores (VNS) were compared through the median (percentile 25–75%) of each protocol and the Kruskal-Wallis Analysis of Variance was used for multiple

Table 1 Demographic and intraoperative variables.

Variables	Anesthetic technique			*p*-value
	P1 (n = 148)	P2 (n = 64)	P3 (n = 59)	
Age[a] (years)	36.13 ± 10.08	37.75 ± 12.38	36 ± 10.91	0.67
Gender[b]				0.54
Female	109 (73.65)	45 (70.31)	39 (66.10)	
Male	39 (26.35)	19 (29.69)	20 (33.90)	
Body mass index[a] (kg.m^{-2})	41.13 ± 5.25	40.69 ± 7.31	40.63 ± 5.38	0.43
Smokers[b,c]				0.54
No	126 (94.03)	51 (89.47)	49 (92.45)	
Yes	8 (5.97)	6 (10.73)	4 (7.55)	
Surgery duration[a] (min)	100 ± 43.87	81.25 ± 34.20	[d]77.71 (27.99)	0.002
Type of surgery[b]				0.074
''Roux-en-Y'' bypass	126 (85.13)	57 (89.00)	44 (74.58)	
''Sleeve'' gastroplasty	22 (14.86)	07 (11.00)	15 (25.42)	

VNS, Verbal Numeric Scale.
[a] Values expressed as mean ± standard deviation – Analysis of variance (ANOVA).
[b] Values expressed as n (%) - Chi-Square test. (P1) sufentanil + remifentanil + morphine (2014-2017).
[c] Smokers: incomplete medical records were observed in 9.5% of charts in P1, 11% in P2 and 7% in P3.
[d] Tukey post-hoc test: P3 < P1-P2; (P2) sufentanil + dexmedetomidine + morphine (2018); (P3) Multimodal Analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).

comparisons, followed by the Dunn post-hoc test in case of *p*-value < 0.05. Prevalence Ratios (PR) were calculated to determine the relationship between independent Variables and Pain Scores (VNS) > 3. Univariate analysis was performed by Poisson regression, with simple robust variance, and estimative of gross Prevalence Ratios (PR) and respective Confidence Intervals (95% CI) to assess the extent of association between variables. Independent variables that were deemed statistically significant (i.e., $p < 0.20$) in the univariate analysis were considered candidates for the multivariable model, which then retained predictors that remained statistically significant at $p < 0.10$ by stepwise selection. Statistical analysis was performed using STATA 12.0 software (Stata Corp, College Station, TX). The research data related to this submission has been published in Mendeley Data (doi:10.17632/txzbhmfxc4.1). The files associated with this dataset are licensed under an attribution non-commercial 3.0 Unported license (CC BY NC 3.0).

Results

The final analysis included 271 patients, of whom 71.2% were female (Table 1). The overall mean age was 36.5 ± 10.4 years. The mean duration of surgery was 92 ± 39.61 minutes. The P3 cohort had shorter duration of surgery. Total number of subjects for each cohort was 148 in P1, 64 in P2 and 59 in P3 (Table 1).

Pain > 3 was documented in 49.8% of patients. Severe pain (VNS > 7) was observed in 28.7% (42) in P1, 9.37% (6) in P2, and 8.47% (5) in P3 (P1 > P2–P3; $p < 0.05$). Figure 2 shows the median (25–75% percentile) of pain scores between anesthetic protocols ($p < 0.05$). Amongst all patients presenting with pain > 3, 93 (68.89%) were submitted to P1 (sufentanil-remifentanil-morphine analgesia), 25 (18.56%) to P2 (sufentanil-dexmedetomidine-morphine analgesia), and 17 (12.59%) to P3 (MMA + methadone)

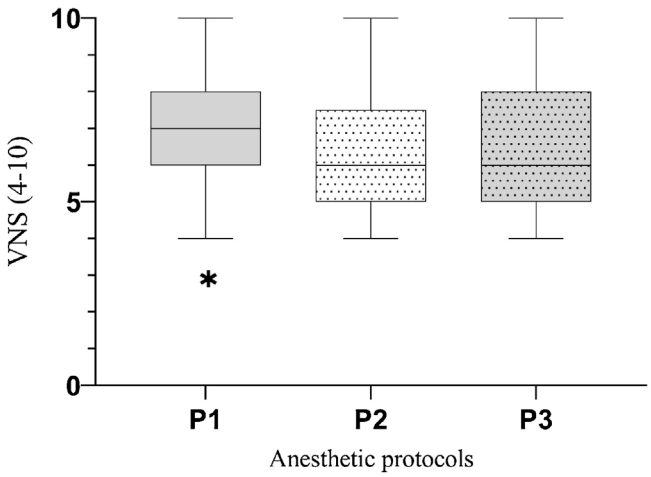

Figure 2 Boxplot: Median (25–75%) of pain scores between anesthetic protocols. (P1) sufentanil + remifentanil + morphine (2014–2017); (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) multimodal analgesia (dexmedetomidine, magnesium, lidocaine) and methadone (2019). VNS, Verbal Numeric Scale; MMA, Multimodal Analgesia – dexmedetomidine + magnesium sulfate + lidocaine. *Analysis of Variance (Kruskal Wallis): $p = 0.01$; Dunn post-hoc test: P1 > P2–P3.

(Table 2). From the factors potentially related to postoperative pain, anesthetic protocol, surgery duration and age presented statistical significance in the univariate analysis (Table 2). In the final adjusted model, anesthetic protocol P3 (MMA-methadone) (PR = 0.10; 95% CI [0.03–0.28]) and P2 (sufentanil-dexmedetomidine-morphine) (PR = 0.42; 95% CI [0.02–0.90]) were associated with lower occurrence of pain > 3 in PACU when compared to protocol P1 (sufentanil-remifentanyl-morphine). Age range 20–29 years-old was associated with higher postoperative pain scores (PR = 3.21; 95% CI [1.22–8.44]) (Table 3).

Table 2 Univariate analysis of demographic and intraoperative variables related to pain score > 3 in the postanesthetic care unit.

Demographic and intraoperative variables	Pain score > 3 (VNS)		Unadjusted PR (CI)	*p*-value
	No	Yes		
Age (years)[a]	38.0 ± 10.9	34.2 ± 10.5	0.97 (0.85–0.99)	0.02
Gender[b]				0.11
Female	91 (66.91)	102 (75.56)	1.00	
Male	45 (33.09)	33 (24.44)	2.30 (0.89–3.88)	
Body mass index(kg.m^{-2})[a]	40.76 ± 5.49	41.07 ± 6.14	1.00 (0.96–1.05)	0.66
Surgery duration (min)[a]	85.6 ± 34.56	96.50 ± 33.29	1.008 (1.002–1.01)	0.01
Type of surgery[b]				0.92
''Roux-en-Y'' bypass	111 (81.62)	116 (85.93)	1.00	
''Sleeve'' gastroplasty	25 (18.38)	19 (14.07)	1.03 (0.44–2.40)	
Anesthetic technique[b,c]				< 0.001
(P1) Sufentanil + remifentanil + morphine	55 (40.44)	93 (68.89)	1.00	
(P2) Sufentanil + dexmedetomidine + morphine	39 (28.68)	25 (18.52)	0.48 (0.74–2.95)	
(3 (P3) MMA + methadone	42 (30.88)	17 (12.59)	0.14 (0.03–0.64)	

VNS, Verbal Numeric Scale; CI, Confidence Interval; PR, Prevalence Ratio.
[a] Values expressed as mean ± standard deviation – Two-sample independent *t*-test.
[b] Values expressed as n (%) - Chi-Square test.
[c] Partitioning test: Incidence of pain score > 3 (VNS) in P1 > P2 and P3; Pain in P3 < P2. (P1) sufentanil + remifentanil + morphine (2014-2017); (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) multimodal analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).

Table 3 Adjusted analysis of independent variables associated with pain score > 3 in the postanesthetic care unit.

Demographic and intraoperative variables	Unadjusted PR (CI)	Adjusted PR (CI)	*p*-value
Age (years)			0.01
20–29	2.54 (1.05–6.64)	3.21 (1.22–8.44)	
Anesthetic technique			< 0.001
(P1) Sufentanil + remifentanil + morphine	1.00	1.00	
(P2) Sufentanil + dexmedetomidine + morphine	0.48 (0.74–2.95)	0.42 (0.20–0.90)	
(3 (P3) MMA + methadone	0.14 (0.03–0.64)	0.10 (0.03–0.28)	

The univariate analysis (presented in Table 2) was followed by multivariable analysis using Poisson regression. (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) Multimodal Analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).
VNS, Verbal Numeric Scale; CI, Confidence Interval; PR, Prevalence Ratio.

Incidence of intraoperative hypotension was 17.46% in the P1 cohort, 20.31% in the P2 cohort, and 39% in the P3 cohort (P3 > P1, P2; $p < 0.05$). Intraoperative arterial hypertension was observed in 5.90% of all patients (P1 = P2 = P3, $p > 0.05$). PONV was observed in 19.93% from analyzed patients, 20.3% from which in P1, 31.25% in P2, and 6.77% in P3 (P3 < P1, P2; $p < 0.05$). The incidence of hypoxemia was 21.40%, with no difference observed between the analyzed anesthetic protocols ($p > 0.05$) (Table 4). Respiratory depression requiring non-invasive ventilatory support occurred in one case in group P1. There was no need for reintubation or other major complications observed in the immediate postoperative period.

Discussion

The main result of this study is that in laparoscopic bariatric surgery, MMA in conjunction with methadone, when compared to techniques based mainly on the intraoperative use of medium-acting and high-potency opioids, significantly reduces the incidence of pain and PONV in PACU. These findings are consistent with similar postoperative pain studies comparing MMA and morphine[7] and studies comparing methadone and morphine[5] in obese and non-obese patients.

The use of methadone in bariatric surgery has shown to be safe and significantly reduce perioperative opioid consumption, postoperative pain (both at rest and with activity), and PONV.[7,8] In the present investigation, intraoperative-high-dose sufentanil (P1) resulted in greater necessity of analgesic rescue in PACU when compared to MMA including methadone. These findings are consistent with previous studies on multimodal opioid-sparing anesthetic techniques, in which methadone was the only opioid used.[8,11] Similarly, perioperative methadone results in lower pain scores in non-obese patients.[12–14]

We also found that age is a risk factor for increased immediate postoperative pain. In Ip et al's literature review, they found correlation between higher postoperative pain and younger age in most, but not all, of the studies.[14]

Table 4 Intraoperative (arterial hypotension and hypertension) and postoperative (PONV and hypoxemia) outcomes in relation to the anesthetic technique employed.

Outcome	Anesthetic technique			*p*-value
	P1 (n = 148)	P2 (n = 64)	P3 (n = 59)	
Intraoperative				
Arterial hypotension	n (%)	n (%)	n (%)	0.001*
Yes	22 (17.46)	13 (20.31)	23 (39.00)	
No	126 (82.54)	51 (79.69)	36 (61.00)[a]	
Arterial hypertension				0.18
Yes	8 (5.40)	7(13.00)	2 (3.38)	
No	140 (94.60)	57 (87.00)	57 (96.61)	
Postanesthetic care unit				
PONV				0.003*
Yes	30 (20.3)	20 (31.25)	04 (6.77)	
No	118 (79.7)	44 (68.75)	55 (93.23)[b]	
Hypoxemia (SpO_2 < 90%)**				0.23
Yes	29 (20.00)	12 (18.75)	17 (28.81)	
No	119 (80.00)	52 (81.25)	39 (71.19)	
Respiratory depression[c]				NA
Yes	01 (0.67)	00 (0.00)	00 (0.00)	
No	147 (99.33)	64 (100)	59 (100)	

NA, Not Applicable; (P1); Sufentanil + remifentanil + morphine (2014-2017); (P2) Sufentanil + dexmedetomidine + morphine (2018); (P3), Multimodal-analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).
PONV, Postoperative Nausea/Vomiting.
* Chi-Square test ($p < 0.05$) – Partitioning test: (a) P3 > P1 ($p < 0.05$), P2; (b) P3 < P1, P2 ($p < 0.05$).
** At admission to PACU.
[c] Respiratory depression requiring ventilatory support.

We hypothesize that cultural factors, modulating social influences, as well as personality and behavior features of different age groups can influence the individual expectation of pain and ultimately their expression in measurement scales. Nonetheless, this finding highlights the importance of a thorough preoperative consultation during which the clinicians (both anesthesiologist and surgeon) must clarify the patient's uncertainties and set up the perioperative expectations accordingly.

Magnesium is the more abundant divalent intracellular cation, implicated in numerous physiologic processes such as blood pressure regulation through modulation of vascular tone and peripheral vascular resistance. The increase in extracellular concentration of magnesium, therefore, results in arterial vasodilation,[15] which may have contributed to the higher incidence of hypotension (39%) observed in P3 (Table 4). Additionally, magnesium modulates pain through antagonism of the NMDA receptors. In obese patients, intraoperative administration of magnesium sulphate is associated with lower postoperative pain scores and opioid consumption.[15,16] Similarly, the well-known hemodynamic (i.e., bradycardia and hypotension) and analgesic/opioid-sparing effects of dexmedetomidine most likely contributed to the higher incidence of intraoperative hypotension and lower incidence (through an opioid-sparing effect) of PONV in P3 (Table 4). Indeed, in a meta-analysis of RCTs, dexmedetomidine significantly reduced postoperative opioid requirements.[17] This was corroborated in our study by a lower incidence of severe pain in P2 and P3 when compared to P1. Finally, intravenous lidocaine (used in P3) can also result in lower opioid requirements, thereby reducing the incidence of PONV.[18]

Interestingly, despite patients in P3 not being given high-potency medium-acting opioids, the incidence of hypoxemia (SpO_2 < 90%) at admission to PACU was similar between groups (Table 4). Several factors may have contributed to this finding such as (1) the incidence and severity of obstructive sleep apnea (not measured) in each group; (2) the somnolence associated with lidocaine combined with the residual effect of other anesthetic agents, leading to obstructive airway episodes; and (3) the respiratory depression associated with methadone (which has a prolonged effect). Notably, even though the incidence of hypoxemia upon PACU admission in the present investigation was in line with previous published data,[19] this study was underpowered to demonstrate differences in this regard.

Historically, the use of potent opioids, such as sufentanil, had been considered the standard practice to promote good quality postoperative analgesia because of its known prolonged residual analgesic effect.[20] Subsequently, multimodal opioid-sparing techniques came to establish a new paradigm, one which targets multiple pain pathways instead of focusing mostly (or solely) on opioid receptors, thereby reducing side effects and improving/accelerating postoperative recovery.[21] Additionally, MMA allows for a reduction in the amount of hypnotic agents required to maintain unconsciousness and anesthetic depth. Hence, multimodal anesthesia has a rather global concept which implies optimization of all pharmacologic agents available in the anesthesiologist's armamentarium to ensure safety

and comfort to patients, while minimizing complications and shortening hospital stay.[21]

This study has several limitations. Since this is a retrospective before-after study, there is the potential that the cohorts in the three different time periods were not similar. Specifically, not all potentially relevant factors that could impact pain, PONV, and desaturation were necessarily analyzed. Before-after studies are susceptible to other biases.[22] For example, the study period spanned 6 years, during which many aspects of care might have changed (historic bias). Clinicians might have been more diligent, perhaps even anticipating the results would be scrutinized, when the new protocol was introduced (Hawthorne effect). Surgery length was shorter in P3, which is usually associated to higher surgeons' experience and potentially lower postoperative pain. Lastly, although the median VNS = 7 for patients in P1 was statistically higher than P2 and P3 (median VNS = 6) (Fig. 2), one may question the clinical relevance of this finding. However, the overall lower incidence of moderate/severe pain (i.e., VNS > 3) in P3 reflects a better efficacy of the MMA regimen including methadone. It was not possible to evaluate the independent effects of MMA technique and methadone. However, the purpose of our review was to validate our strategy of merging MMA and methadone, both of which have been shown to improve postoperative analgesia in our laparoscopic bariatric surgery program. Finally, we did not look beyond the PACU period. Based on previous studies on methadone, however, its analgesic advantages typically extend up to 2–3 days after surgery.[6–8]

Conclusion

Our results show an association of the newer protocol period (MMA + methadone) and a lower occurrence of pain in PACU. Notably, a higher incidence of intraoperative hypotension was also observed in the newer protocol period.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Associations between postoperative analgesic consumption and distress tolerance, anxiety, depression, and pain catastrophizing: a prospective observational study☆

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KEYWORDS
Anxiety;
Depression;
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Pain;
Analgesia

Abstract
Background: Patients' postoperative treatment might be affected by their psychological state. The study aimed to evaluate the effects of anxiety, coping ability (stress tolerance), depression, and pain catastrophizing on analgesic consumption in patients scheduled for sleeve gastrectomy.
Methods: This prospective observational study consisted of 72 patients. The Distress Tolerance Scale (DTS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), and Pain Catastrophizing Scale (PCS) were completed in the preoperative period. In the postoperative period, pain intensity, as measured with the Visual Analogue Scale (VAS), and morphine consumption (mg) were evaluated after 2, 6, 8, and 24 hours. Total morphine consumption was recorded.
Results: The results revealed a strong negative correlation between distress tolerance and postoperative total morphine consumption (r = -0.702, $p < 0.001$). There was a strong positive correlation between total morphine consumption and pain catastrophizing (r = 0.801, $p < 0.001$). A moderate positive correlation was observed between total morphine consumption and anxiety and between total morphine consumption and depression (r = 0.511, $p < 0.001$; r = 0.556, $p < 0.001$, respectively). Linear regression revealed that distress tolerance, anxiety, depression, and pain catastrophizing are predictors of postoperative morphine consumption ($\beta = 0.597$, $p < 0.001$; $\beta = 0.207$, $p = 0.036$; $\beta = 0.140$, $p = 0.208$; $\beta = 0.624$, $p < 0.001$, respectively).
Conclusions: Distress tolerance, anxiety, depression, and pain catastrophizing can be predictive of postoperative analgesic consumption. In the estimation of postoperative analgesic consumption, distress tolerance, as well as anxiety, depression, and pain catastrophizing, were found to be important predictors.
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Introduction

Pain is a subjective condition that is influenced by several variables, such as psychological, social, cultural, and emotional status.[1] Inadequate postoperative pain control can result in a delayed return to daily living in the early postoperative period and chronic pain in the long term.[2] Interindividual differences in pain and analgesic response present difficulties in postoperative pain treatment.

In a study of patients who underwent abdominal aortic aneurysm repair, Liu et al. found that a high body mass index (BMI) was predictive of preoperative depression.[3] In another study, patients who underwent surgery for obesity experienced psychological consequences, which ranged from loss of self-esteem to clinical depression.[4]

Depression has been associated with acute pain (trauma or acute medical condition) and an increased perception of pain severity.[5] Anxiety is an important predictor of postoperative pain. It lowers pain thresholds and exacerbates pain duration. Previous studies have found an association between higher preoperative anxiety and increased postoperative pain.[6] Although anxiety affects analgesic consumption, there are interindividual differences in postoperative pain and analgesic consumption. Thus, it can be speculated that anxiety would not be sufficient to affect analgesic consumption.[7]

The present study hypothesized that the main factor in analgesic consumption would be the lack of anxiety coping skills rather than the presence of anxiety. The present study aimed to evaluate the relationship between postoperative analgesic consumption and distress tolerance, which refers to the ability to tolerate and to endure negative emotions (i.e., distress), pain catastrophizing, which includes the ability to deal with painful conditions and to eliminate pain, depression, and anxiety, in obese patients scheduled for laparoscopic sleeve gastrectomy.

Methods

This prospective observational study consisted of 72 obese patients scheduled for laparoscopic sleeve gastrectomy between July 2017 and January 2018 (Fig. 1). The study was approved by the Gaziosmanpasa University local ethics committee (17-KAEK-077). The data were a subset of a previously registered study (clinicaltrials.gov; Grant Number: NCT03227315). The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines were followed. The inclusionary criteria were as follows: age 18–60 years with a BMI of at least 30 $kg.m^{-2}$, American Society of Anesthesiologists (ASA) physical status I and II, and reading and comprehension ability sufficient to complete the questionnaires. The exclusion criteria were anxiety or depression diagnosis (as indicated in the medical records or patient statements), chronic pain and preoperative analgesic consumption, and contraindications for morphine use. Patients who refused further participation, canceled the procedure, or required open surgery were excluded. To avoid clinical bias, the study was conducted by two experienced surgeons and anesthetists, and it was controlled by a psychiatrist.

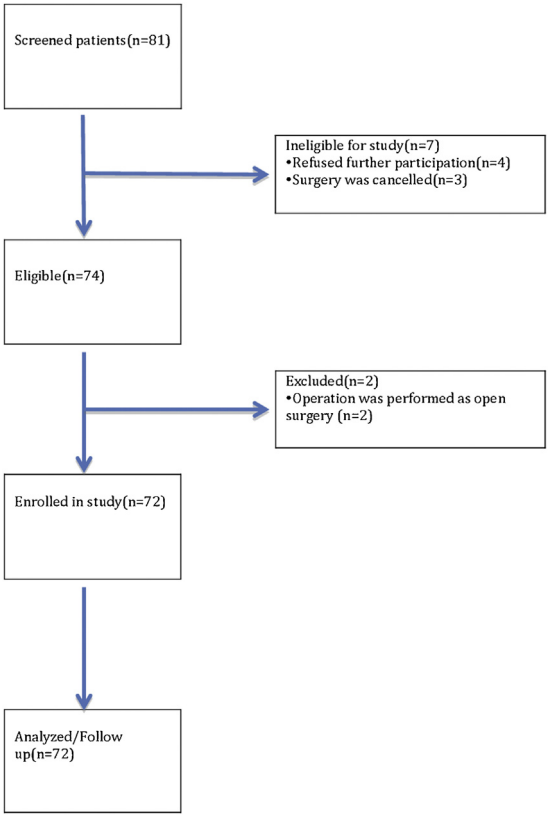

Figure 1 Flow chart. Initially 74 patients of those two were excluded from further analysis because of the intraoperative switch of the surgical technique.

Outcomes

The primary outcome measure was the assessment of the predictive role of distress tolerance in postoperative analgesic consumption and pain intensity. The secondary outcome measure was the assessment of the predictive role of anxiety, depression, and pain catastrophizing in postoperative analgesic consumption and pain intensity.

Measurements

After providing written informed consent, all the patients completed the questionnaires and scales (see below) in the hospital 1 day before surgery. Premedication was not administered before or after the completion of the questionnaire.

Questionnaires and scales

Distress Tolerance Scale

The Distress Tolerance Scale (DTS) developed by Simon et al. is a self-reported measure of the ability to tolerate and to endure negative emotions (i.e., distress). The scale assesses the following areas: (1) tolerability and aversiveness, (2) appraisal and acceptability, (3) tendency to absorb attention and disrupt functioning, and (4) regulation of emotions. It is a 5-point Likert-type scale (1 = *strongly agree*, 2 = *mildly agree*, 3 = *agree and disagree equally*, 4 = *mildly disagree*, and 5 = *strongly disagree*). The DTS comprises 15 items.

High scores indicate the ability to endure adversity.[8] The present study used the Turkish version, which was previously validated by Sargin et al.[9]

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is a three-part questionnaire. The first part, rumination, covers the inability to eliminate pain and worry. The second part, magnification, examines the exaggeration of pain-related situations. The third part, helplessness, covers the ability to deal with painful conditions. The questionnaire consists of 13 items. The scores range from 0 to 52 points, with higher values indicating higher levels of pain catastrophizing.[10] Suren et al. validated the Turkish version of the questionnaire.[11]

Beck Anxiety Inventory

Anxiety severity was measured with the Beck Anxiety Inventory (BAI), which was developed by Beck et al.[12] Responses to this questionnaire are indicated on a Likert scale (none, mild, moderate, and serious), with scores ranging from 0 to 63. The clinician assigns the following values to each response: 0 = *not at all*; 1 = *mild*; 2 = *moderate*; 3 = *severe*. A total score of 0–7 is interpreted as a minimal level of anxiety, 8–15 is interpreted as mild, 16–25 as moderate, and 26–63 as severe. Ulusoy et al. validated the Turkish version of this questionnaire.[13]

Beck Depression Inventory

The Beck Depression Inventory (BDI) measures the severity of depressive symptoms.[14] This questionnaire consists of 21 items. Each item is scored from 0 to 3, for a total score of 0 to 63. A total score of 0–10 is interpreted as a normal level of depression, 11–16 is interpreted as mild mood disturbance, 17–20 as borderline clinical depression, 21–30 as moderate depression, 31–40 as severe depression, and > 40 as extreme depression. The questionnaire was previously validated by Hisli.[15]

Visual Analogue Scale

The Visual Analogue Scale (VAS) is a measure of pain severity. It consists of a scale anchored by ''no pain'' (score of 0) and ''worst imaginable pain'' (score of 100).

Intraoperative period

In all patients, general anesthesia was induced via the intravenous administration of 0.6 $mg.kg^{-1}$ of rocuronium bromide, 2 $mg.kg^{-1}$ of propofol, and 1 $\mu g.kg^{-1}$ of fentanyl. To maintain anesthesia, volatile anesthetic sevoflurane (1 MAC) and a 50% oxygen–50% air mixture were used. During the intraoperative period, morphine was administered in accordance with the patient's ideal body weight. Thus, approximately 6 mg of morphine and 1 g of paracetamol were administered.

Postoperative period

In the postoperative period, a routine analgesic procedure was applied. It involved the administration of 1 g of paracetamol and 100 mg of tramadol 3 times per day. The patients evaluated pain severity on the VAS pain in the recovery room and 2, 6, 8, and 24 hours after surgery. For patients with a self-reported VAS pain greater than 3, the analgesic requirements were fulfilled with the intravenous administration of 2 mg morphine by an anesthesiologist or a nurse. Each patient's total post-surgery morphine consumption was recorded.

Data analysis

In a study by Ali et al.,[16] the total tramadol consumption in patients with high anxiety was found to be 264 ± 29.9 mg. The assumption of an 8% decrease of this dose in patients with low anxiety (accepting a type I error of 0.05 and a power of 0.80) showed that a total of 64 patients was required to discern a statistically significant difference. The normal distribution fitness of the data was assessed with the one-sample Kolmogorov–Smirnov test. The categorical data were expressed as frequencies and percentages, and the quantitative data were expressed as the mean ± standard deviation. The relationship between the questionnaire scores (DTS, PCS, BAI, BDI, and VAS) and analgesic consumption was examined with the Pearson correlation coefficient. The relationships between the variables were evaluated through linear regression. Data analysis was performed in IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY). Statistical significance was set at $p < 0.05$.

Results

Of the 81 potentially eligible patients who were initially assessed, 72 (19 male, 53 female) were included in the study. The flow diagram presents the recruitment and missing data (Fig. 1). The basic characteristics and the patients' preoperative distress tolerance, depression, anxiety, and pain catastrophizing scores and their postoperative VAS pain and analgesic consumption are presented in Table 1. The average 24 -h morphine consumption was 10.7 ± 8.1 mg. The mean distress tolerance, anxiety, depression, and pain catastrophizing values were 49.1 ± 14.2, 22.4 ± 15.9, 8.2 ± 9.3, and 18.5 ± 12.1, respectively. The distress tolerance, anxiety, depression, and pain catastrophizing scores (min-max) were 18–73, 0–59, 0–41, and 1–47, respectively.

The correlations among the predictors and between the predictors and outcomes are presented in Table 2. The patients' VAS pain and morphine consumption in the recovery room and 2, 6, 8, and 24 hours after surgery are presented in Fig. 2.

The Pearson correlation coefficient indicated that there was a strong negative correlation between distress tolerance and total postoperative analgesic consumption (r = -0.702, $p < 0.001$; Fig. 3). There was a strong positive correlation between total morphine consumption and pain catastrophizing (r = 0.801, $p < 0.001$; Fig. 3). There was a moderate correlation between total analgesic consumption and anxiety and depression (r = 0.511, $p < 0.001$; r = 0.556, $p < 0.001$, respectively; Fig. 4).

The multiple linear regression analysis revealed that distress tolerance, anxiety, depression, and pain catastrophizing were important predictors of postoperative morphine consumption (β = -0.597, $p < 0.001$; β = 0.207, p = 0.036; β = 0.140, p = 0.208; β = 0.624, $p < 0.001$,

Table 1 Descriptive analysis of the demographics, predictors, and outcomes.

Variable			n	%	Mean (SD)
Demographics	Gender	Male	19	26.4	
		Female	53	73.6	
	Age (years)				35.5 (10.1)
	Weight (kg)				125.5 (24.9)
	Height (cm)				165.7 (9.9)
	BMI ($kg.m^{-2}$)				45.5 (6.3)
Predictors	Distress tolarance				49.1 (14.2)
	Anxiety				22.4 (15.9)
	Depression				8.2 (9.3)
	Pain catastrophizing				18.5 (12.1)
Outcomes	VAS pain recovery room				4.6 (1.8)
	VAS pain at 2 h				4.9 (1.6)
	VAS pain at 6 h				3.8 (1.7)
	VAS pain at 8 h				3.4 (1.6)
	VAS pain at 24 h				2.4 (1.3)
	Morphine consumption at recovery room				2.6 (3.6)
	Morphine consumption at 2 h				3.3 (1.9)
	Morphine consumption at 6 h				2.0 (1.9)
	Morphine consumption at 8 h				1.8 (1.9)
	Morphine consumption at 24 h				1.0 (1.4)
	Total morphine consumption (mg)				10.7 (8.1)

VAS, Visual analogue scale; BMI, Body mass index.

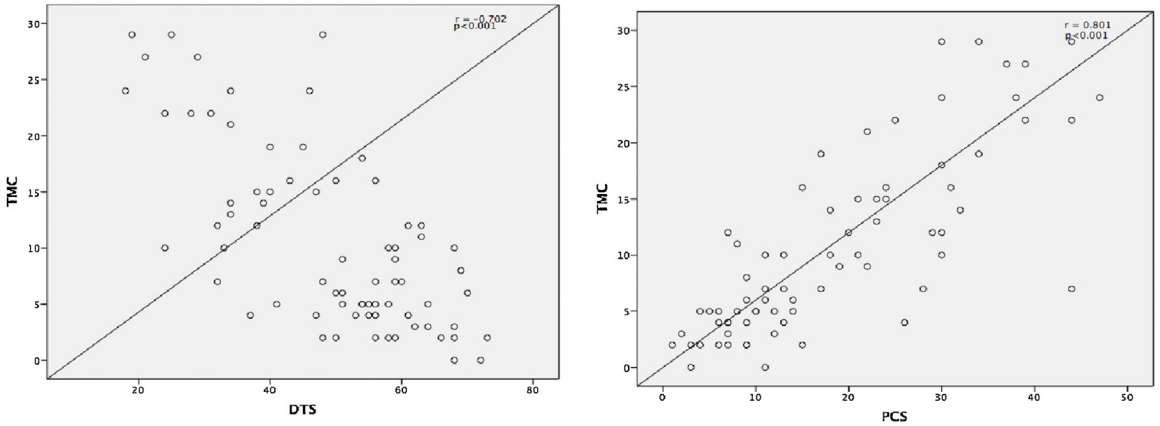

Figure 3 Correlations between analgesic consumption and effect of coping ability and pain catastrophizing on postoperative period. TMC, Total morphine consumption (mg); DTS, Distress Tolerance Scale; PCS, Pain Catastrophizing Scale.

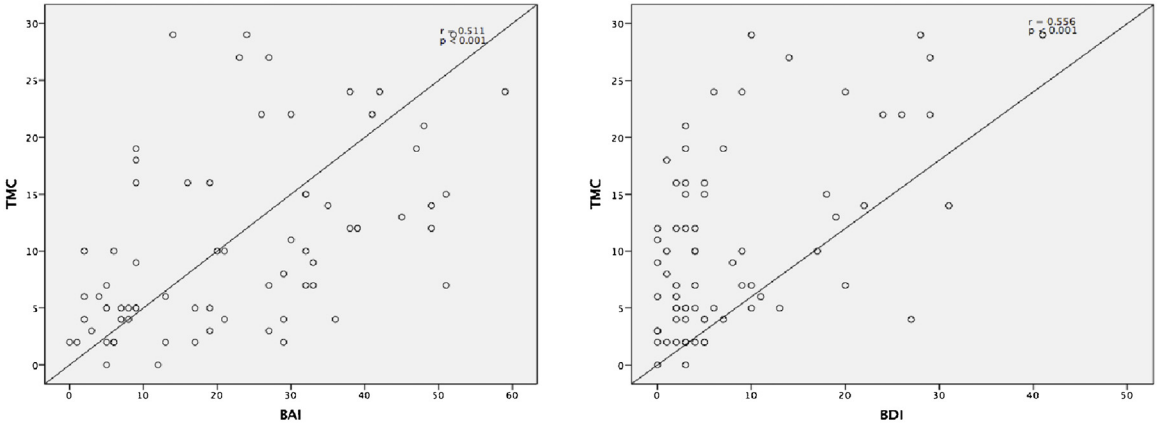

Figure 4 Correlations between analgesic consumption and effect of anxiety and depression on postoperative period. TMC, Total morphine consumption (mg); BAI, Beck anxiety inventory; BDI, Beck depression inventory.

Table 2 Correlations among predictors and outcomes.

Predictors	Predictors or outcomes	n	Correlation coefficients	*p* value
Distress tolerance	Anxiety	72	-0.510	<0.001
	Depression	72	-0.645	<0.001
	Pain catastrophizing	72	-0.791	<0.001
	VAS pain in the recovery room	72	-0.516	<0.001
	VAS pain at 2 h	72	-0.483	<0.001
	VAS pain at 6 h	72	-0.628	<0.001
	VAS pain at 8 h	72	-0.671	<0.001
	VAS pain at 24 h	72	-0.690	<0.001
	Morphine consumption in the recovery room (mg)	72	-0.543	<0.001
	Morphine consumption at 2 h (mg)	72	-0.468	<0.001
	Morphine consumption at 6 h (mg)	72	-0.642	<0.001
	Morphine consumption at 8 h (mg)	72	-0.705	<0.001
	Morphine consumption at 24 h (mg)	72	-0.726	<0.001
	Total morphine consumption (mg)	72	-0.702	<0.001
Anxiety	VAS pain in the recovery room	72	0.359	0.002
	VAS pain at 2 h	72	0.641	<0.001
	VAS pain at 6 h	72	0.395	<0.001
	VAS pain at 8 h	72	0.467	<0.001
	VAS pain at 24 h	72	0.608	<0.001
	Morphine consumption in the recovery room (mg)	72	0.330	0.005
	Morphine consumption at 2 h (mg)	72	0.512	<0.001
	Morphine consumption at 6 h (mg)	72	0.422	<0.001
	Morphine consumption at 8 h (mg)	72	0.477	<0.001
	Morphine consumption at 24 h (mg)	72	0.493	<0.001
	Total morphine consumption (mg)	72	0.511	<0.001
Depression	VAS pain in the recovery room	72	0.548	<0.001
	VAS pain at 2 h	72	0.486	<0.001
	VAS pain at 6 h	72	0.512	<0.001
	VAS pain at 8 h	72	0.551	<0.001
	VAS pain at 24 h	72	0.544	<0.001
	Morphine consumption in the recovery room (mg)	72	0.515	<0.001
	Morphine consumption at 2 h (mg)	72	0.388	<0.001
	Morphine consumption at 6 h (mg)	72	0.415	<0.001
	Morphine consumption at 8 h (mg)	72	0.568	<0.001
	Morphine consumption at 24 h (mg)	72	0.558	<0.001
	Total morphine consumption (mg)	72	0.556	<0.001
Pain catastrophizing	VAS pain in the recovery room	72	0.588	<0.001
	VAS pain at 2 h	72	0.651	<0.001
	VAS pain at 6 h	72	0.717	<0.001
	VAS pain at 8 h	72	0.779	<0.001
	VAS pain at 24 h	72	0.775	<0.001
	Morphine consumption at recovery room (mg)	72	0.613	<0.001
	Morphine consumption at 2 h (mg)	72	0.589	<0.001
	Morphine consumption at 6 h (mg)	72	0.733	<0.001
	Morphine consumption at 8 h (mg)	72	0.805	<0.001
	Morphine consumption at 24 h (mg)	72	0.760	<0.001
	Total morphine consumption (mg)	72	0.801	<0.001
VAS pain	Morphine consumption at recovery room (mg)	72	0.907	<0.001
	Morphine consumption at 2 h (mg)	72	0.887	<0.001
	Morphine consumption at 6 h (mg)	72	0.914	<0.001
	Morphine consumption at 8 h (mg)	72	0.906	<0.001
	Morphine consumption at 24 h (mg)	72	0.858	<0.001
	Total morphine consumption (mg)	72	0.950	<0.001

VAS, Visual analogue scale.

Table 3 Regression analysis between predictors and total morphine consumption.

Outcome	Predictors	N	β	*p* value
Total morphine consumption (mg)	Distress tolerance	72	−0.597	<0.001
	Anxiety	72	−0.207	0.036
	Depression	72	0.140	0.208
	Pain catastrophizing	72	0.624	<0.001

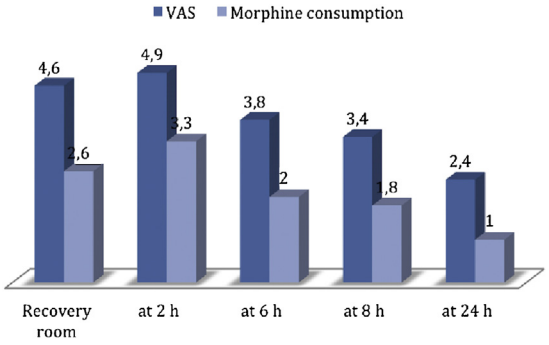

Figure 2 Total morphine (mg) and VAS according to the postoperative follow-up time of the patients. VAS, Visual Analogue Scale.

respectively; Table 3). There was a strong positive correlation between the VAS pain and total postoperative analgesic consumption in the recovery room and 2, 6, 8, and 24 hours after surgery ($r = 0.907$, $p < 0.001$; $r = 0.887$, $p < 0.001$; $r = 0.914$, $p < 0.001$; $r = 0.906$, $p < 0.001$; $r = 0.858$, $p < 0.001$; $r = 0.950$, $p < 0.001$, respectively; Table 2).

Discussion

A review of the literature indicates that the present study is the first to apply the Distress Tolerance Scale to surgical patients. One of the most important findings was the predictive role of distress tolerance, which is a measurement of stress coping ability, tolerance, and acceptance, in the determination of postoperative analgesic requirements.

Patients with anxiety require higher drug doses for anesthesia induction and analgesia. Some studies have found a correlation between preoperative anxiety and postoperative pain; however, this has been contradicted by other studies.[17] According to the literature, psychological factors may explain the differences in postoperative pain intensity and analgesic requirements.[18] These psychological factors include patients' approaches to managing preoperative stress. Thought avoidance regarding a planned surgical procedure resulted in dramatically reduced preoperative anxiety and postoperative recovery.[19] In a study of gynecological laparoscopy patients, Cohen et al. demonstrated that the morphine dosage in the first 48 hours after surgery was affected by stress and stress mitigation techniques. The same study showed that preoperative stress, emotional support, and self-reassurance based on religious convictions were predictive of pain levels 4 weeks after surgery.[20]

Kjolhede et al. examined low and high stress capacity through the administration of the Stress Coping Inventory questionnaire to 162 fast-tracked abdominal hysterectomy patients. The high-stress-capacity patients exhibited lower pain intensity in the surgical area, lower intensity of troublesome symptoms, and less fatigue.[21] Emami et al. found that low distress tolerance was a risk factor for unhealthy eating. The identification of the factors in the link between distress tolerance and unhealthy eating is important for the treatment of obesity and eating disorders.[22] In bariatric surgery patients, low distress tolerance has been found to be associated with depression and anxiety symptoms, disordered eating behaviors, and high BMI. The same study found higher levels of psychological distress in individuals who underwent bariatric surgery. Dialectical behavioral therapy and/or acceptance and commitment therapy have been suggested as options for increasing distress tolerance.[23]

Acceptance means not only overcoming painful situations but also coping with unpleasant situations. It plays an important role in the ability to successfully cope with acute and chronic pain. In acute pain induction, high acceptance was found to be related to higher pain tolerance.[24] In the present study, in accordance with the above information, high distress tolerance scores were negatively correlated with lower analgesic use. The ability to cope with painful and unpleasant situations is an important marker for postoperative analgesia consumption.

Preoperative anxiety is a common occurrence. High anxiety levels can lead to greater postoperative pain and, thus, the need for analgesia. An observational study of 127 adult orthopedic and trauma patients found that anxiety was a predictive risk factor for moderate to severe postoperative pain.[25] A study of the relationship between preoperative anxiety and postoperative pain control in laparoscopic cholecystectomy patients found that those who exhibited greater anxiety had higher postoperative Visual Analogue Scale pain values and analgesic consumption.[16] The results on anxiety in the present study are consistent with those of previous investigations and show that anxiety is a predictor of postoperative pain.

Studies of depression as a prospective predictor of postoperative acute, chronic, and persistent pain found increased pain perception and opioid consumption following total joint arthroplasty in patients with major depressive disorder.[26] De Cosmo et al. found that preoperative depression was significantly correlated with postoperative pain intensity and analgesic requirements.[27] The present study yielded similar results. Depression resulted in higher postoperative Visual Analogue Scale pain and analgesia requirements.

The Pain Catastrophizing Scale was developed to measure individual pain catastrophizing. Pain catastrophizing scores have been found to be predictive of post-trauma variables, such as severe pain and emotional disturbance.[28] Strulov et al. found a positive correlation between preoperative

pain catastrophizing and pain intensity and analgesic use in the first 2 days after a cesarean section.[1] The present study found a positive relationship between not only pain catastrophizing and postoperative analgesic use but also pain catastrophizing and distress tolerance values. This suggests that pain catastrophizing values are an indicator of postoperative analgesic use.

The Visual Analogue Scale pain has been used for evaluating postoperative pain and analgesic requirements. Analgesic drugs are started at a visual analogue scale pain of 3 or 4.[29] In the present study, in which morphine was started in patients with Visual Analogue Scale pain greater than 3, there was a positive correlation between the Visual Analogue Scale pain and morphine consumption.

A limitation of this prospective study is the relatively small sample size. Thus, the use of larger sample sizes might be beneficial in future studies.

Conclusion

In sum, distress tolerance, anxiety, depression, and pain catastrophizing are important predictors of postoperative analgesic consumption.

Conflicts of interest

The authors declare no conflict of interest.

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ORIGINAL INVESTIGATION

Analgesic effect of intercostal nerve block given preventively or at the end of operation in video-assisted thoracic surgery: a randomized clinical trial

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KEYWORDS
Ropivacaine;
Intercostal nerve block;
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Abstract
Objective: To compare the analgesic effect of intercostal nerve block (INB) with ropivacaine when given preventively or at the end of the operation in patients undergoing video-assisted thoracic surgery (VATS).
Methods: A total of 50 patients undergoing VATS were randomly divided into two groups. The patients in the preventive analgesia group (PR group) were given INB with ropivacaine before the intrathoracic manipulation combined with patient-controlled analgesia (PCA). The patients in the post-procedural block group (PO group) were administered INB with ropivacaine at the end of the operation combined with PCA. To evaluate the analgesic effect, postoperative pain was assessed with the visual analogue scale (VAS) at rest and Prince Henry Pain Scale (PHPS) scale at 6, 12, 24, 48, and 72 hours after surgery.
Results: At 6 h and 12 h post-surgery, the VAS at rest and PHPS scores in the PR group were significantly lower than those in the PO group. There were no significant differences in pain scores between two groups at 24, 48, and 72 hours post-surgery.
Conclusion: In patients undergoing VATS, preventive INB with ropivacaine provided a significantly better analgesic effect in the early postoperative period (at least through 12 h post-surgery) than did INB given at the end of surgery.
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Introduction

Video-assisted thoracic surgery (VATS) has largely replaced open thoracic operations because it causes minimal trauma, and has enhanced postoperative recovery.[1] The postoperative pain, however, can still be severe, and this impairs postoperative recovery. In these cases, postoperative INB under thoracoscopic vision is now accepted and used by thoracic surgeons and anesthesiologists.[2–4] It is easy to perform, provides a precise analgesic effect and few complications. While postoperative INB in combination with patient-controlled analgesia (PCA) is effective, postoperative pain is still common. To date, no study has examined the analgesic effect of INB at different timepoints during the operation. Since the trauma and pain fiber stimulation starts at the time of the initial surgical incisions, INB, for example with ropivacaine, after the initial incision but before the intrathoracic operation might be expected to decrease the central nervous system stimulation[5] and achieve a better analgesic effect. Thus, we designed this study to compare the analgesic effects of INB with ropivacaine when given preventively or at the end of the operation in patients undergoing VATS.

Methods

Patient selection

This study was a single-blind, prospective, randomized clinical trial, which was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR1900024877) and approved by the Ethics Committee of Affiliated Hospital of Nantong University (Approval number: 2019-K036). All participants provided signed informed consent before recruitment into the study. Subjects eligible for the study were patients admitted to the hospital from August 2019 to December 2019, aged 35–75 years, American Society of Anesthesiologists (ASA) physical status I–II, and scheduled for elective VATS including pulmonary lobectomy, pulmonary segmentectomy, pulmonary wedge resection, and mediastinal tumor resection. Preoperative exclusion criteria were previous history of thoracotomy, history of alcoholism, and cardiac, lung, liver or kidney dysfunction. Intraoperative and postoperative exclusion criteria included intraoperative conversion from minimally invasive surgery to open thoracotomy, operation time > 3 hours, intraoperative bleeding > 1000 mL, reintubation, or reoperation due to various complications, and incision infection. Patients were randomly divided into two groups via a random number generator. The preventive analgesia group (PR group) received INB with ropivacaine at the start of surgery combined with PCA postoperatively. The post-procedural block group (PO group) received INB with ropivacaine at the end of surgery combined with PCA. PCA was removed 24 h after surgery for all patients.

Anesthesia management

All operations were performed by the same surgical team. On arriving at the operating room, patients were monitored via electrocardiography (ECG), and noninvasive measurement of blood pressure and oxygen saturation. After anesthesia induction with intravenous injection of propofol 2 $mg.kg^{-1}$, midazolam 0.1 $mg.kg^{-1}$, vecuronium 0.1 $mg.kg^{-1}$, and fentanyl 4 $\mu g.kg^{-1}$, patients were intubated with a double-lumen endotracheal tube and ventilated at the following settings: tidal volume (VT) 8–12 $mL.kg^{-1}$, breathing rate (RR) 12–18 times/min, I: E 1:1.5, positive end expiratory pressure (PEEP) 5 cm H_2O. Anesthesia was maintained with propofol and remifentanil. The PR group received INB with 20 mL 1% ropivacaine in three intercostal spaces around every incision and the site where the thoracic drainage tube was placed (generally the observation hole). This was done under the guidance of a thoracoscope after the initial incision and before the intrathoracic manipulation. The specific puncture point was at the posterior adjacent to the spine. The PO group underwent the same injection procedure but at the end of operation. After surgery, a patient was moved to the postanesthesia care unit, and after complete recovery of breathing and muscle tension the endotracheal tube was removed. Postoperative analgesia was administered via a PCA pump with 0.8 mg fentanyl/100 mL 0.9% normal saline at a continuous rate of 2 mL/h (the patient-controlled analgesia dose was 2 mL/time, and the locking time was 15 min). An intramuscular injection of 8–10 mg morphine was given to patients with intolerable postoperative pain (a score of 9–10 on the 10-point visual analogue scale).

Observation index

For pain assessment, both the visual analogue scale (VAS) score at rest and the Prince Henry Pain Scale (PHPS) score were recorded at 6, 12, 24, 48, and 72 hours after surgery. The VAS score ranged from 0 (pain free) to 10 (intolerable pain), and the PHPS score ranged from 0 (no pain when coughing) to 4 (severe pain when quiet). The end point of the study was 72 hours post-surgery. If the patient was discharged within 72 h, the discharge time was used as the end point. The total additional amount of morphine, and adverse reactions such as nausea, vomiting and atelectasis before the end point of the study were recorded.

Statistical analysis

A power analysis was performed on preliminary data with postoperative VAS pain scores at rest as the primary outcome variable. The analysis showed a minimal sample size of 21 subjects in each group would be required to detect a significant between-group difference of 30%, at 5% α and 20% β. In this study, 25 patients were enrolled in each group. Continuous data are presented as mean $\pm$ standard deviation. The Student's *t*-test and Chi-squared test were used to analyze continuous variables and categorical variables, respectively. Statistical analysis was performed with SPSS 20.0 software (SPSS, Inc, Chicago, Ill, USA). Differences were considered statistically significant at $p < 0.05$.

Table 1 Clinical data of two groups.

Index	PA group	PO group	*p*-value
Gender (male/female)	9/16	10/15	0.776
Age (years)	56.2 ± 9.3	57.8 ± 9.7	0.555
BMI (kg/m^2)	24.2 ± 2.3	25.3 ± 2.2	0.090
ASA (I/II)	16/9	15/10	0.776
Time of operation (minutes)	98.4 ± 39.0	92.8 ± 40.1	0.622
Number of thoracic drainage tube	0.68	0.6	0.565
Time of thoracic drainage tube removal (hours)	31.7	29.6	0.768

PA group, preventive analgesia group; PO group, post-procedural block group; BMI, Body Mass Index; ASA, American Society of Anesthesiologists (ASA) physical status.

Table 2 The visual analogue scales at rest of two groups.

Timepoint (hour)	PA group	PO group	*p*-value
6	0.72 ± 0.68[a]	1.52 ± 1.00	0.0020
12	1.72 ± 0.61[a]	2.56 ± 0.87	0.0003
24	2.32 ± 1.03	2.4 ± 1.08	0.7898
48	1.20 ± 0.82	1.48 ± 0.87	0.2470
72	0.60 ± 0.50	0.76 ± 0.66	0.3407

PA group, preventive analgesia group; PO group, post-procedural block group.
[a] $p < 0.05$ vs PO group.

Table 3 The Prince Henry Pain Scales of two groups.

Timepoint (hour)	PA group	PO group	*p*-value
6	0.60 ± 0.50[a]	1.40 ± 0.58	< 0.0001
12	1.36 ± 0.57[a]	2.00 ± 0.65	0.0005
24	1.72 ± 0.74	1.88 ± 0.67	0.4246
48	1.20 ± 0.41	1.24 ± 0.44	0.7392
72	0.92 ± 0.28	0.96 ± 0.20	0.5612

PA group, preventive analgesia group; PO group, post-procedural block group.
[a] $p < 0.05$ vs PO group.

Results

Comparison of clinical data between the two groups

Sixty-two patients were enrolled in the study. Nine patients were excluded as a result of not meeting preoperative inclusion criteria. Three patients were excluded because of conversion to open thoracotomy. Finally, twenty-five patients in each group were analyzed (Fig. 1). The demographic and operation characteristics of the patients are summarized in Table 1. There were no statistically significant differences between the two groups in gender, age, Body Mass Index, ASA physical status, operation time, number of the thoracic drainage tube and time of thoracic tube removal (Table 1).

