Research Article

Comparison of Dexmedetomidine and Dexamethasone as Adjuvants to Ultra-Sound Guided Interscalene Block in Arthroscopic Shoulder Surgery: A Double-Blinded Randomized Placebo-Controlled Study

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Abstract

Background: Interscalene block is one of the popular methods for decreasing pain and analgesic consumption after shoulder arthroscopic surgeries.

Objectives: The objective is to compare the analgesic duration of effects of dexmedetomidine and dexamethasone as adjuvants to 0.5% ropivacaine in ultrasound-guided interscalene blocks for arthroscopic shoulder surgery in an ambulatory setting.

Methods: In this randomized controlled trial, 117 adult patients candidate for ambulatory arthroscopic shoulder surgery under general anesthesia were divided into three groups to perform an ultra-sound guided interscalene block before the surgery. The ropivacaine (control) group received ropivacaine 0.5% 20 mL, group Dexamethasone received ropivacaine 0.5% 20 mL plus 4mg dexamethasone, and group dexmedetomidine received ropivacaine 0.5% 20 mL plus 75 mcg of dexmedetomidine. Time to return of sensory function, of motor function, of first pain sensation, amount of opioid medication consumed at 24 hours and 48 hours post-operatively were measured.

Results: The 24-hour median (25th- 75th percentile) opioid consumption in morphine equivalents was similar between groups 22.5 mg (10 - 30), 15 mg (0 - 30), and 15 mg (0 - 20.6) in the ropivacaine, dexmedetomidine, and dexamethasone groups, respectively (P = 0.130). The median (25th- 75th percentile) 48 hours post-operatively, the median opioid consumption in morphine equivalents was 40 mg (25 - 67.5) in the ropivacaine group, 30 mg (22 - 50.6) in the dexamethasone group, and 52.5 mg (30 - 75) in the dexmedetomidine group (P = 0.278). The median 24-hour pain scores were 6 (5 - 8) in the ropivacaine control group, 7 (5.5 - 8) in the dexamethasone group, and 7 (4 - 9) in the dexmedetomidine group (P = 0.573).

Conclusions: There was no statistical difference in opioid consumption at 24 and 48 hours post-operatively when comparing dexmedetomidine, dexamethasone, and no adjuvant. However, intraoperative opioid use was significantly lower with dexmedetomidine compared to dexamethasone and plain 0.5% ropivacaine. The safe side effect profile of dexmedetomidine makes it a reasonable alternative as an adjuvant for peripheral nerve blockade when dexamethasone use may be contraindicated.

Keywords: Dexmedetomidine, Dexamethasone, Interscalene Brachial Plexus Block, Pain Management, Ambulatory Shoulder Surgeries, Arthroscopic Orthopedic Procedures

1. Background

With the rapidly growing number of surgeries being performed in an ambulatory setting, regional blockade is increasingly used as a modality for controlling pain while reducing common side effects of opioid-centered analgesia (1-4). The addition of adjuvants to local anesthetics for nerve block prolongation is a common practice in regional anesthesia (5-7). Many efforts have studied adjuvants that increase the duration of analgesia while simultaneously maintaining a safe side effect profile (8-10). The most commonly employed agents are perineural dexamethasone and dexmedetomidine (11-13). Our study evalu-

ates whether perineural adjuvants can increase the duration of analgesia that is both clinically safe and effective.

2. Objectives

The objective is to compare the analgesic duration of effects of dexmedetomidine and dexamethasone as adjuvants to 0.5% ropivacaine in ultrasound-guided interscalene blocks for arthroscopic shoulder surgery in an ambulatory setting.

