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Dexmedetomidine Added to Levobupivacaine (S75:R25) in the Brachial Plexus for Arthroscopic Rotator Cuff Repair. A Randomized Controlled Clinical Trial

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ABSTRACT

Background: The use of ultrasound in regional blocks is increasingly more frequent. The use of long-acting local anesthetics may cause long-lasting analgesia, depending on the volume of anesthetics and the concentration of the solution. A recent systematic review recommends the use of adjuvants in peripheral nerve blocks. This study evaluated the effects of adding dexmedetomidine to levobupivacaine in supraclavicular brachial plexus block.

Methods: A prospective, randomized, double-blind, controlled clinical study was performed on 60 patients divided into two groups, after induction and stability of general anesthesia. Groups A (water) and B (dex) received an injection of 0.2ml/kg of levobupivacaine in an enantiomeric mixture (S75:R25) at 0.5% with vasoconstrictor, with 1ml of distilled water added to group A, while in group B 1μg/kg of dexmedetomidine. The Statistical Package for Social Sciences (SPSS) version 2.0 for Windows was used for data analysis. The significant value was 5%.

Results: The demographic data was without significant differences in all variables between the two groups. The used dexmedetomidine, presented a longer shoulder motor block versus group control (water), and lower pain perception by VAS at 18 hours. Regarding adverse effects, there was no significant difference between the groups.

Conclusions: In conclusion, dexmedetomidine associated with 50% enantiomeric excess levobupivacaine with epinephrine in ultrasound-guided interscalene brachial plexus block for arthroscopic cuff repair extending the duration of nerve block and postoperative analgesia.

Keywords: Local: Levobupivacaine; Regional: Supraclavicular Brachial Plexus Block; Adjuvants; Dexmedetomidine; Surgery; Orthopedic

Introduction

The use of ultrasound (US) in regional blocks is increasingly more frequent. The use of local anesthetic peripheral nerve blocks (PNB) for surgical anesthesia and postoperative pain management has increased significantly with the advent of US-guided techniques. The use of long-acting local anesthetics can cause analgesia for an average of 22 hours [1], depending on the volume of anesthetic used and the concentration of the solution, the latter being the greatest determinant of the time of sensory and motor blockade [2]. In 2015, a systematic review of adjuvant-related randomized controlled trials and meta-analyses and provide clinical recommendations for the use of adjuvants in PNB, the clinical trials reported analgesic duration data for the following adjuvants: buprenorphine, morphine, fentanyl, epinephrine, clonidine, dexmedetomidine, dexamethasone, tramadol, and magnesium [3]. However, caution is recommended with use of any perineural adjuvant, as none have Food and Drug Administration approval, and concerns for side effects and potential toxicity persist [3].

In 2020, in a review of adjuvants to local anesthetics in PNB, it was shown that the use of adjuvants to local anesthetics is a continuously evolving field in anesthesiology where newer agents and techniques are being added to improve the efficacy and safety of analgesia [4]. It has become more important to acquire the knowledge of adverse effect profile, associated life-threatening complications, making the user aware of post application monitoring [4]. In 2020, the Brazilian Society of Anesthesiology published the regional anesthesia safety recommendations update, which addresses the use of US in regional anesthesia and safety in drug administration [5]. This study addresses the use of US for interscalene block in anesthetized patients and the use of dexmedetomidine as an adjuvant. We decided to investigate the effects of adding dexmedetomidine to levobupivacaine in supraclavicular brachial plexus block. Our primary aim was to evaluate postoperative analgesia and adverse events in patients undergoing arthroscopic rotator cuff repair surgery under general anesthesia, associated with the use of dexmedetomidine.

Methods

The study project was registered on the Brazil Platform of the State Health Department (CAAE: 61357722.6.0000.5082) and approved by the Ethics and Research Committee (Number: 5,675,381). A prospective, randomized, double-blind, controlled clinical study conducted at the Dr. Henrique Santillo Rehabilitation and Readaptation Center (CRER), after signing the Informed Consent Form (ICF). Sixty patients between 18 and 65 years old, BMI < 35 kg/m^2, of both sexes, American Society of Anesthesiologist (ASA) physical status I and II, who underwent arthroscopic rotator cuff repair surgery. Exclusion criteria were infection at the blockade puncture site, patients with severe lung disease, severe heart disease, coagulopathies, chronic use of corticosteroids, psychiatric disease, brachial plexus neuropathy, chronic use or intolerance to any study medication, and patient refusal. Sixty registration forms were printed with identification data, questions specified in the appendix and a number ranging from 1 to 60 and placed in unmarked and shuffled yellow envelopes. Thirty papers containing the description of group A, and 30 group B were printed and placed in a box. At the time of the patient's admission to the surgical center, an envelope and a paper from the box were randomly removed by the blind researcher who subsequently prepared the solution according to the group drawn and delivered it to an anesthesiologist blinded to the type of solution. This researcher was responsible for performing the procedures and filling out the form. A third blind researcher was responsible for the postoperative evaluation of the patients.