Postoperative pain by VAS at rest

The postoperative VAS pain scores in both groups were low at 6 hours, reached a peak at 12–24 hours, and then gradually decreased at 48 and 72 hours. At 6 and 12 hours postoperative, the VAS scores in the PR group were significantly lower than those in the PO group ($p < 0.05$). There were no statistically significant differences between the two groups in VAS scores at 24, 48 and 72 hours (Table 2).

Postoperative pain by PHPS

The changes and differences in postoperative PHPS pain scores were similar to those for the VAS scores, reaching a peak at 12–24 hours and then gradually decreasing at 48 and 72 hours. At 6 and 12 hours postoperative, the PHPS scores in the PR group were significantly lower than those in the PO group ($p < 0.05$). There were no statistically significant differences between the two groups in PHPS scores at 24, 48 and 72 hours (Table 3).

Postoperative complications

No postoperative complications, including nausea, vomiting and atelectasis, were observed in either of the two groups. No patients experienced severe postoperative pain that required additional morphine.

Discussion

Due to the high degree of trauma with thoracic surgery, patients often experience severe pain at the incision site after surgery especially in the early postoperative period. This pain and anticipation of this pain has some serious consequences. It often prevents patients from coughing, causing retention of respiratory secretions, which in turn leads to pulmonary infection, atelectasis, hypoxemia, and other complications.[6] It increases postoperative bed rest, which increases the risk of deep vein thrombosis and pulmonary embolism,[7] and slows the recovery of pulmonary function. Overall, severe postoperative pain is considered the fifth vital sign that significantly impairs postoperative recovery, and this is also true even for patients after VATS. Enhanced recovery after surgery (ERAS)/fast track surgery (FTS) is a recent evidence-based medicine approach to surgical treatment that integrates and optimizes perioperative management that includes anesthesia, medical treatments, and nursing. The goal is to reduce the stress of surgical trauma and to improve the speed of recovery.[8,9] ERAS has

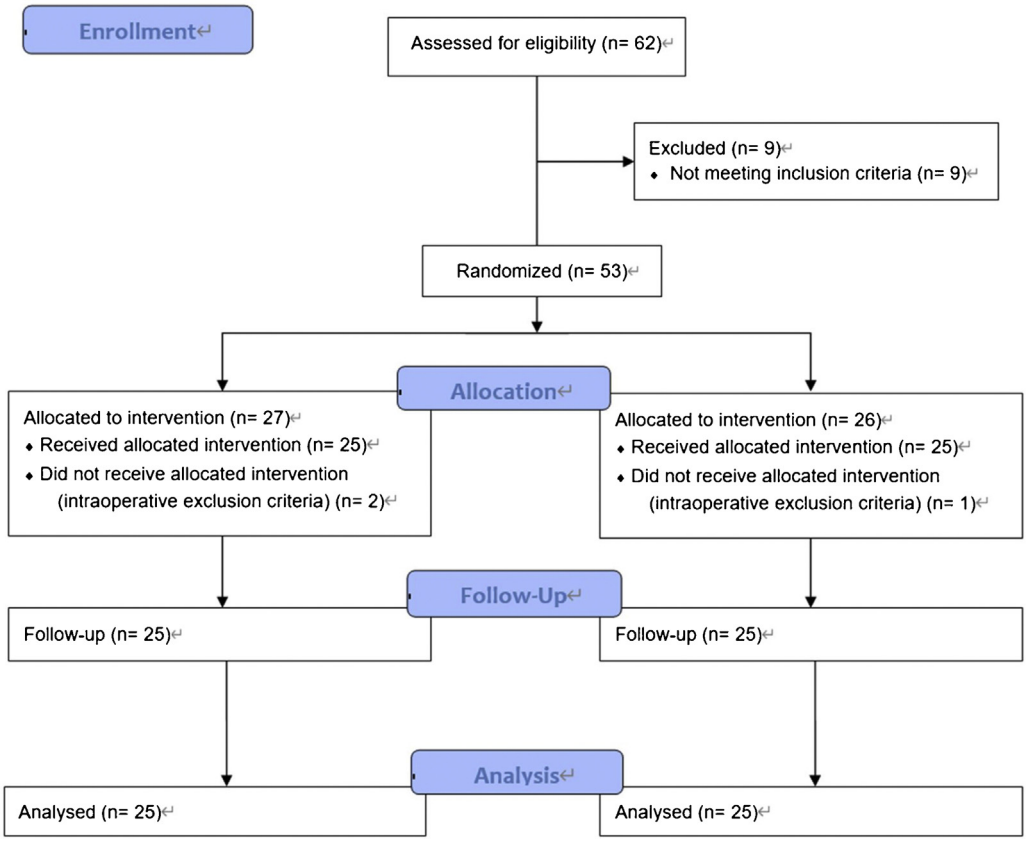

Figure 1 Flowchart showing the progress of participants.

greatly increased awareness of the management of postoperative pain,[10] and thoracic surgeons and nurses should consider this approach to help reduce the pain after VATS, especially in the early postoperative period.

All current commonly used analgesia methods after thoracic surgery have disadvantages and limitations.[11] Epidural anesthesia is effective and easy to control, but has complications such as respiratory inhibition, nausea and vomiting, urinary retention, hypotension, delayed muscular function, epidural hematoma and infection.[12] For PCA plus opioid, the difficulty lies in producing a precise analgesic effect at the incision site. In addition, it has several systemic adverse effects including drowsiness, respiratory depression, gastrointestinal dysfunction, and nausea and vomiting.[13] Oral NSAIDs are well accepted by patients, but can cause gastric ulcers, acute renal insufficiency, platelet dysfunction and other adverse reactions.[14] Compared with these regimens, INB under thoracoscopic vision, is easy to perform without additional discomfort to the patient. It is associated with significantly reduced incidence of postoperative pulmonary complications, urinary retention, and nausea and vomiting, all of which help postoperative recovery.[15]

Ropivacaine is a long-acting local anesthetic. The main pharmacological effect is to block the transport of sodium ions across the nerve fiber membrane, which increases the threshold level of the nerve action potential, reduces the speed of the ascending action potential, and blocks nerve impulse conduction.[16] Clinically ropivacaine is often used as an intercostal nerve blocker given postoperatively because of its definite analgesic effect, long duration of action, and few adverse reactions.[17] Compared with other long-acting local anesthetics such as bupivacaine and levobupivacaine, ropivacaine is less lipophilic, which results in less cardiodepression and less central nervous system inhibition seen as less of a decrease in motor function.[16,18,19] Providing analgesia at the moment of a pain-causing action has been reported to attenuate the sensitization within the central nervous system.[5,20] Based on this, we proposed that intercostal block with ropivacaine just after making the initial incision but before the intrathoracic manipulation would block the stimulation of pain fibers at the beginning of operation, and so decrease the excitatory effect on the central nervous system providing a better analgesic effect.

The results of this study support this hypothesis for the early postoperative period. The pain scores (VAS at rest and PHPS) after VATS were low at 6 hours post-surgery, peaked at 12 to 24 hours, and gradually declined at 48 and 72 hours. In the early postoperative period (6 and 12 h), the pain scores in the PR group were lower than those in the PO group. Although the pain scores in the PR group were numerically lower than in the PO group in the middle and late postoperative period (24–72 h), the differences were not significant. The absorption half-life of ropivacaine from the epidural space is biphasic with a 14-minute fast phase and a 4-h slow phase, and a terminal half-life of > 4 hours.[21] It is also absorbed rapidly from the intercostal space.[22] Due to the short operation time of VATS (in this

study an average of < 100 minutes), intercostal ropivacaine in the PR group would exert an analgesic effect throughout the operation and into the early postoperative period. With the metabolism and elimination of ropivacaine, its analgesic effect gradually disappeared and the lack of significant differences in pain scores between two groups after 24 hours would be expected. In order to try and prevent this, continuous wound infiltration with ropivacaine for postoperative pain management has been tested.[23] This technique, however, required the insertion of a separate catheter into the intercostal space, which increases the difficulty and risk of the operation. One additional observation that might be relevant is that the peak pain score was delayed in the PR group (24 h) vs. the PO group (12 h) and was lower (VAS 2.32 vs. 2.56 and PHPS 1.72 vs. 2.00). These differences were not significant and more data are needed to determine if this is a real effect or not. In addition, our data suggest the elimination rate of ropivacaine may not be an issue since no postoperative complications (such as nausea, vomiting, and atelectasis) occurred in either of the two groups, and no morphine was added for severe pain in any of the patients.

Overall, our data confirm the efficacy and safety of INB with ropivacaine, but the study has some limitations. First, it was not double-blind because the surgeon carried out the analgesia process. Second, 25 subjects per group may be too few to detect differences between groups and to show all potential adverse effects. A double-blind or triple-blind design study with a larger sample size will provide more supportive data for this procedure.

Conclusion

In this study, in patients undergoing VATS, preventive INB with ropivacaine provided significantly better analgesia in the early postoperative period than did INB at the end of surgery. Preventive INB with ropivacaine provided an accurate analgesic effect with few complications and low risk, and is worthy of further study as an effective and safe clinical application.

Conflicts of interest

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The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

The influence of sex and level of physical activity on maximum tolerance to mechanical pain

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KEYWORDS
Pain;
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Abstract
Background: A difference in maximum tolerance to mechanical pain (MTMP) between the sexes is widely studied but there is still no consensus on whether the level of physical activity (PA) influences pain.
Objectives: To compare the MTMP between men and women with different levels of PA.
Methods: Sixty five individuals were divided in female (n = 35) and male group (n = 30). The main outcome measures were PA level and MTMP by pressure algometry. Pressure was applied three times on both sides at the following points: cervical (5th and 7th) and lumbar (3th and 5th) vertebrae; trapezius, rhomboid, gluteus, gastrocnemius, pectoralis major, tibialis anterior, and deltoid muscles, elbow, hand, knee, and ankle.
Results: It was observed that the PA level has little influence on the MTMP at all the assessed points and that men have greater MTMP than women.
Conclusion: Sex, not the PA level, influences the MTMP.
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Introduction

According to the International Association for the Study of Pain,[1] pain is an unpleasant sensory and emotional experience, resulting from current or potential tissue damage or described in relation to such damage. The same definition is used for pain felt by both men and women; however, it is known women are at higher risk for many common pain conditions than men.[2]

Pressure algometry is a known and validated method to induce experimental pain.[3] An algometer is a mechanical device that registers (through an electronic device) the pressure applied on certain surfaces.[3] It has been used for diagnostic, experimental, and medicolegal purposes.[3] In its

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diagnostic applicability, it has been used as a semiquantitative method to measure pain intensity and even to locate tender points in several musculoskeletal and rheumatological disorders.[4–8]

Maximum tolerance to mechanical pain (MTMP) is defined when painful pressure can no longer be tolerated.[3] The pressure pain threshold (PPT) is the point at which the pressure is first painful.[9] The subjective character of MTMP cannot be avoided, since the measurement object itself, that is, the individual's minimal painful perception is a subjective factor.[9–12]

Differences on PPTs or MTMPs have been noted between sexes[9–14] and reveal that women exhibit lower PPT and MTMP to different forms of mechanical stimuli (punctate, pressure, touch).[15,16] However, there is still no consensus on this difference and these studies compare few points. Other authors[17–19] stated that the painful threshold (PT) between men and women is comparable.

Distinct sensitivities are also observed between the different anatomical points of the body. When comparing the PPT in the upper and lower limbs, it was observed that the PPT in the lower limbs is higher. The following are the PT of anatomical points in increasing order: fingertip, palm, forehead, sole of the foot, shoulders, forearm, back of the hand, lumbar spine, anterior thigh, posterior leg, and back of the foot. This increase was analyzed when measuring pain through heat.[20]

Some studies have evaluated the influence of the level of physical activity on pain through heat pain thresholds, heat pain suprathreshold, cold pressor pain, temporal summation of heat pain, conditioned pain modulation, and offset analgesia but not used pressure algometry.[21–23]

Studies comparing the PPT or MTMP through pressure algometry in people with different levels of physical activity (PA) are limited.[24,25] Andrzejewski et al.[24] compared the PPT of 13 body points between different ages and level of PA. The authors found no difference between ages but found that individuals with higher levels of PA had a higher PPT. However, no instrument was used to assess this level of PA, only the participants' self-report. Lemming et al.[25] evaluated the PPT in the tibialis anterior muscle, after mechanical compression by a cuff on the leg, and found that men have a higher PPT than women and that the higher the level of PA, the higher the PPT. The systematic review and meta-analysis by Tesarz et al.[26] suggest that regular PA is associated with changes in pain perception, especially with cold and ischemia. Other studies also found that the higher the level of PA, the higher the PPT, but there were compared among athletes.[27–29] Although there are many studies[15–19] investigating the differences related to pain perception in men and women, the novelty of this article was to verify if there is a difference in such stratified perception according to the level of activity. While several studies have suggested higher PPTs (less sensitive to threshold levels of painful stimuli) are related to PA, very few have considered whether pain tolerance is similarly related to PA.

Thus, the primary objective of the present study was to compare the MTMP in young women and men with different levels of PA and the hypothesis of the study was that the most physically active individuals had a higher mechanical pain threshold. The secondaries objectives were to verify whether there is a difference in the MTMP between the right and left sides and between men and women.

Methods

Study design

This is a cross-sectional study, approved by the Ethics Committee of the Health Sciences of CAEE: 76475417.2.0000.0102. The data collection was carried out at the Physiotherapy Laboratory of Paraná Federal University, Curitiba, Paraná, Brazil, conducted from August 2018 to December 2019.

Participants

Participants included men and women between 18 and 35 years old. Exclusion criteria included those who had an extremely high tolerance to pain (greater than 13 kgf) making it impossible to assess, with neuromusculoskeletal disease, and who had been taking any analgesic and anti-inflammatory medications in the previous 48 hours.

Participants were invited verbally or through social networks, and those who agreed to participate signed the informed consent form (Resolution 466/2012 of the National Health Council).

Evaluating clinical outcomes

Participants were assessed using a specific form containing identification data, anamnesis, and MTMP using pressure algometry.[30] In addition, the Human Activity Profile (HAP) was applied,[31] to assess the participants' level of PA.

Human activity profile (HAP)

This instrument was developed by Daugthon et al.,[32] adapted and validated in Brazil by Souza et al.,[31] and was used to assess functional level and PA, both for healthy individuals, in any age group, and for those with some degree of dysfunction.[31]

The 94 items are arranged in an increasing order of difficulty, that is, as the subject advances in the questionnaire, the activities demand a higher energy level. For each item, there are three possible answers: ''I still do'', ''I stopped doing'', or ''I never did''. An advantage of this instrument is that the answer ''I never did'' is not included in any HAP score or classification, which minimizes the risk of cultural bias, as there are activities that are not considered routine in Brazil.[31]

Based on each answer, the scores are calculated: first, the activities marked ''still do'' are added, and this value is then subtracted from activities marked ''stopped doing.'' The result is used to define the participant's level of activity. If the value obtained is less than 53, the participant is classified as inactive. If this value is between 53 and 74, it is moderately active (MA). Finally, a value between 74 and 94 is considered active.[31]

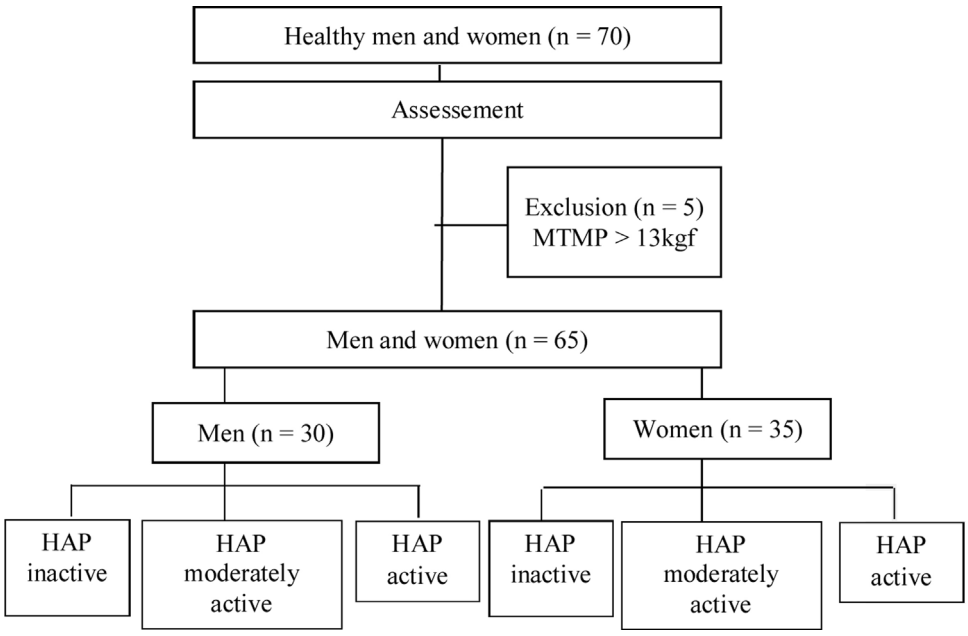

Figure 1 Study design. MTMP, maximum tolerance to mechanical pain; HAP, human activity profile.

Maximum tolerance to mechanical pain (MTMP)

MTMP evaluation was performed using an algometer (EMG system). Fifteen points were demarcated with a dermatographic pencil, frequently affected by myofascial trigger points (Table 1), which were adapted from Fischer,[9] Giesbrecht and Battié,[33] Garcia et al.,[34] Antonaci et al.,[35] Jones et al.,[36] Farasyn et al.,[37] Kroner-Hervig et al.,[38] Alabas et al.[39] Stefania et al.,[40] and Hilberg et al.[41] After that, three collections were performed in each of the points, and finally, the average of the three evaluations was calculated to define the MTMP. In each collection, the subjects were instructed to say ''now'' or ''stop'' when the MTMP was reached, i.e., when they could not tolerate any more. A physiotherapist, previously trained, performed a reliability study for the algometer application. To perform the intra-test reliability test, the expert evaluated ten individuals with an interval of 48 hours. Data analysis indicated excellent reliability for the interventionist results (intra-class correlation coefficient [ICC] = 0.95).

The patients were first placed in prone position for the following points: C5, C7, L3, L5, and trapezius, rhomboid, gluteus, and gastrocnemius muscles. Later, they were instructed to turn in the supine position for the following points: chest, elbow, hand, knee, tibialis anterior muscle, and ankle. Finally, they were positioned in lateral decubitus for the deltoid point. The time between pressure trails was three minutes and the rate was 0,5 kgf/s.

Sample size

The sample consisted of 35 women and 30 men aged between 18 and 35 years. The sample power pos hoc was calculated using the G*Power 3.1.3 program, considering the following criteria: effect size 0.80 and α-error 0.05, resulting in the power (1-β) of 0.93.

Statistical analysis

The parameters were analyzed using SPSS Software (25.0). The results were expressed as mean $\pm$ standard deviation. The normality analysis of the data was performed using the Kolmogorov-Smirnov test and homogeneity using the Levene test. For intergroup comparison four-way mixed repeated measure ANOVA considering sex, PA level, side and anatomical point, and post hoc Bonferroni test were applied. When the data showed normal and homogeneous distribution, the paired Student *t*-tests were applied for intragroup evaluation and the Wilcoxon test for intragroup analyses with nonparametric distribution. For intergroup comparison of normal data, the parametric one-way ANOVA and post hoc Tukey test were applied. While for non-normal data, the Kruskal-Wallis nonparametric test was applied. The data were also analyzed using the ANCOVA 3-way, considering: sex and physical activity level as covariates. The confidence interval between groups were reported. The correlation between the parametric variables was analyzed by Pearson's test and the nonparametric variables by Spearman' correlation; later, a logistic regression analysis was performed for variables with significant correlations, dependent variable was each point measured with the pressure algometer, independent variable was physical activity level and sex was predicted variable. Data were considered significant when $p \leq 0.05$.

Results

Seventy individuals participated in the study, 35 males, with a mean age of 22.6 $\pm$ 3.7 years, and 35 females, with a mean age of 21.3 $\pm$ 2.5 years (Fig. 1). Five male participants were excluded from the study, because MTMP was higher than 13 Kgf, with a total of n = 65. Table 2 shows the sociodemographic characteristics, where the incidences referring to

Table 1 Points selected when applying the algometer.

Decubitus	Point/region	Description
Prone	5th cervical vertebra – C5	3 cm to the right (R) and left (L) of the C5.32
	7th cervical vertebra	3 cm to the R and L of the C7[34]
	Trapezius (medium fibers)	Mean distance of C7 and coracoid process[9,35,36]
	Rhomboid	Mean region of the R and L of the rhomboid[32]
	3rd lumbar vertebra – L3	5 cm to the R and L of the L3[9,32]
	5th lumbar vertebra – L5	5 cm to the R and L of the L5[9,32]
	Gluteus	3 cm below the R and L iliac crest[9,37]
	Gastrocnemius	Mean portion of the R and L gastrocnemius[32]
Supine	Pectoralis major	2 cm below mean the distance of the R and L clavicle[9]
	Elbow	3 cm anterior to the R and L lateral epicondyle of the humerus[38]
	Hand	Middle of the R and L first dorsal interosseous muscle (anatomical snuffbox)[39]
	Knee	5 cm medial to the center of the R and L patella[30]
	Tibialis anterior (TA)	5 cm to the mean distance of the R and L tibia[40]
	Ankle	2 cm below the R and L lateral malleolus[41]
Lateral	Deltoid (medium fibers)	Central region of the R and L deltoid muscle[9,35]

Table 2 Sociodemographic characteristics.

	Females (n = 35)	Males (n = 30)	*p*
Age (mean ± SD)	21.3 ± 2.5	22.6 ± 3.7	0.16
Smokers (n.%)	1 (2.8%)	3 (10%)	0.11
Alcoholic	11 (31.4%)	10 (33.3%)	0.17
Dominant Side			
Right	33 (94.2%)	27 (90%)	0.52
Left	2 (5.7%)	3 (10%)	
HAP			0.07
Inactive	16 (45.7%)	4 (13.3%)	
Moderately Active	9 (25.7%)	17 (56.66%)	
Active	10 (28.5%)	9 (30%)	

WG, women group; MG, men group; HAP, human activity profile.

the sample are being indicated, as well as the classification of individuals from the HAP.

The predicted interaction wasn't significant, F (2.06, 60.84) = 5.36, p = 0.232, and this was qualified by 4-way RM mixed ANOVA interaction anatomical point, side, sex and HPA level on MTMP values F (2.06, 60.84) = 1.198, p = 0.271. Simple interaction analyses revealed the anatomical point on MTMP values *x* sex interaction was significant for both sex, F (1.35, 77.57) = 5.36, p = 0.015 and anatomical point on MTMP values *x* side interaction was significant for both sides F (1.12, 66.07) = 1.16, p = 0.024.

Table 3 shows the assessed MTMP values reached by men and women at 15 points, bilaterally, with the pressure algometer. The analysis of the values is related to the PA. The intragroup difference is related to the right and left sides in both groups. When associating with PA, we observed a difference in the females in the C7 (7.6 ± 3.7 vs. 6.5 ± 2.9) and hand points (5.6 ± 1.7 vs. 6.5 ± 2.1) for those classified as active, and in the deltoid (7.9 ± 3.0 vs. 9.3 ± 4.9) and knee (6.9 ± 2.4 vs. 6.4 ± 3.1) in the inactive groups. In the males a difference was observed in the points C5 (8.3 ± 3.7 vs. 6.4 ± 2), C7 (10.4 ± 4.3 vs. 7.6 ± 2.9), and gluteus (8.8 ± 2.4 vs. 7.3 ± 1.8), and TA muscles (11.7 ± 3.4 vs. 10.6 ± 3.3) for the active; C7 (8.6 ± 2.6 vs. 7.3 ± 2.3), L3 (8.3 ± 2.3 vs. 9.4 ± 2.7), and TA muscle (11.3 ± 2.2 vs. 10.0 ± 1.8) for the MA, and the hand for the inactive groups.

In the intergroup analysis associated with PA, men stood out in relation to women, with predominance for those classified as MA, where 11 of the 15 points evaluated showed differences. Among the active, differences were found on the right side for points C5 (4.5 ± 2.0 vs. 8.3 ± 3.7, d cohen = 1.3), deltoid (8.8 ± 3.5 vs. 12.6 ± 4.6, d cohen = 0.9) and pectoralis major muscles (4.1 ± 1.1 vs. 7.0 ± 3.6, d cohen = 0.9), and on the left side for the deltoid point (8.3 ± 3.2 vs. 14.0 ± 5.0, d cohen = 1.3). In inactive group, a difference was found only in the left TA (7.4 ± 2.6 vs. 9.4 ± 0.4, d cohen = 1.0). It is noteworthy that in all differences, a higher MTMP was observed in men (Table 3).

When comparing the difference between the points according to PA in each sex separately, no difference was found in the WG (Kruskal-Wallis, $p > 0.05$), and a difference was noted only in the left trapezoid point between the inactive and active groups in the WG (Kruskal-Wallis, $p = 0.02$).

Table 4 shows the difference in MTMP regardless of the level of PA. In the females, a difference was observed between the right and left sides only at the trapezoid point (Wilcoxon, $p < 0.05$). Differences were found in the males in the following points: C5; C7; rhomboid, gastrocnemius, and TA muscles; and hand (Wilcoxon, $p > 0.05$). In the intergroup analysis, a higher MTMP was noted in 21 points out of the 30 evaluated (Kruskal-Wallis, $p < 0.05$) (Table 4).

ANCOVA revealed that there is an effect of the sex covariate on the MTMP right C5 [F (1.58) = 11.54; p = 0.001], left C5 [F (1.58) = 4.86; p = 0.031], right trapezius [F (1.58) = 4.58; p = 0.037], right rhomboids [F (1.58) = 8.74; p = 0,004], right deltoids [F (1.58) = 7.18; p = 0.01], left deltoids [F (1,58) = 4.25; p = 0.044], right gluteus [F (1.58) = 7.03; p = 0.01], right gastrocnemius [F (1.58) = 6.41; p = 0.014], left gastrocnemius [F(1.58) = 5.78; p = 0.019], right TA [F(1.58) = 8.37; p = 0.005] and left TA [F (1.58) = 4.82; p = 0.032], such effects were evident in males.

Moreover, ANCOVA revealed that there is an effect of the covariate physical activity level on the MTMP right C7 [F (2.58) = 3.33; p = 0.043], right trapezius [F (2.58) = 3.59;

Table 3 MTMP between women and men by physical activity level.

		Females (n = 35)		Males (n = 30)	
	HAP	R	L	R	L
C5	Inactive	4.4 ± 1.4	4.5 ± 1.3	4.9 ± 0.5	4.7 ± 0.3
	Mod Active	4.9 ± 1.5	4.5 ± 1.6	6.6 ± 1.8[b]	6.0 ± 1.7[b]
	Active	4.5 ± 2.0	4.6 ± 2.0	8.3 ± 3.7[b]	6.4 ± 2.4[a]
C7	Inactive	5.9 ± 1.6	6.1 ± 3.2	6.6 ± 0.9	5.7 ± 0.5
	Mod Active	7.3 ± 2.6	6.9 ± 2.9	8.6 ± 2.6	7.3 ± 2.3[a]
	Active	7.6 ± 3.7	6.5 ± 2.9[a]	10.4 ± 4.3	7.6 ± 2.9[a]
Trapezius	Inactive	5.2 ± 2.1	4.7 ± 1.7	5.4 ± 1.2	4.4 ± 0.1
	Mod Active	6.0 ± 2.1	6.0 ± 2.9	7.2 ± 2.5	6.9 ± 1.9
	Active	6.3 ± 2.4	5.4 ± 2.3	9.7 ± 4.7	8.4 ± 2.6[b]
Romboid	Inactive	7.4 ± 2.3	7.3 ± 2.7	8.5 ± 1.9	7.6 ± 2.1
	Mod Active	7.7 ± 2.9	8.1 ± 2.3	11.0 ± 3.0[b]	10.0 ± 3.0
	Active	7.8 ± 3.9	7.6 ± 2.5	12.0 ± 4.9	10.8 ± 5.0
Deltoid	Inactive	7.9 ± 3.0	9.3 ± 4.9[a]	7.8 ± 1.6	7.6 ± 1.7
	Mod Active	8.8 ± 3.5	9.3 ± 3.5	12.6 ± 4.6[b]	12.5 ± 3.7[b]
	Active	8.5 ± 3.4	8.3 ± 3.2	13.4 ± 5.0[b]	14.0 ± 5.0[b]
L3	Inactive	6.6 ± 2.2	6.5 ± 2.5	6.5 ± 2.1	7.1 ± 0.9
	Mod Active	6.9 ± 1.6	7.0 ± 1.8	8.3 ± 2.3	9.4 ± 2.7[a,b]
	Active	7.6 ± 2.6	7.4 ± 2.4	9.0 ± 3.8	8.7 ± 4.0
L5	Inactive	7.2 ± 2.1	7.3 ± 3.3	7.4 ± 0.9	7.4 ± 0.7
	Mod Active	7.1 ± 2.0	7.5 ± 1.5	9.5 ± 2.9[b]	9.9 ± 2.9
	Active	8.0 ± 2.6	8.0 ± 2.1	9.8 ± 3.9	9.2 ± 3.1
Gluteus	Inactive	5.9 ± 1.9	5.7 ± 2.6	6.5 ± 1.6	6.8 ± 1.9
	Mod Active	6.1 ± 1.7	6.5 ± 1.7	8.0 ± 1.9[b]	8.1 ± 2.4
	Active	6.5 ± 2.4	6.7 ± 2.6	8.8 ± 2.4	7.3 ± 1.8[a]
Gastrocnemius	Inactive	6.6 ± 2.5	6.7 ± 2.3	7.2 ± 0.9	7.1 ± 1.3
	Mod Active	7.0 ± 2.5	7.1 ± 2.3	9.0 ± 1.9[b]	8.6 ± 1.4[b]
	Active	7.5 ± 2.8	6.9 ± 2.2	10.5 ± 3.4	9.9 ± 3.4
Pectoral Major	Inactive	4.5 ± 2.2	4.6 ± 2.6	4.4 ± 1.0	4.8 ± 0.4
	Mod Active	5.8 ± 2.8	6.1 ± 2.4	7.0 ± 2.2	6.9 ± 1.9
	Active	4.1 ± 1.1	4.5 ± 1.5	7.0 ± 3.6[b]	9.9 ± 3.4
Elbow	Inactive	5.7 ± 2.2	5.4 ± 1.7	5.6 ± 0.5	5.2 ± 0.4
	Mod Active	6.3 ± 2.6	6.5 ± 2.0	8.8 ± 2.9[b]	8.3 ± 2.1[b]
	Active	5.8 ± .1.5	5.9 ± 1.7	7.6 ± 3.4	7.5 ± 3.2
Hand	Inactive	5.6 ± 2.1	6.1 ± 2.0	4.8 ± 0.9	5.4 ± 0.7[a]
	Mod Active	6.7 ± 2.6	7.6 ± 2.2	8.4 ± 2.0[b]	9.0 ± 2.2
	Active	5.6 ± 1.7	6.5 ± 2.1[a]	6.8 ± 3.1	7.7 ± 2.9[a]
Knee	Inactive	6.9 ± 2.4	6.4 ± 3.1[a]	6.2 ± 1.1	6.3 ± 1.7
	Mod Active	7.1 ± 1.5	6.9 ± 2.3	9.0 ± 2.2[b]	8.3 ± 1.6
	Active	8.1 ± 3.3	7.2 ± 2.0	7.5 ± 2.0	7.6 ± 2.5
Tibial Anterior	Inactive	7.8 ± 2.5	7.4 ± 2.6	8.9 ± 1.4	9.4 ± 0.4[b]
	Mod Active	8.5 ± 2.9	9.0 ± 3.4	11.3 ± 2.2[b]	10.0 ± 1.8[a]
	Active	8.9 ± 3.2	8.4 ± 2.9	11.7 ± 3.4	10.6 ± 3.3[a]
Ankle	Inactive	6.2 ± 2.0	6.3 ± 2.0	6.4 ± 1.2	6.4 ± 0.6
	Mod Active	6.7 ± 2.6	7.1 ± 2.6	8.2 ± 2.0	7.9 ± 2.0
	Active	6.4 ± 2.2	6.2 ± 2.3	6.5 ± 1.3	7.1 ± 1.7

MTMP, Maximum tolerance to mechanical pain; HAP, Human Activity Profile; Mod, Moderately; C5,5th cervical vertebra; C7, 7th cervical vertebra; L3, 3rd lumbar vertebra; L5, 5th lumbar vertebra.
[a] $p < 0.05$ (within groups, t test).
[b] $p < 0.05$ same side between groups (Kruskall Wallis).

p = 0,034], left trapezius [F (2.58) = 4.78; p = 0.012], left elbow [F (2.58) = 3.71; p = 0.030] such effects were evident for active groups.

Correlations found in male were: right deltoids inactive x active (R = 0.971, p = 0.02), right pectoralis major inactive x active (R = -0.978, p = 0.02); right elbow inactive x moderately active (MA) (R = -0.982, p = 0.018), right hand MA x active (R = 0.741, p = 0.02), right ankle inactive x MA (R = 0.996, p = 0.004), left gastrocnemius MA x active (R = 0.701, p = 0.03), left 3rd lumbar vertebra MA x active (R = 0.692, p = 0.03). In female only correlation was found

Table 4 MTMP Comparison between women and men.

	Females		Males	
	R	L	R	L
C5	4.53 ± 1.63	4.53 ± 1.61	6.58 ± 2.82[b]	5.62 ± 2.26[a,b]
C7	6.74 ± 2.75	6.47 ± 3.02	8.35 ± 3.45[b]	6.88 ± 2.65[a]
Trapezius	5.85 ± 2.24	5.26 ± 2.26[a]	7.45 ± 3.67	6.76 ± 2.64[b]
Romboid	7.55 ± 2.99	7.58 ± 2.57	10.36 ± 4.17[b]	9.20 ± 4.17[a]
Deltoid	8.26 ± 3.23	9.92 ± 4.18	12.38 ± 5.36[b]	11.51 ± 4.54[b]
L3	7.00 ± 2.22	6.85 ± 2.33	8.10 ± 2.97	8.57 ± 3.34[b]
L5	7.42 ± 2.24	7.51 ± 2.60	9.15 ± 3.32[b]	9.11 ± 3.20[b]
Gluteus	6.14 ± 2.00	6.19 ± 2.42	7.92 ± 2.31[b]	7.49 ± 2.91[b]
Gastrocnemius	6.97 ± 2.59	6.88 ± 2.25	9.07 ± 2.70[b]	8.41 ± 2.44[a,b]
Pectoral Major	4.73 ± 2.23	4.99 ± 2.40	6.45 ± 2.97[b]	6.39 ± 2.56[b]
Elbow	5.93 ± 2.17	5.86 ± 1.84	7.69 ± 3.35[b]	7.37 ± 2.84[b]
Hand	5.93 ± 2.18[b]	6.68 ± 2.19	7.00 ± 2.79[b]	7.82 ± 2.81[a]
Knee	7.34 ± 2.54[b]	6.74 ± 2.62	7.90 ± 2.49	7.39 ± 2.11
Tibial Anterior	8.27 ± 2.84	8.06 ± 2.96	10.78 ± 2.86[b]	9.77 ± 2.52[a,b]
Ankle	6.42 ± 2.24	6.52 ± 2.24	7.26 ± 2.11	7.20 ± 2.15

MTMP, Maximum tolerance to mechanical pain; R, rigth; L, left; C5, 5th cervical vertebra; C7, 7th cervical vertebra; L3, 3rd lumbar vertebra; L5, 5th lumbar vertebra.
[a] $p < 0.05$ comparing right and left side within group.
[b] $p < 0.05$ (between groups).

Table 5 Linear regression according to HAP and sex.

Active HAP Classification/sex							
						95 % Confidence Interval for mean	
	R2	R Adjusted	F	*p*	beta	Lower bound	Upper bound
C5R	0.309	0.269	7.615	0.013*	0.55	0.894	6.704
DelR	0.272	0.229	6.359	0.022*	0.52	0.806	9.062
DelL	0.343	0.304	8.864	0.008*	0.58	1.667	9.778
PMR	0.252	0.208	5.723	0.029*	0.50	0.339	5.411
PML	0.216	0.171	4.681	0.045*	0.46	0.059	4.725
Moderately Active HAP Classification/sex							
C5R	0.198	0.165	5.931	0.023*	0.45	0.269	3.257
C5L	0.159	0.124	4.531	0.442*	0.39	0.045	2.913
RbR	0.226	0.194	7.008	0.014*	0.47	0.728	5.882
DelR	0.156	0.121	4.435	0.046*	0.39	0.075	7.426
L5R	0.158	0.123	4.498	0.044*	0.39	0.063	4.625
GLR	0.202	0.166	5.991	0.022*	0.44	0.294	3.462
KR	0.172	0.137	4.972	0.035*	0.41	0.142	3.677
TAR	0.247	0.216	7.868	0.010*	0.49	0.757	4.977
L3L	0.176	0.141	5.117	0.033*	0.41	0.203	4.435
ELL	0.164	0.129	4.695	0.042*	0.40	0.088	3.165

HAP, human activity profile; R, rigth; L, left; C5, 5th cervical vertebra; L3, 3rd lumbar vertebra; del, deltoid; PM, Pectoralis major; Rb, Rhomboid; L5, 5th lumbar vertebra; GL, gluteus; K, knee; TA, tibila anterior; EL, elbow.

on right hand inactive x MA (R = -0.718, $p = 0.02$) and left elbow MA x active (R = -0.670, $p = 0.04$)

Table 5 presents the data of the regression analysis performed between the level of PA and sex. The regression analyses in the inactive group were not significant. Analyzing the regressions in the moderately active and the active groups, it appears that the level of PA influenced less than 30% of the MTMP in both sexes (Table 5).

Linear regression analysis verified that level of physical activity explains only 30% of MTMP right C5 (r2 = 0.30; F = 7.61; $p = 0.013$); 27% of MTMP right deltoids (r2 = 0.27; F = 6.35; $p = 0.022$); 34% of MTMP left deltoids (r2 = 0.34; F = 8.86; $p = 0.008$); 25% of MTMP right pectoralis major (r2 = 0.25; F = 5.72; $p = 0.029$); 21% of MTMP left pectoralis major (r2 = 0.21 F = 4.68; $p = 0.045$) in both active HAP classification sexes.

Furthermore, linear regression revealed moderately active HAP classification explains only 19% of MTMP right C5 (r2 = 0.19; F = 5.93; p = 0.023); 22% of MTMP right rhomboids (r2 = 0.22; F = 7.00; p = 0.014); 15% of MTMP rights deltoids (r2 = 0.15; F = 4.43; p = 0.046); 15% of MTMP right 5th lumbar vertebra (r2 = 0.15; F = 4.49; p = 0.044); 20% of MTMP right gluteus (r2 = 0.20; F = 5.99; p = 0.022); 17% of MTMP right knee (r2 = 0.17; F = 4.97; p = 0.035); 24% of MTMP right TA (r2 = 0.24; F = 7.86; p = 0.010); 17% of MTMP left 3rd lumbar vertebra (r2 = 0.17; F = 5.11; p = 0.033); 16% of MTMP left elbow (r2 = 0.16; F = 4.695; p = 0.042) in male ones.

Discussion

This study showed the following outcomes: the level of PA had little influence on the MTMP, and there was a slight difference in the MTMP between the right and left sides of the body and that men had a higher MTMP than women.

This is one of the first studies to assess the MTMP of individuals with different levels of PA and not related to the sport practiced such as the those studies by Ellingson et al.[21]; Naugle and Riley,[22] Umeda et al.,[23] Manning et al.,[27] Awied et al.,[28] and Leznicka et al.[29]

In our study, there was a minor relationship between PA and the MTMPAndrzejewski et al.[24] found that the higher the PA level, the higher the PPT in 13 points of the body among the different ages and level of PA. However, the level of PA was only reported by the participants as low and moderate according to the number of times per week that the activity was practiced. Lemming et al.[25] also found that the higher the PA level, the higher the PPT; however, it was evaluated in a single point only and after compression of the sphygmomanometer cuff in the leg.

A study by Bertolini et al.[42] observed in animal research with rats that resistance exercise was responsible for reducing nociception through opioids. According to the same authors, other studies with walking and swimming have obtained the same results. Oliveira et al.[43] also pointed out that the same analgesic action resulting from the practice of exercise through the endogenous opioid system occurs in humans, but this is not completely clear yet in the literature.

As a small difference was found between the right and left sides when there is no pathology involved, it is suggested that the MTMP measurement can be performed unilaterally. However, when there is an injury at the site, testing the contralateral side is suggested.

Comparing between the sexes, it was found that men had a higher MTMP than women at eight points bilaterally (C5, L5, elbow, and deltoid gluteus, gastrocnemius, pectoralis major, and TA muscles) and at four points unilaterally (C7, L3, trapezoid and rhomboid muscles, and hand). This might be explained by Mariani et al.,[44] who observed that the PPT was higher in men than in women, as well, and said that biological and psychosocial factors explain these differences, because there is an easier development of painful musculoskeletal disorders in woman.

These results can be related with the studies by Garcia et al.[34] who evaluated PPT in the C5 and gluteus muscle, Widmalm et al.[45] (PPT) and Petrini et al.[46] (MTMP) who evaluated the trapezoid muscle, and Manning and Fillingim[27] who evaluated PPT in the trapezius and pectoralis major muscles. Kroner-Herwig et al.[38] also found greater MTMP in the elbow, the first dorsal interosseous muscle of the hand, and the deltoid muscle.

Binderup et al.[47] evaluated the PPT in lumbar spine of 22 individuals (11 men and 11 women) in addition to the trapezius. While the present study evaluated the points of L3 and L5, the researchers evaluated 27 points in the erector muscle of the spine, both the right and left sides of the lumbar spine. Despite this difference, both studies found a higher MTMP or PPT in men in the lower back.

At the previous tibial point, Stefania et al.[40] and Rivest et al.[48] found no significant differences in PPT between the sexes. In our study, we found difference on MTMP in this point.

At two points (knee and ankle) in our study, no difference was found in the MTMP between men and women. Garcia et al.,[34] when analyzing the PPT in the same point bilaterally on the knee, no differences were found. Nevertheless, in our study, active participants showed a greater MTMP at the gluteus point on the left side.

This study had a single evaluator for all participants, thus ensuring greater data reliability. In addition, the public evaluated is approximately aged, avoiding conflicts in the results regarding this factor. As a limitation, participants with chronic disease or those with menstrual periods were not excluded, factors that can alter the perception of pain, and it was excluded participants with higher MTMP. Other instruments could be used to assess pain as well as the level of PA.

It is suggested to continue the study with a larger number of participants to better elucidate the results of the present study.

Conclusion

It is possible to note that the PA level has little influence on the MTMP, there is a strong correlation between the right and left sides, and the MTMP of young men is higher than that of young women in almost all points evaluated through pressure algometry, except the ankle and the first interosseous muscle of the hand. However, further research is needed to confirm the data found in this study, since literature found is still inconclusive.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Efficacy of serratus anterior plane block versus thoracic paravertebral block for postoperative analgesia after breast cancer surgery - a randomized trial

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KEYWORDS
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Abstract
Background: Breast cancer surgery is associated with considerable acute post-surgical pain and restricted mobility. Various regional and neuraxial anesthesia techniques have been used to alleviate post-mastectomy pain. Ultrasound-guided serratus anterior plane block (SAPB) has been considered a simple and safe technique. This randomized control study was performed to compare the efficacy of SAPB with the thoracic paravertebral block (TPVB) for postoperative analgesia after breast cancer surgery.
Methods: A total of 40 adult ASA physical status I - II female patients undergoing radical mastectomy were randomly allocated into two groups to receive either ultrasound-guided TPVB or SAPB with 0.4 mL.kg^{-1} 0.5% ropivacaine, 30 min before surgery. All patients received standardized general anesthesia for surgery. Injection diclofenac and tramadol were used for postoperative rescue analgesia. The time to first rescue analgesia, total analgesic consumption in the first 24 hours, postoperative pain scores, and any adverse effects were recorded.
Results: The time to first rescue analgesia was significantly longer in the SAPB group (255.3 ± 47.8 min) as compared with the TPVB group (146.8 ± 30.4 min) ($p < 0.001$). Total diclofenac consumption in 24 hours was also less in the SAPB group (138.8 ± 44.0 mg vs 210.0 ± 39.2 mg in SAPB and TPVB group respectively, $p < 0.001$). Postoperative pain scores were significantly lower in the SAPB group as compared with TPVB group ($p < 0.05$). The incidence of PONV was also less in the SAPB group ($p = 0.028$). No block-related adverse effects were reported.

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Conclusion: We found that the serratus anterior plane block was more effective than the thoracic paravertebral block for postoperative analgesia after breast cancer surgery.
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Introduction

Modified radical mastectomy, a common surgical procedure in breast cancer patients, is associated with considerable acute postoperative pain and restricted shoulder mobility leading to delayed hospital discharge.[1] Adequate post-surgical pain management is important for the early mobilization and long-term well-being of these patients. Various regional anesthesia techniques have been used to provide postoperative analgesia in this group of patients including intercostal plane block,[2] local anesthetic infiltration,[3] brachial plexus block,[4] thoracic epidural,[5] thoracic paravertebral block (TPVB),[6–8] and thoracic wall blocks.[9–12] Among these, TPVB is the most commonly used technique for controlling post-mastectomy pain but carries a high failure rate (6 - 10%) and the risk of hypotension, pneumothorax, and vascular puncture.[8]

Recently, thoracic wall blocks (Pecs I and II) have been evolved as less invasive alternatives to the paravertebral block for providing extended postoperative analgesia after breast surgery.[9–11] The serratus anterior plane block (SAPB) is a newer interfacial plane block of the chest wall and appears to be safe and easy to perform as serratus muscle is superficial and easily identifiable under ultrasound.[12] Blanco et al.[13] suggested that SAPB may target the thoracic nerves more selectively than pectoral blocks and provides predictable and effective anesthesia to the anterolateral chest wall. However, literature is scarce about the efficacy of SAPB for postoperative analgesia after breast cancer surgery. Therefore, the present study has been planned to compare the efficacy of ultrasound-guided SAPB with TPVB for the management of postoperative pain after total mastectomy and axillary clearance surgery in breast cancer patients. The primary objective of the study was to evaluate the duration of postoperative analgesia, and the secondary objectives were to observe the pain scores and rescue analgesic consumption for 24 hours postoperatively.

Methods

This randomized control trial was carried out after obtaining approval from the institutional ethics committee (reference number NK/1585/MD/10559-60) and written informed consent from the patients. The study was registered with the clinical trial registry (REF/2017/01/013128) and adheres to the applicable CONSORT guidelines. A total of 40 ASA (American Society of Anesthesiologists) physical status I - II female patients in the age group of 18 - 65 years, scheduled to undergo total mastectomy with axillary clearance under general anesthesia were included. The patients who had local infection at the block site, coagulopathy, morbid obesity (BMI > 40 $kg.m^{-2}$), allergy to local anesthetics, decreased pulmonary reserve, uncontrolled hypertension or ischemic heart disease, renal dysfunction, and pre-existing neurological deficits and psychiatric illness were excluded. The patients were kept fasting overnight and pre-medicated with tablet alprazolam 0.25 mg and tablet ranitidine 150 mg orally the night before and two hours prior to surgery. They have explained the numeric rating scale (NRS, 0 - 10, where 0 stands for no pain and 10 stands for worst imaginable pain) for postoperative pain assessment.

The patients were randomly allocated into two groups using computer-generated random numbers which were kept in sealed opaque envelopes numbered sequentially and opened just before administration of the block. Group 1 patients received thoracic paravertebral block at T4 level (TPVB group) while group 2 patients received serratus anterior plane block at the level of the 5th intercostal space (SAPB group). The blocks were given 30 minutes before surgery by an experienced anesthesiologist (having experience of administration of more than 20 blocks each with the same technique) in the pre-operative room under all aseptic precautions and vital parameters monitoring. The anesthesiologist who performed the blocks did not participate in further management of the patients and data collection.

In TPVB group, the block was performed by placing the patient in a sitting position. The spinous processes of C7 to T6 vertebrae were marked with a permanent skin marker. Both cervical and thoracic paravertebral areas were prepared with 5% povidone-iodine solution and covered with sterile drapes. After covering the USG cable with a sterile ultrasound probe cover, a linear high frequency (5-10 MHz) ultrasound probe (Sonosite, Inc. Bothell. WA 98021 USA) was placed vertically 2.5 cm away from the midline in the sagittal paramedian plane at T4 level on the side of surgery. At this level, the probe was moved laterally and obliquely, until the typical double layer of the internal intercostal membrane (IIM), the transverse process, superior costotransverse ligament, and the pleura were visualized in one image (Fig. 1). After infiltrating the skin with 3 - 5 mL of 2% lignocaine, a 22-G, 80-mm SonoPlex needle was inserted in-plane from caudal to cranial direction. Once the needle tip had reached in between the pleura and costotransverse ligament, 0.4 $mL.kg^{-1}$ of 0.5% ropivacaine was administered after negative aspiration. During the administration of the local anesthetic downward displacement of the pleura was observed.

In the SAPB group, patients were placed in a lateral position with the operating side up and the arm abducted. Under all antiseptic precautions, a linear high-frequency ultrasound probe was placed vertically in the mid-axillary line at the level of the 5thintercostal space. At this level, one can identify subcutaneous tissue and serratus anterior muscle in the superficial plane, the intercostal muscles (external, internal, and innermost) in the intermediate plane and

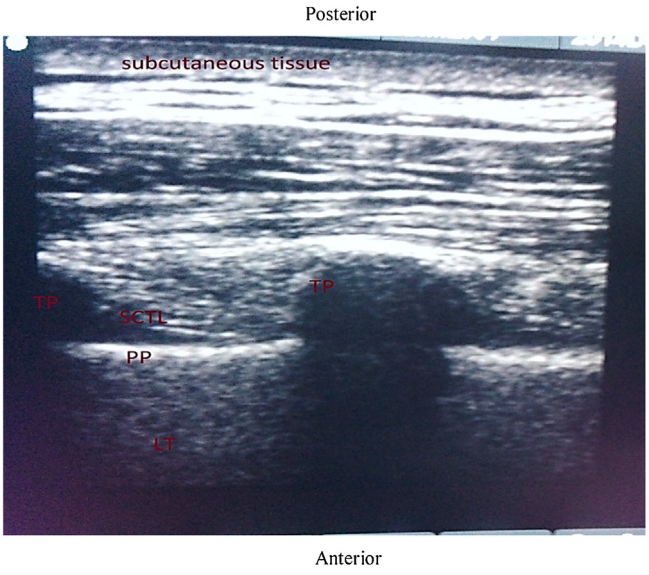

Figure 1 Ultrasound image of thoracic paravertebral space showing the transverse process (TP), parietal pleura (PP), and superior costotransverse ligament (SCTL).