3. Methods

The Institutional Review Board (IRB) approved this study. Patients undergoing ambulatory arthroscopic shoulder surgery at our outpatient surgery center provided written consent to be included in this double-blinded randomized placebo-controlled study. Inclusion criteria included ASA physical score I-III patients between the ages of 18 - 60 years old scheduled for outpatient arthroscopic shoulder surgery. Patients excluded from the study include patients with pre-existing pain disorder on chronic opioid medications, patients with an anatomical abnormality of the upper extremity, patients with known allergy or hypersensitivity to ropivacaine or other amide local anesthetics, patients with coagulopathy disorders, uncontrolled diabetes mellitus, and those with known allergy to dexamethasone or dexmedetomidine. Recruitment of patients occurred between March 2016 and August 2018.

They we received a printed post-surgical questionnaire. They were asked to note several events over the 24 - 48 hours after surgery, including time to first use of pain medication, time to sensory and motor recovery, and total pain medication use. All potential participants additionally filled out a short form of the Pain of Fear Questionnaire pre-operatively. The purpose of this questionnaire was to standardize participants based on their anticipated response to various types of painful stimuli. In other words, it was intended to identify patients that have a significantly low or high pain threshold.

Preoperative and intraoperative procedures followed the routine standard of care practiced in our hospital. All patients received an interscalene brachial plexus block pre-operatively under ultrasound guidance (Sonosite M-Turbo) and sterile conditions. After skin preparation with chlorhexidine, a 21G, 90 mm, echogenic stimulating needle (Arrow StimuQuik insulated peripheral nerve block needle, Arrow International, USA) was advanced under direct ultrasound visualization by a high-frequency linear array probe (5 - 10 MHz) and in-plane method towards the nerve roots of the brachial plexus. Following negative aspiration for blood, the selected local anesthetic with or without adjuvant was slowly injected to surround the brachial plexus. Patients were, as always, continuously asked about the presence of pain or paresthesia during injection to ensure safe needle placement.

A randomization sequence generated by an online program was used to randomize patients into one of the three groups. On the day of surgery, patients were randomly assigned to receive either ropivacaine (Naropin®, APP Pharmaceuticals, USA) 0.5% 20 mL (control) or ropivacaine 0.5% 20 mL plus 4mg dexamethasone (dexamethasone sodium phosphate 4 mg/mL, APP pharmaceuticals, USA) (dexamethasone group), or ropivacaine 0.5% 20 mL plus 75 mcg of dexmedetomidine (Dexmedetomidine HCL Injection, 200 mcg/2mL, Intas Pharmaceuticals, India) (dexmedetomidine group). Randomization was done using pre-sealed envelopes, opened just prior to performing the peripheral nerve block by a nurse or physician not directly involved in patient care. Randomization group assignment envelopes were opened by the same individual who prepared the study medication and the anesthesiologist performed the block. The contents of the solution were blinded to both the patient and anesthesiologist at all times.

General anesthesia was the primary anesthetic for all surgeries. After arrival in the operating room, patients were pre-oxygenation in supine position and underwent induction of anesthesia (intravenous propofol, fentanyl, and midazolam) followed by endotracheal intubation. Patients were maintained under general anesthesia intraoperatively with sevoflurane.

They were positioned in a semi-upright position on a beach chair after airway securement. Additional fentanyl were given during maintenance of anesthesia. All patients were extubated post-operatively in the operating room and recovered uneventfully in the recovery room prior to discharge.

Intra - operatively, analgesia relied mainly on peripheral nerve blockade - often with minimal or no additional opioid administration at the discretion of the anesthesiologist.

Participants underwent motor and sensory assessment postoperatively in the post-anesthesia care unit (PACU) to confirm the effectiveness of the interscalene nerve block. Patients with a failed block, defined for our purposes as intact motor strength, were excluded from further study and follow-up.

Intraoperative data on the total amount of opioids were collected from chart review and converted to morphine equivalents (ME). Other parameters recorded included times to PACU discharge, patient-reported pain scores at 24 hours post-operatively (using numerical rating scale, 0 - 10), time to first opioid consumption, total opioid

consumption at 24 hours (ME), total opioid consumption at 48 hours (ME), and time to return of motor and sensory function. This information was obtained and verified during the post-surgical follow-up interview via phone call.