All patients were evaluated in the hospital's pre-anesthetic outpatient clinic. In the surgical center, they were monitored with cardioscopy, pulse oximetry, thermometer, non-invasive blood pressure and capnography, and venipuncture was performed in the upper limb contralateral to the surgical site with a 20 G catheter. Antibiotic prophylaxis was administered with 30mg/kg cefazolin, and symptomatic intravenous agents were used with dipyrone 30mg/kg, dexamethasone 0.1mg/kg and ondansetron 0.1mg/kg. General anesthesia was performed using a balanced technique. For intravenous induction, fentanyl 3μg/kg, propofol 2mg/kg and rocuronium 0.6mg/kg or cisatracurium 0.15mg/kg or atracurium 0.5mg/kg were used in all patients. Orotracheal intubation was performed under direct laryngoscopy and the patient was connected to a mechanical ventilator in volume-controlled mode using protective parameters. The oxygen flow was adjusted to around 1 L/min combined with compressed air 1 L/min and maintenance was performed with inhalation anesthesia using sevoflurane (1 to 3%).

Ultrasound-guided interscalene brachial plexus block was performed after induction and stability of general anesthesia with an A50 needle, and groups A (water) and B (dex) received an injection of 0.2ml/kg of levobupivacaine in an enantiomeric mixture (S75:R25) at 0.5% with vasoconstrictor, with 1ml of distilled water added to group A, while in group B 1μg/kg of dexmedetomidine. After performing the brachial plexus, patients in both groups were placed in the beach chair position and the mean arterial pressure (MAP) target was adjusted according to the inclination. As the position was in a beach chair, for every 10 cm of head elevation, we increased the target MAP measured in the arm by 7.7 mmHg. After the procedure, the neuromuscular blockade was reversed with sugamadex or neostigmine associated with intravenous atropine and the patients were extubated and transferred to the post-anesthesia care unit (PACU).

The values of heart rate and mean arterial pressure were assessed during the pre-anesthetic visit, at 20 and 40 minutes of the intraoperative period, while oxygen saturation and capnography were only assessed at 20 and 40 minutes, all with the median and interquartile range. The primary outcome consisted of assessing postopera-

tive pain after 0, 6, 12, 18 and 24 hours, using a visual analogue scale (VAS) from 0 to 10 points, with 0 meaning no pain and 10 the maximum level of pain that the patient could bear. This assessment will be performed on all patients by an anesthesiologist who is unaware of the anesthetic procedures performed. As a secondary outcome, the duration of motor blockade, adverse effects such as bradycardia, hypotension, postoperative nausea and vomiting (PONV), the need for rescue analgesia, the rate of blockade failure and complications of the technique were evaluated. Patients were instructed to note the time at which pain appeared and when hand and shoulder mobility recovered.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 2.0 for Windows was used for data analysis. Data normality was verified using the Kolmogorov-Smirnov test and parametric variables were expressed as mean ± standard deviation and nonparametric variables as median (25-75% interquartile range), and nominal variables were expressed as frequency (percentage). The student's t-test was used for parametric variables and its nonparametric equivalent, the Mann-Whitney test. To compare categorical variables, the Chi-square test was used. The significant value was 5%.

Results

The demographic data was without significant differences in all variables between the two groups (Table 1). There was a predominance of females in both groups. Regarding clinical signs, no significant differences were observed between the groups for pre-anesthetic HR and MAP, 20 and 40 minutes after anesthesia, which indicates homogeneity between the groups and no significant hemodynamic repercussions due to the use of dexmedetomidine. SpO2 and ETCO2 also remained at normal values with no significant difference between the groups (Table 2). For the anesthetic effect variables, group B, which used dexmedetomidine, presented a longer shoulder motor block (MB shoulder: GA=18 (16-21) versus GB=20 (18-24) hours, p=0.01)) and lower pain perception by VAS at 18 hours (GA=0.5 (0-3) versus GB=0 (0-0), p=0.01) and 24 hours (GA: 4 (2-4) and GB: 2 (0-3), p=0.01), suggesting that the medication may have minimized the patient's pain (Figure 1). The sensory block had a longer duration in GB (GA=18 (17-21) versus GB=23 (18-26), p<0.01), being another variable that suggests a longer lasting analgesic effect of the medication (Table 3). Regarding adverse effects, there was no significant difference between the groups. In group A, 12 patients presented at least one adverse effect, while in group B only 9 patients (p=0.42). The most prevalent adverse event in group A was the need for analgesics (27%), followed by nausea and vomiting (14%). While in group B, there was a higher prevalence of phrenic nerve block and dyspnea (7%) (Figure 2).