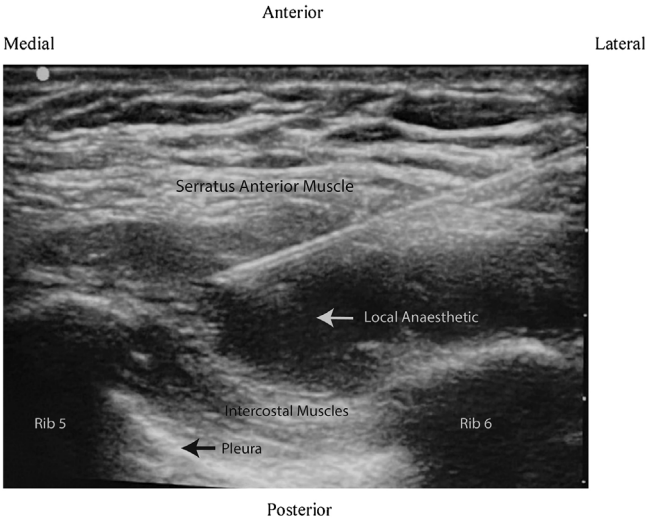

Figure 2 Ultrasound image of serratus anterior plane block (echogenic needle is placed below the serratus anterior muscle between 5th and 6th rib to deposit local anesthetic).

ribs, pleura, and lung in the deep plane. The skin puncture site was infiltrated with 2% lignocaine and a 22-G, 50-mm SonoPlex needle was inserted from caudal to the cranial direction in an in-plane approach until the tip was placed between serratus anterior muscle and intercostal muscles. After negative aspiration, 0.4 mL.kg^{-1} of 0.5% ropivacaine was deposited in this space (Fig. 2).

The patients were monitored continuously for heart rate and oxygen saturation, and the non-invasive blood pressure was recorded at 5-min intervals. The sensory level of the block was assessed by an anesthesiologist blinded to the group allocation, with pinprick sensation every 5 minutes in each dermatomal distribution from T1 to T6 and the number of dermatomes having less sensation as compared with the opposite side was noted. If pinprick sensation did not decrease in any segment until 30 minutes after the block, then it was considered as a block failure. These patients were managed with additional (2 μg.kg^{-1} during induction plus according to the requirement) doses of fentanyl for perioperative analgesia. Any block-related complications like hypotension, vascular puncture, Horner's syndrome, and pneumothorax, were recorded.

The patients were shifted to the operating room 30 minutes after the procedure. Anesthesia was induced with fentanyl 1 μg.kg^{-1} followed by propofol 2 - 3 mg.kg^{-1} until the loss of verbal response. Atracurium 0.5 mg.kg^{-1} was used to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen and isoflurane (MAC 1 - 1.3). The patient's lungs were ventilated with positive pressure ventilation to maintain end-tidal carbon dioxide ($EtCO_2$) between 32 - 36 mmHg. The patients received a continuous infusion of normal saline at the rate of 5 - 8 mL.kg^{-1}.h^{-1}. An increase in mean arterial pressure (MAP) > 25% of baseline was considered as inadequate analgesia and 1 μg.kg^{-1} fentanyl was administered intravenously. Any episode of hypotension (MAP < 25% of baseline) was treated with infusion of normal saline, and if required injection mephentermine in titrated doses. All patients received ondansetron 0.1 mg.kg^{-1} 30 minutes before the end of surgery to prevent postoperative nausea and vomiting. After completion of surgery residual neuromuscular blockade was reversed with intravenous neostigmine 50 μg.kg^{-1} and glycopyrrolate 10 μg.kg^{-1} and the endotracheal tube was removed once they were fully awake and breathing adequately.

The patients were monitored for 24 hours after surgery in the post-anesthesia care room. The vital parameters and pain scores (NRS) were recorded at 0, ½, 1, 2, 4, 6, 8, 12, and 24 hours by an investigator blinded to the group allocation. Patients with NRS more than 3 or those demanding analgesics received diclofenac sodium 75 mg intravenously. If NRS was remained high 30 minutes after administration of diclofenac, then injection tramadol 1 mg.kg^{-1} was given. Time for first rescue analgesia administration (i.e., the time from administration of block to the first demand of diclofenac) and the total analgesic consumption in 24 hours were recorded. Postoperative nausea and vomiting (PONV) were assessed using a 4-point scale system (0 = no PONV, 1 = mild nausea, 2 = severe nausea, 3 = vomiting), and antiemetic ondansetron (4 mg) was given if the PONV score was > 1. Any other adverse effects like hypotension, respiratory depression, shivering and urinary retention were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 22 (Statistical Packages for the Social Sciences, Chicago, IL). The normality of quantitative data was checked by measures of the Kolmogorov-Smirnov test of normality. Continuous and quantitative variables were expressed in mean and standard deviation when normally distributed, and as median and interquartile ranges when non-normally distributed. Categorical variables were expressed in absolute and relative frequencies. Normally distributed data were compared using unpaired t-test and for non-normally distributed data Mann-

Table 1 Demographic data.

Parameters	TPVB group (n = 20)	SAPB group (n = 20)
Age (yr)	48.2 ± 9.8	50.8 ± 9.5
Weight (kg)	59.8 ± 11.6	62.3 ± 9.6
Height (cm)	157.9 ± 4.4	157.5 ± 4.4
ASA 1 : 2 (n)	16:4	15:5
Duration of surgery (min)	71.3 ± 14.6	76.5 ± 15.7
Drug (LA) volume (mL)	23.7 ± 3.7	23.6 ± 3.9

Values are expressed as mean ± SD or number (n) of patients.

Whitney U test was used. The Chi-square test or Fisher's exact test was applied for categorical data. Intragroup comparison of hemodynamic variables from baseline was done by repeated-measures ANOVA followed by Student's t-test. Post-hoc analysis with Bonferroni correction was applied for multiple comparisons. The Kaplan-Meier survival curves were drawn with the time to first analgesic administration in the postoperative period, being considered as the event and log-rank analysis was performed for comparison between the groups. A p value < 0.05 was considered statistically significant.

The sample size was calculated based on a previous study by Kulhari et al,[10] an increase in the duration of postoperative analgesia by 30 minutes with SAPB was considered a clinically relevant difference. For a significance level of 0.05 and power of 0.8, at least 18 patients in each group were needed. Therefore, 40 patients were included in the study.

Results

The groups were comparable regarding the patients' age, weight, height, and ASA physical status (Table 1). There was no significant difference between the two groups in the duration of surgery and the total volume of local anesthetic used for the blocks. Although more patients in the SAPB group had sensory spread at the level of T1, T2, and T6 as compared to the TPVB group, it was not statistically significant (Table 2). One patient in the SAPB group had no sensory deficit and considered as block failure.

The Kaplan-Meier survival curves for the comparative cumulative probability of first recue analgesic requirement in the postoperative period are shown in Fig. 3. Time to first rescue analgesia (duration of analgesia) was significantly longer in the SAPB group (255.3 ± 47.8 min) as compared with the TPVB group (146.8 ± 30.4 min) with a p value of < 0.001. The diclofenac consumption in the first 24 hours after surgery was significantly less in the SAPB group as compared to the TPVB group (p < 0.001) while tramadol requirement was comparable in both the groups (Table 3). Post-operative pain scores were significantly lower in the SAPB group as compared to the TPVB group (p < 0.05) during the first 2 hours and then at 6, 8, and 24 hours after surgery (Fig. 4). The intraoperative and postoperative hemodynamic variables were comparable in both groups except just after induction of anesthesia when MAP in the TPVB group was lower as compared to the SAPB group (p < 0.039). No episode of hypotension or bradycardia was reported in any group of patients. The incidence of PONV was significantly less in the SAPB group (p = 0.028). Eight patients in the TPVB group had PONV (grade > 2) and all received antiemetics whereas two patients in the SAPB group had PONV and only one of them required antiemetics. No block- related adverse effects were reported in any group of patients.

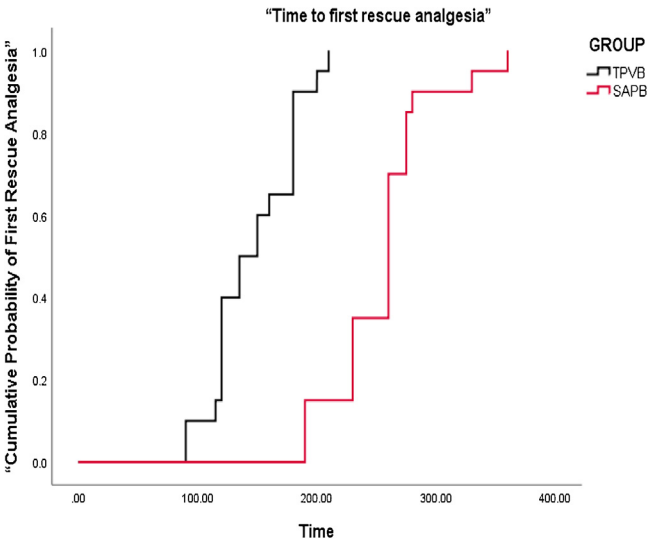

Figure 3 Kaplan-Meier survival curves for the cumulative probability of first recue analgesic requirement in the postoperative period in both the groups (log rank analysis for comparison between groups shows p < 0.001).

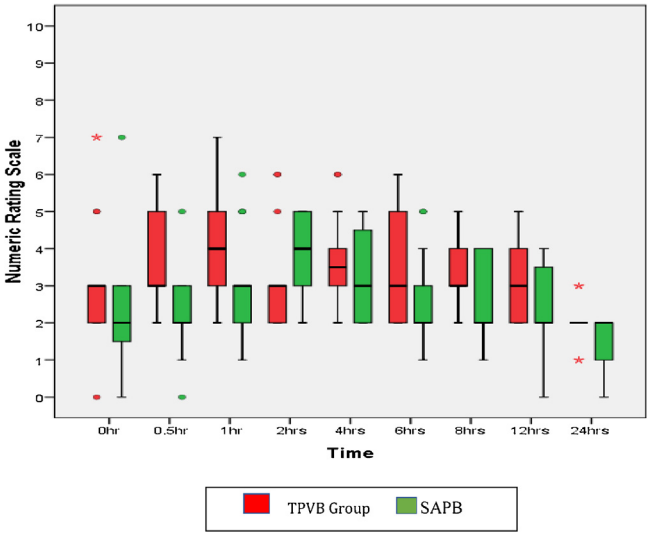

Figure 4 Numeric rating scale (NRS) scores for 24 hours after surgery (median, IQR).
p values: ½ h < 0.001, 1 h = 0.007, 2 h = 0.040, 4 h = 0.167, 6 = 0.040, 8 h = 0.021, 12 h = 0.080, 24 h = 0.032.

Discussion

In this randomized control study, we found that the patients who received SAPB had a longer duration of postoperative analgesia as compared to the patients who received TPVB. The SAPB group patients also showed lower postoperative pain scores and demanded less rescue analgesia in

Table 2 Dermatomal spread of sensory block.

Dermatomal level	TPVB group (n = 20)	SAPB group (n = 20)	*p*-value
T1	0	4 (20%)	-
T2	4 (20%)	6 (30%)	0.465
T3	20 (100%)	19 (95%)	1.000
T4	20 (100%)	19 (95%)	1.000
T5	20 (100%)	19 (95%)	1.000
T6	14 (70%)	17 (85%)	0.451

Values are presented as the number (%) of patients.

Table 3 Duration of analgesia and rescue analgesic requirement.

Parameters	TPVB group (n = 20)	SAPB group (n = 20)	*p*-value
Time to first rescue Analgesia (min)	146.75 ± 30.361	255.26 ± 47.798	< 0.001
Total Diclofenac (mg)	210.00 ± 39.236	138.75 ± 44.036	< 0.001
Total Tramadol (mg)	92.86 ± 18.898	98 ± 12.46	0.626

Values are expressed as mean ± SD.

comparison to the TPVB group. The postoperative tramadol consumption was low in both groups.

Both SAPB and PVPB are attractive regional anesthesia options for providing postoperative analgesia after a radical mastectomy. Although the analgesic efficacy of TPVB versus placebo is well established in various thoracic surgeries, it carries theoretical risks of hypotension and pneumothorax, and not all providers have expertise and are comfortable with the technique.[8] The SAPB has recently gained popularity because of its relative safety, and the ease with which it is learnt and performed.[12] SAPB is usually performed at the level of 5th or 6th rib in midaxillary line via deposition of local anesthetic superficial or deep to the serratus anterior muscle.[13] Although both superficial and deep approaches have been found equally effective for providing postoperative analgesia after breast surgery, Abdulla et al.[14] reported that deep SAPB is more advantageous from a surgical point of view than superficial SAPB. Also, this avoids the possibility of transitory palsy of the long thoracic nerve leading to a winged scapula that can be mistaken with a surgical lesion of this nerve.

SAPB has been used effectively for breast cancer surgery as well as video-assisted trans-thoracic surgery.[15,16] A recent meta-analysis[17] has shown that SAPB reduced postoperative pain scores, decreased opioid consumption in the first 24 hours after surgery, and prolonged time to first analgesia request as well as reduced the incidence of PONV and pruritus as compared with non-block care in breast and thoracic surgery patients. The block appeared safe with no study reporting any block-related complications.[17] The preoperative administration of SAPB also improved the quality of recovery and patient satisfaction following breast cancer surgery.[18]

However, the efficacy of SAPB in comparison with TPVB is not well established. Our results are supported by a recent study,[19] which also found SAPB superior to TPVB in terms of the delayed requirement for the first rescue analgesia and 24 hours reduced analgesic consumption in patients undergoing breast cancer surgery. However, in a previous study, Hetta et al.[20] found SAPB inferior to the TPVB in terms of duration of postoperative analgesia and rescue analgesic requirements. This may be due to multiple injection technique used in the TPVB group (at T2, T4, and T6 levels) in their study.[20]

SAPB targets the lateral cutaneous branches of the intercostal nerves as they traverse between the fascial planes and provide extensive anesthesia of the anterolateral chest wall.[21] Although TPVB targets the spinal nerves directly, the spread of local anesthetic is not predictable, it may spread either laterally to block the intercostal nerves or medially into the epidural space through the intervertebral foramina.[22] A single level TPVB can block one to four dermatomes only. Therefore, a single-level injection of TPVB may not be enough to produce sufficient analgesia after extensive breast cancer surgeries.

In the present study, the duration of analgesia was 255.3 ± 47.8 minutes in SAPB group, which is comparable to the previous reports. Blanco et al.[13] demonstrated 386 (±160) minutes paresthesia in 3 - 5 dermatomes after administration of deep SAPB with 0.4 mg.kg^{-1} local anesthetic in volunteers. Rahimzadeh et al.[23] reported the time to first rescue analgesia as 323.5 ± 49.7 minutes after SAPB in patients undergoing breast cancer surgery. In a recent meta-analysis, Chong et al.[17] have also found the time to first analgesic request in SAPB as 379.2 minutes. However, a longer duration of postoperative analgesia (> 12 hours) has been reported after SAPB in patients undergoing partial or simple mastectomy.[24,25] This may be because the axillary dissection usually requires analgesia up to T1 level while the spread of local anesthetic in the present study was mainly from T2 to T6 segments. Therefore, the pain caused by the axillary dissection might not be effectively controlled by the block. We used about 23 mL local anesthetic while up to 30 - 40 mL of local anesthetic has been used in previous studies.[17,24]

Our success rate was 95% in the SAPB group and 100% in the TPVB group. We used echogenic needles to perform the blocks, as the use of echogenic needles under real-time ultrasound provides better visualization of the needle tip concerning the nearby structures and spread of local anes-

thetics, thus avoids complications. None of our patients had any block- related complications. The low incidence of PONV in patients receiving SAPB might be due to better pain relief (lower pain scores). Previous studies also reported a lower incidence of PONV in patients receiving SAPB.[17]

The main limitation of our study is that the subjects and the anesthesiologist performing the block were not blinded to the group assignment, though the investigator who collected the data was not aware of the group allocation of the patients. In addition, we followed up the patients for only 24 hours after surgery. We did not assess the effect of the block on early hospital discharge and the incidence of chronic pain. Another limitation of this study is that it is a single-center study. Therefore, further multicenter studies are required to generalize our results.

In conclusion, we found SAPB superior to TPVB in terms of prolonged duration of postoperative analgesia and reduced rescue analgesic requirement after radical mastectomy in breast cancer patients. Therefore, SAPB may be a viable alternative to the TPVB, which is technically more challenging and have a higher potential for adverse effects. Further studies are required to compare the efficacy and safety of SAPB with other chest wall blocks. As SAPB usually provides 4 - 6 hours of postoperative analgesia in these patients, the role of additives can also be assessed.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Evaluation of lignocaine, dexmedetomidine, lignocaine-dexmedetomidine infusion on pain and quality of recovery for robotic abdominal hysterectomy: a prospective randomized controlled trial

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KEYWORDS
Quality of recovery score;
Robotic abdominal hysterectomy;
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Lignocaine;
Dexmedetomidine

Abstract
Background: Acute postoperative pain is associated with poor quality of recovery after surgery. Perioperative use of intravenous lignocaine or dexmedetomidine have demonstrated better pain control, early return of bowel function, and effects on quality of recovery.

Methods: Ninety-six women planned for elective robotic abdominal hysterectomy were randomized into four groups. Groups received lignocaine infusion (1.5 $mg.kg^{-1}$ loading, 2 $mg.kg^{-1}.h^{-1}$ infusion) (Group I), dexmedetomidine infusion (1 $\mu g.kg^{-1}$ loading, 0.6 $\mu g.kg^{-1}.h^{-1}$ infusion) (Group 2), lidocaine (1.5 $mg.kg^{-1}$ loading, 2 $mg.kg^{-1}.h^{-1}$ infusion), and dexmedetomidine infusions (1 $\mu g.kg^{-1}$ loading, 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion) (Group 3), and normal saline 10 mL loading, 1 $mL.kg^{-1}.h^{-1}$ infusion) (Group 4). Primary outcome was visual analogue pain scores at 1, 2, 4, 12, and 24 hours after surgery. Secondary outcomes included postoperative fentanyl requirement, time of return of bowel sounds and flatus, QoR15 score on day 1, 2, and discharge.

Results: The VAS was significantly lower in Groups 2 and 3 compared to Groups 1 and 4. Total postoperative fentanyl consumption in the first 24 hours was 256.25 ± 16.36 mcg (Group 1), 177.71 ± 16.81 mcg (Group 2), 114.17 ± 16.19 mcg (Group 3), and 304.42 ± 31.26 mcg (Group 4), respectively. Time to return of bowel sounds and passage of flatus was significantly shorter in Groups 2 and 3 ($p < 0.01$). QoR15 scores after surgery were higher in Group 3 compared to Groups 1, 2, and 4, ($p < 0.01$) respectively.

Conclusion: Combined infusion of lignocaine and dexmedetomidine significantly decreased postoperative pain, fentanyl consumption, and improved quality of recovery score after surgery in patients undergoing Robotic abdominal hysterectomy.
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Introduction

Postoperative pain is a normal physiological response to surgical trauma/manipulations/traction of somatic or visceral structures. Inflammatory, visceral or neuropathic mechanism all contribute to postoperative pain.[1] In the era of fast-track surgeries the anesthesia technique needs to be modified to satisfy surgical needs and early discharge. Minimally invasive surgeries, early mobilization, and preference of short acting anesthetics along with multimodal analgesics postoperatively decrease hospital stay along with increased patient satisfaction.[2] Hysterectomy is a common gynecological surgical procedure done worldwide for a number of reasons. The surgical approaches have evolved with time from open abdominal hysterectomy to laparoscopic hysterectomy to robotic hysterectomy. The advantages for patients are decreased tissue damage, less inflammation and pain, thereby decreasing hospital stay and improving patient satisfaction.[3]

Perioperative use of infusions of lignocaine or dexmedetomidine influence postoperative pain and early home readiness. The advantage postulated is a consequence of opioid sparing effect as well as influence on the inflammatory response of post-surgical insult. Perioperative use of lignocaine or dexmedetomidine as a part of multimodal anesthesia is associated with decreased anesthetic usage as well as reducing postoperative pain.[4,5] Modification of inflammatory markers are one of the proposed mechanisms of their action to decrease pain.[6] Literature regarding perioperative use of combination of lignocaine and dexmedetomidine is sparse and needs further evaluation.

The QoR-15 is a recently developed patient-reported, outcome measurement of postoperative quality of recovery.[7] It was developed from the larger QoR-40, which as extensively used and validated as a measurement of postoperative quality of recovery.[8] The QoR-15 had equivalent, psychometric properties compared to the QoR-40 but was more feasible to use.

With this background, we planned to study the effects of infusions of lignocaine, dexmedetomidine and the combination of lignocaine and dexmedetomidine on postoperative pain, analgesic requirement, and Quality of Recovery (QoR) in patients undergoing elective robotic abdominal hysterectomy. We hypothesized that the combination of lignocaine and dexmedetomidine will provide better analgesia and improved QoR score compared to use of individual agents alone.

Methods

The study was conducted after obtaining Institutional Ethics committee approval of AIIMS, Rishikesh and written informed consent of patients. The trial was registered with Clinical Trial Registry India (CTRI/REF/2019/09/021323). One hundred and twenty females with American Society of Anesthesiologists (ASA) physical status I and II, aged 30 −65 years and scheduled for Robotic Total Abdominal Hysterectomy under general anesthesia were enrolled between October 2019 and March 2020. Patients with BMI $>$ 35 kg.m^{-2}, allergy to study drugs, history of use of opioid, analgesics, psychotropic drugs (or) beta blockers, uncontrolled hypertension, A-V conduction block, history of sleep apnea were excluded from the study.

The patients were randomized to one of four groups utilizing the sealed envelope randomization method available at www.sealedenvelop.com. The numbers were maintained in sequentially numbered opaque envelopes for concealment until 1 hour before induction of anesthesia. On the day of surgery, the envelops were opened and as per group allotment and the drug infusions prepared. An anesthesia support staff prepared the drug infusion as per written instructions. The staff was not involved in the management of cases. Surgeon and patients were blind to the group allotment.

The patients received infusions of Lignocaine 1.5 mg.kg^{-1} over 15 minutes followed by continuous infusion at 2 mg.kg^{-1}.h^{-1} till end of surgery (Group 1), dexmedetomidine 1 mcg.kg^{-1} over 15 minutes followed by continuous infusion at 0.6 mcg.kg^{-1}.h^{-1} till end of surgery (Group 2), infusion of lignocaine 1.5 mg.kg^{-1} and dexmedetomidine 1 mcg.kg^{-1} over 15 minutes followed by infusions at 2 mg.kg^{-1}.h^{-1} (lignocaine) and at 0.5 mcg.kg^{-1}.h^{-1} (dexmedetomidine) until end of surgery (Group 3) and infusion of normal saline 10 mL over 15 minutes followed by infusion at1 mL.kg^{-1}.h^{-1} till end of surgery (Group 4).

Preoperatively on the day before surgery, patient was explained the Visual Analogue Score (VAS) for pain assessment, QoR 15 score and use of the patient-controlled analgesia (PCA) pump. All eligible patients were kept nil per oral for solids for 8 hours and 2 hours for clear liquid and were premedicated with Tablet (Tab). Ranitidine 150 mg and tab. alprazolam 0.25 mg the night before, and 2 hours prior to surgery with sips of water.

On shifting the patient to the operation theatre after achieving intravenous cannulation of peripheral vein, patients were preloaded with 250 mL of Ringer's lactate. Standard ASA monitoring like ECG, noninvasive blood pressure (NIBP), and pulse oximetry (SPO2) were established. Bispectral index (BIS) (Covidien, Singapore) electrode was applied over the forehead and initial readings noted.

Anesthesia induction in all the groups was achieved with inj. fentanyl 2 mcg.kg^{-1}, inj. propofol 1−1.5 mg.kg^{-1} till loss of verbal commands, neuromuscular blockade achieved with inj. vecuronium 0.1 mg.kg^{-1} and intubation completed with an approriate sized cuffed endotracheal tube. Maintenance of anesthesia was achieved with 66% N2O in O2, infusion of test drug as per the group allotment, incremental concentration of isoflurane (MAC 08−1.0), intermittent boluses of inj. fentanyl 1 mcg.kg^{-1} (when heart rate $>$ 20 beats from baseline) and inj. vecuronium 1 mg (as assessed by neuromuscular monitor (Drager Trident, Drager Medical system, Inc, Telford, PA, USA). Ventilation was adjusted to maintain end tidal carbon dioxide value between 35−37 mmHg. BIS maintained between 40−60. Inj. paracetamol 1 g and inj. ondansetron 0.1 mg.kg^{-1} were administered 15 minutes before the end of the surgery. At the end of surgery, the respective infusions were stopped, with resumption of spontaneous effort and BIS between 80−100, achieving the TOF ratio0.9 neuromuscular blockade was reversed by administration of inj. neostigmine (0.05 mg.kg^{-1}) and inj. glycopyrollate (0.01 mg.kg^{-1}), and patient extubated and shifted to PACU.

All the patients received post-operative analgesia with fentanyl (5 μg.mL^{-1}) through IV PCA pump (B Braun Perfusor

Space Pump). A total dose of fentanyl as 1.5 $\mu g.kg^{-1}.h^{-1}$ was utilized, 40% of the calculated dose as continuous infusion and the remaining 60% divided into three equal doses with a lockout interval of 20 minutes. Pain with VAS > 6, an additional 25 mcg of fentanyl administered. The patients were discharged to the ward on achieving Aldrete score of ≥ 9. Postoperative analgesia for the next 24 hours was managed by PCA with fentanyl. Postoperative pain at rest was assessed at time intervals of 1, 2, 4, 12, and 24 hours postoperatively. Total fentanyl requirements in the first 24 hours were recorded. Return of bowel function was assessed by enquiring about time of passage of flatus after surgery and auscultation for bowel sounds. Patients were monitored for nausea, vomiting, itching, bradycardia, hypotension, and any other complications. A 15-point Quality of Recovery score QoR-15 was utilized for assessment on postoperative day 1, 2, and on day of discharge to assess the quality of recovery and total score calculated for each patient.

A power analysis based on a previous study[9,10] revealed that a total sample size of 24 patients in each group was required to achieve a power of 80% and α error of 0.05 for detection of difference in VAS pain score of 1.3. Taking into account a dropout rate of 5% estimated from initial pilot observations, we aimed to include at least 120 patients in our study (30 patients in each group).

Data obtained was analyzed statistically using IBM Statistical Package for Social Sciences (SPSS) for Windows version 26 (IBM Corp., Armonk, NY). For categorical variables, the difference in proportions was assessed using the chi square test. For continuous variables, mean difference between two independent group was tested using the independent *t*-test while for more than three groups One-way Analysis of Variance (ANOVA) test was used. To check the homogeneity of variances, which is one of the assumptions in ANOVA, Levine's test used. For all variables which had a significant *p*-value of < 0.05 on ANOVA, a post hoc test was applied. For quantitative outcomes, the oneway ANOVA test was used to compare the four groups. Data are expressed as numbers, percentage, mean ± standard deviation (SD), median ± IQR and $p < 0.05$ considered as statistically significant.

Results

Ninety-six patients were recruited and randomized, and all the patients completed the study (Fig. 1). Due to

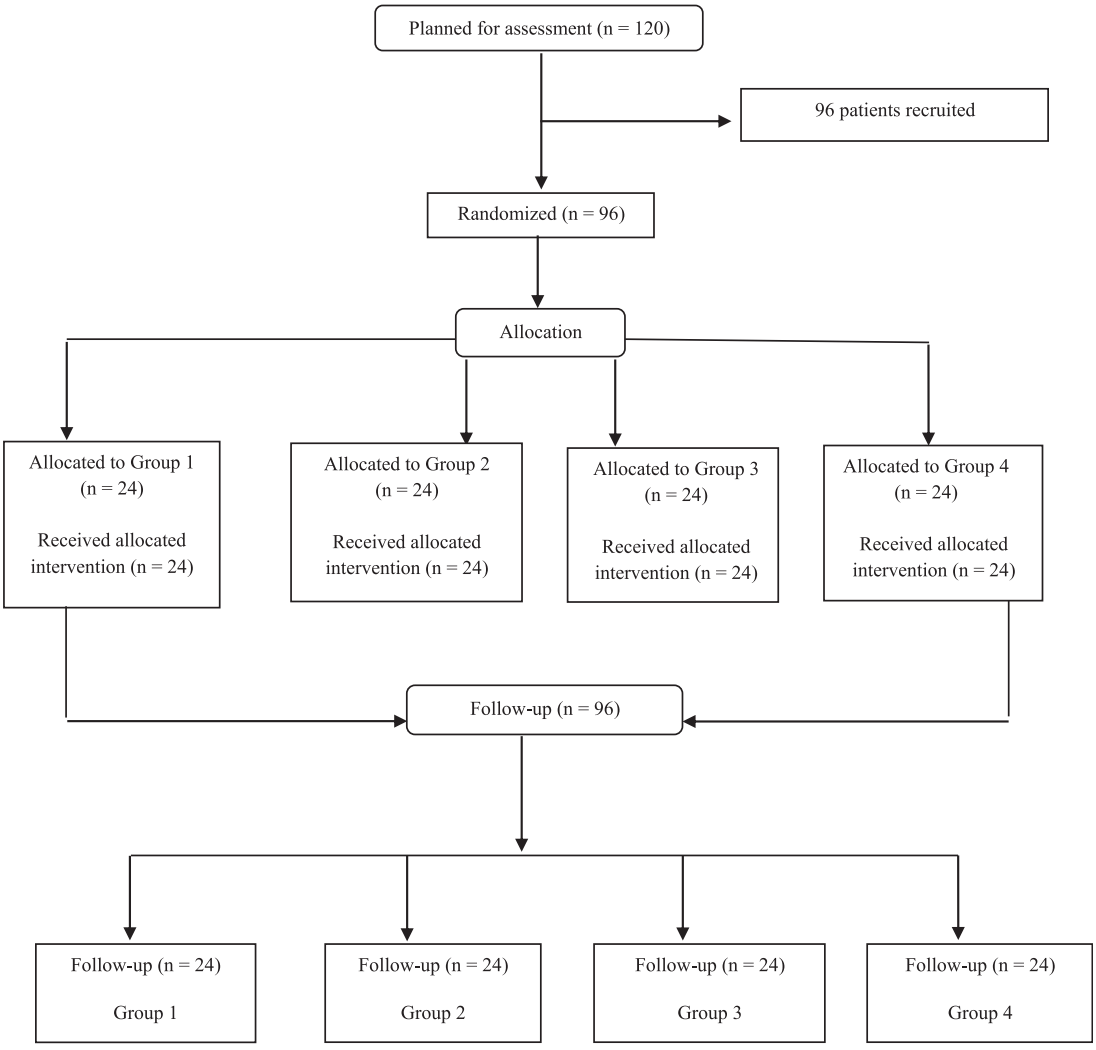

Figure 1 CONSORT flow diagram for this study.

Table 1 Demographic profile of the study populations.

Parameters	Group 1	Group 2	Group 3	Group 4	*p*-value
Age (years)	46.42 ± 5.73	45.79 ± 5.54	45.79 ± 5.54	46.63 ± 5.19	0.47
Weight (kg)	61.96 ± 5.396	62.88 ± 8.02	61.46 ± 3.37	61.75 ± 7.49	0.88
Height (cm)	158.88 ± 5.17	160.38 ± 3.77	159.50 ± 3.79	160.63 ± 3.82	0.44
BMI ($kg.m^{-2}$)	24.57 ± 2.18	24.44 ± 2.84	24.17 ± 1.38	23.93 ± 2.81	0.79
ASA I/II	10/14	15/9	16/8	15/9	0.287

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control; ASA, American Society of Anesthesiologists physical status.

Table 2 Pain assessed by VAS at rest after the surgery.

Parameters	Group 1 (n = 24)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 24)	*p*-value
VAS at 1st h	5.0 ± 1.0	4.0 ± 0.0[a]	3.0 ± 0.0[a,b]	6.0 ± 1.0[a,b,c]	0.00
VAS at 2nd h	4.0 ± 0.0	3.0 ± 0.0[a,b]	2.0 ± 0.0[a,b,c]	4.50 ± 1.0[a]	0.00
VAS at 4th h	3.0 ± 1.0	2.0 ± 1.0[a,b]	1.0 ± 1.0[a,b,c]	3.50 ± 1.0	0.00
VAS at 12th h	2.0 ± 0.75	1.0 ± 1.0[a,b]	1.0 ± 0.0[a,b,c]	2.0 ± 1.0	0.00
VAS at 24th h	1.0 ± 1.0	1.0 ± 0.0[a,b]	0.0 ± 0.0[a,b,c]	1.0 ± 1.0	0.00

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.
[a] Group 1 vs. Groups 2, 3, 4.
[b] Group2 vs. Groups 3, 4.
[c] Group 3 vs. Group 4.

inability to procure instruments for robotic surgery and COVID-19 travel restrictions, only 96 patients could be recruited

The patients were similar in their demographic profile (Table 1).

The VAS at rest were significantly lower in Groups 3 and 2 compared to Groups 1 and 4 (Table 2), and remained so during all times of observation. On comparing VAS between groups 1 and 4, a difference was observed during the first and second hour, however the difference was negligible at 4 hours and beyond. (Table 2)

Total postoperative fentanyl consumption during the first 24 hours via PCA was 256.25±16.36 mcg (95% CI: 249.34, 263.16) in Group 1, 177.71±16.81 mcg (95% CI: 170.61, 184.81) in Group 2, 114.17±16.19 mcg (95% CI: 107.36, 120.98) in Group 3 and 304.42±31.26 mcg (95% CI: 291.21, 317.62) in Group 4, respectively. The requirement was significantly reduced in Group 3 compared to the other three groups ($p < 0.001$). Postoperative fentanyl requirement was also reduced in-groups 1 and 2, compared to Group 4 ($p < 0.001$).

Time to return of bowel function was slowest in Group 4 (34.58 ± 1.84 hours) compared to all other Groups ($p < 0.001$). Return of bowel function was significantly early in group 3 compared to groups 1 and 2 respectively ($p < 0.001$). (Table 3)

The average QoR 15 score preoperatively in all groups was almost equal. There was no statistically significant difference among the four groups ($p = 0.55$). On day 1, improved QoR 15 scores were observed in Group 3 compared to Groups 1, 2, and 4. There is no difference between Groups 1 and Group 4. A statistically significant difference was noted between the four groups in terms of QoR 15 score on Day 1 (*p*-value 0.001). On Day 2 QoR 15 score was high in the group 3 compared to other groups. A statistically significant difference was noted between the four groups in terms of QoR 15 score on Day 2 (*p*-value 0.001). On discharge day, the QoR 15 score in all groups was equal and almost reached to preoperative QoR 15 score values (Table 4).

Complications observed in the perioperative period were hypotension in 23 patients (Group 2) and 24 patients (Group 3). Bradycardia observed in 24 patients (Group 2) and 24 patients (Group 3). None of the patients required treatment with atropine or mephenteramine. Sedation after extubation was observed in 24 patients each in Groups 2 and 3 respectively. Complications like nausea, vomiting, pruritus and hypoxia were not noted in any of the groups during in the postoperative period.

Table 3 Resumption of Bowel function recovery among the groups.

Parameter	Group 1 (n = 24)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 24)	*p*-value
Bowel function recovery (h)	30.38 ± 1.66[a]	26.15 ± 0.74[a,b]	22.65 ± 0.78[a,b,c]	34.58 ± 1.84	0.00

Data are presented as mean ± standard deviation.
Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.
[a] Group 1 vs. Groups 2, 3, 4.
[b] Group 2 vs. Groups 3, 4.
[c] Group 3 vs. Group 4.

Table 4 Comparision of QoR 15 score among the groups.

Parameters	Group 1 (n = 24)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 24)	*p*-value
QoR 15 Preop	144 ± 3.0	144 ± 3.0	145 ± 3.0	144.5 ± 2.0	0.76
QoR 15 Day1	98.0 ± 3.0	107.5 ± 5.0[a,b]	126.0 ± 4.0[a,b,c]	87.0 ± 6.0	0.001
QoR 15 Day 2	122.5 ± 7.0	130.5 ± 4.0[a]	139.0 ± 2.0[a,b,c]	109.5 ± 6.0[a,b]	0.001
QoR 15 Discharge Day	143.0 ± 2.0	143.5 ± 2.0	145.0 ± 2.0	142.0 ± 3.0	0.65

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.
[a] Group 1 vs. Groups 2, 3, 4.
[b] Group 2 vs Groups 3, 4.
[c] Group 3 vs. Group 4.

Discussion

We found that combined infusion of lignocaine and dexmedetomidine provided better recovery with improved postoperative analgesia and better quality of recovery score compared to use of lignocaine or dexmedetomidine infusion alone.

Several studies have reported that lignocaine infusion improved postoperative analgesia, reduced postoperative opioid requirement, accelerated postoperative recovery of bowel function and enhanced early rehabilitation in patients undergoing major abdominal surgery.[11–16]

Our results are similar to the above-mentioned studies. We observed reduced VAS at different point of observations, reduced postoperative fentanyl consumption, early return of bowel function and improved Quality of Recovery 15 score on Day 1 and Day 2 when compared to control group.

Herroeder et al.[17] found that lidocaine infusion significantly accelerated return of bowel function and shortened length of hospital stay by one day compared to control group. But no difference was observed in daily pain ratings between the lignocaine and control group for patients undergoing colorectal surgeries. Herzog et al.[18] in their study observed no beneficial effects on postoperative pain, opioid sparing, bowel function return, and hospital stay after robot-assisted colorectal surgeries in patients administered intravenous lignocaine. The causes of contradictory results may be related to dose, anesthetic time, anesthetic drugs, type of surgery, surgeon experience and duration of lidocaine infusion during the perioperative period We observed that bowel function returned faster in patients receiving lignocaine infusion in the perioperative period.

Use of Alpha-2 adrenoreceptor agonists as anesthetic adjuvants in the perioperative period is increasing due to their beneficial pharmacological effects. Their use provides hemodynamic stability, decreases stress response to surgery by its central sympatholytic action and reduces anesthetic and opioid requirements.[19,20]

Bakhamees et al.[21] demonstrated that intravenous dexmedetomidine (0.8 mcg.kg^{-1} bolus, 0.4 mcg.kg^{-1}.h^{-1}) decreased the total requirement of fentanyl and propofol requirement for maintenance of anesthesia compared to placebo ($p < 0.05$). In the postoperative period, dexmedetomidine decreased pain scores and PCA morphine use significantly and showed better recovery profile as compared to placebo group. Similar results were also demonstrated by Gurbet et al.[22] Our results were consistent with the above studies

Xu et al.[9] were the first to have used the mixture of dexmedetomidine and lignocaine for patients undergoing abdominal hysterectomy and demonstrated the effectiveness of combination compared to either lignocaine or dexmedetomidine infusion alone. Our results were similar to the study of Xu et al. in terms of reduced VAS, decreased postoperative fentanyl requirement, early bowel motility and improved quality of recovery score.

QoR is a global measure of recovery where different aspects of recovery are quantified on a Linkert scale. QoR 15 is an abridged version of QoR 40 scale first used by Myles et al.[23,24] QoR 15 measures the recovery on scale ranging from 0 to 150 with higher the score, better the recovery. Minimal clinical important difference of 8 has been accepted to be significant.

Klief et al. classified the recovery of patient based on QoR 15 score as poor, moderate, good and excellent with corresponding values of 0–89, 90–121, 122–135, 136–150 respectively.[25] Our study demonstrated better perception of psychological benefits along with decreased pain with lignocaine, dexmedetomidine or their combination. Scores on days 1 and 2 were significantly better with dexmedetomidine+lignocaine infusion > dexmedetomidine infusion > lignocaine infusion > control. The pharmacological effects of the drugs as well as their effects on inflammation, analgesic requirement and nausea vomiting may have been responsible for these effects. In a study of use of perioperative lignocaine infusion and early QoR Wang et al. demonstrated a better QoR 40 score on day 1 and 2 in patients receiving lignocaine infusion.[26] Similar results were also observed by Koshyari et al.[27] Similarly in a meta-analysis of use of dexmedetomidine and QoR, Miao et al.[28] concluded that dexmedetomidine as anesthetic adjuvant is associated with enhanced recovery without significant risk of adverse effects.

Hemodynamic effects like hypotension and bradycardia are observed in patients receiving dexmedetomidine. These effects are attributable to inhibition of the central sympathetic outflow overriding the direct stimulating effect as well as stimulation of the presynaptic α2-adrenoceptor, leading to a decreased norepinephrine release. Postoperative bradycardia may occur in as high as 40% healthy patients who were administered dexmedetomidine. The effect is temporary and can be managed with administration of atropine or ephedrine and volume infusions. Increased sedation was observed in our group postoperatively. This maybe an effect of dexmedetomidine as well as fentanyl infusion used for postoperative analgesia

The limitations of the study were small sample size, single centric as well as use in robotic surgeries, which are associated with less pain. Studies in larger populations and varied surgeries may give data on utility of dexmedetomidine-lignocaine combination for use in opioid free anesthesia technique.

In conclusion, we state that the dexmedetomidine—lignocaine combination provides a number of advantages to patients in terms of reduced pain, patient's perception of quality of recovery. These benefits are superior to the use of either agent separately.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Effect of continuous intra-incisional bupivacaine on postoperative pain in non-traumatic spinal fixation surgeries: a randomized controlled trial



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KEYWORDS
Bupivacaine;
Continuous local anesthetics infusion;
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Opioid sparing;
Postoperative pain;
Spine surgery

Abstract
Background: Continuous injection of local anesthetics by using surgical wound catheters for postoperative pain relief has gained acceptance in recent years. However, whether this method can be alternatively used instead of systemic opioids in different surgical procedures has not yet been elucidated.
Objectives: The aim was to investigate the effect of continuous injection of bupivacaine through a catheter inside the surgical wound on reducing the postoperative pain of lumbar spine fusion surgeries.
Methods: In this clinical trial, 31 patients undergoing non-traumatic lumbar spine stabilization surgery were randomly assigned to receive (n = 15) or do not receive (n = 16) bupivacaine through a catheter inside the surgical wound, postoperatively. Pain intensity (NRS), dose of required morphine, and drug-related complications within 24 hours of intervention were assessed and compared by the Mann-Whitney and independent *t*-test.
Results: Mean pain intensity was significantly lower in the case group over the first postoperative hour in the recovery room ($p < 0.001$), which continued for the first 2 hours after entering the ward. The mean morphine intake was lower in the bupivacaine group during the first postoperative 24 hours (16 ± 0.88 vs. 7.33 ± 0.93 mg, $p < 0.001$). The two groups were not significantly different regarding drug-related complications.
Conclusion: Continuous intra-incisional infusion of bupivacaine helped better pain reduction during the early postoperative hours while sparing morphine consumption in the first postoperative day.
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Introduction

Spinal fusion is a painful procedure whose postoperative pain relief has always been a challenging issue. Implementing the appropriate pain reduction protocol not only improves the outcome, but also decreases the pain and likelihood of postoperative morbidity, as well as hospitalization and healthcare costs.[1,2] The systemic inflammatory response causes surgical tissue damage, which is a common mechanism for adverse effects in patients with spinal fusion surgery.[3] Chronic and neuropathic pains are caused by peripheral and central sensitization, which is triggered by nitric oxide, free radicals, and excitable amino acids induced by activated glial cells and the production of cytokines in surgical wounds. The challenge of postoperative pain relief in these patients is most commonly managed via painkillers.[4]

Bupivacaine, an amide local anesthetic with unique properties, is used in regional, epidural, and spinal anesthesia, as well as local infiltration.[5] Local anesthesia commonly increases the threshold for electrical stimulation and consequently blocks the action potential in nerve cells.[6] Local anesthetics have long been administered through local tissue infiltration for pain relief.[7] Topical tissue infiltration with bupivacaine is reported as an efficient pain reliever after lumbar discectomy.[8] Bupivacaine with a half-life of 2.7 hours, being an intermediate-acting local anesthetic, reduces the pain more effectively in continuous infusion.[9] Catheters can be inserted into surgical wounds for topical and continuous injection of bupivacaine.[10]

Neuropathic pain is a common complication following spinal cord injuries and spinal surgeries.[11] Like most traditional treatment protocols, opioids are generally prescribed to reduce pain after spinal surgeries.[12] Morphine sulfate is a classic analgesic opioid that helps manage pain intensity by decreasing the activation of autonomic nervous system. Over the past decade, opioids have been increasingly used after spine stabilization surgery during admission and after discharge.[13] However, concerns exist about the risk of patient long-term dependency on opioid compounds after spine surgeries.[14,15] As already addressed in the literature, alternative methods can prevent such harmful effects.[16]

This study aimed to investigate the effect of continuous injection of bupivacaine via an intra-incisional catheter on reducing the postoperative pain of lumbar spine stabilization surgeries.

Methods

This randomized non-blinded clinical trial was conducted on patients undergoing non-traumatic complex lumbar spine stabilization surgeries at the Chamran Hospital, affiliated to Shiraz University of Medical Sciences, from February to September 2019. The study protocol was ethically approved by the local committee (IR.SUMS.MED.REC.1396.125) and informed written consent was obtained from all participants.

Study population

The trial was performed on patients aged 40 to 75 years with American Society of Anesthesiologists (ASA) physical status I to II who were candidates for complex lumbar spine stabilization surgery with an appropriate mental capacity to cooperate. Those with other chronic pain syndromes, non-degenerative spine pathologies, uncontrolled seizures, history of depression and anxiety, repaired spinal dura mater layer during the operation, severe coagulation disorders, opioids and other types of drug abuse and dependency, sensitivity to the study drugs, and psychosomatic pain disorders were excluded.

Sample size

Based on a previous study,[9] 14 patients were considered per group, with a mean difference of 20 mm on visual analog scale measurements for pain, standard deviation of 16, power of 0.90, and type I error of 0.05. Out of 47 eligible patients, 16 were excluded, and 31 eligible patients met the criteria to be enrolled. Case (n = 15) and control (n = 16) patients were randomly allocated through the permutation block randomization method, based on 15 blocks in 2 permutations (Fig. 1).

Study intervention

Prior to surgery, participants were assessed for using the preoperative pain score and instructed on how to use a PCA pump and the pain assessment tool (numerical rating scale [NRS]). The surgical procedures were all performed by two spine surgeons with comparable techniques accompanied by a single anesthesiologist. A similar drug protocol was followed for both the induction and maintenance phase of anesthesia in all participants: 0.15 $mg.kg^{-1}$ midazolam, 2 $\mu g.kg^{-1}$ fentanyl as premedication plus 0.15 $mg.kg^{-1}$ morphine sulfate in induction and 1−1.2% isoflurane in 50:50 mixture of oxygen, and nitrous oxide for maintenance of anesthesia.

In the bupivacaine group, a 15-cm multiorifice tip catheter (InfilteraLong 600, PAJUNK, Geisingen, Germany) was subfascially placed at the end of the operation. After implantation and fixation, 30 mL of 0.25% bupivacaine (Bupivacain®, Mylan, 100 mg/20 mL vial, Delpharm, France) were injected through the catheter as a bolus dose. Then, the catheter was connected to an elastomeric infusion pump containing 0.25% bupivacaine, the infusion of which was started at a rate of 6 $mL.h^{-1}$. No catheter was inserted in the control group. Intravenous morphine infusion via the PCA pumps was started for both groups in the ward (bolus dose: 1 mg, lockout interval: 7 minutes, no baseline infusion).

Study assessments

In the recovery room, the time interval between the end of the operation and the first request for analgesic was recorded. Moreover, if conscious, the patient's pain intensity was assessed and recorded according to the NRS every 15 minutes (at 15-, 30-, 45-, and 60-minute time points) in static state. Only single modal analgesia with intravenous (IV) morphine was administered to relieve the pain. For NRS < 4 no intervention was made; but for $4 <$ NRS < 7, the patient received 1 mg IV morphine every 5 minutes considering the vital signs until pain intensity dropped below 4; and for NRS > 7, 2 mg IV morphine was administered until the pain score dropped below 7, and thereafter managed with

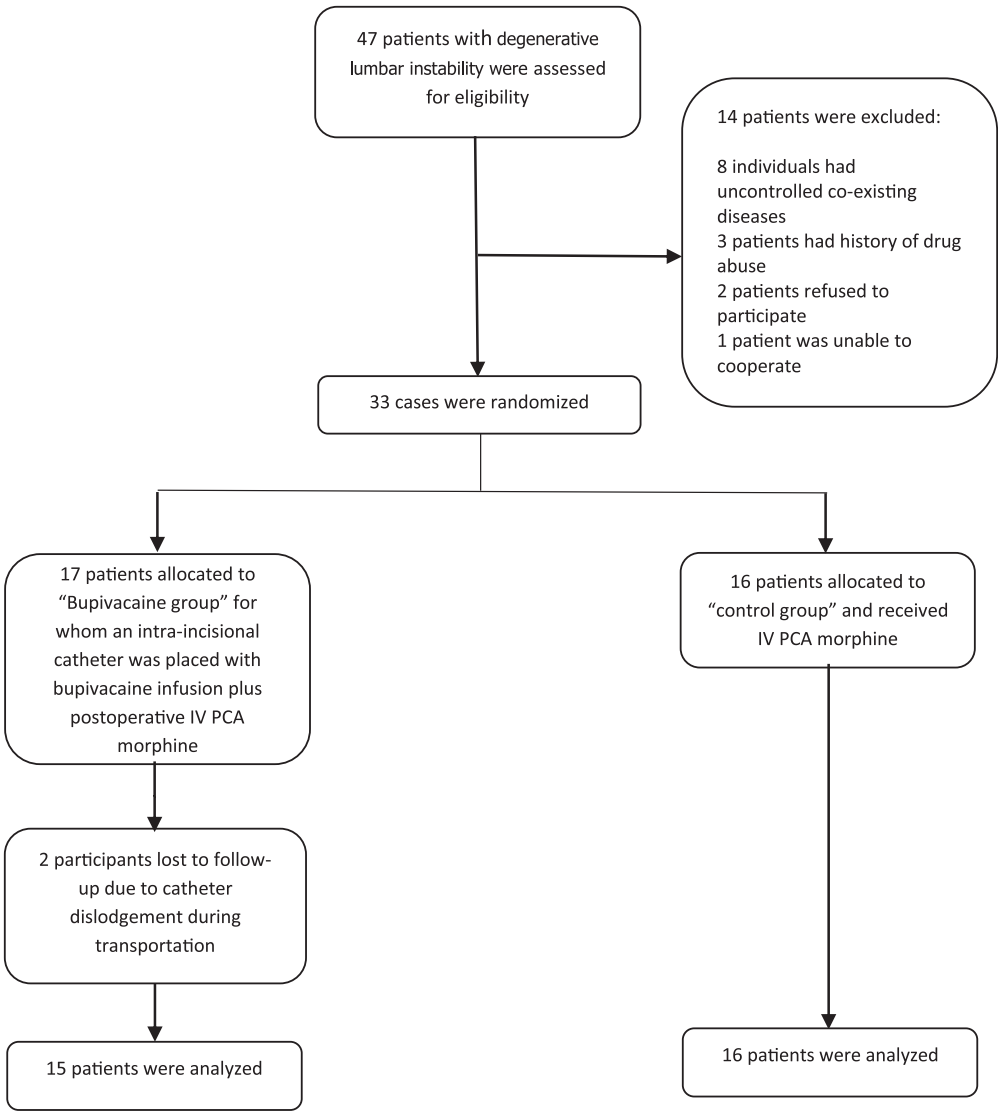

Figure 1 Flowchart of the study.

the protocol used for NRS between 4 and 7. The total amount of morphine consumed in the recovery room was recorded.