3.1. Statistical Analysis

The primary objective of this study was to determine the duration of perineural blockade by looking at 24 hours and 48-hour postoperative opioid consumption of the three groups. Our clinical audit reported the usual requirement of 50 ± 20mg of opioids in the first 24 hours. The study was powered to demonstrate a 20% difference between the dexamethasone group and the dexmedetomidine group as well as a 30% difference between the placebo group and the dexmedetomidine group. Based on a two-sided alpha of 0.05 and a type II error of 20% to achieve a clinically significant 30% difference, 90 subjects were deemed necessary for the study. The secondary outcome was to determine the time to return of sensory function as a marker of block duration. For all the secondary outcomes, time in minutes was calculated from the end of nerve block time to the outcomes mentioned above. All the continuous variables including the opioid consumption between the groups at 24 and 48 hours, were analyzed using the Kruskal–Wallis H test, and for categorical variables, chi-square analysis was performed. For all the analysis a P-value < 0.05 was considered statistically significant.

4. Results

4.1. Baseline Data

A total of 117 patients were enrolled from March 2016 to August 2018. The detailed patient flow chart is depicted in Table 1. A total of 15 patients were withheld from analysis due to protocol deviation, and another 13 patients were excluded due to missing data points. The final analysis included 89 patients. The baseline demographics are depicted in Table 1. In the current analysis, 60% of the participants were male; the mean age was 50 ± 12 years, and 87 % of participants had an ASA physical score of II or blow. There were no significant differences between the study groups at baseline. Indication for the surgery was also similar between all three groups.

4.2. Opioid Consumption

The median (25th - 75th percentile) intraoperative opioid administration was lower in the dexmedetomidine group at 5 (0 - 10) mg versus 10 (4 - 10) mg in the dexamethasone group and 10 (2.5 - 10) mg in the ropivacaine without an adjuvant group (P = 0.056). There was no statistically significant difference in 24-hour opioid usage between the groups. However, the median (25th - 75th percentile) 24-hour opioid consumption was higher in the ropivacaine

group at 22.5 (10 - 30) mg compared to 15 (0 - 30) mg in the dexmedetomidine group and 15 mg (0 - 20.6) in the dexamethasone group, P = 0.130.

Similarly, there was no statistically significant difference between the median (25th - 75th percentile) opioid usages at 48 hours postoperatively. The median (25th - 75th percentile) opioid usage was highest in the dexmedetomidine group 52.5 (30 - 75) mg compared to 30 (22 - 50.6) mg in the dexamethasone group and 40 (25 - 67.5) mg in the ropivacaine group P-value 0.278.

4.3. NRS Pain Scores at 24 Hours

The median (25th - 75th percentile) 24-hour pain scores were not statistically significant between the three groups. The median (25th - 75th percentile) 24-hour pain score was 7 (5.5 - 8) in the dexamethasone group, 7 (4 - 9) in the dexmedetomidine group, and 6 (5 - 8) in the ropivacaine group P-value 0.573.

4.4. Time to PACU discharge

The median (25th - 75th percentile) post-operative care unit discharge time was also not different between the groups. The median (25th - 75th percentile) PACU discharge time was 108 (77 - 153), 139 (122 - 157), and 114 (91 - 162) minutes for dexamethasone dexmedetomidine and ropivacaine alone respectively.

4.5. Return of Sensory Function

The median (25th - 75th percentile) pain onset time was 1130 (854 - 1325) minutes for patients who received dexamethasone additive in the peripheral nerve block, 1280 (977 - 1434) minutes for patients who received dexmedetomidine and 900 (609 - 1348) minutes in patients who received ropivacaine alone, P-value 0.05.

5. Discussion

The increasing emphasis on the benefits of regional analgesia techniques has made peripheral nerve blocks ubiquitous in outpatient and joint centers. There is a greater focus now on anesthesiologists to make the nerve blocks more effective, with a quicker onset and longer duration of action. This has led to much greater use of popular adjuvants include alpha-2 agonists such as dexmedetomidine and clonidine, as well as glucocorticoids such as dexamethasone [14, 15]. The use of other medications including tramadol, nalbuphine, magnesium, and ketamine has also been described [16-20].