Table 1: The demographic data for the two groups.

VARIABLES	Group A=Water n = 30	Group B=Dex n = 30	P-Value
Age (ys)	57.6 ± 5.8	57.3 ± 5.4	0.75
Weight (kg)	71.6 ± 9.7	74.2 ± 12.1	0.45
Height (cm)	163.0 ± 1.0	160.0 ± 1.0	0.40
Gender: F / M	23 / 7	17 / 13	0.10
BMI (kg/m^2)	26.1±3.0	28.2±3.4	0.07
ASA: I / II	3 / 27	0 / 30	0.07

Table 2: Assessment of heart rate, mean arterial pressure, oxygen saturation and capnography.

VARIABLES	Group A=Water n = 30	Group B=Dex n = 30	P-Value
Heart rate (BPM)			
Pre-anesthesia	73 (67-82)	70 (65-80)	0.53
20 minutes	68 (63-73)	65 (60-75)	0.31
40 minutes	63 (56-70)	64 (59-68)	0.77
Mean arterial pressure (mmHg)			
Pre-anesthesia	77 (70-95)	82 (72-91)	0.61
20 minutes	70 (65-88)	76 (65-88)	0.85
40 minutes	72 (63-77)	71 (60-85)	0.90
Oxygen saturation (%)	100 (99-100)	100 (99-100)	0.34
Capnography (mmHg)	37 (34-38)	37 (33-39)	0.98

Note: Data presented as median (interquartile range (25-75%).

Table 3: Variables of the effect of adding dexmedetomidine to the local anesthetic.

VARIABLES	Group A=Water n = 30	Group B=Dex n = 30	P-Value
Motor block hand (hours)	12 (11-14)	12 (10-18)	0.76
Motor block shoulder (hours)	18 (16-21)	20 (18-24)	0.01*
Visual analogue scale (VAS)			
Immediate PO	0 (0-0)	0 (0-0)	0.99
PO 6 hours	0 (0-0)	0 (0-0)	0.99
PO 12 hours	0 (0-0)	0 (0-0)	0.32
PO 18 hours	0.5 (0-3)	0 (0-0)	0.01*
PO 24 hours	4 (2-4)	2 (0-3)	0.01*
Sensory block duration (hours)	18 (17-21)	23 (18-26)	< 0,01*

Note: Caption: PO: postoperative.

Data presented as median (interquartile range (25-75%)).

*p < 0.05 Mann-Whitney test

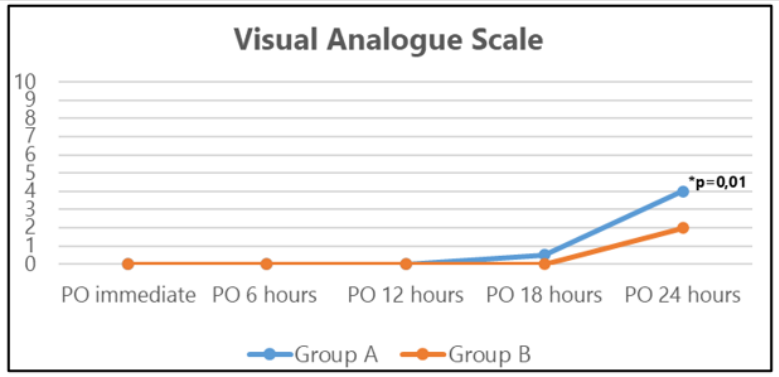

Figure 1: VAS scores over time between groups.

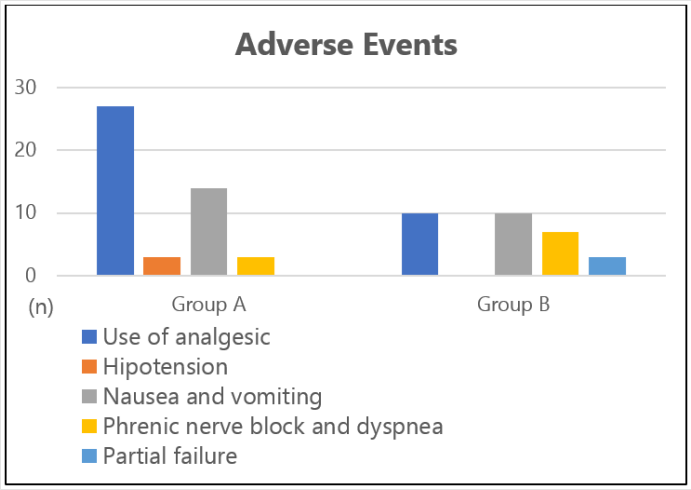

Figure 2: Adverse Events.