In the ward, the patient's pain intensity was hourly assessed and recorded during the first 6 hours, every 2 hours within the next 6 hours, and every 4 hours thereafter till the end of 24 postoperative hours. Morphine complications (respiratory depression, pruritus, urinary retention, nausea, and vomiting) were assessed every 4 hours during the study.

Data analysis

Data were statistically analyzed via SPSS software (version 21, SPSS Inc., IL, USA). Continuous variables were descriptively reported as mean ± standard error of mean (SEM) or median and interquartile range (IQR). Independent sample *t*-test and Mann-Whitney U test were used for continuous variables. Categorical variables were reported as numbers and percentages. The categorical outcomes were compared by the chi-square test. Repeated measure ANOVA was used for the data gathered over a period of time. $p < 0.05$ was considered statistically significant.

Results

The two groups were not significantly different in demographic variables (age, sex, weight, BMI, preoperative pain score) (Table 1). Significant differences existed between the two groups regarding recovery room morphine, ward morphine, and total morphine administration ($p < 0.001$). Yet, they were not different in terms of the time to the first request for analgesic (Table 2).

Pain score in the recovery room

Repeated measure ANOVA revealed a significant relation between the pain score in the recovery room and the time to the first analgesic request ($p = 0.002$), bupivacaine continuous injection ($p < 0.001$), and the interaction of these two variables (time × group) ($p = 0.002$). Considering the

Table 1 Patient demographic data.

Variables/Groups	Bupivacaine (n = 15)	Control (n = 16)	*p*
Age (year) (mean ± SEM)	55.93 ± 2.52	50.37 ± 2.24	0.109
Sex (female)	14 (93%)	11 (69%)	0.172
Weight (kg) (mean ± SEM)	73.80 ± 2.07	77.25 ± 2.15	0.258
BMI (mean ± SEM)	25.66 ± 0.93	26.61 ± 0.89	0.465
Preoperative pain score (mean ± SEM)	7.61 ± 0.74	6.52 ± 0.79	0.323

SEM, standard error of mean; BMI, body mass index.

Table 2 Postoperative morphine consumption.

Variables/Groups	Bupivacaine (n = 15)	Control (n = 16)	*p*
Time to the first request for analgesic (min)	30 (15-30)	15 (10-26)	0.225
Recovery room morphine (mg)	1.73 ± 0.27	5 ± 0.41	< 0.001
Ward morphine (mg)	5.60 ± 0.80	11 ± 0.97	< 0.001
Total morphine consumption (mg)	7.33 ± 0.93	16 ± 0.88	<0.001

significant interaction effect, the Mann-Whitney U test was performed to assess each time independently. Accordingly, the bupivacaine group had a lower pain score than the control group on all time-points in the recovery room (Fig. 2).

Pain score in the ward

Similarly in the ward, the pain score was found to be significantly related to the time to the first analgesic request ($p < 0.001$) and bupivacaine continuous injection ($p = 0.001$); however, the interaction between these two variables (time × group) was not statistically significant ($p = 0.494$). Using independent sample t-test to compare the pain scores (NRS) in the ward at each time-point showed significant differences between the two groups mostly at the first ($p < 0.001$) and second ($p = 0.002$) measurements in the ward (Fig. 3).

Drug-related complications

Neither group showed any drug-related complications such as seizures, arrhythmia, tinnitus, lightheadedness, and dizziness. Only one patient in the case group experienced nausea and vomiting at 4, 8, and 12 hours after the ward admission. The same patient experienced hypotension 4 hours after being transferred to the admission ward. Overall, the two groups were not significantly different regarding the drug-related side effects ($p = 0.707$).

Discussion

Relieving the inevitable severe postoperative pain is a serious concern in patients undergoing spinal deformity surgeries and spine stabilization.[17,18] Acute postoperative pain can have adverse consequences such as delayed wound healing, higher risk of infection, long-term hospitalization, readmission, and cardiovascular complications.[19,20] This randomized clinical trial revealed that at all time-points of the first 24 postoperative hours, the mean pain intensity was lower in patients on continuous injection of bupivacaine through an intra-incisional catheter than in those without catheter implantation; the differences being more prominent during the first postoperative hours. Since the mean preoperative pain score was not significantly different between the two

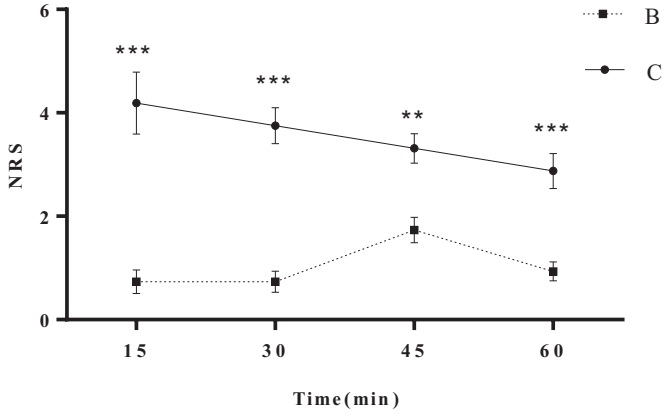

Figure 2 Pain intensity in the recovery room (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

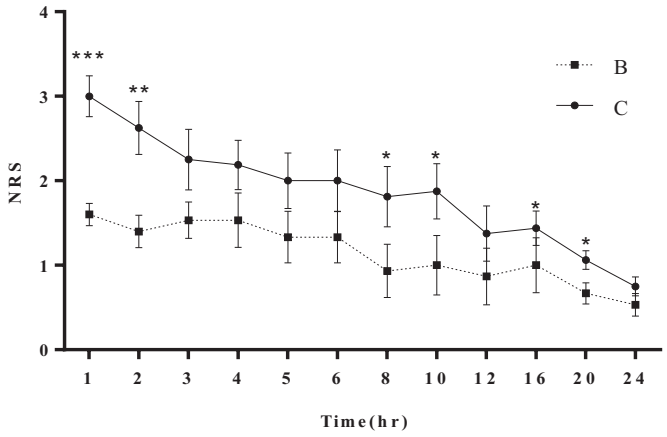

Figure 3 Pain intensity changes during the first 24 postoperative hours (*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

groups, it was not considered as an intervening effective factor.

While the present study aimed to extend postoperative analgesia beyond the effect of a bolus dose of local anesthetic injection, successful pain control was achieved in the period of efficacy of a single-shot injection (the bolus dose). This could be due to the inadequate dose of the running infusion and the wide extent of the surgical incision for this rate of infusion. Increasing the infusion rate might compensate for that; however, the total infusion dose should be regarded. The significant difference in pain intensity recorded in the recovery room which lasted for two hours after transferring to the ward might be attributed to the lower morphine requirement during the recovery room stay in the study group.

The efficacy of such a protocol has also been demonstrated in similar studies as follows. In a study by Bianconi et al.,[21] 38 patients scheduled for spinal stabilization received either intravenous morphine or 0.5% ropivacaine through an intra-incisional catheter. They detected that compared to morphine, ropivacaine significantly decreased pain intensity, analgesic need (diclofenac and tramadol), postoperative blood loss, and the length of hospitalization, with no side effects reported. Their results confirmed that the injection of ropivacaine into the surgical wound through a catheter and its continuous infusion could efficiently alleviate the postoperative pain of spine stabilization.

Xu et al.[22] found no significantly different pain intensity between the patients receiving ropivacaine injection through a catheter into the spinal thoracolumbar surgical wound and those receiving intravenous flurbiprofen, pentazocine, and palonosetron; although, ropivacaine was associated with significantly less nausea, vomiting, and chronic pain. Ali et al.[23] and Manan et al.[24] reported that injection of bupivacaine into the wound site significantly reduced the pain intensity after laparoscopic cholecystectomy.[23] Seelam et al.[25] noted that US-guided erector spinae plane block with bupivacaine in patients undergoing mastectomy resulted in less postoperative morphine consumption and significant postoperative pain relief, as compared with the control group.[25]

Being one of the main drugs for postoperative pain relief, morphine has side effects, and plausible drug-dependency in terms of long use of morphine makes the reduction of postoperative morphine prescription a crucial concern.

This study was strong for being a randomized clinical trial following CONSORT guidelines; however, it was not blinded and had a limited budget for the cost of catheters. Previous similar studies assessed a single-shot bupivacaine wound infiltration or continuous ropivacaine catheter wound infusion in more simple surgeries such as laminectomy. Whereas, the present study was focused on complex spinal fusion surgeries, not single-shot bupivacaine infiltration, and also assessed postoperative pain in continuous bupivacaine wound catheter infusion over 24 postoperative hours. On the other hand, previous studies using medications such as ropivacaine mentioned the high costs; whereas, the present study was superior due to using bupivacaine, which is economically cost-effective and reasonable for the patients. Although the sample size was statistically sufficient to interpret the data, further studies with a larger sample size are recommended.

Conclusion

With respect to the present findings, it can be concluded that using bupivacaine can reduce more efficiently the postoperative pain than morphine, at least in the early postoperative hours, and consequently reduce morphine consumption postoperatively. Continuous injection of bupivacaine through a catheter into a surgical wound to reduce the postoperative pain intensity in non-traumatic complex lumbar spine stabilization surgeries can be considered as a part of an opioid-sparing analgesic protocol.

Conflict of interests

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Assessment of main complications of regional anesthesia recorded in an acute pain unit in a tertiary care university hospital: a retrospective cohort

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KEYWORDS
Anesthesia and Analgesia;
Anesthesia, Epidural;
Anesthesia, Spinal;
Nerve Block

Abstract
Background: Regional anesthesia has been increasingly used. Despite its low number of complications, they are associated with relevant morbidity. This study aims to evaluate the incidence of complications after neuraxial block and peripheral nerve block.
Methods: A retrospective cohort study was conducted, and data related to patients submitted to neuraxial block and peripheral nerve block at a tertiary university hospital from January 1, 2011 to December 31, 2017 were analyzed.
Results: From 10,838 patients referred to Acute Pain Unit, 1093(10.1%) had side effects or complications: 1039 (11.4%) submitted to neuraxial block and 54 (5.2%) to peripheral nerve block. The most common side effects after neuraxial block were sensory (48.5%) or motor deficits (11.8%), nausea or vomiting (17.5%) and pruritus (8.0%); The most common complications: 3 (0.03%) subcutaneous cell tissue hematoma, 3 (0.03%) epidural abscesses and 1 (0.01%) arachnoiditis. 204 of these patients presented sensory or motor deficits at hospital discharge and needed follow-up. Permanent peripheral nerve injury after neuraxial block had an incidence of 7.7:10,000 (0.08%). The most common side effects after peripheral nerve block were sensory deficits (52%) and 21 patients maintained follow-up due to symptoms persistence after hospital discharge.
Conclusion: Although we found similar incidences of side effects or even lower than those described, *major* complications after neuraxial block had a higher incidence, particularly epidural abscesses. Despite this, other serious complications, such as spinal hematoma and permanent peripheral nerve injury, are still rare.
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Introduction

Regional anesthesia (RA) has been increasingly used and plays a prominent role in anesthesiologists' clinical practice. Many advantages are associated with better postoperative pain control, lesser systemic opioids need, diminishing nausea, pruritus and constipation, earlier bowel function recovery, more efficacious breathing, and easier participation in physical therapy.[1]

Despite all the technological and pharmacological advances in RA's safety, side effects and complications occur. The increasing prevalence of risk factors for nerve injury, like obesity, diabetes, potent anticoagulants, and the increasing use of continuous catheter-based peripheral nerve blocks (PNB) may alter the rate of neurological complications.[2] These may range from transient neurological symptoms, urinary retention, nausea or vomiting (NV) to peripheral nerve injury (PNI), central nervous system (CNS) infections, local anesthetic (LA) toxicity, or post-dural puncture headache (PDPH). Spinal cord injury, hematoma or epidural abscess (EA) are rare events, but can become devastating.[3,4] Despite PNI after RA is rare in contemporary anesthetic practice, the real serious complications incidence after RA is still uncertain: there are few recent studies and few include PNB; there are inconsistencies in multicenter data collection and there is a variation in the complications rate between hospitals.[2,5] Accurate data on risk factors and clinical course are also not available and, consequently, there is no evidence on management strategies recommendations.

Acute Pain Units (APU) promotes individualized care in acute pain after surgery, diagnostic procedures, trauma, or medical diseases. They play a key role in pain management and prevention or treatment of side effects and complications related to the techniques.

This study aims to evaluate the main RA complications managed by an APU of a tertiary university hospital.

Methods

Study design and settings

After Ethics Committee approval, a retrospective database analysis of all APU patients from January 1, 2011 to December 31, 2017 was conducted. Clinical data for patients submitted to neuraxial block (NB) and PNB with recorded side effect or complication was collected and analyzed. Pregnant women undergoing labor analgesia, patients under 18 years of age or undergoing other unconventional postoperative systemic analgesia were excluded.

Data collection

Demographic data such as gender, age, weight, height, comorbidities, usual medication, and physical status were collected according to the American Society of Anesthesiologists Physical Status (ASA-PS). Anesthetic technique data were collected from the intraoperative period records; Technique side effects, which are unwanted but generally predictable and expected events, or complications, defined as unexpected events but recognized as possible, were recorded from the postoperative period.

Table 1 Demographic data of patients with reported side effects or complications.

Age, median (IQR), years	61 (50–69)
Weight, median (IQR), kg	70 (60–80)
Height, median (IQR), cm	163 (160–170)
ASA-PS, n (%)	
Class I/II	803 (77.3%)
Class III/IV	290 (27.9%)
Major comorbidities, n (%)	
Diabetes Mellitus	167 (15.3%)
Heart disease	87 (8.0%)
Malignant disease	66 (6.0%)
Chronic kidney disease	44 (4.0%)
Atrial fibrillation with hypocoagulation	31 (2.8%)
Transplant history	7 (0.6%)
Inflammatory bowel disease	7 (0.6%)
HIV	5 (0.5%)
Surgery, n (%)	
Elective	1003 (91.7%)
Urgent	90 (8.2%)
Hospital service, n (%)	
Orthopedics	458 (41.9%)
General surgery	221 (20.2%)
Vascular surgery	170 (15.6%)
Urology	100 (9.1%)
Plastic surgery	53 (4.8%)
Gynecology	45 (4.1%)
Thoracic surgery	21 (1.9%)
Neurosurgery	16 (1.5%)
Intensive care unit	8 (0.7%)
Infectious disease	1 (0.1%)

ASA-PS, American Society of Anesthesiologists physical status; HIV, human immunodeficiency viruses; SD, standard deviation; CSE, combined spinal epidural.

Statistical methods

Statistical analysis of data was performed using the Statistical Package for Social Sciences (SPSS) version 26.0. The descriptive analysis of the variables was used to summarize the data. Ordinal and continuous data did not follow a normal distribution, based on the Kolmogorov-Smirnov test for the normality of the study population. Categorical variables were described as frequency rates and percentages and continuous variables were described using median and interquartile range (IQR) values.

Results

Between January 1, 2011 and December 31, 2017, 10,838 patients were referred to APU with 32,184 consultations. Demographic data of patients with reported side effects/complications are shown in Table 1. There were 9122 NB and 1041 PNB performed. Of these, 1039 (11.4%) submitted to NB and 54 (5.2%) to PNB had side effects or complications, according to Table 2.

Table 2 Anesthetic/analgesic techniques performed in patients with reported side effects or complications.

	Total	Side effects / Complications
Neuraxial block	9122	1039 (11.4%)
CSE	4425 (48.5%)	396 (8.9%)
Epidural	4241 (46,5%)	592 (14.0%)
Spinal	456 (5.0%)	51 (11.2%)
Peripheral nerve block	1041 (11.4%)	54 (5.2%)
Femoral nerve block	101 (9.7%)	8 (7.9%)
Sciatic nerve block	48 (4.6%)	5 (10.4%)
Interscalene brachial plexus nerve block	416 (40.0%)	21(5.0%)
Axillary brachial plexus nerve block	422 (40.5%)	20 (4.7%)
Others	54 (5.2%)	-

CSE, combined spinal epidural.

Table 3 Side effects and/or complications reported in patients undergoing NB.

	Epidural (n = 4241)	CSE (n = 4425)	Spinal (n = 456)
Neurologic			
Sensory deficit	288 (6.8%); 2 days (1–3)	177 (4.0%); 2 days (1–3)	39 (8.6%); 1 day (1–3)
Motor deficit	78 (1.8%); 2 days (1–3)	39 (0.9%); 2 days (1–3)	6 (1.3%); 1 days (1–2)
Spinal pain	19 (0.4%); 12 days (3–20)	14 (0.3%); 3 days (2–8)	2 (0.4%); 2 days (1–4)
PDPH	5 (0.1%); 3 days (1.5–4)	14 (0.2%); 4 days (2–5)	4 (0.9%); 2 days (1–3)
Tinnitus	2 (0.05%); 3 days (1–4)	-	-
Subcutaneous cell tissue hematoma	1 (0.02%)	2 (0.05%)	-
Epidural abscess	1 (0.02%)	2 (0.05%)	-
Arachnoiditis	-	1 (0.02%)	-
Drug related			
Nausea or vomiting	95 (2.2%); 2 days (1–3)	87 (2.0%); 2 days (1–3)	-
Pruritus	43 (1.0%); 1 day (1–2)	40 (0.9%); 1 day (1–3)	-
Sedation	28 (0.7%); 3 days (1–4)	4 (0.09%); 2 days (1–4.5)	-
Urinary retention	9 (0.2%); 1 day (1–2)	8 (0.2%); 1 day (1–2)	-
Respiratory depression	3 (0.07%); 3 days (2–3)	-	-
Metallic flavor	5 (0.1%); 7 days (2–8)	-	-
Perioral paresthesias	2 (0.05%); 6 days (2–7)	-	-
Cardiovascular			
Hypotension	13 (0.3%); 1 day (1–2)	8 (0.2%); 1 day (1–3)	-

N (%); Median days of onset of symptoms after placement of epidural catheter (IQR).
NB, neuraxial block; CSE, combined spinal epidural; PDPH, post-dural puncture headache.

Neuraxial block

During the study period, 1039 patients submitted to NB (11.4%) reported side effects or complications (Table 3). Before performing the RA, 276 of these patients (26.6%) were anticoagulated with enoxaparin at a prophylactic dose with a median suspension time of 14 hours (IQR, 12–16 hours; range 10–36 hours); and 32 (3.1%) at a therapeutic dose with a median suspension time of 25 hours (IQR, 24–28 hours; range 23–42 hours).

In 95.1% of the patients with side effects/complications, the anesthetic/analgesic technique was NB (Table 2): 78.7% lumbar and 21.3% at thoracic level. From those 988 (95.1%) maintained the epidural catheter (EC) for postoperative analgesia. Ropivacaine (0.1%, 0.15% and 0.2%) was the predominant LA (97.8%) for epidural infusion.

Median EC length of stay for patients with side effects/complications was 5 days (IQR, 3–6 days; range, 1–67 days). Signs of infection at the EC insertion point were found in 53 (5.4%), which had a median length of EC stay of 7 days (IQR, 5–11.5 days; range, 2–23 days). The catheter tip microbiological study is presented in Table 4. A patient has died due to refractory septic shock with multiorgan failure, starting on an infected orthopedic prosthesis.

According to APU's protocol, if there are severe, persistent, or worsening neurological deficits, a CNS image study, Magnetic Resonance Imaging (MRI) when clinical situation allows, is performed: Computed Tomography (CT) was performed in 13 patients and MRI in 3. The diagnosis of subcutaneous cell tissue hematoma, EA and arachnoiditis was made in 7, as described in Table 5.

Of the 627 patients with sensory or motor deficits after NB, 204 (32.5%) maintained persistent neurological deficits

Table 4 Type of EC withdrawal from patients with reported side effects or complications and microbiological study result of EC tip.

Removed according to APU protocol	913 (92.4%)
Accidental exteriorization	20 (2.0%)
Signs of infection at the EC insertion point	53 (5.4%)
Microbiological study of EC tip:	
Negative	21 (40.4%)
Staphylococcus epidermidis	10 (19.2%)
Staphylococcus aureus	5 (9.6%)
Klebsiella pneumoniae	4 (7.7%)
Methicillin-resistant Staphylococcus aureus	3 (5.8%)
Pseudomonas aeruginosa	3 (5.8%)
Polymicrobial	2 (3.8%)
Staphylococcus capitis	1 (1.9%)
Staphylococcus haemolyticus	1 (1.9%)
Staphylococcus hominis	1 (1.9%)
Proteus mirabilis	1 (1.9%)
Removed at the operating room	1 (0.1%)
Removed after death	1 (0.1%)

EC, epidural catheter.

at hospital discharge. Sixteen patients with neurological deficits and pain before surgery were referenced to chronic pain unit (CPU) and 56 patients to telephone surveillance: follow-up was lost in 4; 48 had early symptoms' resolution, on average until 5 days after hospital discharge; 4 were referred for APU's ambulatory consultation. The remaining 132 patients were directly sent to APU's ambulatory consultation. Of these patients, 13 (9.6%) underwent electromyographic (EMG) study: 7 had PNI, requiring continuous follow-up in APU and physical rehabilitation medicine (PRM).

Patients with subcutaneous cell tissue hematoma had complete neurological symptoms resolution before hospital discharge. Arachnoiditis patient was sent to APU's ambulatory consultation with sensory deficits and spinal pain, with complete resolution 8 months after the diagnosis. The 3 EA patients were surgically approached for emergent decompression on average 8 hours after MRI confirmation. After hospital discharge, follow-up included PRM and APU's ambulatory consultation. Only one had complete resolution of neurologic symptoms.

Peripheral nerve block

During the study period, 54 patients submitted to PNB (5.2%) reported side effects/complications, described in Table 6. Of these, 26.0% (n = 14) had continuous regional postoperative analgesia during a median of 1 day (IQR, 1–4 days; range 1–6 days). All catheters were removed according to APU's protocol.

Sensory deficits were the main side effects and 21 patients maintained follow-up due to persistent symptoms after hospital discharge: 16 of them were evaluated by telephone with complete early symptoms resolution and 5 were directly managed at APU's ambulatory consultation. Two patients with persistent sensory deficits performed EMG study: one was submitted to femoral block without evidence of nerve damage; the other to interscalene brachial plexus block and revealed persistence of neurologic deficits with

Table 5 Description of patients with severe neuraxis complications.

	Age	ASA-PS / Relevant medical history	Surgery	Anesthetic technique/Number of attempts	EC length of stay (days)	Symptoms (days after EC placement)	EC tip – Microbiologic study	Treatment
Epidural abscess	39	II /Inflammatory Bowel Disease	Major digestive	Lumbar Epidural / 3	3	Spinal pain and fever (D4), sensory deficit (D12)	MRSA	Antibiotic and neurosurgical decompression
	65	IV / Heart Transplant; DM	Major orthopedic	Lumbar CSE / 4	13	Spinal pain (D13), sensory and motor deficits (D33)	MRSA	
	61	II / Prostate cancer; DM[a]	Peripheral vascular	Lumbar CSE/ 3	6	Spinal pain and fever (D11)	Negative	
Subcutaneous cell tissue hematoma	62	III / DM; HF	Major orthopedic	Lumbar CSE/1	16	Spinal pain and inflammatory signs (D11)	Negative	Antibiotic
	70	III / CRD; HF	Major orthopedic	Lumbar CSE/ 1	5	Spinal pain and inflammatory signs (D14)	MRSA	Antibiotic
	62	III/ Epilepsy; Malignant disease	Major digestive	Lumbar Epidural / 2	4	Sensory and motor deficits (D4)	Not applicable	Surveillance
Arachnoiditis	69	III / Obesity	Peripheral vascular	Lumbar CSE / 3	5	Spinal pain and sensory deficits (D13)	Negative	Antibiotic

ASA-PS, American Society of Anesthesiologists Physical Status; CRD, chronic renal disease; CSE, combined spinal epidural; DM, diabetes mellitus; EC, epidural catheter; HF, heart failure; MRSA, methicillin-resistant staphylococcus aureus.

[a] Patient with Methicillin-resistant Staphylococcus aureus (MRSA) bacteremia sepsis.

Table 6 Side effects and/or complications reported in patients undergoing PNB.

	PNB (n = 1041)
Sensory deficit	51 (4.9%); 1 day (1–2)
Motor deficit	18 (1.7%); 1day (1–3)
Nausea or vomiting	9 (0.9%); 1 day (1–1)

N (%); Median days of onset of symptoms after placement of peripheral catheter (IQR).
PNB, peripheral nerve block.

inconclusive EMG study after 12 days; A posterior MRI showed a pseudomeningocele, requiring continuous PRM and CPU follow-ups.

Discussion

RA's complications decreased in recent decades mainly due to technological and pharmacological advances, better patients' selection and greater attention in timely complications diagnosis. Permanent neurologic complications are effectively rare but also underreported probably due to lack of surveillance or symptoms recognition, so it's extremely difficult to obtain reliable and consistent incidence data.[3,4]

Complications/ Side effects after NB

According to Cameron et al. in 2009, the risk of developing a serious complication after NB was 1:35,000.[6] In 2018 a higher incidence of *major* adverse neuraxial events related to epidural analgesia in non-obstetric patients, 1:6000 to 1:1000, was described.[5–7] In this study, from a single center, we found an incidence of NB *major* adverse events of 1.5:1000.

Neurologic complications

Sensory and motor deficits

As described in the literature, sensory (48,5%) and motor deficits (11.8%) were the most frequent side effects related to NB in our study. Paresthesia had an overall incidence of 5.5% and it was more frequent after spinal block (8.6%) then epidural (6.8%) or combined spinal epidural (CSE) blocks (4.0%). Paresthesia is frequently described during NB technique (6.3%) but if occurs during needle or catheter placement, there is an increased risk of permanent lesion.[8–10] These techniques' details weren't collected in our database. New motor block after NB assessed by the modified Bromage scale[11] had a global incidence of 1.4% after NB (1.8%, 1.7% and 0.9% after epidural, spinal and CSE blocks, respectively).

Neurologic deficits may result from neural or vascular damages, ischemia, or drug-related neurotoxicity.[3–5] Although most LA in clinical doses does not cause nerve damage, prolonged exposure, higher doses, or concentrations may be deleterious. LA neurotoxicity is most associated with intrathecal lidocaine, mepivacaine and prilocaine.[4] None of these LAs were used in our patients.

The majority of sensory/motor deficits were temporary and 67.5% of our patients had complete resolution before hospital discharge. The remaining (32,5%, n = 204) and who had follow-up by APU (n = 200), 83.5% (n = 167) had early symptoms resolution until 3 months after discharge and 5% (n = 10) between 3 months to 1 year. We recorded an incidence of 7.7:10,000 (0.08%) of new permanent PNI after NB, documented by EMG study, similar to the literature: Horlocker et al. point an incidence of permanent neurological damage after NB from 0-8:10,000 cases and Naithani et al. between 0–0.16% after spinal and epidural anesthesia.[8,9]

The 16 patients referred directly to the CPU had neurological deficits or pain previous to surgery. Pre-existing spinal condition or other neurological diseases are known to increase the incidence of postoperative neurological complications.[4,12]

Transient neurologic symptoms (TNS) have a variable incidence, up to 37% after spinal block.[13] It is characterized by lumbar/gluteal pain that can irradiate for legs, usually without neurologic deficits.[10,14] Cauda equina syndrome (CES) is an unusual (1:33,000 to 1:100,000) and severe complication of NB induced by sacral roots damage.[8,14] It presents with lumbar pain, lower extremities neurologic deficits, sexual, intestinal and vesical sphincter dysfunctions.[10] According to the deficits presented in this study, without bladder, sexual or intestinal disfunction and with early recovery in the majority, CES or TNS are a rare complication not detected in our database.

PDPH

It remains a common complication after NB. Its prevalence is about 1% in non-obstetric population.[4,7] PDPH is due to cerebrospinal fluid (CSF) loss through a leak in the meninges and headache results from intracranial support loss, with traction and pressure on pain-sensitive structures and cerebral vasodilatation.[15] In our study, a 0.3% incidence of PDPH after NB was documented: 61% submitted to CSE block, 22% to epidural block and 17% to single-shot spinal block. Related symptoms, like diplopia and tinnitus, were recorded. Almeida et al. reported higher rates of PDPH by inexperienced providers and residents.[15,16] Given the university hospital context of our hospital, a higher headache prevalence would be expected. Age or prolonged immobilization of our patients may be the cause of these results.

According to the risk factors described, young females are at increased risk of developing PDPH and our data also showed a higher incidence (74%; median of 49 years). Higher needle size and tip design are the most important procedural factors.[15] In our patients, PDPH occurred mostly after CSE blocks, which were performed using the available kit at the hospital – 18G Touhy epidural needle and 27G pencil point tip spinal needle. Only in two cases were used, as a rescue, larger and beveled spinal needles (22G and 25G); In 50% and 43% of cases, respectively, the epidural and subarachnoid spaces were reached after more than one attempt. The accidental dural puncture with 18G Touhy epidural needle was only reported in two cases. In the literature, approximately 50% of cases resolve spontaneously within 5 days and in 90% of cases in 10 days.[10] All cases of our study resolved with prophylactic approaches, maximum at 7th day.

Infection

The development of major CNS infections may range from 1:6000 to 1:1000 in epidural procedures.[4] In this study, EC's insertion point infection was clinically evident in 0.6% of patients, which presented a median length of EC stay of 7 days (IQR, 5–11.5 days; range, 2–23 days). EC tip microbiological study was positive in 60% of these cases although we do not do this exam by routine.

The incidence of EC tip colonization varies from 0% to 55% in the literature. According to our and several other studies, despite colonization of the EC tip, epidural space infection is uncommon, and the presence of positive tip culture is not a reliable predictor of infection. Thus, routine culture of EC may not be indicated.[16] According to APU protocol, patients with positive microbiological study and no symptoms are followed-up in ambulatory consultation during a minimum of 12 months.

Positive microbiological EC tip is mainly due to Staphylococcus epidermidis, human skin commensal, and Staphylococcus aureus, resulting from probable tip contamination. Harde et al. identified the same microorganism in skin swab and EC tip cultures performed in the same patient, showing a significant correlation between bacterial colonization of the skin around the EC's insertion site and its tip.[17]

Infection of CNS depends on several maneuvers, since the EC's placement until its removal: sterile dressing, skin disinfection, LA solution or catheter handling, removal and ward handling protocols.[9,17] Although we do not have data about patient skin wash, disinfectant solution type neither disinfection times, according to our protocol, we should do skin wash with neutral solution, skin disinfection with 10% povidone iodine nonalcoholic solution with adequate drying times.

Patients with Klebsiella pneumoniae and Pseudomonas aeruginosa on EC tip had respiratory and urinary tract infections with the same organism isolated, according to certain studies about the possibility of hematologic spread through the spinal cord from the remote side.[17]

Epidural abscess (EA)

EA can be neurologically devastating if unrecognized. According to data reviewed by The Second ASRA Practice Advisory on Neurologic Complications Associated with RA and Pain Medicine in 2015, EA has an incidence of 13 in 1.7 million NB. Cook et al. described an incidence of 1:40,000 to 1:100,000 NB.[4,18]

In our study, the EA incidence was higher: 1:3040 (0,03%). This may be a consequence of a greater monitorization performed in our hospital since 2007, with APU patients' referral, but also probably due to the lack of protocols related to the entire process of regional technique: from its execution to the EC's removal in the ward.

Patients with EA were immunocompromised, namely with malignancy, history of heart transplantation, inflammatory bowel disease under chronic corticotherapy or diabetes mellitus. These are in line with previous studies that point these as risk factors. Difficulty in EC's placement often leads to an asymptomatic epidural or subcutaneous hematoma which also allows for infection proliferation.[7,10,18,19] According to the APU's data, two patients with EA had a record of moderate difficulty in EC's technique.

Catheterization length of stay is also an important risk factor: several studies reported EA development after an EC stay of at least 3 days.[7,9] In this study, only one (0,7%) of the 140 patients (13,5%) who maintained the EC for more than 7 days, developed EA. The others maintained the EC for a median of 3 days. What's the infection cause: the length of EC stay? EC and drugs handling in the ward? EC's placement/removal techniques?

NB in patients with previous or coexisting infection is a controversial issue.[19] During the study period, 327 patients with EC admitted in the intensive care unit (ICU) were assessed by APU: 148 with sepsis or bacteremia during hospitalization and only one developed an EA. There were no reports of other *major* neurological complications. The incidence of epidural analgesia in critically ill patients remains poorly investigated, despite its benefit on pain control, pulmonary function, ventilatory weaning, intestinal, cardiovascular and immune functions. ICU patients may present relative contraindications to NB, such as coagulation disturbances, severe hypovolemia, hemodynamic instability, neurological assessment, and technical difficulties. However, the risk-benefit balance of epidural analgesia may be favorable. More prospective studies should be carried out to evaluate NB risk factors and complications in critically ill patients.

Two of the three patients with an EA had Methicillin-resistant Staphylococcus aureus (MRSA) isolation at EC's tip: one was an older patient, with MRSA bacteremia, secondary to orthopedic prothesis infection; the other was a young individual with inflammatory bowel disease submitted to abdominal surgery, without evidence of systemic infection in the postoperative period.

All patients diagnosed with EA were submitted to emergent surgical decompression on median 8 hours (IQR, 6–11 hours; range, 6–11 hours) after MRI confirmation, and started immediately intravenous empirical antibiotic therapy. Several studies found favorable neurological outcomes in patients treated within the first 12 hours from symptoms onset.[9] After hospital discharge, our patients were observed in ambulatory APU consultation during a minimum of one year. After this period, the youngest patient had complete resolution of the symptoms and the other two were referred to CPU due to the persistence of sensory deficits and low back pain, although without significant functional disability.

Spinal hematoma (SH)

SH is particularly catastrophic as it may go unnoticed until there is permanent neurologic compromise.[20] The incidence of SH in patients undergoing NB is extremely variable. A study carried out in Sweden between 1990 and 1999 showed a rate of 1:3600 to 1:29,000 in patients undergoing orthopedic surgery.[21] ASRA described in 2015 an incidence of epidural hematoma of 33 in 1.7 million NB.[4]

Female gender, increased age, spine's anatomical abnormalities, changes in hemostasis during NB, or catheters' removal and traumatic spinal puncture/ EC placement are considered risk factors.[7,10] In this study, there were 3 cases of subcutaneous cell tissue hematoma, probably due to moderate difficulty in EC's placement, but development

of SH was not evident. A vast majority (92.4%) of EC were placed and removed according to the APU's protocol, respecting hypocoagulation suspension times and normal analytic results. Accidental displacement rate of EC was only 0.23%. Some researchers reported that one-third of all SH occurred in patients in the absence of any previously known risk factors, respecting thromboprophylaxis suspension times. Therefore, adherence to guidelines regarding hypocoagulation, anti-aggregation and NB may reduce, but not completely extinguish its occurrence.[5–8]

Arachnoiditis

Adhesive arachnoiditis can be a severe complication of NB and with incidence reports between 1:10,000 to 1:25,000.[23] This diffuse inflammatory meninx reaction to injurious stimulus results in subarachnoid scarring. It may be associated with alcohol-containing antiseptic solutions and is rarely related to EC *per se*.[7,22] Because of the varied symptomatology, clinical diagnosis can be difficult, and the number of cases can be underestimated.[9] In our study, we only recorded one case of arachnoiditis (0,01%). The course of arachnoiditis commonly starts slowly and include back pain, decrease in muscle strength and changes in lower extremities and perineum sensitivity. Critical cases can lead to bladder and intestinal disfunction or complete paraplegia.[23] In our study, the patient was submitted to CSE block in the operating room for vascular surgery. In the ICU postoperative period, due to a non-functioning EC, a new one was placed on the 3rd postoperative day. After 5 days, the EC was removed and 5 days later the patient developed persistent low back pain and sensory deficits in the lower limbs. The diagnosis of arachnoiditis was performed through MRI. The patient was followed-up in APU's ambulatory consultation with complete resolution of the deficits in about eight months later.

Drug-related side effects

Nausea and/or vomiting

It was the most frequent complaint recorded and it affected 2.1% of all patients submitted to NB. Prospective studies reported postoperative retching and vomiting in 11.1% of patients after spinal anesthesia. There are several patients, anesthetics, and surgical factors that influence their incidence and severity.[24] Spinal anesthesia does not always reduce NV compared to general anesthesia (GA) possibly because of hypotension, intrathecal opioid additives, or sympathetic blockade, resulting in a vagally mediated overactivity of the gastrointestinal system.[1]

Hypotension

Of the patients submitted to epidural analgesia in the postoperative period, 0.23% reported hypotension episodes. The injected LA leads to vasodilatation by affecting sympathetic efferences, with temporary sympathicolysis, blood pressure fluctuation and hypotension. This can also be related to the LA's concentration and method of administration, with higher concentrations and bolus regimens being more often associated with hypotension episodes than infusions.[24,25]

Pruritus

It can be troublesome neuraxial opioids side-effect. We recorded an incidence of 0.9%, which is smaller than the reported in several studies: 83% in postpartum patients; 69% in non-pregnant patients including males and females; and 30% to 60% after intrathecal opioid for orthopedic surgery.[26] In fact, in the majority of epidural analgesia cases sufentanil was the opioid of choice and actually pruritus, invoked by lipid-soluble opioids, is of shorter duration, which can underestimate the cases.[26]

Urinary retention

In this study we only report an incidence of evident urinary retention in 0.18% of patients submitted to NB. The majority of patients with EC can experience urinary retention, but in our center they usually remain with a bladder catheter in the postoperative period. Postoperative urinary retention can result from intraoperative damage of the pelvic autonomic nerve, use of sympathomimetic and anticholinergic drugs and stress-induced activation of inhibitory sympathetic reflexes. Type and length of surgery, intraoperative fluid management, early postoperative ambulation and previous history of micturition problems could play a more important role in immediate postoperative urinary retention than the type of postoperative pain control.[1,27]

Complications/ Side effects of PNB

In the early postoperative period, mild paresthesia may be present in up to 15% of patients that undergo PNB.[4] In this study, 4.9% (n = 51) of patients submitted to PNB complained of an early sensory deficit, on median 1day after the technique. Motor deficits were present in 1.7% (n = 18).

After hospital discharge, only 30.4% (n = 21) had prolonged sensory or motor deficits, but as in the literature, most of these symptoms disappear within days to weeks.[4,28] Our patients were evaluated by telephone or ambulatory consultation within one month and 72.6% of cases had complete deficits' resolution within the first week; the remaining until 2 months. There was only one case of persistent sensory deficits one year after surgery, due to a pseudomeningocele, with follow-up in CPU. The patient was submitted to shoulder surgery under interscalene plexus block. These arthroscopic surgeries are associated with PNI, ranging from 0.1% to 10%, mainly caused by surgical traction to improve exposure or by arthroscopic portal placement.[4] Pseudomeningoceles are more frequent after forceful distraction, causing neuropraxia and tears in the dura and arachnoid mater with CSF leak, usually self-limited and asymptomatic. Occasionally, CSF may accumulate in the supraclavicular tissues and cause local pain and symptoms related to liquid hypotension in orthostatism.[29]

Similar to neuraxial injury PNI is commonly linked to needles' or catheters' trauma, ischemia or drug toxicity. It is also associated with patient factors like advanced age, extreme biotypes, history of chemotherapy, diabetes mellitus or previous neurologic disease. Surgical technique with retractor stretches, direct nerve injury, compressive dressings, use of tourniquets, improper or prolonged positioning, are also important factors.[4,28]

In a large prospective study of Neal et al., serious PNI are reported in 2.4:10,000 PNB and Auroy et al. described permanent neurologic complications in 1.5:10,000 cases.[4,12]

Theoretically, recent studies showed that nerve location with ultrasound increased the rate of successful PNB compared with electrical stimulation and reduced the rate of vascular puncture.[30] In future studies, it would be equally important to record the type of technique used for PNB.

The small number of complications associated with PNB may be due to our small sample. However, PNB are increasing in our hospital and surveillance of these patients by APU will allow us to follow-up its rare but possible complications.

In general, all candidates for RA should be rigorously evaluated and informed of any potential side effects or complications of these techniques and the decision to perform it must be made on an individual basis considering its benefits and the risk factors for complications. The APUs are fundamental in monitoring, following-up and guiding the treatment of patients with complications, and in the future will serve as a link between hospitals and primary health care to define the most appropriate therapeutic strategies. They can also provide useful information and education to health care providers, patients, and tutors. In this new era, in which APUs exist in all national hospitals, we need to carry out more frequent and rigorous audits, which allow us to better monitor the frequency and severity of each RA's complications.

Despite this, we recognize some limitations of our study, namely due to its retrospective character with recording and information bias such as the lack of data in the APU's electronic records related to the anesthetic technique, disinfection type and complications registration.

Conclusion

Although we found incidences of side effects similar or even lower than those described in the literature, *major* adverse events/complications after NB had a higher incidence, with particular emphasis on EA cases. Despite this, other serious complications, such as SH and permanent PNI, are still rare.

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.2021.03.011.

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ORIGINAL INVESTIGATION

Validation of the Brazilian version of the child pain catastrophizing scale and its relationship with a marker of central sensitization

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Catastrophizing;
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Validation studies as topic;
Children;
Brain-Derived Neurotrophic Factor (BDNF)

Abstract

Objectives: The Pain Catastrophizing Scale-Child version (PCS-C) allows to identify children who are prone to catastrophic thinking. We aimed to adapt the Brazilian version of PCS-C (BPCS-C) to examine scale psychometric properties and factorial structure in children with and without chronic pain. Also, we assessed its correlation with salivary levels of Brain-Derived Neurotrophic factor (BDNF).

Methods: The Brazilian version of PCS-C was modified to adjust it for 7–12 years old children. To assess psychometric properties, 100 children (44 with chronic pain from a tertiary hospital and 56 healthy children from a public school) answered the BPCS-C, the visual analogue pain scale, and questions about pain interference in daily activities. We also collected a salivary sample to measure BDNF.

Results: We observed good internal consistency (Cronbach's value = 0.81). Parallel analysis retained 2 factors. Confirmatory factor analysis of our 2-factor model revealed consistent goodness-of-fit (IFI = 0.946) when compared to other models. There was no correlation between visual analogue pain scale and the total BPCS-C score; however, there was an association between pain catastrophizing and difficulty in doing physical activities in school (p = 0.01). BPCS-C total scores were not different between groups. We found a marginal association with BPCS-C (r = 0.27, p = 0.01) and salivary BDNF levels.

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Discussion: BPCS-C is a valid instrument with consistent psychometric properties. The revised 2-dimension proposed can be used for this population. Children catastrophism is well correlated with physical limitation, but the absence of BPCS-C score differences between groups highlights the necessity of a better understanding about catastrophic thinking in children.
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Introduction

Pain is a multidimensional experience with a complex and dynamic interaction among physiological, psychological, and social factors that can perpetuate or worsen it. The biopsychosocial approach views the pain as an experience; thus, we must identify the variables that account for the initiation, exacerbation, waning, maintenance of pain, and suffering.

The emotional reaction to pain is intrinsically unpleasant, causing suffering and distress. While the acute pain is an adaptive reaction to physical injuries, chronic pain is a maladaptive process. Chronic pain induces dysfunctional changes in the central nervous system function, both in adults and children. The prevalence of chronic pain in childhood reaches 20–35%.[1,2] It is associated with decreased quality of life, higher incidence of school absenteeism, and prevalent symptoms of depression, anxiety, and catastrophic thoughts about life.

Intense pain may trigger adverse emotional reactions, especially catastrophic thinking. Such reactions may modify the subjective experience of pain and amplify its transmission process; they constitute an exaggeratedly negative mental state that appears during actual or predicted pain experience, representing a dysfunctional way of coping with stressors.[3] Previous studies in adults, children, and adolescents, showed that high scores of catastrophizing were associated with greater emotional distress,[4–7] severe physical disability,[8,9] and higher pain scores.[4,6,11] In this context, the Pain Catastrophizing Scale-Child version (PCS-C) allows identifying children who are prone to catastrophic thinking and at risk of suffering from its psychological consequences. The PCS-C is validated and well established in other countries, yet there is no study to measure catastrophic thinking in Brazilian children with or without chronic pain.

The present study aimed to adapt the English version of the PCS-C to be used with Brazilian children and evaluate its psychometric properties. We investigated the internal consistency, the factor structure, and the correlations of the PCS-C and functional capabilities in a sample of children with chronic pain and healthy ones. We also hypothesized that the degree of catastrophic thoughts in children could be associated with their salivary levels Brain-Derived-Neurotrophic Factor (BDNF).

Methods

The Institution ethics committee approved the project. We obtained Informed Consent from every parent or guardian before starting the study. The scale validation was divided into three standardized phases, as recommended by Beaton[12] and presented in Figure 1.

Instrument validation

Adapted from the Pain Catastrophizing Scale for adults, the Pain Catastrophizing Scale-Child version[6] is a validated self-report measure[13] including a 13-item questionnaire that assesses the extent of catastrophizing thoughts of child patients in pain. It comprises three domains (helplessness, magnification, and rumination) that can be rated according to a 5-point Likert-type scale that considers intensity and frequency. The total score is the sum of points from the three domains.

Phase I

Translation, synthesis, and back translation

We carried out both the translation of the PCS-C scale (original English version) into Brazilian Portuguese and its adaptation to our culture according to previously published guidelines.[12] In order to adapt the wording of the answers, we made some changes in the keywords.

Two native English speakers with Brazilian Portuguese as their second language were responsible for back-translating the scales. Both translators worked under blinded conditions. A third bilingual person highlighted the conceptual errors and contradictions of the translated versions for later examination by a committee of experts. For feedback, we sent the back-translated scales to the original authors.

Delphi method to assess the semantics and the conceptual content of each item

A panel of experts, including translators, back-translators, methodologists, clinical researchers, and the English-language authors of the PCS-C verified the semantic, idiomatic, experimental, and conceptual equivalence of the scales. The aim was to confirm that the translated version reflected the same content of the original one.

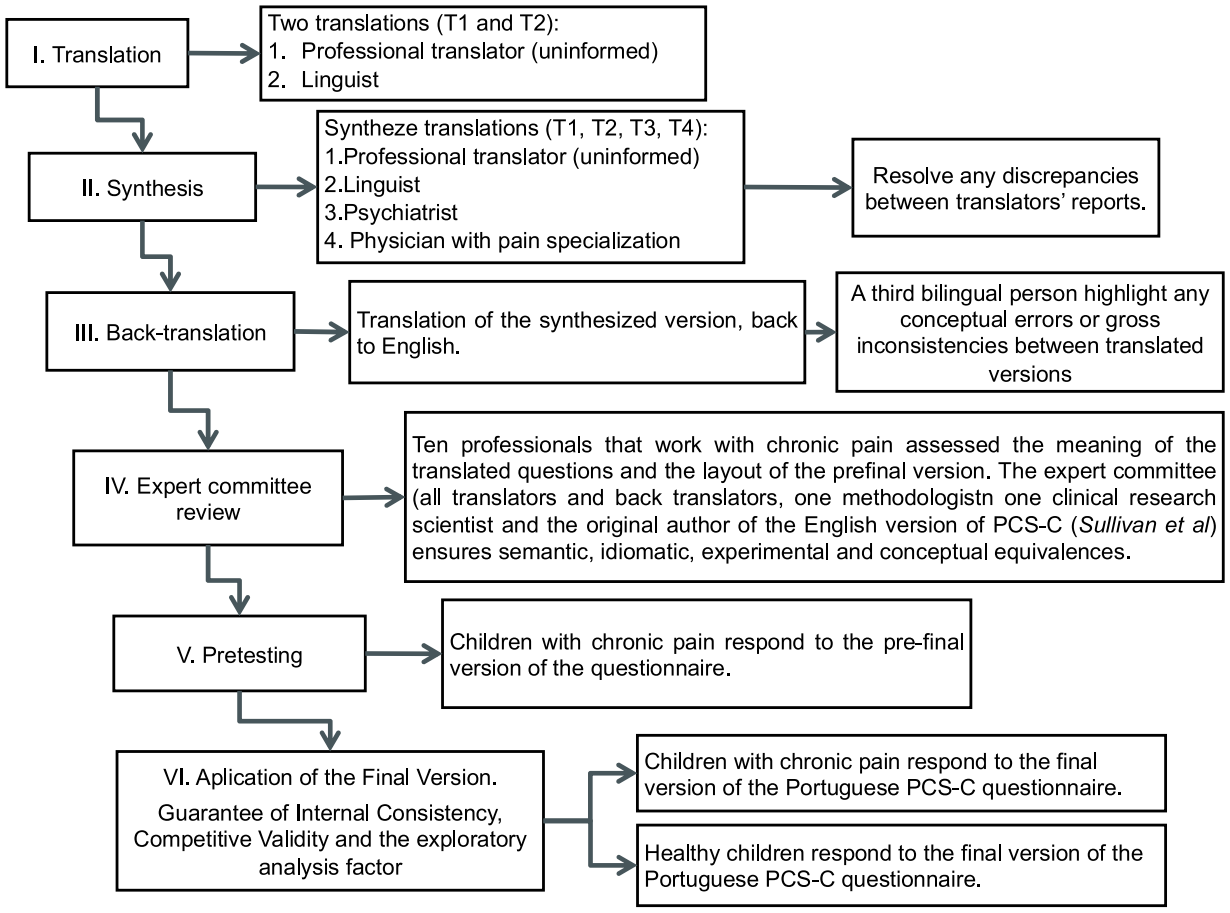

Figure 1 Flow of the multiple standardized phases of the study 20.

Phase II

Pretesting the PCS-C in the pilot version

To check comprehension, we selected a small group of children of both genders to explore the subjective thoughts that each question and answer could arouse. Also, fifteen professionals who work daily with children, related or not with the health area, were asked to participate.

We used a visual 10-cm analogue scale, ranging from zero (completely incomprehensible) to 10 (comprehensible), to gauge understanding of each question from both questionnaires. The mean ± SD of the comprehension degree of the 13 questions on the PCS-C scale was 9.19 ± 1.10. After gathering information, we made small adaptations for better understanding from the children. The ultimate goal was to obtain idiomatic and conceptual equivalence rather than the literal equivalence of the scales. The final version of the Brazilian PCS-C is in Figure 2.