No singular mechanism of action determines the efficacy or utility of adjuvants in enhancing local anesthetics. However, evidence exists to support that many have inherent analgesic properties. Various trials and meta-analyses have attempted to characterize the effects of the

Table 1. Baseline Demographics [a]

Variables	Dexamethasone (n = 28)	Dexmedetomidine (n = 30)	Ropivacaine (n = 31)	P Value
BMI	29 (26.2 - 31.2)	31 (27 - 33)	29 (25 - 32)	0.108
Age (y)	52 (45 - 57)	54 (49 - 59)	52 (39 - 57)	0.344
Sex (M), No. (%)	19 (55.9)	12 (41)	19 (61.3)	0.250
ASA physical status	2 (2 - 2)	2 (2 - 2)	2 (1 - 2)	0.271
Operative time (min)	169 (130 - 190)	170 (146 - 186)	173 (150 - 190)	0.746
Intraoperative opioids (mg)	10 (4 - 10)	5 (0 - 10)	10 (2.5 - 10)	0.056

[a] Values are expressed as median (25th - 75th percentile) unless otherwise indicated.

various adjuvants but remain inconclusive (16, 21). There is a paucity of data to support the superiority of one adjuvant over another, and little evidence-based guidelines exist to help direct usage. Additionally, there is a lack of long-term studies to determine the side effects of these additives, if any, as well as their potential for neurotoxicity.

Dexamethasone is one of the better studied and more widely used local anesthetic adjuvants (22-24). It is anti-inflammatory, analgesic, immunosuppressive and antiemetic effects are the result of inhibition of phospholipase A2. Parrington found that dexamethasone as an adjuvant to mepivacaine prolonged peripheral nerve blockade from 228 minutes to 332 minutes relative to placebo (24). As another example, Cummings found that the addition of 8 mg of dexamethasone to local anesthetic for interscalene block almost doubled the time before the first need for pain medication (23). Although animal studies have suggested that potential for neurotoxicity does exist, human studies have not found similar outcomes at this time (23, 24). With the exception of hyperglycemia, dexamethasone as an adjuvant to peripheral nerve block is well tolerated by the majority of patients.

Alpha-2 agonists are thought to prolong nerve blockade effectively by hyperpolarization of cyclic-nucleotide-gated cation channels (25). Dexmedetomidine, an alpha-2 agonist with seven times greater affinity for the alpha-2 receptor than clonidine, has shown promise as an adjunctive medication for regional anesthesia (22, 25). Brummet showed enhanced sensory and motor blockade when dexmedetomidine was used as an adjuvant in rats (26). Marhofer demonstrated a prolonged duration of peripheral nerve blocks by up to 60% with the addition of dexmedetomidine to 0.75% ropivacaine when compared to ropivacaine alone (13). Similarly, other studies showed prolongation of axillary brachial plexus block by up to 25% with the use of 100 ug dexmedetomidine added to 0.5% ropivacaine (25).

For interscalene nerve block and shoulder surgery, there is little information in the literature on which adjuvant is more effective at block prolongation. The studies on dexmedetomidine and dexamethasone tend to vary immensely in terms of design and methodology, are often underpowered, or carried out with non-standard dosing (25). This study was designed to provide a direct and unbiased look at which of the two adjuvants – dexmedetomidine or dexamethasone – provide improved characteristics for interscalene block in ambulatory shoulder surgery in comparison to the ropivacaine control group. Our study outcomes were a prolongation of analgesia postoperatively, time to first pain medication, total opioid consumption (in morphine equivalents).