Discussion

This study demonstrated that the addition of dexmedetomidine to levobupivacaine in enantiomeric excess (S75:R25) as a vasoconstrictor in US-guided interscalene brachial plexus block for arthroscopic rotator cuff repair resulted in increased duration of sensory and motor blocks, contributing to decreased postoperative analgesic consumption. Patients who received dexmedetomidine had prolonged postoperative analgesia of approximately five hours, with a higher prevalence of phrenic nerve block and dyspnea (7%) than in the control group. The study of the chirality of substances is an important field in the pharmaceutical industry and agrochemicals. In Brazil, an enantiomeric excess local anesthetic containing 75% of the S-enantiomer and 25% of the R-enantiomer was investigated, and later approved for use in regional anesthesia [6]. This new solution was patented by the National Institute of Industrial Property, the regulatory body of the Brazilian Government (INPI) and registered with ANVISA (National Agency of Sanitary Surveillance), and marketed under the name Novabupi, in its S75:R25 formulation, for use in regional anesthesia, being used in several techniques such as epidural, brachial or lumbar plexus block, postoperative analgesia by bilateral pudendal nerve block, there is no report of toxicity with cardiac arrest [6].

For this safety, this solution containing epinephrine was used in this study in patients previously subjected to general anesthesia, to evaluate the addition of dexmedetomidine. Dexmedetomidine, an α-2 adrenoceptor agonist, has been associated with prolonged analgesia after the administration of local anesthesia in a variety of routes and mechanisms, including neuraxial, perineural, intraarticular, and possibly even IV [3,4]. Another α-2 adrenoceptor agonist and local anesthetic adjunct, clonidine, has been reported to prolong the duration of analgesia when administered IV in conjunction with local anesthetic–based PNB [7], the authors concluded that IV but not perineural clonidine (1μg/kg) prolongs analgesia after PCB without increasing the incidence of adverse effects [7]. Therefore, the issue of adding α-2 adrenoceptor agonist to local anesthetics in NPB remains controversial.

In a randomized, triple-masked, placebo-controlled trial to date, the study aimed to define and compare the efficacy of perineural and IV using 15 ml ropivacaine, 0.5%, with 0.5 μg/kg dexmedetomidine in prolonging the analgesic duration of single-injection interscalene brachial plexus block for outpatient shoulder surgery, showed that both routes reduced the pain and opioid consumption up to 8 h postoperatively and did not prolong the duration of motor blockade [8]. Different from our study with 0.5% levobupivacaine in enantiomeric mixture (S7:R25) with epinephrine and at a dose of 0.2ml/kg added to dexmethedomidine (0.1μg/kg) it reduced pain and opioid consumption but increased the duration of both sensory and motor blockades. Epinephrine has been used for over a century as an additive to local anesthetics. Epinephrine, a vasoconstrictor, reduces absorption into the bloodstream when used as an adjuvant to local anesthetics. With a typical dose range of 5–10μg/mL, epinephrine is believed to prolong duration by its vasoconstrictive properties that prevent systemic reabsorption of local anesthetics [9]. In groups of 10 patients comparing dexmedetomidine (1μg/kg), epinephrine (200μg) with a control group associated with 1% mepivacaine 40 ml, it was shown that both dexmedetomidine and epinephrine the sensory block duration, motor block duration and time to sense first pain were prolonged significantly compared to the control group [10]. In this study, the combination of epinephrine and dexmedetomidine in group B showed that there was a significant increase in the duration of sensory and motor blocks, compared to group A with only epinephrine.

Regarding adverse effects, there was no significant difference between the groups, with hypotension, bradycardia, nausea and vomiting not being observed more frequently in the group that received dexmedetomidine. No intraoperative complications were observed, but in the postoperative period there was a higher prevalence of phrenic nerve block and dyspnea in the group that received dexmedetomidine. In a study with 30 ml of enantiomeric excess levobupivacaine (S75:R25) with epinephrine associated with 6 mg of dexamethasone compared with the control group in interscalene block with US and neurostimulator, it was shown that it significantly prolonged the sensory block of levobupivacaine in the interscalene brachial plexus block, reduced the intensity of pain and the need for rescue analgesia by the patient in the postoperative period [11]. The mean duration of the sensory block was 24 hours, like other studies [1-6].

Conclusion

Dexmedetomidine can cause systemic effects such as sedation and relief of anxiety as well as complications such as hypotension and bradycardia as the dosage is increased [12]. In conclusion, dexmedetomidine associated with 50% enantiomeric excess levobupivacaine with epinephrine in ultrasound-guided interscalene brachial plexus block for arthroscopic cuff repair extending the duration of nerve block and postoperative analgesia. Because epinephrine and dexmedetomidine have opposite effects on heart rate, dexmedetomidine may be considered a good alternative as an adjunct to local anesthesia in patients in whom epinephrine should be used with caution.

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