Phase III

Assessment of psychometric properties and the validation of the PCS-C's final version

Subjects

Participants were 7–12 years old children divided into two subsamples: one with 56 healthy children recruited from the 5th grade of a state school in Southern Brazil; the other with 44 children with chronic pain recruited from the gastroenterology ambulatory, and the pediatric oncology, and reumatology clinics in a quaternary university hospital. All the children with chronic pain and their caregivers were recruited through a convenience sample. Before the interviews, participants were asked to answer a questionnaire exploring social and health issues including questions about chronic disabilities and psychiatry disorders. The children with chronic pain did so using mobile devices while their parents/caregivers, paper forms. The healthy children wrote answers to the same questions during school time. The consent from their parents/caregivers was obtained previously.

Additional measures

In addition, the chronic pain group completed two further self-report measures.

Pain intensity

Severity was assessed with a Visual Analogue Scale (VAS). Children rated their ''average pain intensity'' in the previous 2 weeks on a 10-cm VAS (0 cm, ''no pain'', 10 cm, ''the worst pain possible''). They were also asked about pain medications and hospital stays.

Disability

To correlate total catastrophism score with functional disabilities, we asked the participants a simple ques-

Escala de Catastrofização – Versão Infantil, Crombez et al. (PCS-C)

Pensamentos e sentimentos durante a dor

Abaixo, há 13 frases sobre diferentes pensamentos e sentimentos que você pode ter quando está com dor.

Ao ler cada frase, marque a palavra que melhor define com qual FORÇA você tem cada pensamento.

1. Quando eu estou com dor, me preocupo o tempo todo se ela vai acabar				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
2. Quando eu estou com dor, penso que é impossível continuar assim por muito tempo				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
3. Quando eu estou com dor, penso que ela é terrível e que nunca vai melhorar				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
4. Quando eu estou com dor, é horrível e sinto que ela vai tomar conta de mim				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
5. Quando eu estou com dor, penso que não aguentarei mais				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
6. Quando eu estou com dor, tenho medo de que a dor piore				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
7. Quando eu estou com dor, penso em outras situações de dor				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
8. Quando eu estou com dor, desejo que a dor vá embora				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
9. Quando eu estou com dor, não consigo pensar em outra coisa				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
10. Quando eu estou com dor, fico pensando no quanto ela dói				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
11. Quando eu estou com dor, fico pensando no quanto eu quero que a dor pare				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
12. Quando eu estou com dor, nada que eu faça faz a dor parar.				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*
13. Quando eu estou com dor, penso que algo grave pode acontecer				
NUNCA	*POUCO*	*MAIS OU MENOS*	*MUITO*	*MUITÍSSIMO*

Figure 2 Final version of the Brazilian Catastrophizing Scale-Children's version.

tion about their abilities to perform physical activities or sports at school. They reported their difficulties using an ordinary scale (1–3), from little to extreme.

Salivary biological marker

Salivary samples were passively collected by expectoration for BDNF dosing. After harvest, the samples were stored on ice until biochemical evaluation, which was performed

Table 1 Participants characteristics (n = 100).

Characteristic	Healthy children	Chronic pain	*p*
	n = 56	n = 44	
Gender (female)	23 (41.07%)	21 (47.72%)	0.1
Age (y)	11.16 (0.73)	9.7 (1.63)	0.001
Years of education (mean)	5.57 (0.49)	4.38 (1.59)	0.001
Psychiatric disease		6 (13.63%)	
Months of pain		39.84 (SD = 37.4)	
Pain diagnosis			
Abdominal		34 (77.27%)	
Oncologic		3 (6.81%)	
Rheumatologic		7 (15.9%)	
BDNF	2,814 (1.57)	1,875 (1.41)	0.008
Catastrophism score	20.32 (7.69)	20.16 (9.19)	0.9

Data are presented as mean and Standard Deviation (SD) or frequency and percentual.

within one hour. The samples were frozen at -80 °C after centrifugation at 5000 rpm for 10 minutes at 4 °C. Afterwards, samples were thawed, centrifuged, and analyzed as described by Mandel et al to optimize the detection of BDNF by ELISA kits.[14]

Statistical analysis

To identify the relevant dimensions of the PCS-C we conducted a parallel analysis[15] of the 13 items. Then, we performed an exploratory factor analysis with squared multiple correlations for the prior communality estimating Kaiser measures of sampling adequacy, with promax rotation to confirm the factor retention.

Given that PCS-C was a previously validated measure, we used a Confirmatory Factor Analysis (CFA) with structural equation model to evaluate if the original 3-factor model proposed by Crombez[6] and the other models fit a sample from a new population. We assessed the models' fit by using root mean square error of approximation (RMSEA – values should be < 0.05), the Bentler Comparative Fit Index (CFI), and the Bollen Non normed Index (IFI – values close to 1 indicate a very good fit).[16] The latter is preferred because it is the least affected by the sample size.[17] Internal consistency was assessed through Cronbach's alpha using the data from the baseline questionnaires. We calculated descriptive statistics for all demographic and study variables. We tested continuous variables for normality using the Shapiro-Wilk test. Comparisons between continuous variables were performed using *t*-test for independent samples. Categorical variables were compared using the χ^2 or Fisher exact test. The association of the catastrophizing scale and pain variables was analyzed by Spearman Rank correlation. Moderate positive correlation coefficients were expected not to exceed 0.7.[18] One-way ANOVA was used to understand how the variables ''total months of pain'' and ''physical activity at school'' related to the child pain catastrophizing scores in the group of children with pain. For all statistical analysis, the significance was set at $p < 0.05$. Data were analyzed using SAS 9.4.

Results

Participants were divided in healthy and chronic pain groups. Most of the children with chronic pain (77%) were recruited from the pediatric gastroenterology ambulatory of abdominal pain. Table 1 shows the demographic characteristics.

Internal consistency of the PCS-C and item variability

The Supplementary Table shows the distribution of item scores. There was a good internal consistency with Cronbach's alpha of 0.813, indicating that each of the items contributed similarly to the construct we intended to measure. Reliability testing further revealed good factor stability with only a negligible gain in Cronbach's value by omitting item 8, which had the lowest total correlation.

Parallel and exploratory factor analysis

In order to determine the instrument dimensions, we ran a parallel analysis which retained two factors. These two dimensions were confirmed by the exploratory factorial analysis.

Confirmatory factor analysis

It was used to evaluate the aforementioned model and other models already proposed. Model 1 is a 1-factor model in which the 13 items are assumed to be indicators of a single latent trait (pain catastrophizing). Model 2, proposed by Pielech,[20] has two factors: one composed of the items measuring rumination and magnification, and the other, with items measuring helplessness. Model 3 is the original 3-factor model (magnification, rumination, and helplessness) proposed by Sulivan in adult scale and by Crombez for the child scale. Model 4 is the 2-factor model found in our analysis. Our model retained different items in two factors that could be included in the rumination domain (1,8,9,11,12) and in the magnification and help-

Table 2 Goodness-of-fit values for the different models tested (n = 100).

		IFI	RMSEA	95% IC; RMSEA	CFI
Model 1	1 factor (13 itens)	0.8790	0.0694	(0.0279; 0.1025)	0.8726
Model 2	2 factors (5 + 8 itens)	0.8762	0.0709	(0.0301; 0.1040)	0.8690
Model 3	3 factors (6 + 4 + 3 itens)	0.8962	0.0662	(0.0195; 0.1006)	0.8894
Model 4	2 factors (5 + 8 itens)	0.9467	0.0465	(0.0000; 0.0849)	0.9437

Model 1, 1 factor, 13 items; Model 2, factor structure by Pielech[20]; Model 3, factor structure suggested by Crombez[10]; Model 4, model revealed by the current study.
CFI, Comparative Fit Index; IFI, Incremental Fit Index; RMSEA, Root Mean Square Error of Approximation.

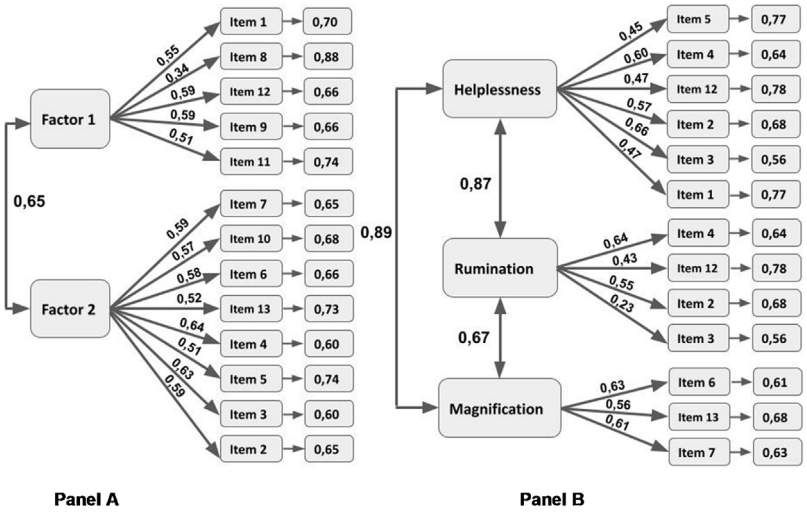

Figure 3 Factorial structure of the Brazilian Portuguese Version of Pain catastrophizing scale for Children (Panel A: 2-factor model revealed by the current study; Panel B: the classical 3-factor model).

lessness domain (2,3,4,5,6,7,10,13). Item 8 revealed the lowest close fit (0.34), as was already demonstrated in other models.[20,21] To realize how well the models fit the data, we computed several goodness-of-fit indices in Table 2. The 2-factor model (Model 4) revealed the best goodness-of-fit values with IFI and CFI close to 1, followed by the classical 3-factor model.[13] Figure 3 shows the diagrams and the factor loading generated for the hypothesized model by Sulivan and for the new factorial analysis proposed by the authors (Model 4).

Demographic and pain factors and concurrent validity

The PCS-C total score was not different between chronic pain and healthy children, whose age and schooling years varied. We performed a general linear model analysis with ''age'' and ''years of schooling'' in relation to the catastrophism score of healthy and pain children, but it showed no significant results. Also, it was not identified a correlation between a single measure of visual analogue scale and catastrophism (r = 0.17). But there was a negative moderate Spearman correlation (r = -0.387, p = 0.009) between the ''time of pain'' diagnosis in months and the catastrophism in the group of pain children. One-way ANOVA was used to examine differences in child pain catastrophism scores utilizing ''time of pain'' diagnosis and gauging progressive difficulty in doing physical education at school. There was significant difference just for physical school activities (p = 0.019). When examining post-hoc pairwise comparisons by Tukey test, the means of catastrophism for the group with great difficulty to do school physical activities were higher than for the groups with some and lower difficulties (Table 3).

Table 3 One-way ANOVA between child pain catastrophizing, months of pain, and physical activity at school (n = 44).

	Catastrophism score		
Variable	Means	F-value	p
Months of pain	-	2.36	0.135
Physical activity at school		4.34	0.019
Any difficult	18.28[a]		
Some difficult	19.74[a]		
Much difficult	30.49[b]		

Means with different superscripts differ significantly at $p < 0.05$ (e.g., a is significantly different from b).

Relationship between the PCS-C and salivary BDNF

Samples with a concentration of salivary BDNF below the lower limit were excluded from analysis (n = 18). PCS-C total scores were moderately correlated with levels of BDNF

($r = 0.27$, $p = 0.012$). The Supplementary Figure presents the scatter plot of the raw PCS-C and BDNF.

Discussion

The adaptation of the Brazilian Portuguese version of PCS-C was carried out by a panel of experts and included both linguistic translation and cross-cultural adaptation to maintain the content validity of measures throughout the contexts. Strict and well-established guidelines were followed during the translation and validation steps. This process yielded a Brazilian Portuguese version that can be easily understood by Portuguese-speaking children and adults. The translation process was followed by the evaluation of the psychometric properties, and by a number of validity analysis, including association with objective biological marker of central sensitization.

The test for internal consistency, Cronbach's alpha (0.81) showed adequate consistency of participant's responses. In our initial approach, we conducted a parallel analysis that identified two dimensions. The parallel analysis provides a superior alternative to other techniques for the same purpose, since it is minimally affected by the sample size.[19] The retention of psychometric properties reflects their validity despite the presence of differences in dimensions from the original one.

In the subsequent confirmatory factor analysis CFA, we evaluated our model structure and the framework of other models already described for children and adults.[6,20,22,23]

The CFA showed that our 2-dimension model provides a good fit (RMSA = 0.046, CFI = 0.94) and all items loaded on its original factor (> 0.5), except item 8 (Supplementary Table). This item (''When I am in pain, I want it to go away'') was the most highly endorsed in our study and in previous ones,[20,21] and probably reflects the tendency children have to worry about pain more than about their catastrophic thoughts.[21] The second model with a good fit was the original Sulivan's adult and Crombez's children 3-factor model (RMSA = 0.06 and CFI = 0.88), even showing correlations lower than 0.5 on items 1, 5, 8, 11 and 12. This result could express the difference between adults and children comprehension of the three original dimensions of the scale. The three separated dimensions of original adult scale were adapted for children, and should be interpreted with caution, considering cultural differences and educational levels between participants. The same authors of the first proposal of PCS-C validation suggest a reappraisal of the catastrophism thinking in children. The way children appraise threat and its potential consequences, and how they cope with it is different. Some social-cognitive development features like emotional control, magical thinking, egocentric distortion, and fragile coping differ a lot between adults and the young, and we should consider this[24,25] Because of these differences, the dimensions may not reflect the same constructs as in adult thinking. Furthermore, despite the establishment of PCS-C subscales and dimensions, the assessment of catastrophizing thinking in children with pain has been focused on the total score. Measuring the dimensions is unlikely to impact treatment decisions.[20,26]

We also examined the concurrent validity of PCS-C by investigating the strength of the relationship between the PCS-C scores and the scores for other pain-related aspects. The absence of correlation between moderate pain score on VAS and the catastrophizing score could be explained by the lack of consistency of just one pain measurement in an ordinary scale. Furthermore, the measure of pain intensity may be more accurate for acute pain than for chronic pain, since chronic pain is a multidimensional experience.

Likewise, we found a negative correlation between total months of pain and catastrophism. Resiliency could explain this finding. Those familiar with their diagnosis might know what to expect, suffer less from anxiety, and have fewer negative feelings.

Furthermore, catastrophizing relates to functional disability.[10,20] Difficulty in doing daily activities shows how much a disease affects the functionality and hinders day-to-day life.[27] When it comes to reflecting the consequences of pain and child fragility, assessment of pain-related disabilities seems a better measure than a visual scale to measure pain. In our chronic pain sample, we were able to show the dependence of the catastrophizing score on physical activity abilities.

We also examined the relationship between catastrophism (PCS-C total scores) with salivary BDNF, finding a modest positive correlation. Otherwise, healthy patients had higher levels than chronic pain children. The presented BDNF's association with higher catastrophism and probable lower resilience, even without definite disease, corroborates previous studies which demonstrated that BDNF has to do with cerebral modulation and is higher in patients under chronic pain.[28,29] Our findings suggest that it is not possible to assess directly and singly the effect of each one of these potential modifier factors on BDNF secretion and on the psychological constructs. Unfortunately, it is not established that salivary BDNF has an acceptable correlation with serum or central nervous system values.[14] Although the salivary measure of this biological marker demonstrated good feasibility, future studies should best define the significance of human salivary BDNF and its correlation with central nervous plasticity.

This study has some limitations. First, it was based on a sample of children from one single institution and from one single public school. Therefore, the findings may not generalize to community samples. Secondly, the limited sample could not be sufficient to infer conclusions about the psychometric properties of the tested scale. Hence, the reliability of factorial analysis does not depend exclusively on the sample size. Moreover, the magnitude of the loadings of the components could be more significant than the isolated sample size.[30] We could, however, demonstrate a relevant internal consistency and adequate loading factors even with limited sample.

Thirdly, catastrophism is a complex construct associated with psychiatric variables such as depressive symptoms or anxiety.[20] A better understanding of children catastrophizing thinking involves assessing their psychological state and evaluating their personality traits and other components of health and wellness such as health conditions, lifestyles, social support, and socioeconomic conditions.

This study provides evidence for consistent psychometric properties of the Portuguese version of PCS-C. Our factorial analysis suggests that we can apply both the revised 2-dimension proposal and the original 3-dimension scale on

Brazilian children. Children catastrophism is well correlated with physical limitations, but the absence of PCS-C score differences between healthy children and those with chronic pain highlights the necessity of a better understanding about catastrophic thinking in children.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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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.2021.02.057.

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ORIGINAL INVESTIGATION

Predictive model for difficult laryngoscopy using machine learning: retrospective cohort study

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KEYWORDS
Intratracheal intubation;
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Abstract
Background: Both predictions and predictors of difficult laryngoscopy are controversial. Machine learning is an excellent alternative method for predicting difficult laryngoscopy. This study aimed to develop and validate practical predictive models for difficult laryngoscopy through machine learning.
Methods: Variables for the prediction of difficult laryngoscopy included age, Mallampati grade, body mass index, sternomental distance, and neck circumference. Difficult laryngoscopy was defined as grade 3 and 4 by the Cormack-Lehane classification. Pre-anesthesia and anesthesia data of 616 patients who had undergone anesthesia at a single center were included. The dataset was divided into a base training set (n = 492) and a base test set (n = 124), with equal distribution of difficult laryngoscopy. Training data sets were trained with six algorithms (multilayer perceptron, logistic regression, supportive vector machine, random forest, extreme gradient boosting, and light gradient boosting machine), and cross-validated. The model with the highest area under the receiver operating characteristic curve (AUROC) was chosen as the final model, which was validated with the test set.
Results: The results of cross-validation were best using the light gradient boosting machine algorithm with Mallampati score x age and sternomental distance as predictive model parameters. The predicted AUROC for the difficult laryngoscopy class was 0.71 (95% confidence interval, 0.59–0.83; $p = 0.014$), and the recall (sensitivity) was 0.85.
Conclusion: Predicting difficult laryngoscopy is possible with three parameters. Severe damage resulting from failure to predict difficult laryngoscopy with high recall is small with the reported model. The model's performance can be further enhanced by additional data training.
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Introduction

Difficult airway (DA) is a clinical situation in which a traditionally trained anesthesiologist experiences difficulty in ventilating the facial mask of the upper airway, intubation, or both.[1] The incidence of difficult laryngoscopy, difficult intubation, and failed intubation was 12.3%, 9%, and 0.47%, respectively.[2] Although difficult airways are uncommon in anesthesia or resuscitation, improper airway management can result in fatal outcomes. Therefore, predicting DA in patients requiring airway management becomes crucial. DA includes difficult laryngoscopy (DL), in which case visualizing any portion of the vocal cords is not possible.[1] Many methods and guidelines for evaluating and predicting DL exist[1,3–8]; however, there is still debate on the best methods and anatomical landmarks to predict DL.[9]

Machine learning (ML) is a category of algorithms that allows accurate software applications predict results. Machine learning is increasingly used for medical diagnose and disease predictions. The basic premise of machine learning involves writing an algorithm that receives input data, uses statistical analysis to predict an output, and updates it as new data becomes available. ML has the power to quickly synthesize and analyze complex multivariable combinations. Thanks to ML, predicting difficult intubation is also changing.[10]

There are several predictive models for DL or DA. However, the use of multiple predictors reduces practicality,[10–14] and most models lack sufficient validation.[10,11] This study aimed to develop and validate practical predictive models for DL through ML using only a few predictors.

Methods

This retrospective cohort study was approved by the Institutional Review Board/Ethics Committee of the Chuncheon Sacred Heart Hospital, Hallym University (IRB No. 2019-07-012-001). The requirement for written informed consent was waived by the ethics committee. The study was conducted retrospectively, and the diagnosis of DL was considered predictors and evaluated by comparing it with the diagnosis of anesthesia record. Data of patients who had undergone surgery under anesthesia at Hallym University Chuncheon Sacred Heart Hospital between January 18, 2019 and November 6, 2019 were collected from preanesthesia and anesthesia records. Exclusion criteria were as follows: < 18 years old, regional anesthesia, major external facial or neck abnormalities, laryngeal abnormalities or tumors, laryngeal mask or mask ventilation, use of video laryngoscopes or fiberoptic scope for tracheal intubation, intubation performed by a resident with < 2 years of anesthesiology experience, insufficient records, and endotracheal intubated states before anesthesia. Of the 3676 selected patients, 3060 were excluded, and 616 were finally included in the study.

Parameters for prediction of difficult laryngoscopy

The parameters for prediction of DL included age, body mass index (BMI), Mallampati grade, sternomental distance (SMD), and neck circumference (NC). The Mallampati score classifies the ease of endotracheal intubations as Class I glottis – fully exposed glottis including the anterior and posterior commissures; Class 2 glottis – partly exposed glottis and not visualized anterior commissure; Class 3 glottis – glottis not exposed and only corniculate cartilages visualized; and Class 4 glottis – corniculate cartilages not exposed. SMD was defined as the straight distance between the upper border of the manubrium sterni and the bony point of the mentum after fully extending the neck with the mouth closed.[8] Neck circumference was measured in cm at the level of the thyroid cartilage.[7] All missing values were removed.

Intubation and laryngoscopy grade

The routine procedures for tracheal intubation are standardized at our hospital. If the vocal cord was not visualized at first attempt, the anesthesiologist would try the laryngoscope manipulation again. Then, depending on the situation, a laryngoscope manipulation was attempted by another anesthesiologist or a video laryngoscope was attempted. Difficult laryngoscopy was defined when all direct laryngoscopy attempts did not visualize the vocal cords. In the anesthesia record, if multiple attempts are made, the number of attempts is recorded and the final Cormack-Lehane grade is recorded. Standard Macintosh metallic single-use disposable laryngoscope blades (INT; Intubrite Llc, Vista, CA, USA) were employed. In total, seven attending anesthesiologists and three resident anesthesiologists classified direct laryngoscopy views in accordance with the Cormack-Lehane grades as Grade 1 = most of the glottic opening is visible; Grade 2 = only the posterior portion of the glottis or only arytenoid cartilages are visible; Grade 3 = only the epiglottis but no portion of the glottis is visible; Grade 4 = neither the glottis nor the epiglottis is visible. Cormack-Lehane 3 and 4 indicated DL and were combined into the difficult class. Cormack-Lehane 1 and 2 were combined into the non-difficult class.

Imbalance learning

The five prediction parameters mentioned were included as variables. A dataset was created with the variables of 616 patients. However, the difficult class (n = 64) included less patients than the non-difficult class (n = 552), resulting in imbalanced data. To solve this problem, we combined over- and under-sampling by the synthetic minority oversampling technique (SMOTE).[15,16]

Variables and algorithm selection

The dataset was randomly divided into a base training set (80%, 492) and a base test set (20%, 124) with equal distribution of difficult class patient data. Through logistic regression of the base training set, we found variables with significant odds ratios ($p < 0.05$) for DL occurrence and created several training datasets with different variable combinations. We used the base test set to create test sets corresponding to the variables in each training

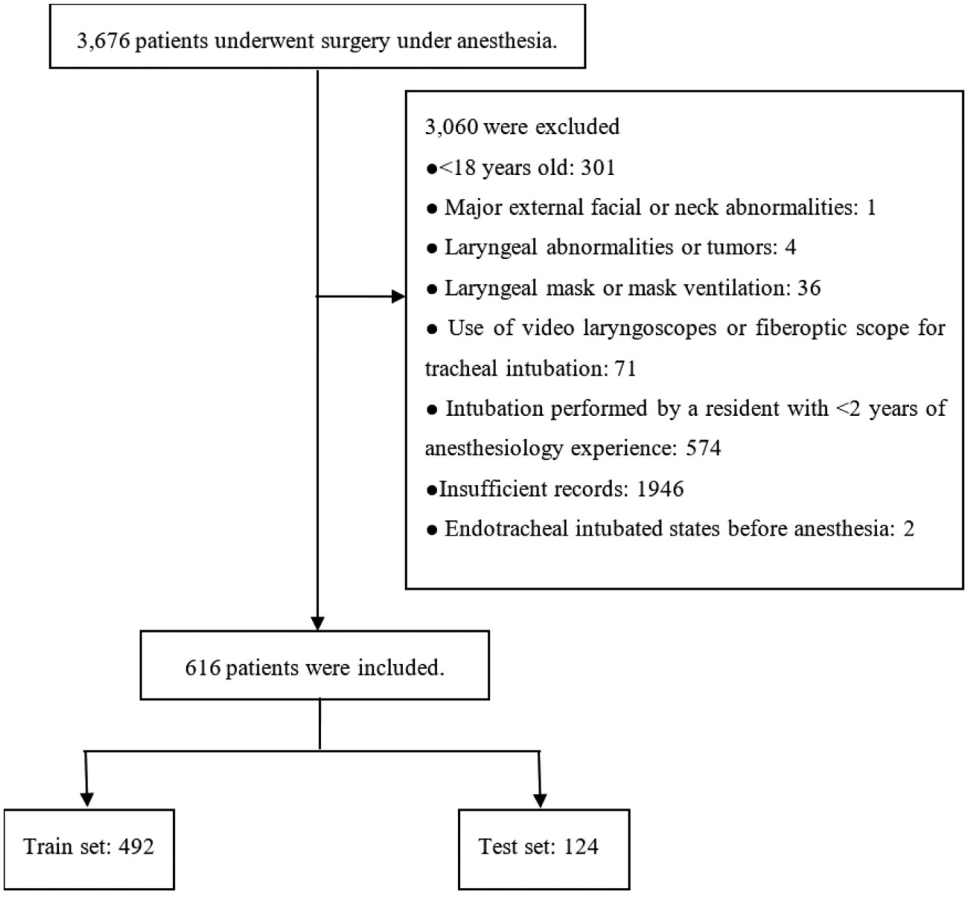

Figure 1 Flow diagram.

set. Because the purpose of this study is to develop a predictive model with a small number of variables and good performance, a model trained with the basic training set is needed to compare with a model with fewer variables than the basic training set. Also, in addition, a corresponding test set is required to evaluate each training set, including the basic training set. Each training set was normalized by min–max scaling after applying SMOTE, while each test set was normalized by the min–max scaling of the training set. All training sets were trained with six algorithms including multilayer perceptron, logistic regression, supportive vector machines, balanced random forest, extreme gradient boosting, and light gradient boosting machines (LGBM). The developed prediction models applied training sets to algorithms, after which a 10-fold cross-validation was performed and the area under curve of the receiver operating characteristic curve (AUROC) calculated. The results were evaluated by the mean AUROC, and the best model chosen as the final one.

Model evaluation and statistics

The final model was completed after tuning the hyperparameters of the selected model. The performance of the complete model was evaluated through a separate test set, and its performance evaluated by AUROC. Additionally, precision (positive predictive value, ratio of patients with true DL among patients predicted as DL) and recall (sensitivity, ratio of patients predicted as DL among true DL) were calculated. Underdiagnosis is DL, but it is predicted and diagnosed as NDL. If DL leads to airway management failure, it can have serious consequences for the patient. Conversely, overdiagnosis is predicting and diagnosing NDL as DL, and because the practitioner recognize that airway management may be difficult and prepare for it, investment in time, manpower, and equipment due to overdiagnosis may be wasted.

All data were processed and analyzed by Anaconda (Python version 3.7; https://www.anaconda.com). Data set variables were analyzed by SPSS (version 26.0, IBM). Continuous variables were compared with the *t*-test or Mann-Whitney test and categorical variables with the chi-squared test. The odds ratio of the variables was determined by logistic regression (method: enter).

Results

Figure 1 shows enrolment, progress and allocation of study. Table 1 shows the patient's DL prediction parameters in the base training and base test dataset. Table 2 shows the odds ratio of DL variables in the base training set. Age, Mallampati grade, and SMD showed statistical significance. A separate training set was created from the base training set using the three statistically significant variables. In addition, by combining the variables, new potential variables and training

Table 1 Prediction variables of difficult laryngoscopy in base train and base test datasets.

	Base train dataset (n = 492)			Base test sets (n = 124)		
	NDL (n = 441)	DL (n = 51)	*p*-value	NDL (n = 111)	DL (n = 13)	*p*-value
Age (years, mean ± SD)	52.7 ± 16.4	57.6 ± 14.9	0.044	54.2 ± 16.9	68.5 ± 10.8	0.004
Mallampati grade (number, %)			0.008			0.057
Grade 1	97 (22.0)	7 (13.7)		30 (27.0)	2 (15.4)	
Grade 2	167 (37.9)	13 (25.5)		46 (41.4)	3 (23.1)	
Grade 3	115 (26.1)	19 (37.3)		23 (20.7)	5 (38.5)	
Grade 4	62 (14.1)	12 (23.5)		12 (10.8)	3 (23.1)	
SMD (cm, years, mean ± SD)	17.5 ± 2.3	16.6 ± 1.9	0.006	17.3 ± 2.0	16.4 ± 1.5	0.103
NC (cm, years, mean ± SD)	37.1 ± 3.6	37.3 ± 3.3	0.628	37.3 ± 5.1	37.8 ± 3.1	0.717
BMI	25.5 ± 3.9	25.3 ± 4.0	0.714	25.6 ± 4.0	25.6 ± 4.6	0.723

NDL, not difficult laryngoscopy class; DL, difficult laryngoscopy class; SMD, sternomental distance; NC, neck circumference; BMI, body mass index; SD standard deviation.

Table 2 Odds ratio of variables in the base train set.

		Odds ratio (95% CI)	*p*-value
Age		1.02 (1.00–1.04)	0.046
Mallampati grade			0.049
	Grade 1	reference	
	Grade 2	1.08 (0.42–2.80)	0.876
	Grade 3	2.29 (0.92–5.68)	0.074
	Grade 4	2.68 (1.00–7.18)	0.050
SMD		0.81 (0.70–0.94)	0.005
NC		1.02 (0.94–1.10)	0.627
BMI		0.99 (0.91–1.06)	0.713

SMD, Sternomental distance; NC, neck circumference; BMI, body mass index.

Table 3 Ten-fold cross validation AUROC after applying each training set to each algorithm.

	Base train set	Train set 1	Train set 2	Train set 3	Train set 4
MLP (mean ± SD)	0.66 ± 0.03	0.60 ± 0.02	0.62 ± 0.04	0.60 ± 0.03	0.62 ± 0.05
LR (mean ± SD)	0.69 ± 0.1	0.63 ± 0.08	0.75 ± 0.09	0.71 ± 0.15	0.67 ± 0.19
SVM (mean ± SD)	0.68 ± 0.09	0.63 ± 0.08	0.75 ± 0.1	0.72 ± 0.18	0.68 ± 0.19
BRF (mean ± SD)	0.92 ± 0.08	0.90 ± 0.09	0.98 ± 0.03	0.98 ± 0.03	0.98 ± 0.04
XGB (mean ± SD)	0.86 ± 0.1	0.84 ± 0.13	0.99 ± 0.03	0.95 ± 0.05	0.98 ± 0.04
LGBM (mean ± SD)	0.94 ± 0.08	0.92 ± 0.12	0.99 ± 0.02[a]	0.96 ± 0.06	0.97 ± 0.03

Base train set: Mallampati grade, age, sternomental distance, body mass index, neck circumference.
Train set 1: Mallampati grade, age, sternomental distance.
Train set 2: Mallampati grade x age, sternomental distance.
Train set 3: Mallampati grade x sternomental distance, age.
Train set 4: Mallampati grade, sternomental distance x age.
AUROC, area under the receiver operating characteristic curve; MLP, multilayer perceptron; LR, logistic regression; SVM, supportive vector machine; BRF, balanced random forest; XGB, extreme gradient boosting; LGBM, light gradient boosting machine.
[a] The model applying training set 2 to LGBM showed the best performance in cross-validation.

sets based on the new combination variables were created. The variables included in the data set were the following:

- Base train set & Base test set: Mallampati grade, age, SMD, BMI, NC
- Train set 1 & Test set 1: Mallampati grade, age, SMD
- Train set 2 & Test set 2: Mallampati grade x age, SMD
- Train set 3 & Test set 3: Mallampati grade x SMD, age
- Train set 4 & Test set 4: Mallampati grade, SMD x age

The results of cross-validation after applying each train set to each algorithm are shown in Table 3. Model performance was best when Mallampati grade x age and SMD were applied to LGBM in the cross-validation. Therefore, we selected the model applying Mallampati grade x age, and SMD variables to LGBM as the prediction model for DL. The final model was completed after hyperparameter tuning. The test set was applied to the final model to evaluate the final model's performance, which showed an AUROC of 0.71 (95% confidence interval, 0.59–0.83; $p = 0.014$) (Fig. 2). The

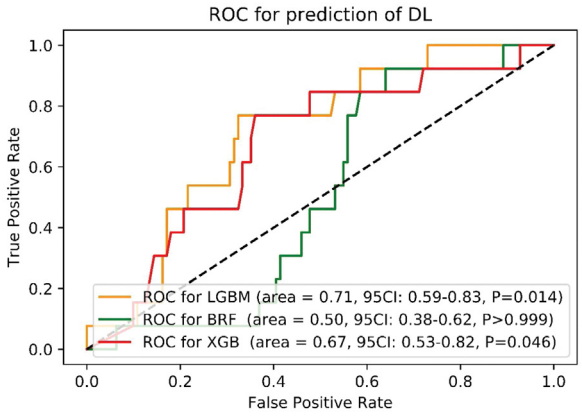

Figure 2 AUROC for difficult laryngoscopy prediction model algorithms: light gradient boosting machine (LGBM), extreme gradient boosting (XGB), balanced random forest (BRF). Predictors: Mallampati grade x age, sternomental distance (SMD). AUROC, area under the receiver operating characteristic curve; DL, difficult laryngoscopy; NDL, no difficult laryngoscopy; 95CI, 95% confidence interval.

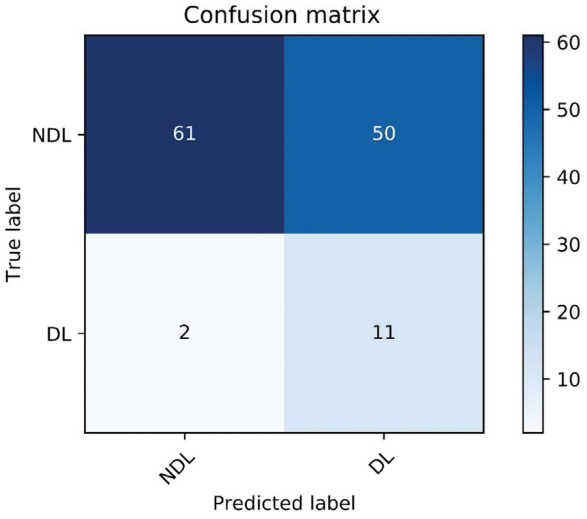

Figure 3 Confusion matrix of difficult laryngoscopy prediction model. DL, difficult laryngoscopy; NDL, no difficult laryngoscopy.

confusion matrix shows the results of counting the number of matches between the original class of the test set target and the test set class predicted by the model (Fig. 3). The precision for DL prediction was 0.18 (ratio of true DL patients among patients predicted as DL, 11/60) and the recall 0.85 (ratio of patients predicted as DL among patients with true DL, 11/13). The importance of the predictors used in the final model is shown in Figure 4.

Discussion

Numerous studies have reported various parameter combinations and results in an attempt to predict DA intubation. In a meta-analysis predicting difficult intubation, the combination of Mallampati score and thyromental distance predicted the most difficult intubation,[17] however, the lack of heterogeneity and the small number of studies limited the conclusions. L'Hermite et al. predicted difficult intubations using the passive scores of five airway parameters but suggested that such predictions of difficult intubation were unlikely to be useful.[18] Some studies have used ML to predict DL or difficult intubation. However, those study results were not validated and evaluated using a test set. Moustafa et al. used ML with a positive predictive value of 76%, a negative predictive value of 76%, and an AUROC of 0.79 for DL.[11] However, even with nine predictive parameters, their cross-validation results were worse than the current study (AUROC, 0.79 vs. 0.99). On their study, Langeson et al. concluded that even though difficult intubation using computer-assisted calculation was predictive, each parameter used for difficult intubation had a poor predictive value.[10] Their ultimate predictive target was difficult intubation, which slightly differs from our predictive target – DL prediction with less variables. They reported significant variables in BMI, age, and Mallampati score, but in our study, the result of cross-validation of models without BMI was better.

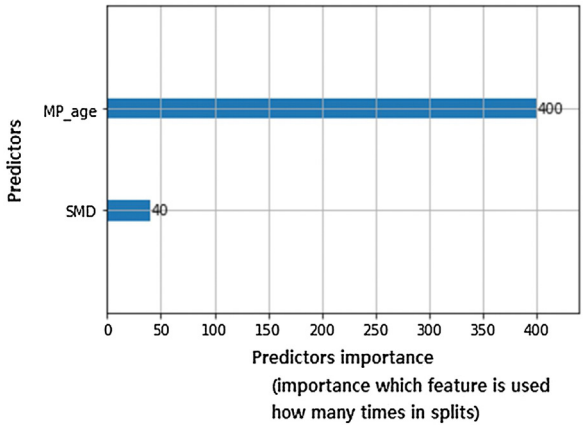

Figure 4 Predictors importance in last model. MP_age, Mallampati grade x age; SMD, sternomental distance.

Despite the differences in prediction targets, some prediction models of difficult tracheal intubation not employing ML perform better than ours. The validated results for those models range from 0.79 to 0.87 in AUROC.[11] However, previous models used 4 to 9 predictors.[10–14] The Arne model employed seven variables, and showed the highest AUROC among the validated models.[13] Although many predictors can be used for accurate predictions, increasing its number is not practical. In this study, the objective was to create predictive models that perform well with few predictors. Airway prediction with few parameters is a good target for ML because of its power to quickly synthesize and analyze variable combinations. On the other hand, models with high precision and recall are ideal for DL prediction. High precision during DL prediction can save time and money in DA preparation. Recall is even more critical considering the serious problem of unpredictable DL. However, when the test set was applied to our model, it did not show the same result as the cross-validation results, and precision was low. This can be attributed to training data overfitting. In general, the solution to overfitting is collecting more training data.[19] Indeed, the small proportion of patients with DL did

not provide a sufficient number of datasets. In such cases of unbalanced data, the data amount becomes even more critical.

In our model, the cross-validation results improved despite reducing the number of predictors. In addition, the model cross-validation results using the newly combined Mallampati grade x age were better than that with Mallampati grade and age as separate predictors. In ML predictions, the model performance can be improved by removing irrelevant information for predictions or by combining features to create potentially new features.[19]

We showed a model that predicts DL with as few predictors as possible, and could identify important predictors for classifying DLs in machine learning models. However, it is difficult to interpret how those predictors behave in machine learning models. Machine learning is often referred to as a black box. Data comes in and decisions come out, but the process between input and output is opaque.[20] In our model, we can see that Mallampati grade x age is the most important predictor in the model, but it is difficult to understand the meaning of the number.

Difficult intubation can often lead to unexpected and complex consequences, harming the patient. In 2015–2018, there was a difference in hospitalization costs in the United States between patients with difficult airway intubation and those who did not, and the median value was about $20,000 higher in patients with difficult airway intubation.[21] Difficult laryngoscopy is different from difficult tracheal intubation but may cause difficult tracheal intubation. In some studies, half of the difficult laryngoscopy reported a high intubation difficult scale $\geq$ 5 points.[22] Appropriate difficult laryngoscopy prediction can help to anticipate difficult airways and be an effective way to reduce medical costs.

Our study has some limitations. First, similar to previous machine learning studies, it does not apply to pediatric patients as it applies to adult populations. Second, because both training and testing were conducted on Asian subjects, the results could differ in other races. For example, Asian populations have statistically different dimensions from Caucasian populations for chin arch, face length and nose protrusion.[23] In order to generalize to global anesthesia patients, studies with additional variables may be needed. Recently, video laryngoscopes have been used in difficult airways, so difficult airway management is better than in the past. However, in situations where video laryngoscopes are not available, difficult laryngoscope prediction can be useful. Third, the use of video laryngoscope or fiberoptic endoscope for tracheal intubation was excluded in our study. It reduces the incidence of difficult laryngoscopy results, which may limit the variability of predictors.

In conclusion, the proposed novel model can predict DL with only three predictors (Mallampati grade, age, and sternomental distance). This small number of predictors makes the prediction simple and with high recall. Thus, the likelihood of serious problems caused by DL prediction failure is low. However, for the improvement of the model's overall performance and generalizability more data from patients with DLs and from different races is required.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparison of anesthesia management in transcatheter aortic valve implantation: a retrospective cohort study

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KEYWORDS
Heart valve prosthesis;
Aortic stenosis;
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General anesthesia

Abstract
Background and objectives: We aimed to investigate the effects of two different anesthetic techniques in our patients who underwent transcatheter aortic valve implantation (TAVI).
Methods: In this study, 303 patients who underwent TAVI procedure with a diagnosis of severe aortic stenosis between January 1, 2012 and December 31, 2018 were retrospectively evaluated. The patients were divided according to the type of anesthesia given during each procedure as; general anesthesia (GA), local anesthesia (LA).
Results: LA was preferred in 245 (80.8%) of 303 patients who underwent TAVI, while GA was preferred in 58 patients (19.1%). Median ages of our patients who received LA and GA were 83 and 84, respectively. The procedure and anesthesia durations of the patients in the GA group were longer than the LA group ($p< 0.00001$, $p < 0.00001$, respectively). Demographic and pre-operative clinical data were similar in comparison between two groups ($p > 0.05$) except for peripheral artery disease. Hypertension was the most common comorbidity in both groups. While the number of inotrope use was significantly higher in patients who received GA ($p < 0.00001$), no significant differences were found between LA and GA patients in terms of major complications and mortality ($p > 0.05$). Intensive care and hospital stays were significantly shorter in the LA group ($p = 0.001$, $p = 0.023$, respectively).

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Conclusion: The anesthetic technique of TAVI procedure did not have a significant effect on outcomes including; complications, mortality and success of the procedure. LA provides shorter duration of procedure and hospital stay.
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Introduction

Severe aortic stenosis is an increasingly important health problem in elderly people.[1,2] If symptomatic aortic stenosis is not treated, it has a poor prognosis and results in mortality shortly.[3–5] Surgical aortic valve replacement (AVR) and transcatheter aortic valve implantation (TAVI) are the methods used in the treatment of aortic stenosis.[6,7] TAVI is an up-to-date treatment approach that is frequently preferred because it is less invasive than AVR, which is a superior surgical method compared to medical treatment.[7]

The fact that patients undergoing TAVI are high-risk and elderly patients may cause many difficulties in anesthesia management. General anesthesia (GA) and local anesthesia (LA) are the preferred anesthesia methods during TAVI procedure in our clinic and in many hospitals around the world.[7,8] Although GA was used more commonly in the beginning of our clinical studies, LA became more widespread with the increasing experience of those performing the procedure.[9] Comorbidities observed in each patient provides information regarding which anesthetic technique may provide advantage and be more suitable during the TAVI procedure.[10,11] In this study, we aimed to investigate the effects of two different anesthetic techniques on outcomes including complications, mortality, and success of the procedure in our patients who underwent TAVI procedure.

Methods

Within the scope of the retrospective cohort study, 337 patients who underwent TAVI with a diagnosis of severe aortic stenosis between January 1, 2012 and December 31, 2018 in Trabzon Ahi Evren Training and Research Hospital were evaluated. The study was initiated after obtaining the local ethics committee approval (2019/07), in accordance with the principles of Helsinki declaration. The consents of the patient and/or patients' relatives were obtained through informed patient consent forms for TAVI procedure and for anesthetic management. The inclusion criteria was defined as patients over 18 years of age who underwent TAVI under GA, LA or conversion from LA to GA. Exclusion criteria was defined as patients under 18 years of age, with prior cardiac arrest before the procedure, open heart surgery during or after the procedure, and patients with missing data. The data were collected retrospectively from the patient files, hospital automation system, and anesthesia follow-up charts. The collected data includes: demographic data of the patients, comorbidity illnesses, American Society of Anesthesiologists (ASA) physical status, EuroSCORE (European System for Cardiac Operative Risk Evaluation) or STS (Society of Thoracic Surgeons) scores, ejection fraction (EF), anesthethic technique, anesthesia and procedure times, use of anesthetic drugs, type of valve used, hemodynamic data, patients who needed inotropes, blood and blood products, duration of intensive care and hospital stay, incidence of complications, and mortality. Thirty-day mortality data were obtained according to hospital records and by phone calls. The patients were divided according to the type of anesthesia given during each procedure as general anesthesia (GA), and local anesthesia (LA).

Pre-TAVI procedure

The TAVI procedure was decided on by the council consisting of a cardiac surgeon, a cardiologist, and an anesthesiologist. The severity of aortic stenosis was assessed by transthoracic echocardiography. Severe aortic stenosis was defined as aortic valve area of <1 cm^2, peak aortic-jet velocity of $\geq$ 4 $m.s^{-1}$ and mean aortic-valve gradient $\geq$ 40 mmHg. In the pre-anesthesia examination, detailed patients' history, comorbidity, physical examination, laboratory examination, consultation results, ASA, EURO, and STS score results were evaluated. The criteria for high risk for conventional surgical aortic valve replacement was included; logistic EuroScore $\geq$ 20% and/or STS predicted risk of mortality $\geq$ 8%, porcelain aorta, prior cardiac surgery, prior chest radiation, severe obstructive pulmonary disease, and frailty. Blood and blood products were prepared.

Routine anesthesia procedure during TAVI

The procedures were performed in the angiography unit of our hospital under sterile conditions and fluoroscopy. Apart from the anesthetic technique planned, the equipment and drugs required for GA were available in the operation room. Arterial blood pressure was measured and recorded by invasive radial artery catheterization from the nondominant arm, and all patients were monitored with routine electrocardiography (ECG), Bispectral index (BIS), and peripheral oxygen saturation (SpO_2). After intravenous peripheral venous cannulation was performed with 16G and 18G needles, two venous access routes were established and appropriate crystalloid solution infusions were started. Central venous catheterization was not used routinely. Central venous catheterization was performed only in some of the patients, and the reasons include the severity of the illness that required central venous pressure measurement and/or inotrope therapy or as there was no possibility to perform peripheral vascular access.

Anesthesia type was decided after evaluating the patient's general condition along with the details of the procedure, and either GA or LA was administered. Sedation and

analgesia were also administered to LA group. After radial artery cannulation, blood samples were obtained from all patients for ACT (activated clotting time) and blood gas measurement. In patients that received GA, intravenous midazolam at a dose of 1 or 2 $mg.kg^{-1}$ (Zolamid, And Pharmaceutical Industry, Turkey) was administered. Anesthesia was induced with intravenous fentanyl at a dose of 1–2 $\mu.kg^{-1}$ (Talinat, And Pharmaceutical Industry, Turkey), propofol at a dose of 2 $mg.kg^{-1}$ (Propofol, Fresenius vial, Germany), and rocuronium at a dose of 0.6 $mg.kg^{-1}$ (Myokron, et Pharmaceutical Co., Turkey). The patients were intubated endotracheally and ventilation was provided with an anesthesia device (Drager Primus, Germany). Normoxic and normocapnic conditions were targeted in the ventilation parameters. Sevoflurane (Sevorane, Abbott, USA) was used as inhalation to maintain anesthesia. In LA group, 2 $L.min^{-1}$ of O_2 was administered via nasal cannula. The targeted sedation and analgesia level was determined as a report of Ramsey sedation score of 3 or 4. Intravenous doses of fentanyl (1 $\mu g.kg^{-1}$) and midazolam (0.05 $mg.kg^{-1}$) were administered. If adequate patient comfort could not be provided, intravenous doses of midazolam (1–3 mg), propofol infusion (Fresenius vial, Germany) (2–5 $mg.kg^{-1}.h^{-1}$), and remifentanil infusion (Ultiva 2 mg/vial, Glaxo Smith Kline, United Kingdom) (0.025–0.2 $\mu g.kg^{-1}.min^{-1}$) were used as necessary by the anesthesiologist.

During LA technique,patients who needed deep anesthesia developed complications due to open surgery or who developed respiratory depression were intubated and GA was applied. The combination of LA and sedation has advantages such as early detection of neurological complications, shorter duration of the procedure, rapid recovery from anesthesia, and decreasing the need for postoperative care. In addition, in cases where the transapical, subclavian or aortic approach is used, GA provides advantages such as managing a difficult airway, planning transesophageal echocardiography, increased patient compliance, and transition to emergency surgery if necessary. If LA is preferred, the patients avoid the occurrence of adverse events related to GA.

A decrease in intraoperative systolic blood pressure more than 25% of the control values or a decrease below 90 mmHg was accepted as hypotension. After fluid bolus and infusion of normal saline for low blood pressure, if a response was not observed in 5 minutes, 5–10 mg IV (intravenous) ephedrine was administered. Later, if there is no response, noradrenaline infusion at a dose of 0.03–0.05 $\mu g.kg^{-1}.min^{-1}$ was planned. Also, it was planned to add dobutamine infusion at a dose of 2–20 $\mu g.kg^{-1}.min^{-1}$ dobutamine to patients whose hypotension did not improve despite these treatments and who had severe hemodynamic instability.[12,13]

Routine cardiology procedure during the TAVI procedure

The transfemoral approach is used in most of the patients. For patients who are not eligible for the transfemoral approach, alternatives are the subclavian/axillary, transaortic, and transapical approach. One of the femoral arteries was cannulated for contrast agent injection and one of the femoral veins for the pacemaker. All TAVI patients require a temporary pacemaker, which is usually performed by insertion of a temporary pace electrode through the femoral vein. A pigtail catheter was placed in the aortic root, and a pacemaker lead was placed in the right ventricle. Then the contralateral femoral artery was cannulated surgically or percutaneously. The calcified valve was passed through with the stiff guidewire advanced through the AL2 diagnostic catheter. Anticoagulation was provided with 70–100 $IU.kg^{-1}$ unfractionated heparin to maintain ACT > 250 seconds. The stiff wire in the left ventricular cavity was replaced with a stiff wire with a flexible tip to minimize the risk of rupture with the aid of a pigtail catheter. Before valve implantation, the stenotic valve was dilated by balloon valvuloplasty. The Edwards-Sapien valve was brought to the aortic root with the help of the delivery system and inflated with the help of a balloon, which was then placed. The Medtronic-CoreValve was released slowly under fluoroscopy at the aortic root with the help of a conveyor system and automatically expanded and placed in place. During the balloon valvuloplasty procedure and valve implantation, short-term ventricular pacing was performed at a rate of 180–200/min to minimize heart movement and prevent the prosthetic valves from slipping.

After the procedure, paravalvular leakage was evaluated by aortography. If paravalvular leaks and/or pericardial effusion is suspected with fluoroscopy, transthoracic echocardiography was performed to evaluate quantify paravalvular leaks or effusion was significant. The femoral artery entry site was closed surgically or by using a percutaneous vascular closure device (Prostar XL, Abbott Vascular, Redwood City, CA, USA). Peripheral angiography was performed to evaluate vascular leak. The pacemaker is usually removed at the end of the TAVI procedure, but if a complete atrioventricular block occurs during the procedure and when using the CoreValve valve, which is more associated with conduction complications, the temporary pacemaker is removed 24 hours later.

Routine procedure after TAVI

Among those who received GA, patients with stable hemodynamics and sufficient respiratory effort were extubated in the procedure room. Patients who could not be extubated because they did not meet these criteria were transferred to the coronary intensive care unit intubated. All patients, including those who underwent LA, sedation, and analgesia after the procedure were transferred to the coronary intensive care unit.