We found that there was no difference in the total amount of opioid consumption for the first 24 hours between the groups; however, the median opioid consumption in the control group was highest at 22.5 mg morphine equivalents compared to 15 mg morphine equivalents in both the dexamethasone and dexmedetomidine groups. At 48 hours postoperatively, there was no difference in opioid consumption between the adjuvant groups. Furthermore, we found no statistical significance between the adjuvant groups in terms of overall pain scores. Regarding pain onset (Table 2), a surrogate for block duration, although there was no statistically significant difference between the dexamethasone and dexmedetomidine group, both did show overall nerve block duration up to 40% more than the control. This is in keeping with the findings of similar studies. Further, we think that the block duration with ropivacaine alone could have been influenced by the perioperative use of intravenous dexamethasone to combat postoperative nausea and vomiting. Finally, intraoperative opioid consumption was less in the dexmedetomidine group when compared to both the control and dexamethasone groups.

The search for an appropriate adjuvant that results in a denser, prolonged, and higher quality nerve blockade would result in decreased pain scores, decreased pain medication requirement, and thus decreased opioid consumption, in turn reducing side effects of narcotic medication such as sedation, constipation and respiratory depression. However, this study showed that although the peripheral nerve blockade was prolonged, it did not result in a significant difference in opioid consumption when compared to control.

The use of adjuvants for local anesthetics is still off-

Table 2. Study Outcomes at 24 And 48 Hours [a]

Variables	Dexamethasone (n = 28)	Dexmedetomidine (n = 30)	Ropivacaine (n = 31)	P Value
PACU time (min)	108 (77 - 153)	139 (122 - 157)	114 (91 - 162)	0.81
Pain onset (min)	1130 (854 - 1325)	1280 (977 - 1434)	900 (609 - 1348)	0.05
Opioid use 24 h (mg)	15 (0 - 20.6)	15 (0 - 30)	22.5 (10 - 30)	0.130
NRS pain score 24 h	7 (5.5 - 8)	7 (4 - 9)	6 (5 - 8)	0.573
Opioid use 48 h (mg)	30 (22 - 50.6)	52.5 (30 - 75)	40 (25 - 67.5)	0.278

[a] Values are expressed as median (25th - 75th percentile) unless otherwise indicated.

label and no single drug has been approved by the FDA for this purpose. Higher doses of dexamethasone have demonstrated neurotoxicity only in in vitro animal models, and recent in vivo animal safety models have shown no adverse outcomes (27, 28). Additionally, recent RCT analysis has indicated that perineural dexamethasone can prolong analgesia by up to three hours when compared to the use of IV dexamethasone for the same purpose (29). There is also some degree of neuroprotection and antihyperalgesia observed with clinically relevant dosing of dexamethasone in animal models (22).

In regard to dexmedetomidine as an adjuvant to local anesthetics in peripheral nerve block, no studies have shown neurotoxic effects. Nevertheless, at high doses, a systemic effect on the cardiovascular system remains a potential concern for patients with pre-existing cardiac disease (30).

Our study is with several limitations - one of which is the use of a modified intention - to treat analysis method. As we mentioned in our result section, a total of 28 patients were not included in the final analysis. Omission of these patients from the final analysis could potentially introduce bias and lead to misleading results. However, protocol deviations and missing data points were evenly distributed among all three groups, and missing data points were at random patterns. In addition, due to the ambulatory nature of this study, the majority of data was obtained postoperatively by telephone. Even though patients were informed about the importance of keeping a time log for the return of motor function and pain onset, some patients did not comply with the study requirements, which may have an impact on the validity of the results.

5.1. Conclusion

Our data support the use of adjuvant medications for prolongation of interscalene nerve block duration for ambulatory shoulder surgery. Although significant block duration was observed in both adjuvant groups, no statistically significant difference in opioid consumption at 24 or 48 hours post-operatively were found.

Both adjuvant medications were shown to have similar nerve block prolongation. However, dexmedetomidine was associated with a significant decrease in intra-operative opioid consumption. Both medications, therefore, give the provider two safe and effective choices when selecting adjuvants for peripheral nerve blockade. Dexmedetomidine may be a reasonable alternative adjuvant for peripheral nerve blockade when dexamethasone use may be contraindicated.

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