Statistical analysis

The normally distributed data are presented as mean ± standard deviation, and non-normally distributed data as median (interquartile range). Categorical variables are expressed in numbers and percentages. SPSS 24 (Statistical Package for Social Sciences software, SPSS Inc. Chicago, Illinois, USA) program was used in the analysis of the study. In group comparisons, chi-square test was used for frequency comparisons in categorical variables. Independent sample *t*-test was utilized for comparison of mean values among continuous variables, whereas Mann-Whitney non-parametric test

Table 1 Comparison of patients' demographic and pre-procedural data.

	Local anesthesia (n = 245)	General Anesthesia (n = 58)	*p* value
Age (years)	83 (78.5–86)	84 (77.7–86.2)	0.543
Male gender (%)	104 (42.4)	26 (44.8)	0.748
ASA 3 (%)	197 (80.4)	40 (68.9)	0.368
ASA 4 (%)	48 (19.5)	18 (31)	0.123
EF (%)	60 (50–60)	55 (40–60)	0.201
Logistic EuroSCORE	21 (18–25)	22 (17.5–25)	0.661
STS risk score	12 (8.6–20)	13.5 (10–17.2)	0.418
HT (%)	167 (68.1)	43 (74.1)	0.615
DM (%)	85 (34.6)	21 (36.2)	0.906
COPD (%)	68 (27.7)	13 (22.4)	0.396
CVD (%)	25 (10.2)	6 (10.3)	0.944
CRF (%)	19 (7.7)	5 (8.6)	0.810
CAD (%)	154 (62.8)	36 (62)	0.929
PAD (%)	1 (0.4)	5 (8.6)	**0.011**

Values are median (interquartile range).
ASA, American Society of Anesthesiologists; EF, Ejection Fraction; DM, Diabetes Mellitus; COPD, Chronic Obstructive Pulmonary Disease; CVD, Cerebrovascular Disease; CRF, Chronic Renal Failure; CAD, Coronary Artery Disease; PAD, Peripheral Artery Disease.

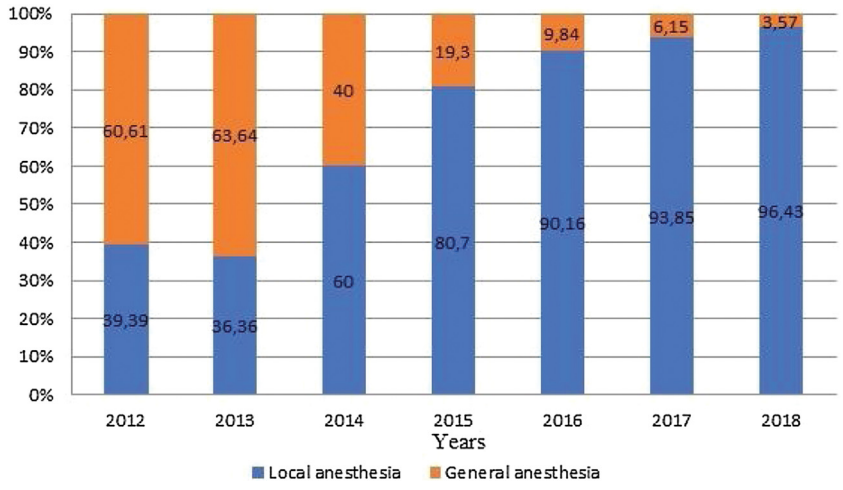

Figure 1 Distribution of the anesthesia technique throughout the years.

was used for comparison of median values. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 337 patients who underwent TAVI between January 1, 2012 and December 31, 2018 were screened and 303 patients were included in the study. The median age of our patients was 83 (78–86) years. Clinical and demographic characteristics of the patients before the procedure are shown in Table 1. When the demographic and pre-procedural data were examined between the two groups, no significant difference was found ($p > 0.05$) except for peripheral artery disease ($p = 0.011$) (Table 1). Hypertension was the most common comorbidity in both groups.

The rate of patients who underwent LA increased and that of patients who underwent GA gradually decreased from 2012 to 2018 (Fig. 1). In Table 2, intraoperative data of patients who underwent LA and GA are compared. Considering the findings obtained, it is seen that the duration of anesthesia, the duration of the procedure and the amount of fluid administered during the procedure were significantly higher in patients who underwent GA ($p < 0.00001$, $p < 0.00001$ respectively). In addition, no significant difference was found between the use of blood and blood products, ephedrine use, valve types, and transfemoral approach rates in patients undergoing GA and LA ($p > 0.05$). It was found that peripheral artery disease was comorbid in 5 patients who underwent the transapical approach. Although hemodynamic instability was higher in the GA group, the difference was not statistically significant ($p = 0.052$) (Table 2). On the other hand, the rate of inotrope use was significantly higher in patients who had GA in comparison to patients who underwent LA ($p < 0.00001$).

The postoperative data and major complications of the patients who underwent LA and GA are compared in Table 3. According to the results, it is seen that the duration of stay

Table 2 Comparison of patients' data during the procedure.

	Local anesthesia (n = 245)	General anesthesia (n = 58)	*p* value
Duration of anesthesia (min)	95 (75–120)	160 (135–191.25)	**< 0.00001**
Duration of the procedure (min)	80 (60–110)	147.5 (120–181.25)	**< 0.00001**
Fluid administered during the procedure (ml)	760 (650–900)	1215 (977.5–1705)	**< 0.00001**
Use of blood products (%)	76 (31,20)	20 (34.8)	0.622
Hemodynamic instability (%)	32 (13.06)	15 (25.4)	**0.052**
Ephedrine use (%)	29 (11.8)	13 (22.4)	0.086
Inotrope use (%)	5 (2.0)	12 (20.6)	**< 0.00001**
Edwards-Sapien valve (%)	198 (97.1)	57 (98.2)	0.943
Medtronic-Core valve (%)	7 (2.8)	1 (1.7)	0.655
Transfemoral approach (%)	245 (100)	53 (93.3)	0.614
Transapical approach (%)	–	5 (8.6)	–

Values are median (interquartile range).

Table 3 Comparison of postoperative data and major complications.

	Local anesthesia (n = 245)	General anesthesia (n = 58)	*p*-value
Duration of stay in the intensive care unit (days)	2 (1–3)	3.5 (2–6)	**0.001**
Length of hospital stay (days)	6 (5–7.75)	7 (5–10)	**0.023**
Pacemaker requirement (%)	28 (11.4)	6 (10.3)	0.827
Arrhythmia (%)	32 (13)	7 (12)	0.841
Vascular complications (%)	18 (7.3)	5 (8.6)	0.617
Infection (%)	8 (3.2)	2 (3.4)	0.806
Neurological dysfunction (%)	5 (2)	3 (5.1)	0.257
Paravalvular leak (%)	7 (2.8)	1 (1.7)	0.101
Myocardial infarction (%)	3 (1.2)	2 (3.4)	0.180
Renal dysfunction (%)	14 (5.7)	4 (6.8)	0.782
30-day mortality	19 (7.7)	5 (8.6)	0.808

Values are median (interquartile range).

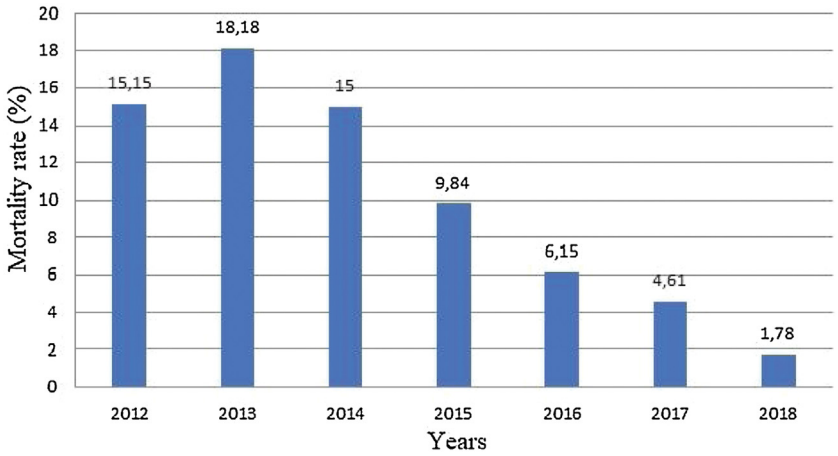

Figure 2 Distribution of mortality rate throughout the years.

in the intensive care unit of the patients who received GA was significantly longer in comparison to patients with LA (p = 0.001). In addition, the length of hospital stay was significantly shorter in the LA group (p = 0.023). No significant difference was found between patients who underwent LA and GA in terms of major complications and mortality (Table 3). The rate of mortality was observed to decrease from 2012 to 2018 (Fig. 2).

Discussion

In our study, where we retrospectively investigated the data of patients who underwent TAVI due to severe aortic valve stenosis with regard to the anesthesia method, the duration of intensive care and hospital stay were significantly shorter in the patient group who underwent TAVI procedure along with LA. On the other hand, no significant differences were

found between the two anesthetic techniques in terms of outcomes, including complications and thirty-day mortality, and success of the procedure.

TAVI is a noninvasive treatment option that is frequently preferred in high-risk AD cases, such as those with advanced age and comorbidity related factors. In the PARTNER study, one of the important researches on TAVI, it has been shown that the procedure is a safe and effective treatment.[10] Anesthesia applications are an integral part of this noninvasive approach, which requires multidisciplinary work. It includes applications ranging from GA to LA or regional anesthesia.[8] In our study, LA was preferred in 245 (80.86%) of the 303 patients, while GA was preferred in 58 (19.14%) (Table 1). Regional anesthesia was not preferred. The main reason for this is the necessity to perform an antiplatelet treatment procedure performed prior to, during, and after the intervention. Spinal hematoma risk limits the application of regional anesthesia. In addition, patients should be investigated in terms of bleeding diathesis in the preoperative period against possible bleeding from the vascular intervention site.[11,14] Blood and blood products should be prepared.

In the studies by Gürcü et al. and Azizoğlu et al.,[7,9] the mean ages of patients who underwent TAVI were 78.30 ± 6.44 and 77.78 ± 6.60, respectively. These results are also dependent on the application of TAVI treatment to patients with advanced valves. The results of our study are consistent with these studies, as the median age in ours was 83 (78–86) years. There was no significant difference in the distribution by gender. Comorbidities of the patients are one of the factors in determining the type of anesthesia and surgical risk score calculation. In our study, hypertension was the most common comorbid factor, which also included diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, chronic renal failure, and peripheral artery disease. Both the most common and other commodities found in our study were consistent with the studies in the literature.[7,9] Peripheral artery disease was statistically significantly higher in the GA group compared to LA group (Table 1). This was due to the preference of the transapical approach and GA in these patients.

Preoperative surgical risk assessment is important for the TAVI procedure. According to the logistic EuroSCORE and STS surgical risk scoring, high-risk and inoperable patients constitute the potential patient group for TAVI. The patient group with high surgical risk is constituted by those with Logistics EuroSCORE > 20% and STS scores above 10%.[15] In our patients, the logistic EuroSCORE value was 22.80 ± 8.36 in GA patients, and 21.73 ± 6.76 in patients with LA. The STS score was 14.81 ± 7.49 in GA patients and 14.07 ± 7.39 in patients who underwent LA (Table 1). In the literature, it is known that LA should be preferred instead of GA due to the risk of increased mortality for patients with high EuroSCORE values.[16] However, especially in the first years where TAVI procedure became more widely performed throughout the world, there was an opposing view in the literature that GA was more appropriate and safer. Factors such as the size and diameter of the catheters, delivery systems, and team experience were important in the choice of GA.[17] It was also stated that general anesthesia is a more appropriate anesthesia method, both to facilitate the management of possible hemodynamic instability and enable the operating team to work more comfortably.[18] In addition, in cases where the transapical, subclavian, or aortic approach is used, general anesthesia provides advantages such as managing a difficult airway, planning transesophageal echocardiography, increased patient compliance, and transition to emergency surgery if necessary.[19]

On the other hand, the increase in the experience of the operators and the advances in technology have raised the application of local anesthesia.[17] The increase in the frequency of transfemoral approach is also a factor in this preference.[17] According to the results of our study, the application of LA technique increased in the following years compared to GA technique (Fig. 1). Transfemoral approach was also significantly preferred.

In a study comparing LA and GA during TAVI procedures, more stable hemodynamics, shorter procedure time, and earlier mobilization were reported with LA.[20] It has been demonstrated that the combination of local anesthesia and sedation has advantages such as early detection of neurological complications, shorter duration of the procedure, rapid recovery from anesthesia, and decreasing the need for postoperative care. Another published research stated that patients having GA showed longer procedure times than those of the LA group.[21] Therefore, LA is preferred more frequently in high-volume centers.[10,11,14,20–22] Among our patients, in GA group the procedure and anesthesia durations were significantly longer than patients in LA group.

The prominent effect of GA during the TAVI procedure is hemodynamic. It is also stated in some publications that the use of vasopressors and inotropic agents is more common during general anesthesia.[23,24] In the literature, it has also been reported that GA increases the need for inotropic support compared to LA applications, and at least two vasoactive drug infusions are required due to severe hemodynamic stability.[12,13] These patients may be hypovolemic due to the diuretic treatment that may be administered before the procedure, and the vasodilator and cardiac depressant effects of general anesthetic agents may lead to hemodynamic instability.[24] Adequacy of left ventricular preload must be ensured to avoid hypovolemia. According to the results of our study, intraoperative fluid use was the highest in the general anesthesia group due to the length of the procedure (Table 2).

The use of blood and blood products for our patients is based on the anemia criteria of the World Health Organization (WHO). The WHO defined anemia as hemoglobin values below 13 $g.dL^{-1}$, in males, and below 12 $g.dL^{-1}$, in females.[25] In TAVI patients, in the presence of additional symptoms and signs such as angina, dyspnea, edema, heart failure, and in patients with severe ischemic heart disease, the planned procedure is a major surgical procedure. In our institution, in conjuction with cardiology and cardiac surgery clinic protocols, for patients undergoing TAVI procedure, the hemoglobin value is kept at a level of 10 to 12 $g.dL^{-1}$. Based on this criterion, in our clinic, blood and blood products were used in 76 patients (31.2%) in LA group, whereas 20 patients (34.8%) in GA group, and the comparison between groups were similar ($p > 0.05$).

Hemodynamic instability and the use of inotropic agents were significantly higher in our study in the GA group and this result is consistent with the literature.[23,24] We

think this may be due to the general anesthetic agents. Azizoğluet et al. stated the anesthetic agents they used in their study were propofol, thiopental, midazolam, and fentanyl, in order of frequency.[9] In our patients, midazolam, fentanyl, and propofol were the most commonly used anesthetic agents in both groups. In the GA group, the agent used for neuromuscular blockade was rocuronium. In our anesthesia applications, in addition to dose titration, vasopressor and inotropic agents were also administered according to the protocol of our study. Melidi et al. also stated that dose titration is more important than the agent in keeping hemodynamics stable and that a medium-effective agent such as rocuronium can be used as a muscle relaxant for intubation.[22]

With the advancing technology, different valve models were developed for use in TAVI. The expansion of the EdwarsSapien (Edwards Lifesciences) model valve occurred through a balloon in the early years. The CoreValve (Medtronic Inc, MN), which was developed later, is a self-expandable model.[26] There was no difference between the groups according to the types of valves used in our study. There are cardiac and non-cardiac complications in the TAVI procedure. In a meta-analysis, TAVI patients undergoing general and local anesthesia were compared, and it was reported that there was no difference in terms of stroke, myocardial infarction, arrhythmia, annular rupture, cardiovascular mortality, permanent pacing, vascular complications, major bleeding, and renal failure.[27] When the patients in our study were compared in terms of complications related to the procedure, no statistically significant difference was found between the two groups. It was also stated in another study that the complication rates do not depend on the type of anesthesia.[17]

In the studies conducted, the length of stay in the intensive care unit and in the hospital were investigated according to the type of anesthesia applied in the TAVI procedure. It has been reported that local anesthesia significantly shortened these periods.[28–30] In our study, consistent with the literature, the length of hospital stay and the duration of intensive care unit stay were significantly shorter in the local anesthesia group. Although there was no investigation about cost effectiveness in our study, we think that shortening the length of stay in the hospital and the intensive care unit will decrease the cost. The cost-effectiveness could have been studied, and this is a limitation of our study.

Ehret et al. reported that thirty-day mortality rates were similar in their systematic review and meta-analysis, in which they compared GA and LA.[29] Again, in different studies, they found that thirty-day mortality did not differ according to the types of anesthesia.[12,28] In our results, no statistically significant difference was found in terms of thirty-day mortality when the groups undergoing GA and LA were compared. Factors such as the procedure itself and the patients' comorbidities are more determinant on the prognosis. In addition, according to our data, the mortality rate showed a diminishing rate throughout the years (Fig. 2). We think that the increase of experience over the years is also effective in this decrease in mortality.

The first of the limitations of our study is that it, could not be conducted in a prospective, randomized study design. The reason is that we had little experience at the beginning of these procedures and later we read the advances in the literature. The other limitation is that the group of patients in LA is much larger than the group in GA. The choice of anesthesia was made according to the severity of the illness and comorbidities that required the use of LA technique instead of GA, due to possible adverse events related to GA and difficult airway. Another limitation is that cost effectiveness was not included in the study. However, we believe that sharing experiences covering 303 cases is also important in terms of contributing to the literature.

Conclusion

Multidisciplinary team management is essential for the success of the procedure, regardless the anesthesia technique during TAVI procedures. The role of the anesthesiologist is important in all stages of the procedure, and these include evaluation preoperatively, during the, operation where titration of anesthetic agents and other essential drugs are administered as well as in the immediate intervention of potential life-threatening complications. Early diagnosis of adverse events related to both surgical and anesthetic techniques requires adequate knowledge and experience for both surgical and anesthetic teams. Therefore, the task of selecting the most appropriate anesthesia technique in line with patient and surgical procedure requirements is important. In our study, we have retrospectively evaluated our experience on outcomes including: complications, mortality and success of the procedure that was done under GA or LA, and no differences were found in comparison between two different anesthesia techniques. However, LA shortens the duration of intensive care and hospital stays.

Conflict of interests

The authors declare no conflicts of interest.

Ethical approval

The study was initiated after obtaining the local ethics committee approval (2019/07), in accordance with the principles of Helsinki declaration.

Acknowledgment

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NARRATIVE REVIEW

Efficacy of opioids and non-opioid analgesics in the treatment of post procedure pain of burned patients: a narrative review

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KEYWORDS
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Pain management;
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Lidocaine;
Gabapentin

Abstract
Introduction: Burns are a common trauma that cause acute severe pain in up to 80% of patients. The objective of this narrative review is to evaluate the efficacy of opioids, non-steroidal anti-inflammatory drugs, paracetamol, gabapentinoids, ketamine, and lidocaine in the treatment of acute pain in burn victims.
Methodology: The databases explored were PubMed, Embase, ClinicalTrials, and OpenGrey. The included randomized, controlled clinical trials assessed the analgesic efficacy of these drugs on hospitalized patients, had no age limit, patients were in the acute phase of the burn injury and were compared to placebo or other analgesic drugs. Studies describing deep sedation, chronic opioid use, chronic pain, and patients taken to reconstructive surgeries were excluded. The Jadad scale was used to evaluate quality.
Results: Six randomized controlled clinical trials (397 patients) that evaluated the analgesic efficacy of fentanyl (n = 2), nalbuphine (n = 1), ketamine (n = 1), gabapentin (n = 1), and lidocaine (n = 1) to treat post-procedural pain were included. Fentanyl, nalbuphine, and ketamine were effective, while lidocaine was associated with a slight increase in reported pain and gabapentin showed no significant differences. Two studies were of high quality, one was of medium high quality, and three were of low quality. No studies on the efficacy of NSAIDs or paracetamol were found.
Conclusion: Evidence of efficacy is very limited. Fentanyl, nalbuphine, and ketamine seem to be effective for controlling acute pain in burn patients, whereas gabapentin and lidocaine did not show any efficacy.
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Introduction

Burns are a common type of injury that is associated with morbidity and mortality. In the United States, estimates are that 450,000 people suffer from burn injuries every year. Although most of these injuries are mild, approximately 40,000 people require hospitalization to complete treatment.[1] In Europe, the annual incidence of severe burns is 0.2 to 2.9/10,000[2] and global mortality varies between <1% and 60.8%.[3]

People with second- to third-degree burns experience acute pain due to the injury and the therapeutic procedures carried out to treat the initial burn and other related complications. Along with initial pain, there may be incidental pain with significant severity variation, leading to changes in analgesic requirements.[4] In the acute phase, it is estimated that 84% of patients experience severe to intolerable pain, 100% report daily pain, and 92% suffer night pain that awakens them.[5]

Opioids are generally recommended as the first-line treatment for moderate to severe acute pain in these patients, despite insufficient evidence of their use.[6] There are also co-adjuvant drugs that act on the receptors of the nociceptive pathways and have an additive or synergic action,[7] such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, lidocaine, and gabapentinoids.[8]

The management of acute pain in burn patients is a challenge as reports of high-quality analgesia studies are scarce and existing treatment schemes have information gaps.[6] The objective of this narrative review is to evaluate the efficacy of opioids, NSAIDs, paracetamol, gabapentinoids, ketamine, and lidocaine in the treatment of acute pain associated with wound care procedures in burn patients.

Methods

Databases and eligibility criteria

A structured search was done between November 12 and 17, 2019, in PubMed (Medline) and Embase. Unpublished articles were collected from ClinicalTrials and OpenGray. Randomized clinical trials (RCT) of burn patients with clinical treatment indications and/or second-degree burns or higher that met the following criteria were included: evaluation of the efficacy of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) (ketorolac, diclofenac, parecoxib), paracetamol, gabapentinoids, ketamine, lidocaine vs. intravenous, or oral placebo or another drug with analgesic properties used for acute pain relief according to the authors' opinion; a minimum follow-up period of six hours and a maximum follow-up period of 15 days; written in Spanish or English; and assessment of analgesia as a primary or secondary outcome. No filter for age or publication date was applied.

Ketamine trials involving doses of <1 $mg.kg^{-1}$ intravenously or <8 $mg.kg^{-1}$ rectally, as well as and dexmedetomidine <1 $\mu g.kg^{-1}.h^{-1}$ intravenously were considered for inclusion. Studies with intubated patients, anesthetic doses of ketamine at a dose of $\geq$ 1 $mg.kg^{-1}$ intravenously or $\geq$8 $mg.kg^{-1}$ rectally, dexmedetomidine at a dose of $\geq$1 $\mu g.kg^{-1}$, and propofol at a dose of $\geq$1 $mg.kg^{-1}$, or in combination with hypnotic sedative agents used for analgesia or procedural sedation related with the care of burn injuries, studies in patients with chronic use of opioids or previous chronic pain, and studies with burn patients taken to reconstructive surgery were excluded.

Outcomes

Reported pain sensitivity using the verbal numeric scale, the visual analog scale, or the verbal assessment scale was the primary outcome (absent, mild, moderate, severe, intolerable). Based on Woo study, equivalence between these scales was established (1–4 equals mild pain, 5–6 equals moderate pain, and 7–10 equals severe/intolerable pain).[9] The need for rescue analgesia to treat the pain crisis and the side effects associated with the drug used were the secondary outcomes. The full text of the articles included in this study was reviewed to analyze outcomes other than pain control.

Search strategy

The MeSH terms used to conduct the search in Medline-PubMed were ''burns'' AND ''acute pain'' OR ''pain management.'' The subheadings used for the term ''burns'' were ''drug therapy'' OR ''metabolism'' OR ''physiology'' OR ''physiopathology'' OR ''prevention and control'' OR ''therapy.'' In turn, the subheadings used for the term ''acute pain'' were ''drug therapy'' OR ''metabolism'' OR ''physiology'' OR ''physiopathology'' OR ''rehabilitation'' OR ''therapy.'' Finally, for the term ''Pain Management'', the subheadings used were ''adverse effects'' OR ''classification'' OR ''pharmacology'' OR ''therapeutic use'' OR ''therapy.''

Simultaneously, an independent search was conducted with all the drugs of interest for the study using the MeSH term ''burns'' and the Boolean operator AND plus the following MeSH terms: ñarcotics,¨ketamine," "lidocaine," "anti-inflammatory agents, non-steroidal," "acetaminophen," "gabapentin," "pregabalin." The following subheadings were used for each of the drugs: ädministration and dosageÖR ädverse effectsÖR ägonistsÖR änalogs and derivativesÖR äntagonists and inhibitorsÖR c̈lassificationÖR m̈etabolismÖR p̈harmacokineticsÖR p̈harmacologyÖR p̈hysiologyÖR ẗherapeutic useÖR ẗherapy.. Lastly, the following filters were applied to the search: Clinical Trial; Controlled Clinical Trial; Observational Study; Randomized Controlled Trial; studies in humans.

The search in www.clinicaltrials.gov was done using the terms ''burned'', ''burns'' AND ''pain,'' applying the following filters: completed, terminated studies, interventional studies, observational studies. On the other hand, the search in OpenGray was done using the terms ''burn'' and ''burns'', as well as the following filters: medicine (discipline) and Spanish and English languages (Appendix 1).

Study selection process

Two independent reviewers selected the studies based on the titles and abstracts according to the inclusion criteria. These references were included in a result extraction

matrix (Appendixes 2 and 3) and pre-selected studies were thoroughly reviewed. In case of disagreement during the process, a third reviewer decided whether the analysis should be included in the qualitative syntaxis or not. To summarize this information, one of the authors extracted detailed information from each selected study (author, year of publication, name and design of the study, population characteristics, size of the population, pharmacologic intervention, control group, and results evaluated).

Data analysis and synthesis

A narrative approach was utilized to synthesize the findings of the included studies. Data could not be pooled using meta-analytic methods due to their heterogeneity and were thus described individually. The estimation of effect sizes was hampered by a limited data reporting and a high degree of clinical heterogeneity.

Evaluation of biases and heterogeneity

The 5-point Jadad scale[10] was used to assess quality and probability of bias, having in mind randomization, blinding, and description of the reasons for abandonment or exclusion of participants. Since clinical heterogeneity was so strong between studies, no statistical heterogeneity analysis was performed (regarding the drugs used).

Results

Search results

Initially, 540 references were found using the search criteria above mentioned. A total of 127 references were duplicates, consequently, they were excluded. The titles and abstracts of the remaining 413 references were reviewed and 51 were pre-selected. After conducting a thorough full-text review of these articles, six were included in the final analysis (Fig. 1). The methodological quality of the included studies was variable (Table 1).

Description of the studies

High levels of clinical heterogeneity between the studies in terms of the type of drugs used were identified, so a statistical heterogeneity analysis was not performed. Regarding quality, it was found that 2 of the studies scored 5 points, 1 study scored 4, and 3 studies scored below 3.

The six selected studies included 397 patients, of whom 231 received at least one treatment and 166 were assigned to the control group (68 placebo, and 98 another drug). One of the studies evaluated the use of intravenous lidocaine as an adjuvant in postoperative pain management,[11] and another evaluated the efficacy of gabapentin as an adjuvant immediately after thermal injury.[12] One research the efficacy of ketamine for pain management during and after dressing change and compared it to dexmedetomidine while dressings were being changed.[13] Two studies compared the analgesic efficacy of fentanyl changing dressings; one of them reported different doses of the drug through a patient-controlled analgesia pump (PCA),[14] and the other used a pediatric formulation intranasally versus oral morphine.[15] Finally, one study compared the analgesic efficacy of nalbuphine to morphine for pain control during wound care of burn injuries.[16]

Primary outcome

The included studies evaluated analgesic efficacy of gabapentin (n = 1), lidocaine (n = 1), fentanyl (n = 2), nalbuphine (n = 1), and ketamine (n = 1) (Table 2). All of them were carried out to assess analgesic efficacy for pain management during burn care procedures, specifically dressing changes (Table 2).

Kundra[13] randomly assigned patients to 2 groups to receive ketamine 5 $mg.kg^{-1}$ and dexmedetomidine 4 $\mu g.kg^{-1}$ orally (Table 2). When compared to the baseline value, pain intensity decreased by 67% in the ketamine group and 44% in the dexmedetomidine group. Pain scores in the ketamine group were significantly lower than in the dexmedetomidine group ($p < 0.05$) (Table 2).

In Prakash's study,[11] each adult patient (n = 60) received an initial loading dose of fentanyl 1 $\mu g.kg^{-1}$ for 10 minutes intravenously before changing the dressings. During the procedure, patients were given various bolus doses of fentanyl via a PCA pump, finding that the optimal dose was 30 μg per bolus when using a PCA pump, with a total mean fentanyl dose administered of 155.00 ± 40.71 μg. In turn, Borland,[15] in a study with a cohort of 24 pediatric patients, found that intranasal fentanyl (1.4 $\mu g.kg^{-1}$ every 15 minutes) prior to wound dressings was as effective as oral morphine and did not cause respiratory depression. The study concluded that intranasal fentanyl is as effective as oral morphine for pain management during dressing change in pediatric patients.

Furthermore, in a randomized study, Lee et al.[16] compared nalbuphine 0.4 $mg.kg^{-1}$ and morphine 0.2 $mg.kg^{-1}$ intravenously (n = 50), finding no significant differences in the doses used or in pain scores after a wound treatment procedure in burn patients. Wibbenmeyer et al.,[12] on the other hand, compared gabapentin to placebo to identify differences in pain and opioid use (n = 50); the gabapentin group received a daily dose ranging between 300 mg and 3,600 mg. There was no difference in pain scores or opioid use between groups.

Lastly, Wasiak et al.[11] conducted a randomized trial in which they compared the administration of lidocaine 1.5 $mg.kg^{-1}$ intravenously followed by an infusion run at 2 $mg.min^{-1}$ during the dressing process to placebo (n = 45). The difference in pain intensity score was slightly lower for lidocaine [difference (95%CI) = 0.36 (0.17–0.55)] than for placebo.

Secondary outcomes

The six studies evaluated the presence of adverse events associated with drug administration, even though the sample size was not based on this parameter in any of the studies. Rescue analgesia was assessed as an outcome in four of the studies and was defined need for rescue analgesia to manage a pain crisis.

Table 1 Study quality score on Jadad scale.

Author, year	Study name	Quality of the study according to Jadad scale					
		Is the study described as having randomized assigning?	Is the study described as being double blind?	Are the dropouts and exclusions described?	Is the method of randomized assignment the appropriate one?	Is the blinding method the adequate one?	Total score
Wibbenmeyer et al, 2014	Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period	1	1	1	1	1	5
Jason Wasiak et al, 2011	Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double-blind, placebo-controlled, cross-over trial	1	1	1	1	1	5
Prakash et al, 2004	Patient-Controlled Analgesia with Fentanyl for Burn Dressing Changes	1	1	0	-1	1	2
Lee, Marvin, Heimbach, 1989	Effectiveness of nalbuphine for relief of burn debridement pain	1	1	0	-1	-1	0
Kundra et al, 2013	Oral ketamine and dexmedetomidine in adults' burn wound dressing—A randomized double-blind cross over study	1	1	0	-1	-1	0
M.L. Borland et al., 2005	Intranasal fentanyl is an equivalent analgesic to oral morphine in pediatric burns patients for dressing changes: A randomized double-blind crossover study	1	1	1	0	1	4

Table 2 Description of the included studies.

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Wibbenmeyer et al., 2014	Patients older than 18 (n = 53) with a burn injury compromising at least 5% body surface area and a predicted hospitalization of 48 hours.	Gabapentin	Day 1: 1200 mg (only dose).	Placebo	Pain intensity according to Numeric Rating Scale: Average (SD)	There is no difference in the pain intensity reported after procedure between groups
Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period, RCT			Day 2,3: 300 mg TID, 900 mg.day^{-1}		Group I (n = 27) 5.4 ± 2.5	
			Day 4-7 of study: 600 mg TID 1800 mg* Daily. Day 8-11 of study: 800 mg TID 2400 mg* Daily. [Optional raising to 2400 if pain score continues at 4 in NPR scale] Day 11 of study: 1200 mg TID 3600 mg* Daily [Optional raising to 3600 if pain score continues at > 4 in NPR scale]		Group C (n = 26) 5.5 ± 2.5 p = 0,57	
Jason Wasiak et al., 2011	Adult patients (n = 90) admitted to the Victorian Adult Burn Service, with a burn injury affecting between 3 and 55% body surface area. And that were taken to injury care procedures as in: Debridement ± change of dressings in within two days and analgesia was prescribed with opioids as part of the treatment	Lidocaine	Initial Dose: 1.5 mg.kg^{-1} (30 minutes post procedure)	Saline solution 0.9%	Pain intensity according to according to numeric scale (Numeric Rating Scale): Median (RIC)	Mild increment in reported pain in lidocaine group

Table 2 (*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double-blind, placebo-controlled, cross-over trial, RCT			Bolus: 0,5 mg.kg^{-1} (two boluses after initial dose every 5 minutes)	Administered in equal volume, dose, and speed as lidocaine		
			Infusion: 2 mg.min^{-1} (during the duration of the changing of dressings)		Group I (n = 45) Group C (n = 45) 1 (0-2) 1 (0-3) Change in NRS	
Prakash et al., 2004	Adult patients (n = 60) with thermal burns of more than 20% body surface area and programmed to the change of dressings	Fentanyl	Initial dose: 1 μg.kg^{-1} (10 minutes before the procedure of every patient) Dose on demand of fentanyl divided in four groups: 10, 20, 30 and 40 μg	PCA-fentanyl demand doses 10, 20, 30, and 40 μg.	Size of demanded dose of fentanyl (μg)	Optimal on demand dose of fentanyl controlled by the patient (PCA) was 30 μg (5-minute interval) after the initial dose of fentanyl 1 IV μg.kg^{-1}
Patient-Controlled Analgesia with Fentanyl for Burn Dressing Changes, RCT					Score VAS scale: average (SD) Group 10 μg: 7.73 (1.33) Group 20 μg: 7.20 (1.21) Group 30 μg: 4.47 (0.83)* Group 40 μg: 3.90 (0.63)* *$P \leq 0,05$	
Lee JJ, et al., 1989	Adult male patients (n = 50) between 18-65 years hospitalized with second and third degree burns and taken to debridement of injuries	Nalbuphine	0,4 mg.kg^{-1}	Morphine 0,2 mg.kg^{-1}	Pain intensity nominal scale: none, mild, moderate, severe	Nalbuphine and morphine have a comparable analgesic efficacy

(*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Effectiveness of nalbuphine for relief of burn debridement pain, RCT					Nalbuphine (n = 25) Morphine (n = 25) p 10 minutes after treatment 2,6 ± 0,2 2,4 ± 0,1 > 0,05 Pain intensity VAS scale: 0 = none, 10 = severe Nalbuphine (n = 25) Morphine (n = 25) p 10 minutes after treatment 4,5 ± 0,6 3,4 ± 0,5. > 0,05	
Kundra et al., 2013	Adult hospitalized patients (n = 120) with a burn injury compromising 20% to 50% body Surface area.	Ketamine (Group K)	5 $mg.kg^{-1}$	Dexmedetomidine 4 $mcg.kg^{-1}$ (Grupo D)	Pain intensity evaluated with visual analog scale: average (SD) Grupo K (n = 60): 2,6 ± 0,6 cm	VAS score was improved in 67% in group K and 44% in group D from baseline values. VAS scores improved significantly in group K vs group D in every time interval, $P < 0.05$
Oral ketamine and dexmedetomidine in adults' burn wound dressing—A randomized double-blind cross over study, RCT					Grupo D (n = 60): 3,8 ± 0,8 cm	
M.L. Borland et al., 2005	Children with burn injury aged up to 15 years (n = 24).	Intranasal fentanyl	1,4 $\mu g.Kg^{-1}$	Oral morphine 1 $mg.kg^{-1}$	Intranasal fentanyl	Intranasal fentanyl is an adequate analgesic agent used in changes of dressings for pediatric burns, by itself or in combination with oral morphine as a titratable agent.

(*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomized double blind crossover study, RCT				Group A	Baseline 0 (0–1)	
				(Day 1: oral morphine + intranasal placebo	1 (0–1.3)	
				Day 2: oral placebo + intranasal fentanyl)	0.31	
				Group B	Pre-procedure	
				(Day 1: Intranasal fentanyl + oral placebo	4.3 (0–6)	
				Day 2: oral morphine + intranasal placebo)	2 (1–3.1)	
					0.47	
					Post procedure	
					0 (0–4) a	
					1.5 (0.8–2.5)	
					0.45	
					Data are presented as median and interquartile range a = lost values for a patient b = lost values for two patients	

* Statistically significant difference.

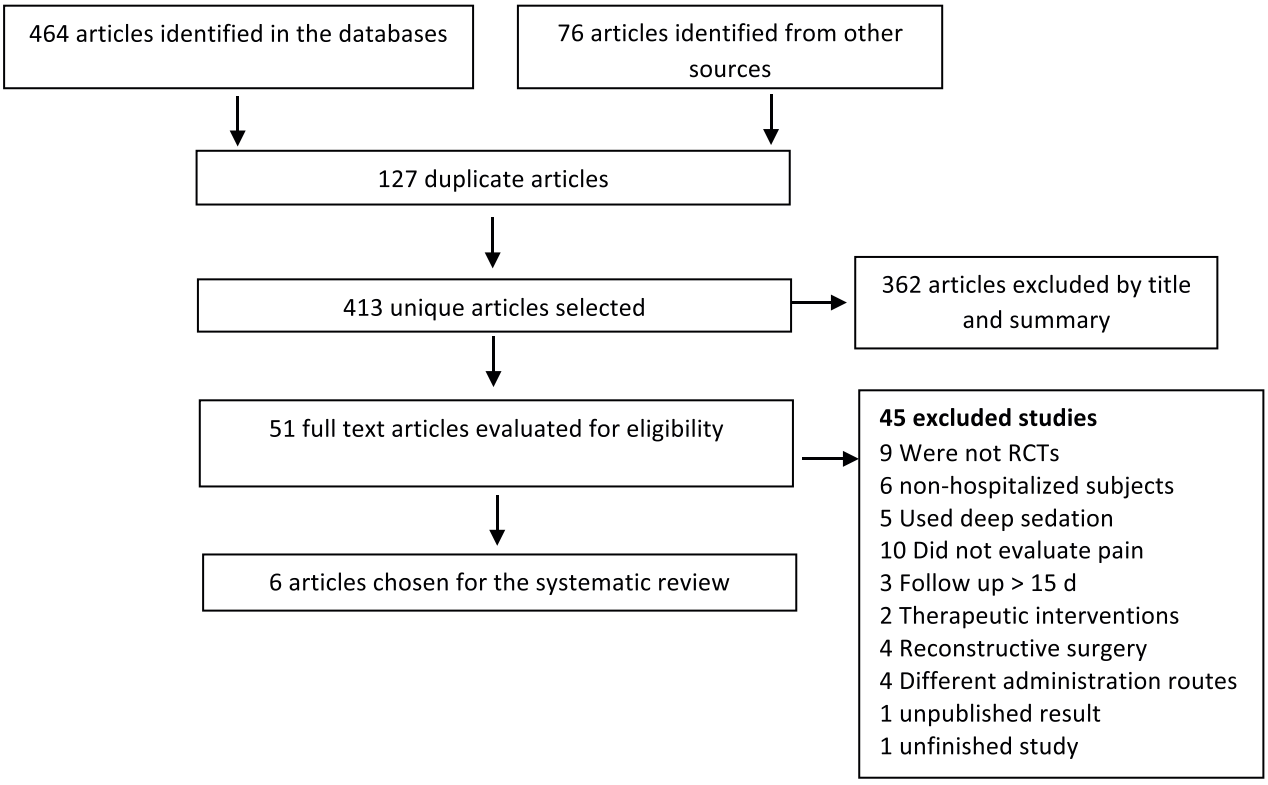

Figure 1 Flowchart diagram.

Firstly, Wibbenmeyer[12] evaluated secondarily the impact of gabapentin on patient anxiety measured using the Hospital Anxiety and Depression Scale (n = 53); no difference in anxiety scores was observed between the placebo group and the gabapentin group (HADS-anxiety $p = 0.13$).

Wasiak et al. (2011),[11] who compared the effect of intravenous lidocaine to placebo, also assessed patient satisfaction (n = 45) with treatment and anxiety in relation to lifestyle changes; no differences in these two aspects were observed in the treatment groups.

Moreover, Lee et al.,[16] in a study with male patients (n = 50) who received morphine or nalbuphine, investigated analgesic acceptability using a categorical scale, finding no differences between analgesic acceptability scores in both groups; this study did not include functional scales.

Kundra et al.[13] carried out a crossover study to compare the effects of oral ketamine to dexmedetomidine (n = 60). The incidence of delirium and excessive salivation was evaluated, finding that they were significantly higher in the ketamine group ($p < 0.05$); however, the post-procedure assessment showed that most patients (63.3%) preferred ketamine over dexmedetomidine ($p < 0.05$). In turn, Prakash et al.[14] reported outcomes other than pain intensity (n = 60), demonstrating that patients who received a dose of 30 μg were satisfied with pain relief.

Finally, Borland et al.[15] performed a crossover study in pediatric patients (n = 24) that compared oral morphine and nasal fentanyl, reporting no statistically significant associations between treatment and certain recovery variables. For example, the average time to resume daily activities were 145 minutes for patients receiving oral morphine compared to an average time of 125 minutes for patients receiving nasal fentanyl.

Discussion

The objective of this narrative review was to evaluate the analgesic efficacy of six drugs or drug groups during wound care in burn patients, namely, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, gabapentinoids, ketamine, and lidocaine. One of the first conclusions drawn from the results is that the clinical trials comparing the efficacy of various pharmacologic treatments for acute pain in burn patients are scarce. However, six studies that met the inclusion criteria evaluated the analgesic efficacy of fentanyl, nalbuphine, gabapentin, ketamine, and lidocaine. Efficacy was assessed in patients whose dressings were replaced during follow-up.

Regarding fentanyl, analgesic efficacy was observed when administrated intravenously via PCA pump[14] or intranasally.[15] Due to the fast onset of its action, fentanyl is often used in burn patients to relieve background and breakthrough pain associated with procedures.[17] Nevertheless, regular administration of opioids has been linked tolerance, dependence, and abstinence after suspension, so they must be used as part of a multimodal scheme that allows reducing the doses.[18]

In this regard, the ketamine–propofol combination is the most commonly used drug combination for procedural sedation and analgesia in the treatment of burns in children.[19] Since nasal fentanyl spray is not available in many countries, its use may be limited; however, fentanyl citrate for intra-

venous use, due to its lipophilic nature, can be successfully administered by nasal route.[20] While this result indicates a mechanism for scheduling an appropriate dose within the analgesic plan for burn victims, it should be interpreted with caution due to the poor methodological quality of the Jadad score. Despite being prescribed for the treatment of acute continuous pain,[21] no studies comparing the efficacy of opioid drugs to other agents, such as methadone or tapentadol, were identified.

The lack of information on patients receiving hospital-based care and prolonged exposure to opioid use clearly indicates the need for further studies on this issue in burn patients. Few studies evaluate the role of agonists-antagonists. Only a randomized clinical trial compared the efficacy of nalbuphine vs. morphine[16] and was published in 1989; delving into this topic would open the door to new findings in this area.

Kundra et al. conducted a report on ketamine.[13] These researchers found that, compared to dexmedetomidine, ketamine is more effective for pain control, reducing pain intensity in approximately 3 out of every 4 patients. A systematic review published in 2011 that included 4 experimental studies involving voluntary subjects had already established the analgesic efficacy of ketamine in burned patients, demonstrating a decrease in secondary hyperalgesia and pain amplification.[22] The randomized clinical trial included in the present review had a low-quality evaluation score; however, it has an additional value because it includes hospitalized patients, implying that the findings can be applied to clinical practice.

It should be noted that adverse effects were more frequent (mild delirium and excessive salivation) and statistically significant in the ketamine group, without indicating whether these secondary effects forced its suspension. Ketamine has been linked to psychiatric side effects such as hallucinations, delirium, increased secretions, and sympathetic activation, resulting in tachycardia and higher blood pressure, especially at doses higher than 1 $mg.kg^{-1}$.[18]

Regarding lidocaine, although it has been demonstrated that it has analgesic, anti-hyperalgesia, anti-inflammatory, and opioid-sparing effects,[4,23] only one study, published by Wasiak et al.,[11] evaluated its effect as an analgesic adjuvant for burn patients in the acute phase. This trial showed that when lidocaine was added to PCA, the pain level increased compared to the placebo. While clinically irrelevant, the fact that the average improvement in pain score was less than 1 on the visual analog scale makes evident the importance of being cautious when selecting patients for treatment with this drug.

Furthermore, Wibbenmeyer et al.[12] found no significant difference in pain severity following wound treatment when comparing gabapentin to placebo. This finding is consistent with the findings of a historic cohort reported in 2019 that suggested that the early (less than 72 hours after burn injury) or later use of gabapentin does not improve the short- or long-term hospital discharge of burned patients[24]; this result agrees with several investigations on gabapentinoids that show little benefit and the presence of side effects. Consequently, the use of opioids to treat acute pain in burn patients should be reconsidered since up to 60% of the patients experience adverse effects (particularly drowsiness and fatigue).[25] There was no study assessing the impact of pregabalin that could be included in the current analysis.

This review has various strengths. To the best of the authors' knowledge, this is the first study of its kind that evaluates the efficacy of a group of drugs used to treat acute postoperative pain in burned patients and is based on strict inclusion criteria that allowed selecting studies that could be applied to clinical practice. The included studies were randomized controlled clinical trials of hospitalized patients, excluding patients with experimental burns induced under laboratory conditions, and assessed drugs commonly used for acute pain management. Moreover, there were no restrictions on the publication dates of the studies, and unpublished articles were actively searched for in two databases, minimizing the probability of publication bias.

On the other hand, one of the reported weaknesses of the present review is that statistical heterogeneity was not calculated due to the clinical heterogeneity of the findings; as a result, no meta-analysis was performed using the collected data. Another shortcoming was the use of the publication language filter, which limited the number of controlled clinical trials retrieved to English and Spanish only.

Most of the articles included in this review do not address multimodal analgesia, which is widely used today,[4] and involve NSAIDs, dipyrone and acetaminophen as part of the analgesic scheme. In addition, although with limited evidence, intravenous lidocaine infusions may be a useful treatment option in some patients.[26] Intravenous ketamine in sub-anesthetic doses is also recommended in patients who have developed an opioid tolerance.[27] However, due to the high intensity of pain and exposure to multiple painful procedures, non-pharmacological therapies that contribute to analgesia should be considered, such as virtual reality. In this regard, Lauwens et al.[28] found that virtual reality had an outstanding effect in reducing pain in pediatric patients when compared to traditional care (n = 104) ($p < 0.00001$).

Solid recommendations for analgesia in burn patients cannot be made based on the studies included in this review since they involved a small number of patients, efficacy was described as a decrease in the use of opioid analgesics in some studies and a decrease in pain in others, and patient characteristics were quite different. Additionally, non-opioid analgesics are often difficult to compare because of the variety of drugs and doses used in clinical trials. Based on these considerations, the authors propose using fentanyl for background and breakthrough pain and ketamine in subanesthetic doses for breakthrough pain. In a multimodal approach, acetaminophen and nonsteroidal anti-inflammatory medications are viable options.

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.2021.07.022.

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NARRATIVE REVIEW

Chronic non-cancer pain in adolescents: a narrative review



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Abstract
Introduction: Chronic pain is defined as a pain lasting more than 3–6 months. It is estimated that 25% of the pediatric population may experience some kind of pain in this context. Adolescence, corresponding to a particular period of development, seems to present the ideal territory for the appearance of maladaptive mechanisms that can trigger episodes of persistent or recurrent pain.
Methods: A narrative review, in the PubMed/Medline database, in order to synthetize the available evidence in the approach to chronic pain in adolescents, highlighting its etiology, pathophysiology, diagnosis, and treatment.
Results: Pain is seen as a result from the interaction of biological, psychological, individual, social, and environmental factors. Headache, abdominal pain, and musculoskeletal pain are frequent causes of chronic pain in adolescents. Pain not only has implications on adolescents, but also on family, society, and how they interact. It has implications on daily activities, physical capacity, school performance, and sleep, and is associated with psychiatric comorbidities, such as anxiety and depression. The therapeutic approach of pain must be multimodal and multidisciplinary, involving adolescents, their families and environment, using pharmacological and non-pharmacological strategies.
Discussion and conclusion: The acknowledgment, prevention, diagnosis, and treatment of chronic pain in adolescent patients seem not to be ideal. The development of evidence-based forms of treatment, and the training of health professionals at all levels of care are essential for the diagnosis, treatment, and early referral of these patients.
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Introduction

The underappreciation of pain in pediatrics affects the health of children and adolescents, leading to physical disability and psychological distress in adulthood.[1] Up to 60% of the children and adolescents with chronic pain end up having pain in adulthood, which is associated with a higher burden on healthcare services, affecting labor productivity, and causing social marginalization.[2] However, the prevention and treatment of pain in children and adolescents does not seem to be ideal. It is often underdiagnosed and undertreated.

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with or similar to actual or potential tissue damage, thus demonstrating the difficulty to have an objective definition and description, given its multidimensional character.[3,4] Chronic pain is defined as pain that lasts longer than 3–6 months.[3]

Adolescence corresponds to a specific period of physiological, psychological, emotional, and social development, and seems to present the ideal ground for the emergence of maladaptive mechanisms that trigger pain phenomena.[2] All adolescents experience acute pain along their development. Although most of them recover without further complications, some end up having persistent or recurring pain, which culminates with the process of chronic non-cancer pain in adolescents. In this manner, it is urgent to know, understand, and work on the many factors that contribute to the chronification of pain in adolescents.[5]

The aim of this review is to summarize the evidence available on the etiology, pathophysiology, diagnosis, and treatment of chronic non-cancer pain in adolescents.

Methods

In this review, we followed the assumptions of a narrative review,[6,7] aiming to answer the investigation question: what is the evidence available on the etiology, pathophysiology, diagnosis, and treatment of chronic non-cancer pain in adolescents?

We conducted a search on the PubMed/Medline database, on July 2nd, 2020, using natural language terms, and MeSH Subject Headings: ''chronic pain'', ''adolescent'', ''paediatric'', and ''pediatric'', combining them with the Boolean operators ''AND'' and ''OR'', which led to a total of 405 results. After reviewing abstracts, 166 papers were initially selected and analyzed, which in turn, allowed identifying other relevant complementary publications. We included papers written in English and Portuguese published in the past ten years, whose titles stated they were experimental, observational prospective, or retrospective trials, clinical case reports, or systematic reviews that addressed adolescents with chronic pain.

We defined the concept of adolescence using the definition of the World Health Organization (WHO), as the period of development comprehended between 10 and 19 years of age.[8] We did not apply geographical or cultural limitations for the studies included in this review.

Results

Epidemiology

Chronic pain is a global public health problem whose estimated average prevalence is approximately 35%. Globally, its etiology, type, and location seem to vary according to sex, and the age group considered. It is more frequent in the female sex, above 65 years of age, and located on the lumbar region or lower limbs.[9,10]

Chronic pain in the pediatric population is more expressive in adolescence and its prevalence is estimated to be 25%, with peak incidence between 14 and 15 years of age, affecting disproportionally more the female sex, with prevalence rates almost twice as high as that of the male sex.[11] About 30% of adolescents show interference in their daily life activities and 8% present severe incapacity.[12,13] The most prevalent types of pain are headaches (23%–51%), abdominal pain (2%–41%), and musculoskeletal pain (4%–40%).[11,14]

In a multicenter trial coordinated by Gobina et al., which intended to assess the prevalence and demographic characteristics of chronic pain in adolescents, using questionnaires applied on 11-, 13- and 15-year-old students in secondary schools of 42 countries, they found that about 44.2% of them reported weekly chronic pain during the past 6 months, and chronic pain in several areas was more frequent (13.2%–33.8%), than pain on a single site.[15]

Current data allow the observation that, although chronic pain in adolescents is a global problem, there are differences in prevalence, whether due to sampling differences, form of description, and acquisition of data, or even due to the very definition of pain used, pain pattern, and demographic characteristics of adolescents, with age and sex being important predictors.[15]

Pathophysiology

Pain has been classified as to its mechanism in three major groups: nociceptive, neuropathic, and nociplastic (Table 1).[3]

Nociceptive pain results from tissue lesion with the activation of nociceptors and, depending on the area where the noxious stimulus occurs, it is differentiated in somatic pain and visceral pain. Visceral pain originates from the activation of nociceptors located in internal organs. Neuropathic pain is the result of a lesion or disease in the somatosensorial nervous system.[16] Nociplastic pain encompasses all situations in which there is a lesion that is not on the somatic tissue, visceral or somatosensorial system, but in which there is an alteration in the nociception mechanism.[17,18]

Although practical and with predominant implications in the clinical and therapeutic approach, this classification of pain is increasingly seen as too reductionist because it is limited to only two dimensions, physical and functional. In that sense, in 2019, IASP and the WHO developed, through the International Classification of Diseases (ICD-11), a more robust, systematized, and dynamic classification system. In this manner, chronic pain is classified in 7 groups: (1) Chronic primary pain, which includes chronic pain whose etiology is unknown or cannot be attributed to another chronic condition; (2) Chronic cancer-related pain, which includes pain caused by oncological diseases or by their treatment; (3)

Table 1 Classification of pain according to the underlying mechanism. Pathophysiological and clinical differentiation of nociceptive, neuropathic, and nociplastic pain.[21]

	Nociceptive pain	Neuropathic pain	Nociplastic pain
Stimulus	Noxious or inflammation	Nervous system lesion	No lesion identified. Abnormal central processing
	Somatic – skin, bones, deep tissues. Well localized	Peripheral – peripheral somatosensorial nervous system	
Area	Visceral – smooth muscle, solid organs. Diffuse, poorly localized, referred	Central – central somatosensorial nervous system	Brain cortex
Clinical characteristics	Sharp/continuous, stabbing, throbbing, palpitating	Burning, pins, and needles, breakthrough, hypoesthesia, hyperesthesia, allodynia, irradiation	Multiple areas, diffuse, undefined
Context	Trauma, Post-operative pain, Burn, Ischemic pain	Polyneuropathy, Neuralgia, Chemotherapy, Radiotherapy	Fibromyalgia, Irritable bowel syndrome, Headaches

Chronic postsurgical or posttraumatic pain, when pain persists beyond normal healing time; (4) Chronic neuropathic pain, caused by a disease or lesion of the somatosensorial nervous system; (5) Chronic headache or orofacial pain; (6) Chronic visceral pain, whose origin is secondary to internal organs (head, neck, chest, abdominal, and pelvis); and (7) Chronic musculoskeletal pain, secondary to diseases of the bones, joints or related soft tissues.[19]

Today, chronic pain is interpreted as a complex, and sometimes dysfunctional, network resulting from neuronal communications between peripheral nerves, spine, and brain. All information is processed, and modulated in the brain, where consciousness of the experience of pain takes place.[20,21] Patients with chronic pain present facilitation of the nociceptive circuits, with increased signal transduction and reduced response threshold to noxious stimuli, originating phenomena of peripheral and central sensitization, often without any identifiable structural cause.[20,21] Currently, pain is interpreted as a complex multidimensional process with the integration of biological, psychological, individual, sociocultural, and environmental factors, based on the biopsychosocial model (Fig. 1).[22] In this manner, the interaction of genetic and environmental aspects, like physical health, sex, maturity, cognitive development, emotions, cultural influences, and socioeconomic level results in pathophysiological mechanisms that perpetuate pain.[23] In chronic non-cancer pain in adolescents, these factors have yet to be interpreted from a developmental perspective.

The psychological dimension has been widely investigated and seems to play a predominant role in the pathophysiology of chronic non-cancer pain in adolescents.[24] Several models try to explain the influence of these psychological processes in the augmentation and perpetuation of pain. The Fear Avoidance Model says that pain, when interpreted as a threat, leads to repetitive behaviors of fear and avoidance, which may result in loss of function.[25] It is a vicious cycle that may condition more avoidance, more pain and incapacity, as well as an increased risk of persistent

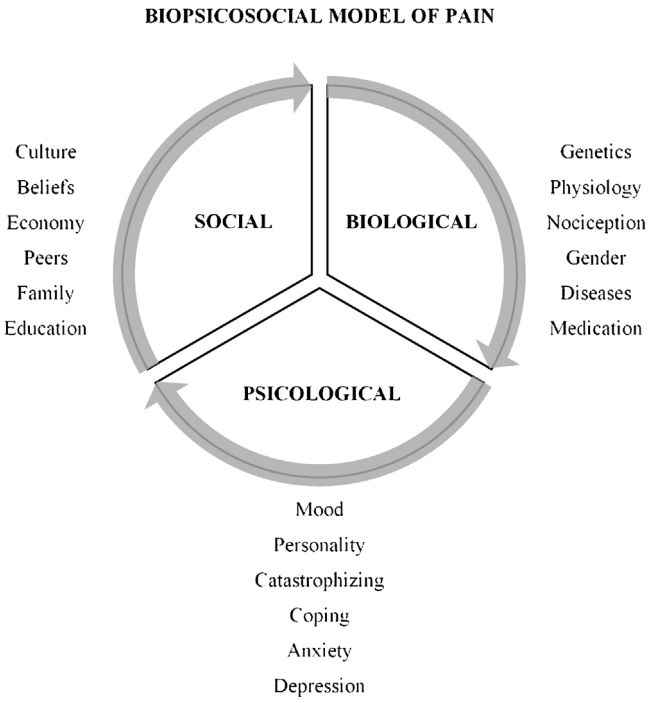

Figure 1 Biopsychosocial model of pain. Pain is interpreted as a dynamic interaction between each individual's typical biological, psychological, and social factors.

pain.[26] If, on one hand, catastrophizing (negative posture and mentality of overreacting to pain), depression, and anxiety are facilitators and individual risk factors in the chronic pain process, on the other hand, an overprotective family and chronic disease models are interpersonal risk factors and mechanisms, that is, they are important predictors for central sensitization, and persistence of pain.[27]

However, not all psychological states are maladaptive. According to the Ecological Risk-Resilience Model of Pediatric Chronic Pain, several resources and mech-

anisms may lead to adaptive experiences with chronic pain. This model identifies individual and interpersonal resilience as a key aspect. Resilience is defined as someone's capacity to respond effectively to adversity and is influenced by developmental, social, cultural, and environmental factors.[28] As an example, optimism, self-efficacy, cognitive flexibility (capacity to respond in an effective and flexible way to adverse events), and positive emotions are considered individual resilience resources. Positive relationships with peers, social engagement, and the support of family and teachers are interpersonal resilience resources. These specific resilience mechanisms may be activated when adolescents are confronted with pain and may modulate and positively influence nociceptive pathways.[29]

In a more integrative way, and at the light of the models described above, the Self-determination Theory suggests that pain mechanisms influence three basic psychological needs: autonomy, competence/efficacy, and interpersonal relationships.[30] Autonomy is considered a fundamental acquisition in adolescent development and may be negatively affected by pain. In the presence of pain, the incapacity to perform school, leisure, and mastery and physical activities may contribute to avoidance and frustration behaviors, leading to difficulties in social interaction, victimization, and rejection by peers.[31]

Impact

Chronic non-cancer pain in adolescents impacts the adolescent's individual, family, and social structure and dynamics, giving grounds for clinical assessment, diagnostic investigation, and referral, which sometimes generate or perpetuate uncertainty, stress, and anxiety.[32,33]

The presence of comorbidities like anxiety, and depression is frequent, and more common in this group than in the general pediatric population. It is estimated that about 80% of the adolescents with chronic pain have anxiety in some phase of the treatment.[34,35] The consequences of fear and anxiety, including attention biases, somatization, and avoidance behaviors, contribute to a vicious cycle that perpetuates and exacerbates pain.[36]

This psychosocial aspect may be the only manifestation of the painful process adolescents go through at the time of assessment. In 2006, when John D. Loeser put forth the Onion Model, the author structured the pain experience in layers, comparing it to an onion formed, from the center to the periphery by: nociception, pain, suffering, and pain behaviors. The inner layers are not visible on the outside, being private experiences that only the adolescent is subjected to. The external layer is the pain behavior, which translates through words, actions, or expressions all the experience of the biopsychosocial process involved.[37,38]

Pain may affect school performance, absenteeism, and academic progress, reason for which it should always be assessed.[39,40] Adolescents with chronic pain tend to present a lower level of schooling in adulthood, higher probability of joining the labor market earlier, and of having precarious jobs.[41,42]

Adolescents with chronic pain frequently show anxiety, a frail, dependent or obsessive-compulsive personality, delayed development, and difficulties in learning, concentration, memory and cognition, previous traumatic experiences, poor coping strategies, overprotective parents, chronic disease models, or dysfunctional families.[23,27,43–45] They are exposed to a series of conditions, including the physical manifestations of pain, which translate into lower functional status, quality of life, school performance, and social life engagement.[39,46]

Diagnosis

The care of adolescents with chronic pain is challenging, and as previously described, the problem goes beyond reporting their pain, often being associated with other symptoms, behaviors, and disabilities.[33]

The assessment of pain should start with the adolescents' report, in their own words, of their experiences, and beliefs.[24] The information provided by parents, caretakers, peers, teachers, and other professionals is also fundamental, and essential to complement and provide details of the clinical history.

The thorough description of symptoms should include their location, distribution, time characteristics, intensity, character, and relief and worsening factors.

A complete physical examination is an essential complement to the clinical history, including for example, the observation of the overall appearance of the adolescent, vital signs, growth, inspection, palpation, and neurological examination, which help define the etiological diagnosis. Additional diagnostic tests, upon the hypothesis of a structural cause or a specific disease, should be directed and complement the investigation.[47,48]

The Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, in an attempt to standardize procedures, suggests the assessment of physical and emotional aspects, sleep, family interaction, quality of life, previous treatments, and history as key aspects to take into account in the diagnosis (Table 2).[23,49–52]

State-of-the-art treatment

The therapeutic approach to chronic non-cancer pain in adolescents should be based on the biopsychosocial model, using a multimodal (pharmacological and non-pharmacological) and interdisciplinary strategy, integrating several professionals (physicians of different specialties, nurses, psychologists, physical therapists, occupational therapists, and social workers) contributing and sharing treatment objectives.[12,53–55]

Initially, a plan of care is outlined with the active participation of the patient, both in the definition of the goals to reach, and in the acquisition and application of coping strategies (ideally active), in which the physician plays the role of a mentor.[56,57] The goal of the treatment is to have an effective control of the pain, although frequently functional recovery (physical activity, regular sleep, school attendance, and social life) usually comes first.[57–59] The family plays a key role in the results and should be involved in the treatment plan from the beginning.[52,60]

Today, according to recommendations, the management, follow-up, and treatment of part of these patients do not require consultation at a Pediatric Chronic Pain Unit, that is,

Table 2 Examples of multidimensional assessment instruments for adolescents with chronic pain. Adapted from Liossi C. et al. (2016).[50,51]

Dimension		Parameter	Assessment[a]
Biological	Pain symptom	Intensity	VAS, NRS, Pain Diaries
		Characteristics	DN4, LANSS
		Distribution	Body maps
	Comorbidities	Fatigue	PedsQL (MFS)
		Functional status	FDI
		Quality of life	PedsQL
		Sleep	CSHQ
Psychological	Emotional status	Depression	CDI, RCADS, PI-ED,
		Anxiety	STAI, RCADS, PI-ED,
	Cognition	Coping	PCQ
		Catastrophizing	PCS-C
		Self-efficacy	PSEQ
Social	Environment	Family dynamics	PSI-SF
		Parental catastrophizing	PCS-P
		Parental anxiety	BAI, STAI
		Parental depression	HADS, BDI-II

BAI, Backache Index; BDI-II, Beck Depression Inventory-II; CDI, Children's Depression Inventory; CSHQ, Children's Sleep Habits Questionnaire; DN4, Douleur neuropathique 4; FDI, Functional Disability Inventory; FPSS-R, Faces Pain Scale-Revised; HADS, Hospital Anxiety, and Depression Scale; LANSS, Leeds Assessment of Neuropathic Symptoms, and Signs; MFS, Multidimensional Fatigue Scale; NRS, Numeric Rating Scale; PCQ, Pain Coping Questionnaire; PCS-C, Pain Catastrophizing Scale-Child; PCS-P, Pain Catastrophizing Scale-Parent; PedsQL, Pediatric Quality of Life; PI-ED, Paediatric Index of Emotional Distress; RCADS, Revised Child Anxiety, and Depression Scale; STAI, State-Trait Anxiety Inventory; PSI-SF, Parenting Stress Index/Short Form; STAI, State-Trait Anxiety Inventory; STAXI, State- Trait Anger Expression Inventory; STAXI-2, State-Trait Anger Expression Inventory-2; STAXI-2 C/A, State-Trait Anger Expression Inventory-2 Child, and Adolescent; VAS, visual analog scale; VRS, Verbal Rating Scale.

[a] Some of the abovementioned instruments have not yet been translated and validated in Portuguese.

these patients may be followed up in any context of primary or differentiated care. However, there is a recommendation that they should be referred early in cases of refractory or complex chronic pain.[12,61]

Education on pain neuroscience

The understanding of pain and its mechanisms, through education on the neuroscience of pain, may have a therapeutic benefit. When the origin of chronic pain is not understood, maladjusted beliefs may be developed (kinesiophobia and catastrophizing) that support the vicious cycle of chronic pain.[62,63] These interventions intend to provide informational and emotional support that facilitates behavior change, and the acquisition of active coping strategies.[64] It consists of using the knowledge on the neurobiology and neurophysiology of chronic pain, addressing (a) The nociceptive system and its operation, focusing on the role of the CNS in the interpretation, processing, and positive and negative modulation of nociceptive stimuli, under the influence of the biopsychosocial model; (b) The adaptation of the nociceptive system to persistent pain (central and peripheral sensitization); and (c) Its practical application in every-day life, especially the factors likely to worsen or attenuate pain.[56,65] Empathetic adolescent-centered communication is fundamental, and evidence suggests that adolescents learn better through metaphor, metonymy, short stories, and images, adapted to their cognitive capacity and environment.[66] Sometimes, educational interventions at school may also be beneficial.[58,67]

In parallel, education toward a healthy lifestyle, focusing on its fundamental pillars (ex., nutrition, bowel microbiota) should also be encouraged.

Pharmacological treatment

Despite the common use and clinical usefulness of many pharmacological agents, currently there is no evidence supporting their use in chronic non-cancer pain in adolescents. Systematic reviews conducted so far do not permit drawing conclusions about a beneficial or harmful effect of using drugs for chronic non-cancer pain in adolescents.[61] Even though the absence of scientific evidence does not mean evidence of no effect, there is an urgent need for data on the efficacy, safety, and tolerability of analgesic drugs on the pediatric population, as well as the development and licensing of new drugs for this age group.[68–72]

Many drugs are used in this context: peripheral analgesic agents, Non-Steroidal Anti-inflammatory Drugs (NSAIDs), opioids, local anesthetics, and adjuvant medications like antidepressants, and anticonvulsants. This review does not intend to explore the characteristics of each option. However, they are available in the recommended literature (WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses), currently under revision.[73] The decision to start a new pharmacological treatment must be based on the pathophysiology of pain and on the mechanism of action of the drug.[12] The WHO's analgesic ladder provides, depending on the intensity of the pain, an orientation for the prescription of drugs. It has two

steps: the first, mild to moderate pain for which the use of peripheral analgesic drugs and NSAIDs are recommended, in isolation or in combination; and for the second step, moderate to severe pain, the administration of an opioid should be considered.[73,74] The correct use of analgesic drugs is also based on their administration at regular intervals, with the possibility of salvage doses, through the simplest, most effective, and least painful route of administration.[73] Sometimes, for example in neuropathic pain, peripheral analgesic drugs may be insufficient and the association of adjuvant drugs (antidepressants, anticonvulsants) is possible.[69,70] In refractory or complex pain, it may be necessary to resort to opioids.[71] In this context, there is no consensus on their use in pediatrics. Today, it is suggested that they be prescribed in the context of consultations at Chronic Pediatric Pain Units, at the lowest effective dose and for the shortest time possible, in order to keep the surveillance of potential secondary effects.[75] Morphine is the drug of choice and the rotation of opioids or route of administration is recommended whenever the analgesic effect is insufficient and/or intolerable secondary effects appear.[73] Using mild opioids (codeine, tramadol) is not currently recommended by the Food and Drug Administration for children under 12 years of age nor for obese teens between 12 and 18 years with severe respiratory disease or Obstructive Sleep Hypopnea-Apnea Syndrome. European organizations recommend using low doses of tramadol.[76]

Intervention techniques for peripheral nerves and neuroaxis may constitute a diagnostic and therapeutic strategy as part of the multimodal strategy, although there is not much evidence for their use.[73]

Physical therapies

There is a wide variety of frequently used techniques, like the application of heat or cold, Transcutaneous Electric Neuromuscular Stimulation (TENS), desensitization, and cardio exercise.[73] Every adolescent should have an individualized rehabilitation plan, supported on a cognitive-behavioral approach that includes active physical interventions, defining goals to be reached (ideally defined by the teenager), gradual physical exercise, rhythmic activity (progressing to regular physical exercise) that they are interested in so as to optimize compliance. Today, neuromuscular physical practice and cardio exercise are emerging as promising interventions.[77]

Psychological interventions

Psychological interventions are the treatment modality that presents the highest level of evidence.[61] They are based on cognitive or behavioral therapy or a combination of both (cognitive-behavioral therapy). Their focus are maladaptive emotions, cognitions, and behaviors related to pain, present in adolescents, and their families, and have as therapeutic goals: to prevent recurring pain; to mitigate severe pain; to reduce sociocultural, environmental, family, emotional (anxiety, depression, and post-traumatic stress), and behavioral (passive coping, pain fear-avoidance, kinesiophobia, catastrophizing, poor sleep hygiene, low acceptance of pain, parental overprotection, and other) risk factors, and to increase adaptative functioning.[78] They may be provided individually or in group, and currently there is growing interest in their implementation with the use of digital tools (apps for cell phones, videos, websites), because of their accessibility and ease of use.[79]

Integrative medicine

Integrative medicine is an emerging field that encompasses alternative and complementary medicine based on evidence, on conventional medicine, integrating individuals to their environment as a whole. It comprehends several approaches: utilization of natural products (vitamins, minerals, plant-based products); mind-body therapies (meditation, relaxation); physical and movement therapies (massage, yoga); energy therapies (acupuncture, reiki); traditional Chinese medicine, naturopathy, and others. The modalities most frequently used in the treatment of chronic non-cancer pain in adolescents are acupuncture, creative arts, herbal medicine, homeopathy, and massage, despite the scarce evidence for their use in the pediatric population.[80]

Intensive interdisciplinary treatment

Some centers have instituted intensive interdisciplinary treatment for adolescents with severe incapacity. It consists of a treatment program lasting about 3 weeks, with 3 to 5 sessions per day, and involves several therapeutic modalities in an inpatient or outpatient regimen. Although parents do not stay in together, they are also focused by the intervention (family interventions/parenteral education/group therapy). The cost is high, but everything indicates good cost effectiveness and high satisfaction.[81]

Discussion and conclusion

The current information on pain in the pediatric population, particularly on adolescence, makes it difficult to standardize and describe it because of the heterogeneity of this group.[2,16,21] In this age group, the problem is particularly evident as to the epidemiological characterization and treatment of pain.

Overall, chronic non-cancer pain in adolescents seems to be frequent and have impact on several daily-life activities, and its underappreciation and perpetuation contribute to make it chronic, with physical limitations and psychological suffering in adulthood.[1] However, this impact seems to be frequently ignored or underappreciated, and pain is accepted as something ''normal''.

The study and description of the pathophysiology of pain is undergoing clear evolution. The approach according to its mechanism and based on the biopsychosocial model is fundamental for the institution of adequate treatments. However, it looks like this strategy is not yet generalized, which contributes to make chronic pain misunderstood, and mistreated, perpetuating its negative consequences.

Chronic non-cancer pain in adolescents should always be treated, regardless of the context or level of care. The capacity of health services to detect and respond to

these patients should be cross-sectional, and not exclusive with super dedicated and highly specialized teams. Primary health care, because of its community activity, constitutes a privileged area for the diagnosis and detection of chronic non-cancer pain in adolescents.[6,54] It should be an integral part of the initial approach, diagnosis, treatment, and whenever necessary, severe or complex pain should be referred.

Early detection and diagnosis, like interdisciplinary treatment, sharing common treatment goals, has a positive impact on the rational and effective use of health services, reduces costs, and translates into economic and social return to the country.

Chronic Pediatric Pain Units may also play an important role in the training of healthcare workers and to the population, and schools are an excellent environment to build awareness and promote intervention strategies for pain in adolescents.

On the other hand, it is urgent to study and design therapeutic measures with proven treatment effectiveness, considering the potential effects in the development and efficacy from the standpoint of patients.[61–65]

In conclusion, the awareness of the problem of chronic pain in adolescents is fundamental for adequate treatment, requires joint work of several professional groups, with the aim of minimizing its impact on the day-to-day and future of adolescents.

Conflicts of interest

The authors declare no conflicts of interest.

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SYSTEMATIC REVIEW

Identifying patient safety competences among anesthesiology residents: systematic review

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Abstract
Introduction and objective: Patient safety is a concept of great importance to managers, health professionals, and patients and their families, given patient safety promotes more effective care and reduces costs. Moreover, while analyzing the area of anesthesiology, one can realize the epidemiological changes, increased complexity and number of procedures, and the adoption of a new matrix of essential skills mandatory for residents of anesthesiology in Brazil. Thus, it is relevant to identify current patient safety competences among anesthesiology residents.
Methods: A systematic review was elaborated using PubMed, SciELO, BVS, Cochrane Library, LILACS and CAPES databases with the descriptors "anesthesiology", "patient safety", "residency" and "competence".
Results and conclusions: Thirteen articles published in the past 10 years were analyzed. The articles depicted competences grouped into three categories: knowledge (identification, prevention and management of adverse events; use of correct and up-to-date information; understanding of human factors; and continuous learning), skills (efficient communication; teamwork; leadership; decision-making; and self-confidence), and attitude (management of stress and fatigue; and infection control). All these skills can be developed and assessed through simulation and active learning methods, profiting from a multidisciplinary approach. Studies also reveal that residents perform poorly in certain patient safety domains due to lack of effective in-depth understanding, appreciation of the topic and ineffective teaching. As a result, greater investment in the topic is needed by teaching and health institutions and researchers.
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Introduction

The expression "patient safety" dates from the 19th century, when the English nurse Florence Nightingale, working in the Crimean War and observing the precarious conditions of battlefield soldiers, proposed changes in hospital organization and hygiene, fundamental factors for satisfactory quality of care.[1]

Early in the 21st century, the Institute of Medicine of the United States of America included patient safety as one of the parameters of patient care quality. It can be defined as

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the extent to which health services dedicated to patient or population care increase the likelihood of producing desired outcomes based on current scientific evidence.[2] In this scenario, patient safety can be recognized as the process seeking to reduce, to an acceptable minimum, preventable injury and damage that may result from health care to patients.[2]

This concept has acquired, all over the world, great importance not only for health professionals, but also for managers, patients and family members, in order to offer safer assistance.

Given the significance of the matter, the World Health Organization (WHO) has prioritized two measures to reduce the risks that result in harm to patients: the worldwide campaign of hand hygiene and the promotion of safer surgery. The latter, for example, is based on performing a checklist before, during, and after surgery.[3]

Moreover, in the past 10 years there have been epidemiological changes, such as aging of the population, introduction of new technological devices, and scientific progresses in healthcare. Worldwide, such changes have resulted in a significant increase in the number of surgeries and in the complexity of anesthetic procedures, demanding more investigation on patient safety practices in the domain of anesthesiology.

In the complex setting of an operating room, anesthesiology is configured as a clinical specialty which intensively applies concepts and knowledge of the basic sciences in a practical context. Familiarity and proficiency in these domains are critical for delivering good practice, attaining satisfaction in professional activity and achieving the safe patient care criteria established by WHO.[2]

Thus, as dictated by Resolution No. 2174/2017 of the Federal Council of Medicine (CFM)[4], physician duties regarding the confirmation of safety conditions are the basis of the new CFM guidelines for routine clinical practice in anesthesiology. Consequently, it is necessary to understand the patient safety competences that anesthesiology residents acquire during their training.

The term competence, according to Fernandes et al.,[5] was initially defined as a set of knowledge, skills and attitudes, that when collectively applied, make it possible to improve the use of technical and cognitive resources to diagnose and treat patients and promote lower morbidity and costs to health institutions. However, they must be performed considering professional ethics and current scientific evidence. Govaerts[6] further develops this concept by adding that competences are context dependent, require experience and reflection on medical practice itself, in addition to the ability to keep continuous medical education activities throughout one's professional life.

Still in relation to the anesthesiology residency program, the skills to be acquired, and which are necessary for the training of residents, vary according to the country in which the training takes place.

In the US, for example, in 2013 the Accreditation Council on Graduate Medical Education (ACGME) proposed the creation of the Anesthesiology Milestone Project to assess physicians participating in American residency and fellowship programs. According to the Milestone Project, the resident can be assessed in the following 5 different domains: patient care (perioperative management); medical knowledge (biomedical, clinical, epidemiological and sociocultural); systems-based practice (coordination of care with the health system and patient safety); practice-based learning and improvement (improvement in patient safety during clinical practice; autonomous learning; knowledge about patients, families, students, residents, and other health professionals); professionalism (responsibility, honesty, integrity and ethical behavior; proposing and accepting suggestions; maintaining personal health); interpersonal and communication skills (dealing with everyone involved in health care; leadership and teamwork skills).[7]

On the other hand, in Brazil through Resolution No. 11 of April 8, 2019, the National Medical Residency Committee (CNRM) created the competence matrix for Medical Residency Programs in Anesthesiology.[8] The matrix became mandatory on March 1, 2020 and it has general and specific objectives, and competences for each year of the training program (at the end of the first, second and third year of residency).

Regarding patient safety, the matrix presents as one of its specific objectives "to carry out anesthesia safely throughout all its stages".[8] Moreover, it values medical practice based on ethics and respect for sociocultural differences. It also states that the resident should show respect toward all those involved in health care at the end of the third year of anesthesiology residency (patients, family members, colleagues, and assistants); communication skills; emotional control; leadership skills and teamwork. Finally, the matrix declares that it is essential for anesthesiologists to be aware of their own limitations to constantly enable opportunity for improvement.

Thus, by analyzing the current competences that anesthesiology residents have regarding patient safety, it will be possible to point out whether there is a need for improvement and how to achieve it. In addition, an opportunity will be created to analyze, in the future, how the progress of competences took place following the implementation of several curriculum matrices worldwide during the past decades.

Therefore, the guiding question of this study was: "What are the patient safety competences of anesthesiology residents?". To answer this question, the objective of this systematic review study was to identify the competences, that is, knowledge, skills and attitudes of anesthesiology residents regarding patient safety.

Methods

As this is a systematic review, the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA)[9] checklist were followed. In addition, the study was registered on the international database PROSPERO,[10] under the identification code CRD42020176724.

Search strategies

The systematic review used the following databases: PubMed, SciELO, BVS, Cochrane Library, LILACS and CAPES. The descriptors "anesthesiology" AND "patient safety" AND "residency" AND "competence" were used for searching articles. Such descriptors were defined using Medical Subject Headings (MeSH).[11] Furthermore, they were contained either in the title or in the abstract of the selected study. The articles were published in the past 10 years, between January 2011 and April 2020, and they were all written in Portuguese, English or Spanish. Table 1 summarizes the initial search results.

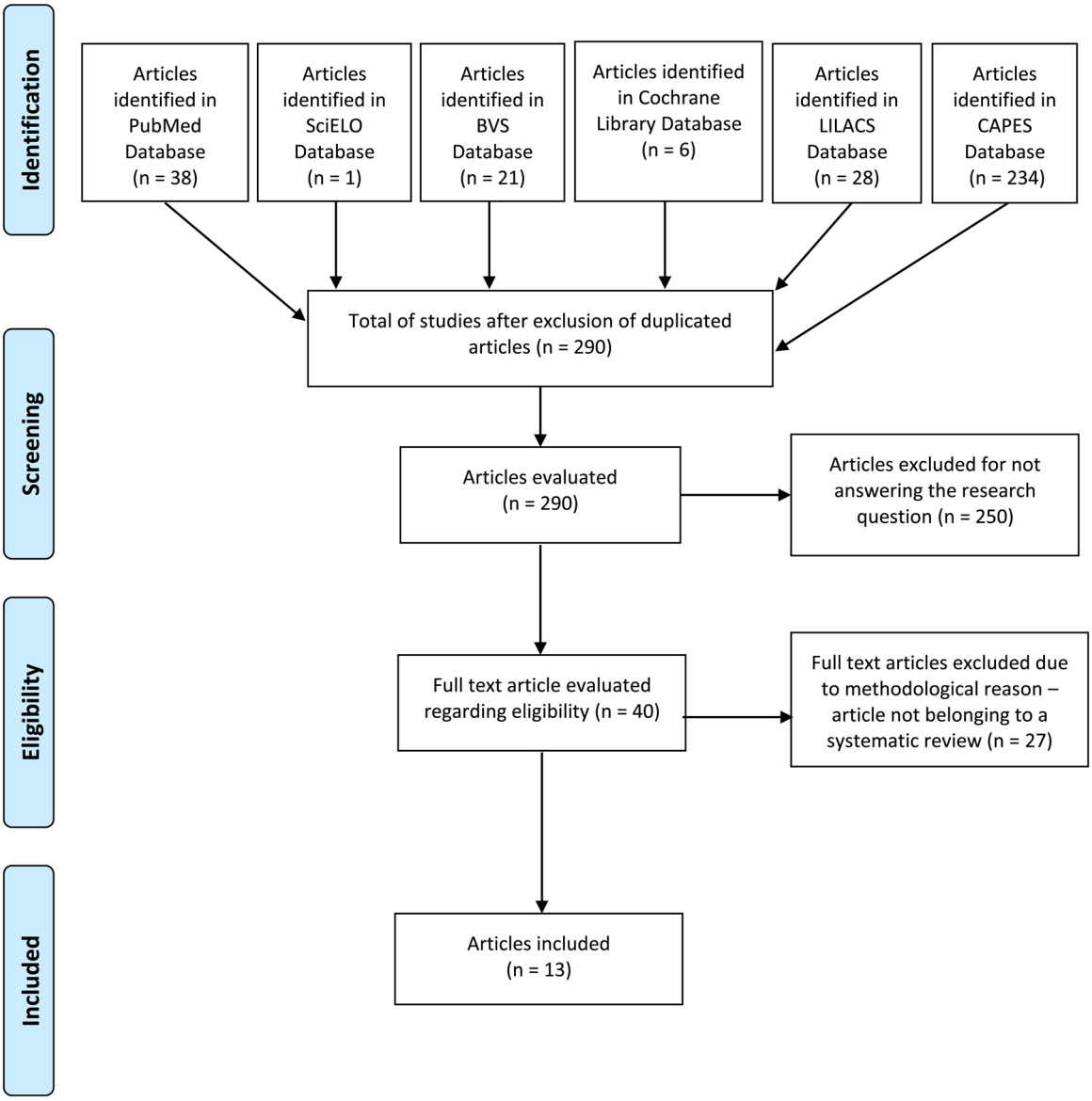

Figure 1 Flowchart of the article selection process according to the PRISMA model.[9]

Selection of articles

Duplicate studies were removed based on each article's title and authors. After this process, articles underwent a first reading by independent researchers, and were assessed according to inclusion and exclusion criteria. For inclusion, study participants of the article had to be anesthesiology residents. On the other hand, the following were excluded: (I) studies with resident physicians from other areas; (II) studies with participants that were already trained anesthesiologists; (III) or studies that had no correlation with the objectives of this systematic review.

A second reading of the abstract was carried out followed by an in-depth reading of the full articles that made up the final sample of the present study. Figure 1 depicts the selection process of the articles.

Presentation and discussion of results

After searching the databases depicted in Table 1, initial evaluation, and elimination of articles incompatible with this systematic review, a total of 13 articles were obtained for analysis and discussion.

The articles were tabulated according to their authors, title, journal, year and country of publication, as presented in Table 2.

Table 1 Number of articles found in the databases, according to search period and items.

Database	Search period	Search items	Number of articles found
PubMed	2011—2020	All fields	38
SciELO	2011—2020	All indexes	1
BVS	2011—2020	Title, abstract, topic	21
Cochrane Library	2011—2020	Title, abstract, keyword	6
LILACS	2011—2020	Words	28
CAPES	2011—2020	Any	234

Table 2 Characteristics of selected articles.

Article number	Authors/Journal	Title of publication	Year of publication	Country of publication
1	Fehr et al.[12] / Anesthesiology	Simulation-based Assessment of Pediatric Anesthesia Skills	2011	USA
2	Riem et al.[13] / British Journal of Anaesthesia	Do technical skills correlate with non-technical skills in crisis resource management: a simulation study	2012	UK
3	Oliveira Junior et al.[14] / Anesthesia & Analgesia	The prevalence of burnout and depression and their association with adherence to safety and practice standards: a survey of United States anesthesiology trainees	2013	USA
4	BLUM et al.[15] / Anesthesiology	Simulation-based Assessment to Identify Critical Gaps in Safe Anesthesia Resident Performance	2014	USA
5	Iblher et al.[16] / BMC Medical Education	What motivates young physicians? — a qualitative analysis of the learning climate in specialist medical training	2015	UK
6	Doyle et al.[17] / BMJ Quality and Safety	Self-reported patient safety competence among Canadian medical students and postgraduate trainees: a cross-sectional survey	2015	UK
7	Dalband; Mohseni; Rosani[18] / Advances in Natural and Applied Sciences	The impact of anesthesiologists' level of expertise on orodental injuries in patients undergoing general anesthesia	2015	Jordan
8	Kumar et al.[19] / Anesthesia Essays and Researches	Perioperative communication practices of anesthesiologists: A need to introspect and change	2016	India
9	Corvetto et al.[20] / BMC Anesthesiology	Validation of the imperial college surgical assessment device for spinal anesthesia	2017	UK
10	Gauger et al.[21] / International Journal of Pediatric Otorhinolaryngology	A Multidisciplinary International Collaborative Implementing Low Cost, High Fidelity, 3D Printed Airway Models to Enhance Ethiopian Anesthesia Resident Emergency Cricothyroidotomy Skills	2018	Netherlands
11	Blum et al.[22] / Anesthesiology	Simulation-based Assessment to Reliably Identify Key Resident Performance Attributes	2018	USA
12	Komasawa; Berg; Minami[23] / PLoS ONE	Problem-based learning for anesthesia resident operating room crisis management training	2018	USA
13	Kumari et al.[24] / Saudi Journal of Anesthesia	Assessment of procedural skills in residents working in a research and training institute: An effort to ensure patient safety and quality control	2018	India

Table 3 Characteristics of selected articles.

Article number	Objective	Type of study
1	a) Develop a relevant set of pediatric perioperative simulations and determine their effectiveness in evaluating anesthesia residents and pediatric anesthesia fellows. b) Determine how experience and training time in pediatric anesthesia has affected a resident's ability to care for a variety of critical events in pediatric anesthesia.	Cross-sectional study
2	Assess the relationship between technical (T) and non-technical (NT) skills during a simulated intraoperative crisis scenario.	Cross-sectional study
3	Determine the prevalence of burnout and depression in anesthesiology residents in the USA.	Cross-sectional study
4	Design and test the use of an anchored behavioral scale, as part of a multiple scenario and a simulation-based rating system to elucidate the high and low performance characteristics of first-year anesthesia residents.	Prospective observational study
5	a) Investigate the preferences and concerns that German residents have about their learning. b) Highlight how German residents assess the quality of their postgraduate training and learning environment.	Qualitative study
6	a) Describe and compare self-reported patient safety competence acquired in lectures and clinical settings. b) Compare self-reported patient safety along the years of the residency program.	Cross-sectional study
7	a) Determine the impact of anesthesiologists' level of expertise on orodental injuries in patients under general anesthesia during oral intubation. b) Determine the prevalence of orodental injuries during oral intubation.	Descriptive Cross-sectional study
8	a) Check (using a questionnaire) communication skills during the perioperative period of anesthesiology residents. b) Report the level of psychosocial support anesthesiology residents provided to patients and family members. c) Report communication among residents and colleagues in the operating room.	Cross-sectional study
9	Assess (by video) hand movement in a simulated spinal anesthesia model.	Cross-sectional study
10	Assess the knowledge and ability of anesthesiology residents to perform needle cricothyroidotomy using a simulator	Cross-sectional study
11	a) Assess whether there are important gaps in the performance of anesthesiology residents. b) Validate an assessment based on several simulation scenarios for residents (regarding patient safety).	Cross-sectional study
12	a) Teach anesthesiology residents emergency airway procedures, pain and venous access using PBL. b) Additionally assess the non-technical skills of residents (self-confidence, for example).	Cross-sectional study
13	a) Evaluate the competence of residents and the impact of various corrective measures using educational lectures and of clinical skill demonstration in providing several anesthesia procedures. b) Evaluate such procedures by PSC and GRS scores.	Cross-sectional study

Regarding the articles chosen for analysis, 38.46% of the studies were carried out in North America, 38.46% in Europe, and 23.07% in Asia. The US and UK had the highest number of publications, with 5 (38.46%) and 4 (30.77%) articles, respectively.

On the other hand, concerning the research design, 11 (84.60%) articles were cross-sectional studies, 1 (7.70%) was observational prospective, and 1 (7.70%) was qualitative, as revealed in Table 3, which depicts the specific characteristics of each article selected.

All articles were submitted to an analysis of risk of bias using the QUADAS-2[25] tool. During this process, four domains were examined: selection of residents, index test, reference standard, and flow and time. Such data are shown in Figure 2.

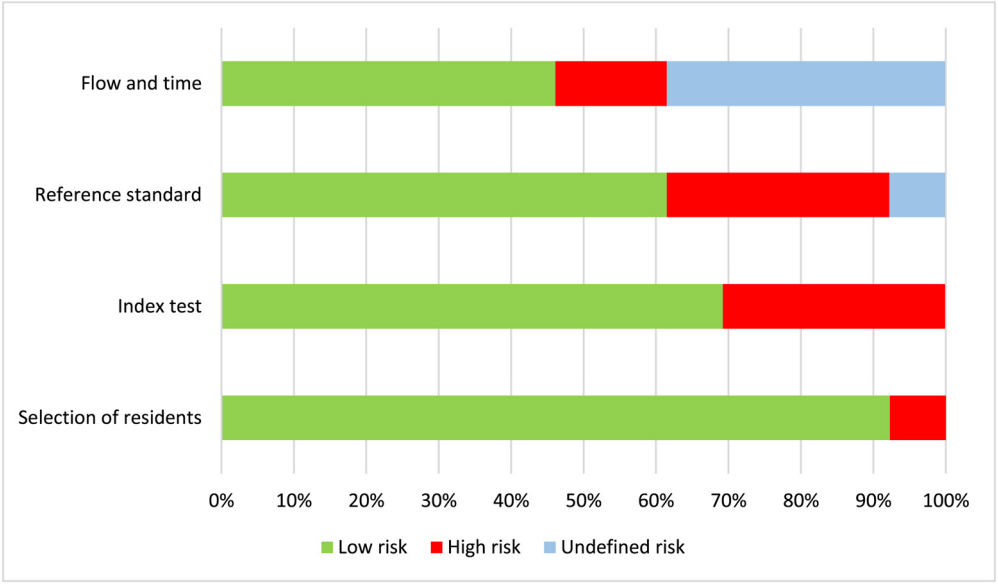

Figure 2 Proportion of articles with low, high or undefined risk of bias according to the QUADAS-2 tool.[25]

As for the first domain, that is, how study participants were selected, 92.3% of the articles had a low risk of bias. These studies reported the total number of residents who participated in the survey and avoided unnecessary exclusions. However, article 7 reported only the number of patients seen by residents during the study.

Regarding the index test, that is, the instrument applied by the author in the research, 69.2% of the articles had a low risk of bias (authors described the tool and how it was used and interpreted), while 30.7% had a high risk of bias. For example, articles 2 and 5 offered a comprehensive description of the instruments, however, both tools were original and have not been validated by other authors, increasing the risk of bias. On the other hand, article 8 did not offer a satisfactory description of the tool or describe how it was interpreted. Article 13 did not elucidate whether residents were assessed in simulation or in a clinical practice setting and, consequently, did not assess the risk of bias that both settings may have.

As for the reference standard, that is, other non-authorial instruments that inspired the authors during the research, 61.5% of the articles had a low risk of bias (they offered an adequate tool description); 30.7% presented high risk of bias (in articles 4, 5, 7 and 12 tools are only mentioned, but not described); and 7.7% had an undefined risk of bias (article 8 did not elucidate whether the tool used has devised by the article's author or based on other studies).

On the other hand, in the flow and time domain, that is, how the study was conducted, 46.1% of the articles had a low risk of bias (there was suitable time between pre- and post-test; the tool was applied to each resident, at the same time and in the same manner, and all data were included in the analysis); 15.4% had a high risk of bias (articles 5 and 6 did not discriminate the study results by medical specialty); and 38.4% had an undefined risk of bias. As to the latter, articles 1, 2, 4 and 13 did not specify whether the study was conducted using the same residents and at the same time. Article 7 had no description on how the study was conducted.

In general, the 13 articles selected presented different types of patient safety competences that can be classified into three categories: (1) knowledge, (2) skills and (3) attitude, that are described below.

Category 1: knowledge

Regarding the knowledge category, a set of theory knowledge acquired by the rationale, experience or information received, the articles underline as fundamental: the identification, prevention and management of adverse events and possible errors arising from the comprehensive assessment of the patient, and from the understanding and training of the procedures and medications to be used, recognition and reporting of errors[14, 16-18]; the use of accurate and updated information by practicing Evidence-Based Medicine and using technology[12, 15, 21]; the understanding of human factors[13, 15, 17, 18, 22]; and continuous learning, that is, learning and teaching at the workplace, and the existence of dedicated and receptive teachers and active methodologies can help in this process.[16, 17, 23]

Category 2: skills

Regarding skills, the ability to put acquired knowledge into practice, a great emphasis was given to efficient communication, a factor that directly impacts interpersonal relationships. Hence, during clinical care or adverse events, residents must always honestly report what is the actual situation to the patient and family; obtain consent to perform procedures; perform shared (with patient and team) and individual anesthetic plans; be clear and assertive; show mutual respect; be interactive, empathetic and a good listener; be willing to give and receive feedback.[12, 15-17, 19, 22, 24] Teamwork and the demonstration of leadership through recognition of their role and that of other team members; decision-making; self-confidence; and good communication were also valued.[13, 15-17, 22-24] In order for all the aforementioned skills to be developed, interdisciplinarity during the

anesthesiology residents' learning is critical in order to ensure an integral perception of the health-disease process.[17, 21]

Category 3: attitude

In the attitude category, that is, the behavior while facing a scenario, was underlined: the management of stress and fatigue through the awareness of one's self-limitations, acting according to an adequate workload, use of coping techniques, and requesting help when required[14-16, 22]; and infection control by hand hygiene, antiseptic techniques and proper use of personal protective equipment (gloves, mask and gown).[14, 17, 24]

Additionally, it is possible to point out the Six International Patient Safety Goals, advocated by the World Health Organization, whose objective is to achieve high standards of quality in care, with measures that help this development, such as behavioral changes and technological innovation in care[1]. Knowing and applying the assumptions emanating from them is vital so that the anesthesiology resident can provide a positive attitude towards patient safety.

All skills regarding patient safety, and even in other areas, can be developed, improved and evaluated through simulations, a matter explored in most of the articles selected in this systematic review. Fehr et al.,[12] for example, submitted 35 residents and fellows to 10 scenarios using pediatric perioperative simulation, while Blum et al.[15] submitted 30 residents and fellows to seven scenarios focusing on perioperative care pertaining to first-year residents, together with a behavioral scale.

Both concluded that this method was able to assess the actual level of the residents, since the performance of a scenario was related to overall performance. In the study by Fehr et al.,[12] the lowest scores were achieved in the scenario of appendicitis with sepsis, and the highest in the scenario of bronchospasm.

In the study by Blum et al.,[15] based on the average performance of participants, scenario 5 (management of anaphylaxis in a patient with transurethral resection of the prostate and bladder biopsy) was considered the most difficult, and scenario 6 (management of one patient presenting delayed awakening in the operating room after transurethral resection of the prostate) was considered the easiest. In this study, the authors report that 98% of the residents rated the simulations as more instructive than a day in the operating room, demonstrating the importance of such a teaching method for learning patient safety, especially regarding communication skills. Simulation in multiple scenarios helps to identify gaps in residents' performance and enables adjusting teaching-learning programs.

Additional studies were carried out by other investigators, like Gauger et al.,[2] who assessed 12 residents after being trained to perform needle cricothyroidotomy; Kumari et al.,[24] in which 95 residents received suggestions on corrective measures during lectures and practical training sessions; and Blum et al.,[22] who enrolled 67 residents to participate in seven simulation scenarios focusing on perioperative care. These three groups of investigators revealed that, after the administration of simulation scenarios and feedback, there is significant improvement in residents' skills in the three categories (knowledge, skills, and attitude). Moreover, in Blum's study, 98% of the residents indicated simulation scenarios as more educational than actual routine situations in the operating room.

Corvetto et al.[20] enrolled 30 residents to perform spinal anesthesia simulations and evaluated the number of movements made by trainees, and time for executing the procedure. The authors observed that the highest scores were obtained by third-year residents. According to the authors, the analysis was carried out with procedures in compliance to patient safety. Such teaching methodology demonstrates that there was improvement in the way procedural skills are taught when the authors state and acknowledge that the traditional method must be replaced by a structured method for acquiring technical skills.

Fehr et al.[12] used 10 pediatric perioperative simulation scenarios for 35 residents and fellows and reported that higher scores were obtained by participants with more training and experience. They also identified that simulation, as a learning method, enables characterizing residents' progress during the different years of residency. Thus, it is still possible to identify likely gaps while teaching residents and provide support to resolve these issues before residents are granted specialist status.

Furthermore, Komasawa, Berg and Minami[23] analyzed the skills of 35 residents before and after training and reported performance improvement for all scenarios, and Gauger et al.[21] also stated that study methods such as Problem Based Learning (PBL) or other types of simulations can enhance a resident's self-confidence. This is a fundamental factor for residents to put into practice everything they have learned and to question the procedures performed by themselves and by others around them.

Articles such as those by Riem et al.,[13] in which improvement in technical and non-technical skills in 50 residents followed their exposure to a simulated scenario of intraoperative cardiac arrest secondary to a malignant arrhythmia; by Doyle et al.,[17] in which medical students, 13 residents of anesthesiology and other areas answered a questionnaire on patient safety; and by Komasawa, Berg and Minami[23] also reported a close correlation between technical (hand hygiene; infection control; safe medication practices) and non-technical (trust; decision making; teamwork) skills. Therefore, developing one of these domains automatically improves overall performance by residents. Despite this, in the survey by Doyle et al.,[17] most residents claimed to have more confidence in learning technical patient safety skills and less confidence in learning patient sociocultural aspects.

Regarding this matter, similarly, Iblher et al.[18] asked 198 anesthesiology residents about what would be the fundamental factors for medical training. From the responses obtained, 10 categories were created. Among them appear learning methodology, with the benefits of simulations and active methodologies already evidenced here; patient safety; supervision; and personal safety.

As for supervision, the study done by Doyle et al.,[17] enrolling medical students and residents, including 13 anesthesiology residents, indicated that the majority (78%) believed it was hard to question authority, and 39% agreed that there is consistency in how patient safety is dealt with by different tutors.

Based on these data, the need to guarantee that the anesthesiologists trained before the curricular changes have access to patient safety knowledge is evident. In addition, as a professional requirement, these specialists must continue learning and improving themselves.

Personal safety is another category created in the study by Iblher et al.[16] On this topic, Oliveira Junior et al.,[14] administering a questionnaire to 1508 residents, concluded that 41% of the participants had a high risk of burnout and 22% had positive results for depression. Risk factors included excessive workload (> 70h per week); alcohol intake (> 5 drinks per week); tobacco use; and female gender. Among respondents, the authors identified a percentage of 33% at high risk of burnout and depression, who reported making medication errors, and concluded the study discussing the actual prevalence of depression and even suicidal ideation, relating such symptoms to patient safety or lack of safety.

These data underlined the significance of physical, but also mental care for residents. In this sense, it is possible to rely on the emotional support of colleagues and superiors and gain new insights from the experiences they have already undergone. It is also crucial that residents recognize their limits and seek professional help when needed. Finally, education and health institutions must maintain a firm inspection to ensure that residents do not exceed the maximum workload established — 60 hours per week.[26]

Oliveira Junior et al.[14] state that residents with burnout or depression had worse practical performance, compromising quality of care and patient safety. Dalband, Mohseni and Rosani[18] also corroborated this concept by reporting after questionnaire administration to 683 patients undergoing orotracheal intubation during general anesthesia, that 67% of tooth damages caused by residents were due to negligence during the procedure and lack of adequate training, and were considered as adverse events.

Communication with the team and with patients and their families is another fundamental factor ensuring patient safety and appropriate resident performance. Kumar et al.[19] verified, in a questionnaire administered to 127 anesthesiology residents and professionals in the area, that anesthesiologists practicing in private settings are more communicative than those who are tutors at a teaching institution or residents; that there is greater interest in intraoperative communication than in relation to the anesthetic plan; and that the discussion with the surgeon on the postoperative pain control strategy is not prioritized, even in university centers. This lack of communication among team members reduces care efficiency and places patient safety at risk. Furthermore, it does not contribute to promoting a harmonious and less stressful work environment.

Doyle et al.[17] also stated that only 78% of respondents reported having enough opportunities to learn and interact with members of interdisciplinary groups. Thus, it is necessary that practicing good communication be fostered and developed.

None of the authors of the selected articles demonstrated improvement in health care quality associated with a Hospital Accreditation process. It is known that this procedure greatly assists in raising the quality of care, mainly by providing organized and strategic management. Health institutions that undergo accreditation advance in their daily reflection on work processes, and consequently, towards the promotion of a positive organizational culture.

Final considerations

Given what was exposed in this research, the absence of more in-depth and effective understanding, or of residents' appreciation of the topic places quality of care at risk, which is reinforced by the lack of conformity when working with the subject at graduation or residency. In addition, many residents praise technical skills over non-technical and sociocultural aspects, which impacts on the quality of care. Communication, one of the International Patient Safety Goals, is yet another area that needs to be much improved in all its scopes, demanding better interaction among colleagues, professionals from other areas and tutors, including when posing questions and criticism. Finally, a great devaluation of residents' self-safety is still observed, reflecting on their physical and mental health and resulting in increase in medical errors.

When revisiting the proposed objective, evidence indicates that anesthesiology residents, to ensure the safety of their patients, must have appropriate skills, such as: identification, prevention and management of adverse events and possible medical errors; use of accurate and updated information that best favors patient clinical outcome; understanding of human factors; continuous learning; efficient communication among team members, patients and their families; empathy and respect for those around; willingness to provide and receive feedback; team work; showing leadership and decision making; self-confidence; managing stress and fatigue, always seeking to recognize self-limitations and asking for help when required; and infection control through good hygiene and antisepsis practices and the use of personal protective equipment.

Regardless of the specialty, patient safety is a fundamental theme in medical education. Therefore, it is necessary that faculty staff and institutions value teaching during graduation and residency, facilitating discussions and constructive feedback. Simulations and active methodologies are effective strategies for this purpose, as they enable the improvement of technical and non-technical skills and the identification of gaps in resident competences.

In this scenario, interdisciplinarity enhances such methods and prepares future anesthesiologists for the reality of the specialty. In addition, further studies are required given the lack of data on the competences needed for providing safe care, especially in the area of anesthesiology residency, which limited the present study. We suggest that other databases should be consulted for searching publications that identify evidence on the matter arriving from different countries, with regional specificities regarding their teaching programs on patient safety.

Author's contribution

FSHP contributed to the study design, data collection and analysis, and wrote and reviewed the manuscript. DBG contributed to study design, wrote and reviewed the

manuscript. ERR coordinated all phases of the study and contributed to the study design and reviewed the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Unilateral lingual nerve and hypoglossal nerve injury caused by a novel laryngeal mask airway: a case report



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KEYWORDS
Case report;
Complication;
Cranial nerve injury;
The laryngeal mask airway

Abstract
Cranial nerve injury by a laryngeal mask airway is rare but a serious complication. The nerve injuries must be prevented during the intubation using a laryngeal mask airway. We report a female patient who complained of tongue numbness, slurred speech, and slight difficulty in swallowing solid food after a hand surgery. She was then diagnosed with unilateral lingual nerve and hypoglossal nerve injuries. Extreme head rotation, relatively small oral cavity, and wide rigid composition at the lower part of the novel laryngeal mask probably resulted in cranial nerve injury.
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Introduction

The laryngeal mask airway (LMA) is a supraglottic airway device between the face mask and the endotracheal tube. It has been widely used in certain surgical procedures. Complications related to the LMA during surgery are commonly not life-threatening. However, serious and rare complications like aspiration of gastric contents, trauma, nerve injuries, and compression of vascular structures have been reported.[1—3] Here, we report a rare case of unilateral lingual nerve and hypoglossal nerve injuries during the use of a novel laryngeal mask airway.

Case report

A 57-year-old female patient (weight, 65 kg; height, 155 cm) with no significant medical history underwent exploratory release of the right brachial plexus under general anesthesia. Anesthesia was induced with 1 mg of midazolam, 20 μg of sufentanyl, 100 mg of propofol, and 6 mg of cisatracurium. A novel size-4 laryngeal mask was then inserted smoothly. The location of LMA inserting was confirmed by capnography, with the absence of sounds over the epigastrium. The maintenance of anesthesia consisted of continuous intravenous infusions of propofol and remifentanyl under mechanical ventilation, with a peak inspiratory pressure of 15 cmH_2O. Neuromuscular blockers were not administered during the operation due to the requirement for intraoperative electromyography monitoring. The surgery lasted approximately 1 hour. No clinical

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meaningful changes in cardiovascular or respiratory parameters during the operation. The LMA was gently removed after the surgery when spontaneous respiration was adequate and the patient was fully awake. She was then relocated to the recovery room with no complaints. Two hours later, she complained of tongue numbness, and slurred speech as well. Physical examination indicated the decrease in sensation and loss of taste in the anterior two-thirds of the tongue. Meanwhile, when she was requested to stick out her tongue, it deviated toward the left side. The limb muscle strength and tone were not seen any abnormal. On day 2 (1 day postoperative), her speech recovered to some extent. After receiving a normal diet, she complained of a slight difficulty in swallowing solid food, but no concern in drinking water. A cranial MRI plain scan ruled out the diagnosis of acute cerebral infarction. MRI scan for this patient indicated small double frontal parietal lobe ischemic foci without diffusion weighted imaging (DWI) hyperintensity lesions. DWI is a commonly performed MRI sequence for evaluation of acute ischemic stroke, which is sensitive and specific in the detection of small and early infarcts. No DWI hyperintensity lesions in this patient and her speech impairment gradually recovered without sudden limb dysfunction, limb numbness, and disturbance of consciousness, suggesting the acute cerebral infarction was very unlikely. In addition, laryngoscopy showed a good movement of both vocal cords. According to her symptoms and examinations, a clinical diagnosis of unilateral lingual nerve and hypoglossal nerve injury was suggested. She was then given intravenous dexamethasone for three days. Her symptoms improved substantially, with slight numbness of her tongue and mild difficulty in swallowing a week after. After six weeks, she completely recovered without any residue symptoms.

Discussion

Cranial nerve injury following the use of LMA is rare but a serious complication. Branches of the trigeminal, glossopharyngeal, vagus, and hypoglossal nerves are considered involved in the cranial nerve injury. As summarized by a systematic review, lingual nerve injury was the leading report, then followed by recurrent laryngeal, hypoglossal, glossopharyngeal, inferior alveolar, and infra-orbital nerves.[3]

The clinical manifestation depends on the cranial nerve revolved in the injury. Lingual nerve lesions are generally related to loss of taste and sensation in the anterior region of the tongue; hypoglossal nerve damage leads to dysphagia and tongue deviation to the affected side, and the lesion of the recurrent laryngeal nerve causes postoperative dysarthria and aspiration. In the current report, this patient initially showed the decrease in sensation in the anterior two-thirds of the tongue and tongue deviation, as well as the difficulties in speaking and swallowing, which suggested a result of lingual and hypoglossal nerve damages.

Cranial nerve paralysis can be caused by the damages from somewhere along the nerve. When the lingual nerve runs beneath the mucosa on the inner surface of the mandible below the roots of the third molar tooth, it is prone to compression at the periosteum close to the molar by the shaft of the LMA.[4] The hypoglossal nerve located above the greater horn of the hyoid bone at the angle of the mandible before turning forward and medially toward the tongue. The nerve is vulnerable to damage from compression against the hyoid bone by the cuff of the LMA (Fig. 1).

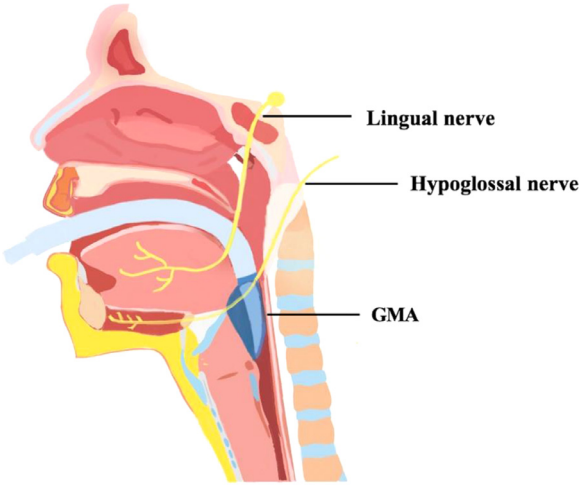

Figure 1 Insertion of the laryngeal mask airway and the surrounding nerves.

The etiology of cranial nerve injury by LMA was considered to be multifactorial, including anesthesia-related factors (e.g., incorrect or forceful insertion and excessive cuff pressures), patient-associated factors (like diabetes mellitus patients vulnerable to ischemia injury) and surgery-dependent factors incorporating lateral position and prolonged duration.[3]

Regarding this reported case, the LMA was placed gently and smoothly, and it was confirmed to be in the appropriate position without any leakage. The operation lasted approximately 1 hour. A novel LMA with FDA approval named glottis mask airway (GMA) (Fig. 2), manufactured by Chinese Tianjin Medan Medical Crop, was used for this patient. It was a bowl-shaped glottis mask airway with a non-inflatable cuff that was specifically designed to match the anatomy of the laryngeal aperture. As many reports in the literature, the cranial nerve injury was associated with the high pressure of the over-inflatable cuff of the LMA. However, nerve injury in association with the i-gel has also been described despite its lack of a cuff. It was speculated to be attributed to some of the design features of the i-gel device.[5] Being similar to i-gel, GMA has a soft gel-like cuff, but without the necessity of inflation. Unlike other LMA, there was a distinctive tongue base rest for GMA as the device stabilizer and a C-channel for gastric tube insertion on the side of the tube. The wide stabilizer and the integral bite block design resulted in the tube a bit bulkier and harder than other types of LMA (Fig. 2). The tongue base rest of GMA was a horizontal plane to hold a tongue base and stabilize the glottis mask airway, especially in case of position shift during anesthesia, as shown in Figure 3. During the operation, the patient was in supine position, but her head was tilted to the left side as much as possible for the convenience of the surgeons. Extreme head rotation and wide rigid composition at the lower part of the tube, probably resulted in an increase in the pressure on the lingual nerve at the medial aspect of the inner surface of the mandible, which was close to the third molar and hypoglossal nerve at the site of the angle of the mandible. Moreover, the distinctive tongue base rest for

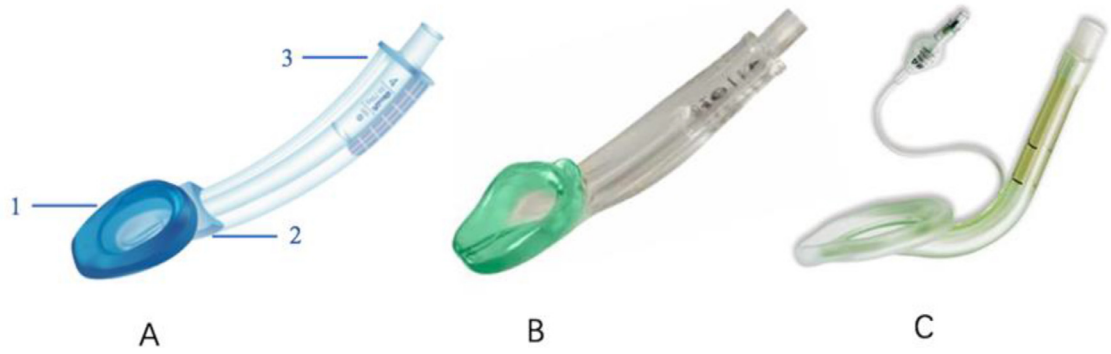

Figure 2 The view of 3 types of laryngeal mask. A, GMA; B, i-gel; C, inflatable LMA; 1, non-inflatable gel-like cuff; 2, tongue base rest; 3, C-channel for gastric tube insertion.

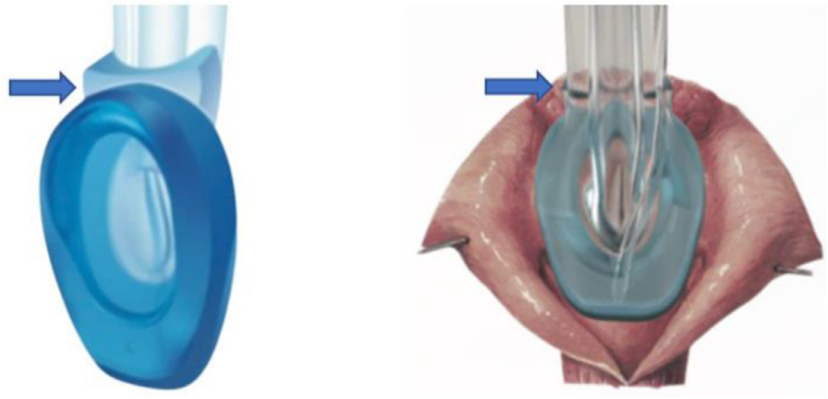

Figure 3 **A,** the tongue base rest of GMA (blue arrow); **B**, a schematic view of the contrasted position between the human larynx and GMA. Blue arrow indicates the tongue base rest.

GMA was likely to increase the risk of lingual nerve compression at the lateral edge of the tongue base, in case of extreme head rotation for this patient.

In addition, the size of the LMA should also be considered. The small size of LMA which could lead to an overinflated cuff, was likely to cause cranial nerve injury.[3] The current choice of LMA size was mainly based on body weight. In this case, the female patient with bodyweight of 65 kg used the size-4 GMA with a non-inflatable cuff. Again, her oral cavity was relatively small for the wide shaft of the GMA, thereby increase the pressure on the cranial nerve substantially, especially during head rotation.

This report suggests the differences in device design, such as the width of the shaft or the material quality of the LMA, might influence their propensity to cause nerve injury. The caution should be taken to prevent cranial nerve injuries during the use of the LMA.

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.2021.10.014.

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CASE REPORT

Anesthesia or analgesia? New block for shoulder surgery: pericapsular nerve group block



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KEYWORDS
Regional anesthesia;
Shoulder surgery;
Pericapsular Nerve Group Block (PENG);
Postoperative analgesia

Abstract Interscalene brachial plexus (ISB) block is considered the analgesic technique of choice for shoulder surgery. However, the hemidiaphragmatic paresis that may occur after the block has led to the search for an alternative to the ISB block. In this case report, the pericapsular nerve group (PENG) block was performed for both surgical anesthesia and postoperative analgesia in two patients who underwent shoulder surgery. It is suggested that the PENG block can be safely applied for analgesia and can be part of surgical anesthesia, but alone is not sufficient for anesthesia. The block of this area did not cause motor block or pulmonary complications, nor result in muscle laxity, blocking only the shoulder and the upper third of the humerus. It was demonstrated that the PENG block may be safely applied for both partial anesthesia and analgesia in selected shoulder surgery cases.
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Introduction

Early postoperative pain immediately following shoulder surgery is a major concern and cause of distress for patients and orthopedic surgeons.[1] Adequate pain control is vital for all aspects of the patient's recovery.

Multimodal pain management is recommended for early postoperative pain control. Regional anesthesia (RA) is preferred in shoulder surgery as an effective means of providing anesthesia and postoperative analgesia.[1]

Commonly used techniques for shoulder surgery include interscalene brachial plexus (ISB) blocks, continuous ISB (CISB) blocks, suprascapular nerve blocks (SSB), supraclavicular nerve blocks (SCB), local infiltration (LI), and ISB with adjuvants.[2]

In this case report, the pericapsular nerve group (PENG) block was performed for both postoperative analgesia and surgical anesthesia in two patients who underwent shoulder surgery.

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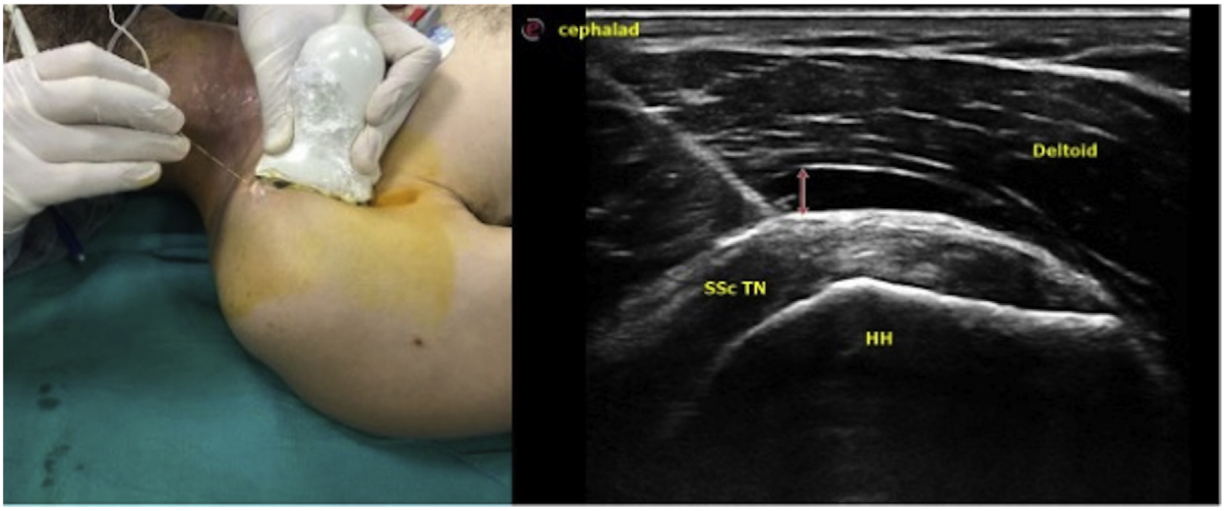

Figure 1 Position of the US probe (A) and the needle (B). HH, humerus head; SSc Tn, subscapularis tendon; Deltoid, deltoid muscle.

Case 1

A 43-year-old male patient was brought to the emergency room due to a traffic accident. He had right femoral neck fracture, right upper humerus fracture, and multiple rib fractures between the 3–10 ribs at seven levels on the left side. The patient had neither hemothorax nor pneumothorax, but lung contusion was detected. During the preoperative evaluation, conscious communication could not be established with the patient and it was learned from his relatives that he had a known diagnosis of schizophrenia. The patient was tachypneic and his breathing was irregular. We observed that peripheral oxygen saturation (SpO2) was 92% (with oxygen). Open surgical reduction was planned for the upper humerus fracture by the surgical team. A PENG block was planned in the right shoulder in order to avoid any regional anesthesia that would cause lung complications, due to left-sided rib fractures and lung contusion. The patient was administered 2 mg of midazolam, and the right shoulder was prepared sterile.

PENG block

The patient's arm was placed in external rotation and abducted at 45 degrees. A linear ultrasound probe was placed longitudinally between the coracoid and the humeral head. After defining the humeral head, the tendon of the subscapular muscle and the deltoid muscle over it, a 50-mm needle was inserted using the ''in plane'' technique. When the needle passed through the deltoid muscle and touched the subscapularis tendon, a bone-like hard tissue was felt and the needle could not be advanced further. The needle tip was placed between the deltoid muscle and subscapularis tendon, and 20 cc of 0.5% bupivacaine hydrochloride was injected (Fig. 1).

Surgery started successfully with skin incision 30 minutes after the block procedure. However, the patient felt pain during the skin incision in the distal of the upper third of the arm. At this stage, 150 mg of ketamine (2 $mg.kg^{-1}$) and 100 mcg of fentanyl were added. Although it is known that ketamine may cause schizophreniform symptoms, since we did not want to encounter respiratory problems in this case, it was administered as a single dose after considering the risk-benefit analysis. When it was observed that the block did not provide muscle relaxation, 50 mg of propofol was added at three separate times during the two-hour long surgery. Surgically, open reduction was performed with one proximal humeral plate and a few screws (Fig. 2). The case was completed without any problem. The patient was taken to the intensive care unit. Tramadol 100 mg administered 2 $\times$ 1 intravenously in intensive care was sufficient for postoperative analgesia. The 24-h visual analog scale (VAS) for pain scores did not exceed 4. The next day he was transferred to the orthopedic department.

Case 2

A 45-year-old female patient was admitted to the orthopedic clinic with left shoulder pain. Bankart arthroscopic repair was planned, and general anesthesia was given with intravenous (IV) induction, which was achieved with 100 mcg fentanyl, 200 mg propofol, and 50 mg rocuronium. Maintenance of anesthesia was provided by a mixture of 2 MAC sevoflurane + 50% oxygen + 50% air. For postoperative analgesia, 1000 mg IV paracetamol before the end of the operation and a PENG block with ultrasound was planned before the patient was roused after the operation. As described in the previous case, 15 cc of local anesthetic (0.5% bupivacaine) was injected between the deltoid and the subscapularis tendon (Fig. 3). At the end of the procedure, the patient was awakened with neostigmine + atropine, without any problem, and was taken to the postoperative care unit. The patient reported a VAS score of 0 and was taken to the ward after being kept under observation for half an hour. The first subsequent analgesic need was seen 16 hours later, and the patient received 1.000 mg IV paracetamol. The patient was discharged the next day without any complications.



Figure 2 Procedure of surgery.

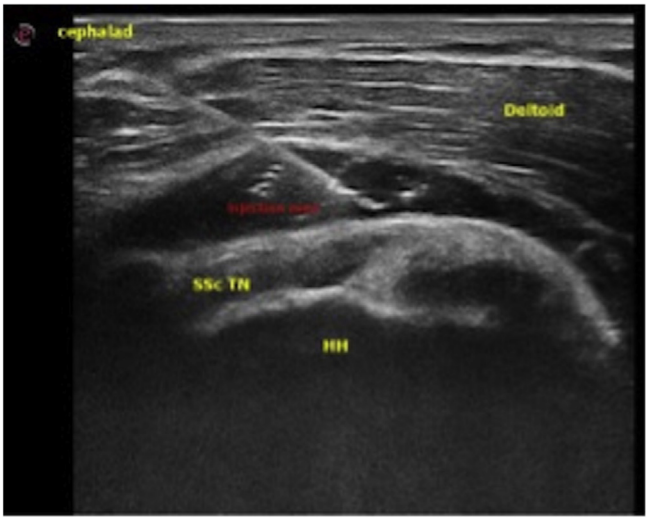

Figure 3 Local anesthetic infiltration between the deltoid and the subscapularis tendon. HH, humerus head; SSc Tn, subscapularis tendon; deltoid, deltoid muscle.

Discussion

In these cases, it was demonstrated that the PENG block can be effectively and safely applied under ultrasound guidance in selected shoulder surgery cases for postoperative analgesia. In addition, PENG block was a useful and effective part of anesthetic management but was not sufficient alone for effective anesthesia.

Shoulder surgery is one of the most common outpatient orthopedic procedures. The glenohumeral joint (GHJ) contains the glenoid of the scapula and the humeral head, which are surrounded by a capsule consisting of a fibrous sheath. To ensure adequate postoperative pain control, nerve supply to the synovium, capsule, joint surfaces, ligaments, periosteum, and shoulder muscles should all be blocked.[1,3]

There has been a great deal of research on perioperative pain management and optimal block techniques for shoulder surgery.[4] Interscalene block (ISB) is the most common. ISB targets the brachial plexus, resulting in both sensory and motor blockage in the upper limb. ISB has been studied extensively and is a good method of providing analgesia following shoulder surgery, being considered the gold standard mode of RA.[2] A potential complication of ISB is the spread of local anesthetic to the phrenic nerve.

Tran et al. showed that the posterosuperior quadrant of the GHJ was innervated by the suprascapular nerve and the posteroinferior quadrant was innervated by the posterior branch of the axillary nerve. In addition, the same group reported that the anterosuperior quadrant of this joint is innervated by the subscapularis superior branch and the anteroinferior by the main branch of the axillary nerve.[4] These anatomical data indicated that it would be possible to define new blocks that mainly target the GHJ sensory branches and thus minimize motor blockage. For example, it was suggested that deep pericapsular infiltration of local anesthetic towards the subscapularis may cover the axillary and subscapularis branches that feed the anteroinferior and superior quadrants of the GHJ. Similarly, Altınpulluk et al., in their cadaver studies using methylene blue injection hypothesized that this technique provided a pericapsular distribution and most likely reached the joint branches that innervate the GHJ.[3] Pericapsular nerve block was successfully and safely applied in our patients and contributed to both anesthesia and analgesic management.

PENG block has been studied extensively in hip surgeries,[5] but its place in shoulder surgeries is not yet clear. We achieved successful results with 20 cc 0.5% bupivacaine hydrochloride in our patient for whom we requested surgical anesthesia, and 15 cc 0.5% bupivacaine in our patient requiring postoperative analgesia. For the arm position, we applied the block in external rotation, as described by Altınpulluk et al.[3]

It is notable that while performing these PENG blocks the subscapularis tendon was very hard and was impervious to anesthetic needle penetration. In addition, in our patients this area block did not cause motor block or pulmonary complications and did not provide muscle laxity, blocking only the upper third of the shoulder and humerus. It has some limitations for surgical anesthesia appearing to be more suitable for shoulder arthroscopy. Although our cases appear to show that shoulder PENG block is effective in postoperative analgesia and as a part of anesthesia, there is need for more data including comparative studies with ISB plexus block, SCB, LI, and combined suprascapular and axillary nerve block.

Conclusion

In this case report, it was demonstrated that the PENG block can be safely applied for both anesthesia and analgesia in selected shoulder surgery cases, can be a part of surgi-

cal anesthesia, but might not be sufficient for anesthesia alone. We believe that with further prospective randomized studies, optimal technique and safety of this block will be clarified.

Informed consent

The two patients provided consent for the publication of this report.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL IMAGES

Next generation in ultrasound imaging to assess upper airway



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KEYWORDS
Anesthesia;
Airway management;
Difficult laryngoscopy;
3D/4D images;
Ultrasonography

Point of Care Ultrasound (POCUS) is well established in anesthetic practice but underused for and during airway management. In addition to 2D images, three/four Dimensional (3D/4D) ultrasound technology provides clearer and more accurate imaging for airway, and additional visual information to diagnose potential pathological conditions more efficiently.[1] Moreover, POCUS facilitates rapid screening for possible difficult laryngoscopy[2] and identification of the cricothyroid membrane.[3] We present a complete four-step upper airway assessment in 2D (Column 1) images and the correspondence with 3D/4D images (Column 2), and the position for ultrasound probe (Column 3).

Figure 1 shows four-step measurements of ultrasound parameters that assess upper airway anatomy suggesting difficult laryngoscopy. Picture 1a and 1b corresponds to Hyomental Distance (HMD) in Midline Sagittal Plane (MSP); Picture 2a and 2b is the Distance from Skin to Hyoid bone (DSH) in Transversely Plane (TP); Picture 3a and 3b shows the Distance from Skin to Epiglottis (DSE) in TP; Picture 4a and 4b displays the Distance from Skin to Vocal Cords (DSVC) in TP.

Figure 2 shows four-step tracheal structures to identify the cricothyroid membrane. Pictures 1a and 1b corresponds to Cricoid cartilage in TP; Pictures 2a and 2b, to tracheal rings in TP; Pictures 3a and 3b, to Cricoid cartilage and tracheal rings in MSP and Pictures 4a and 4b, to cricothyroid membrane in MSP.

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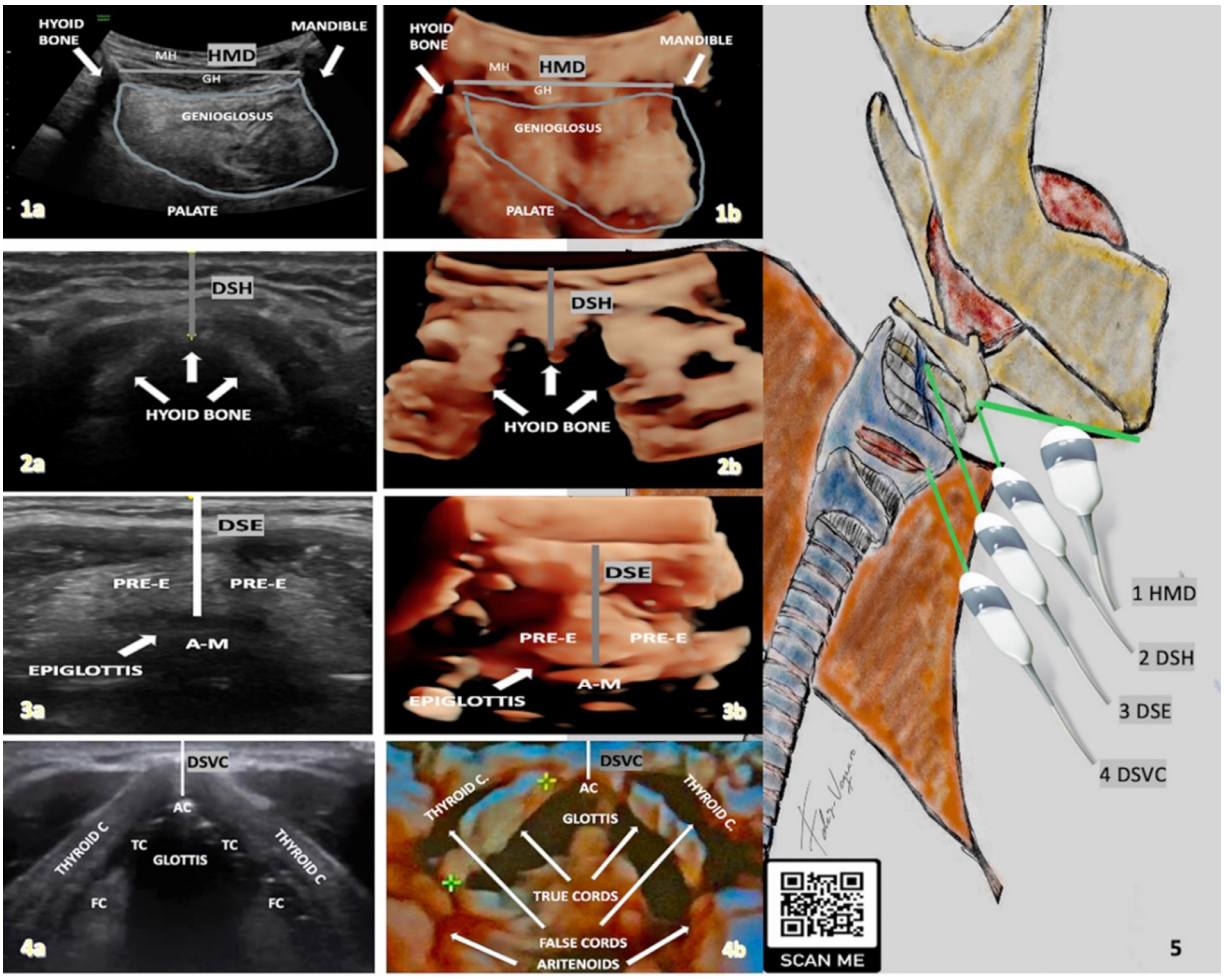

Figure 1 Four-step measurements of ultrasound parameters that assess upper airway anatomy suggesting difficult laryngoscopy. Column 1: 2D images; Column 2: 3D/4D images. Gained from a Voluson Swift ultrasound machine and a Convex Array Volume Probe (GE; Little Chalfont, UK). QR available. Picture 1a/b Midline sagittal scan of Hyomental Distance (HMD); Hyoid bone; Mandible; Genioglossus muscle; Palate; Mylohyoid Muscle (MH) and Geniohyoid Muscle (GH). Picture 2a/b transverse midline scan of Distance from Skin to hyoid bone (DSH) and Hyoid bone. Picture 3a/b transverse midline scan of Distance from Skin to Epiglottis (DSE); Pre-Epiglottic Space (PRE-E); Epiglottis and Air-Mucosa interface (A-M). Picture 4a/b transverse midline scan of Distance from Skin to Vocal Cords (DSVC); Anterior Commissure (AC); True Cords (TC); False Cords (FC); Arytenoids and Thyroid cartilage. Picture 5 the position of the ultrasound probe for pictures 1-2-3-4 respectively.

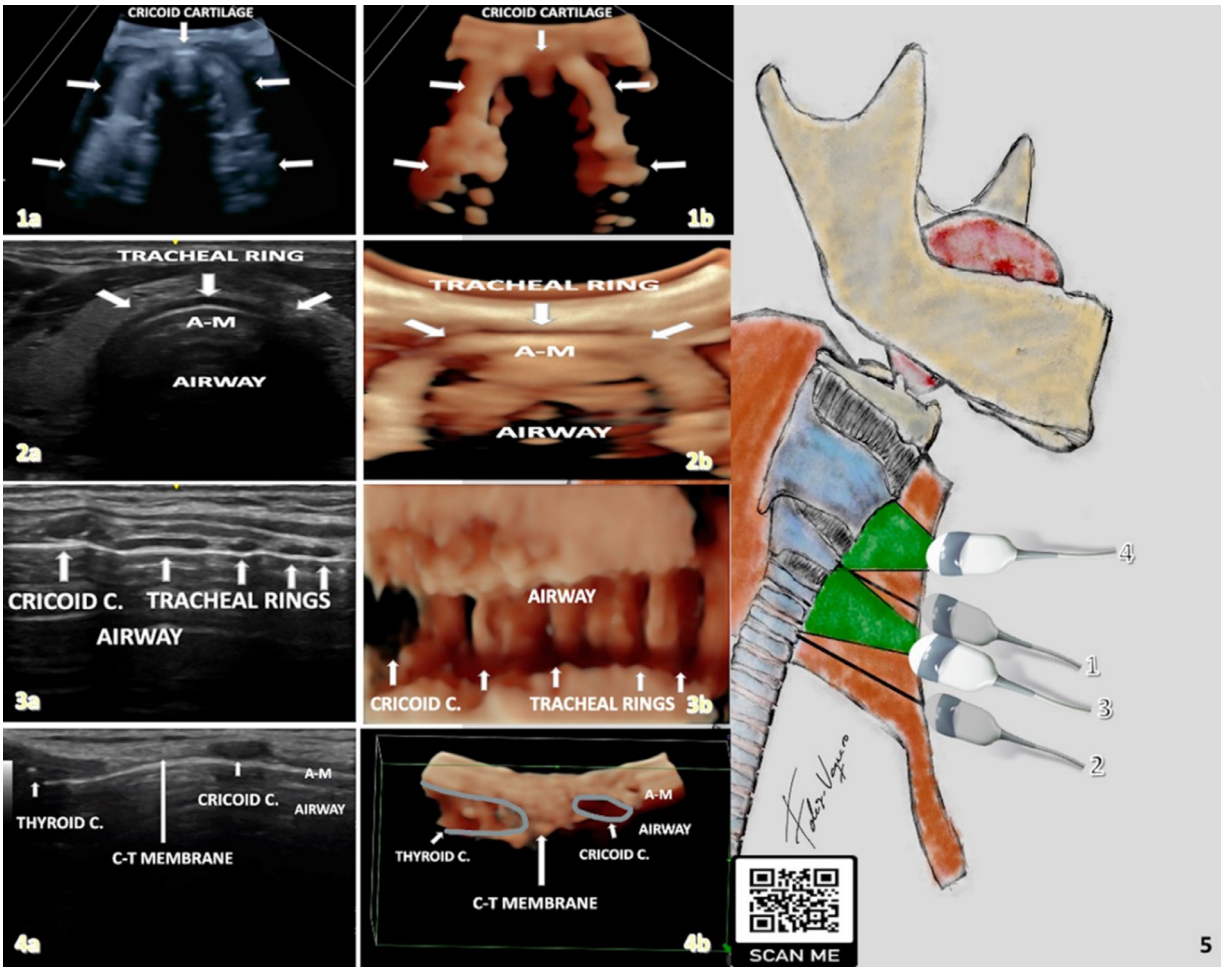

Figure 2 Four-step tracheal structures to identify the cricothyroid membrane. Column 1: 2D images; Column 2. 3D/4D images. Gained from a Voluson Swift ultrasound machine and a Convex Array Volume Probe (GE; Little Chalfont, UK). QR available. Picture 1a/b transverse midline scan of Cricoid cartilage. Picture 2a/b transverse midline scan of a tracheal ring; Airway and Air-Mucosa interface (A-M). Picture 3a/b midline sagittal scan of Cricoid cartilage; Tracheal rings and airway. Picture 4a/b midline sagittal scan of Thyroid Cartilage (Thyroid C.); Cricothyroid Membrane (C-T Membrane); Cricoid cartilage (Cricoid C.); Airway and Air-Mucosa interface (A-M). Picture 5 the position of the ultrasound probe for pictures 1-2-3-4 respectively.

Presentation

The images have been accepted for presentation at Euroanaesthesia (June 2022 Milan, Italy), the annual conference of ESAIC (European Society of Anaesthesiology and Intensive Care).

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.2022.05.008.

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

CLINICAL IMAGES

Surgical treatment of huge orbital retinoblastoma under general anesthesia in a three-year old child

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Retinoblastoma is the most common primary intraocular cancer in pediatric age.[1] We describe a 3-year-old boy refugee with orbital extension of retinoblastoma due to delayed treatment because of war in his country (Fig. 1). There was no evidence of metastasis. He received 3 cycles of chemotherapy including vincristine, etoposide, and carboplatin. Hemoglobin level was 5.4 $g.dL^{-1}$ and blood transfusion was given preoperatively. Left orbital exenteration with tumor – free margins under general anesthesia – were performed (Fig. 2) Anesthesia induction was provided using in situ Intravenous (IV) route with 2 $mg.kg^{-1}$ (50 mg) propofol, and endotracheal intubation was facilitated with IV 3 mg rocuronium with wired tube (ID = 4.0 mm). Then anesthesia was maintained with 2% sevoflurane inhalation in 50% oxygen-air mixture and remifentanil infusion (0.1 $\mu g.kg^{-1}.min^{-1}$). Operation ended uneventfully in 90 minutes. The patient was followed by pediatric oncologist, and systemic chemotherapy was completed. Retinoblastoma is a curable malignancy if detected while it is still limited to the globe.[1,2] The 5-year survival rate has been reported to be 96% in the USA.[2] However, due to late diagnosis and presentation of the tumor with advanced disease, retinoblastoma still continues to be a life-threatening problem in low-income countries.[3]

Conflicts of interest

The authors declare no conflicts of interest.

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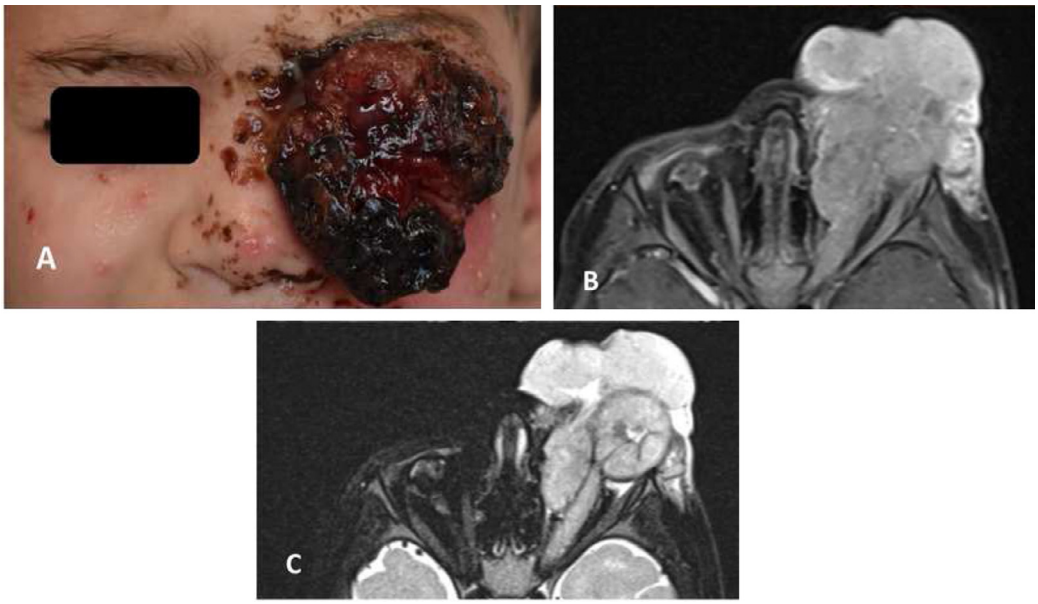

Figure 1 (A) Orbital extension of an intraocular retinoblastoma at the initial clinical presentation, manifesting with massive proptosis of the left eye. (B and C) T1 and T2 magnetic resonance imaging of the orbit.



Figure 2 (A) Image of the patient after three cycles of chemotherapy. (B and C) Peroperative images of the patient. (D) The exenteration spesimen was measured to be 20 × 16 × 11 cm.

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LETTERS TO THE EDITOR

Postoperative analgesia efficacy of erector spinae plane block in patients submitted to cardiac surgery: randomized clinical trial

Dear Editor,

In view of the importance of postoperative analgesia for patients undergoing cardiac surgery and the need to achieve a consensus regarding the indication of nerve block techniques for postoperative pain control for those patients, we performed a randomized, controlled, and blinded study comparing postoperative analgesia efficacy of using Erector Spinae muscle Plane Block (ESPB) associated with multimodal general anesthesia versus only using multimodal general anesthesia. The study was approved by our institution's Research Ethics Committee (CAAE 25758919.8.0000.5138) and included in the Brazilian Clinical Trials Registry (RBR-9djgjv). We recruited patients from both sexes, ages 18 to 75 years, scheduled for cardiac surgery via sternotomy, included after obtaining informed consent. We excluded patients with hemodynamic instability, coagulation disorders, cognitive disorders, and undergoing urgent or emergency surgery. By using a table of random numbers, participants were randomly allocated into block or control group. Upon operating room arrival, routine monitoring was installed, in addition to invasive arterial blood pressure, collection of blood samples for laboratory tests, and Foley catheter for urine output monitoring. In the block group, before anesthetic induction, ESPB was performed bilaterally, with the patient in lateral decubitus and sedated with dexmedetomidine. An ultrasound-guided technique was performed using an A50 needle, at the T4–T6 level. After injecting 20 mL of 0.5% ropivacaine bilaterally, we observed the spread of the local anesthetic solution in the erector spinae muscle plane. No block techniques were performed in the control group. General anesthesia was performed in all patients using remifentanil (0.1 to 0.5 $\mu g.kg^{-1}.min^{-1}$), dexmedetomidine (0.1 to 0.3 $\mu g.kg^{-1}.h^{-1}$), etomidate (0.1 to 0.2 $\mu g.kg^{-1}$), cisatracurium (0.15 $\mu g.kg^{-1}$), isoflurane (up to 2%), ketamine (0.1 to 0.3 $mg.kg^{-1}$), magnesium sulfate (20 to 30 $mg.kg^{-1}$), and sevoflurane. Pain scores were assessed by a blind examiner as to which group the patient was allocated, using a Visual Analogue Scale (VAS) postoperatively. Morphine was administered as rescue analgesia, as follows: 10 $mcg.kg^{-1}$ if VAS = 2 to 3; 30 $mcg.kg^{-1}$ if VAS = 4 to 6; and 50 $mcg.kg^{-1}$ if VAS = 7 to 10.

Study conducted at the Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte, MG, Brazil.

The sample size calculation was based on a pilot study that revealed mean ± standard deviation of morphine consumption in the first 24 hours equal to 5.90 ± 5.25 (mg) in the block group, and 5.50 ± 6.00 (mg) in the control group. In order to detect a difference of 5 mg between the groups, attain 90% power and a type I error of 5%, 25 patients were estimated for each group (n = 50). A $p < 0.05$ value was considered statistically significant for data analysis. Data were recorded and analyzed using SPSS 23 software.

From October 14 to December 16, 2020, a total of 74 patients were eligible to participate in the study. Nine patients from the block group and six from the control group were excluded due to loss during follow-up. Data from 54 patients were analyzed, 25 and 29 patients in the block and control group, respectively. Groups were similar regarding age, weight, and sex ($p < 0.05$). When the intensity of postoperative pain was analyzed, VAS scores were significantly lower in the block group at the 6th postoperative hour, but no difference between groups was revealed at the 12th postoperative hour and 24th postoperative hour. The block group had lower morphine consumption in the period from the end of surgery and 6th postoperative hour, while there was no difference from the 6th postoperative hour to the 12th postoperative hour, and from the 12th postoperative hour to the 24th postoperative hour (Fig. 1). Both groups showed similar total consumption of morphine, ranging from 0 to 18 mg in 24 hours, with a median of 3 mg and 5 mg in the block and control groups, respectively ($p = 0.779$ by the Mann-Whitney Test). No block-related complications were reported.

After comparing multimodal general anesthesia alone with multimodal general anesthesia associated with ESPB, we can suggest that ESPB promotes a beneficial outcome up to the 6th postoperative hour after cardiac surgery, confirmed by the lower pain score and lower morphine consumption. However, no statistically significant difference was seen at the 12th and 24th postoperative hours, indicating that such benefit is restricted to the early postoperative hours. This agrees with previous studies which also evaluated the single-shot ESPB technique.

Early analgesia in cardiac surgery was studied by other authors comparing ESPB versus paracetamol and tramadol intravenous analgesia. Pain in the group of patients receiving ESPB was lower at the 6th hour, a beneficial effect lasting up to the 12th postoperative hour.[1] However, a meta-analysis published later revealed a difference restricted to the 6th postoperative hour, given a difference in pain control in favor of ESPB was observed at the 6th postoperative hour ($p < 0.02$), and there were no differences in the subsequent assessments, up to the 24th postoperative hour.[2] Corroborating that finding and our results, a recent clinical study published,

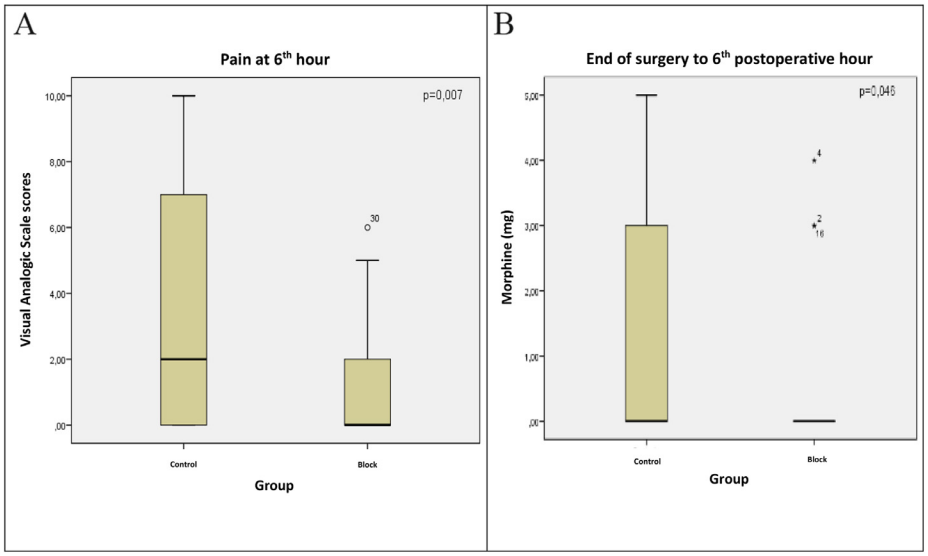

Figure 1 Comparison between control group and erector spinae muscle plane block group regarding, (A) pain score at 6th postoperative hour, and (B) morphine consumption up to the 6th postoperative hour, for patients submitted to cardiac surgery.

assessing patients undergoing cardiac surgery, revealed pain scores significantly lower in the ESPB group compared to the sham block group up to the 6th postoperative hour and no difference in the subsequent pain assessments.[3] The present study showed no difference between groups in total rescue morphine consumption in 24 hours, a finding in disagreement with other investigations that revealed a reduction in the total consumption of rescue opioids in the ESPB group.[2-4] The difference can be explained by the use of multimodal general anesthesia in both groups in the present study, resulting in low morphine consumption in both groups, so that the difference in total consumption was not detected or was irrelevant. Nevertheless, current evidence suggests that a multimodal strategy, combining drugs such as dexmedetomidine, ketamine, and magnesium sulfate, is the best indication for postoperative pain management of patients submitted to cardiac surgery. The multimodal strategy promotes a synergistic effect and pain reduction with fewer adverse effects,[5] justifying its choice. The present study has limitations, such as the probable interference of multimodal general anesthesia on morphine consumption and not having measured robust outcomes such as mortality. Notwithstanding, the study indicates that ESPB improved pain management and reduced morphine consumption up to the 6th postoperative hour in patients undergoing cardiac surgery, and this may be the rationale for using ESPB for these patients.

Conflicts of interest

The authors declare no conflicts of interest.

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Brazilian Journal of ANESTHESIOLOGY



LETTER TO THE EDITOR

In reference to "Downregulation of CSF-derived miRNAs miR-142-3p and miR-17-5p may be associated with post-dural puncture headache in pregnant women upon spinal anaesthesia"

Dear Editor,

We read the article by Dr. Yucel with interest and appreciated the study showing the association of downregulation of CSF-derived miRNAs with post-dural puncture headache after cesarean delivery.[1]

However, we would like to contribute to this essential issue and present our criticisms to the author's work in terms of both anesthesia and genetics literature.

The author stated that pregnant women who underwent elective cesarean section with spinal anesthesia and were classified as a physical condition I according to the American Society of Anesthesiologists (ASA) physical status were included in the study. In contrast, the author excluded from the study pregnant women classified as ASA II–IV. However, according to the ASA physical status classification system, pregnant women cannot be classified as ASA I. According to its 2020 guideline update, pregnancy is not considered a disease, but even pregnant women who do not have any systemic disease are classified as ASA II due to physiological changes during pregnancy.[2] Therefore, pregnant women who were excluded from the study because they were classified as ASA II are patients who should have been included in the study, according to the literature. Although there is a clear and strong association between ASA physical status and complications and all-cause mortality, this system was not originally designed or developed to predict perioperative risk.[3] The purpose of this classification system is to summarize, document, and compare the preoperative health status of surgical patients. In this way, the ASA physical condition classification system has become a component of clinical studies in both anesthesia and surgical departments. It enables to identify and document demographic characteristics of subjects, similarities or differences between study groups in clinical trials.[4]

On the other hand, the author used only the real-time PCR method for miRNA profile analysis in patients Cerebrospinal Fluid (CSF) samples. It is correct to choose the best reference gene among many reference genes in the literature using NormFinder. However, using just one reference gene or a short non-coding RNA element (SNORD61, SNORD68, SNORD72, SNORD95, SNORD96A, RNU6B-2) for normalization is not an appropriate approach as for miRNA profile analysis, a negative control, a positive control (or spike-in control element), and a short non-coding element should be evaluated together.

In addition, the author stated that target miRNA expression levels were investigated by the delta CT method. But, standard deviation values were not given next to the delta CT values in the results and supplementary sections. It is essential to provide these values as the author did not provide the number of repetitions (duplicate, triplicate, etc.) in each sample.[5]

Finally, the results would be more objective if the sensitivity and specificity of downregulation of miR-142-3p and miR-17-5p were investigated by ROC analysis.

In conclusion, complete and accurate ASA physical status is essential to obtain objective data in clinical studies. And target genes of miR-142-3p and miR-17-5p may be the focus of future studies on PDPH.

Conflicts of interest

The authors declare no conflicts of interest.

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