IV and Perineural Dexmedetomidine Similarly Prolong the Duration of Analgesia after Interscalene Brachial Plexus Block

A Randomized, Three-arm, Triple-masked, Placebo-controlled Trial

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ABSTRACT

Background: Perineural and IV dexmedetomidine have each been suggested to prolong the duration of analgesia when administered in conjunction with peripheral nerve blocks. In the first randomized, triple-masked, placebo-controlled trial to date, the authors aimed to define and compare the efficacy of perineural and IV dexmedetomidine in prolonging the analgesic duration of single-injection interscalene brachial plexus block (ISB) for outpatient shoulder surgery.

Methods: Ninety-nine patients were randomized to receive ISB using 15 ml ropivacaine, 0.5%, with 0.5 μg/kg dexmedetomidine administered perineurally (Dex_P group), intravenously (Dex_{IV} group), or none (control group). The authors sequentially tested the joint hypothesis that dexmedetomidine prolongs the duration of analgesia and reduces the 24-h cumulative postoperative morphine consumption. Motor blockade, pain severity, hemodynamic variations, opioid-related side effects, postoperative neurologic symptoms, and patient satisfaction were also evaluated.

Results: Ninety-nine patients were analyzed. The duration of analgesia was 10.9 h (10.0 to 11.8 h) and 9.8 h (9.0 to 10.6 h) for the Dex_P and Dex_{IV} groups, respectively, compared with 6.7 h (5.6 to 7.8) for the control group ($P < 0.001$). Dexmedetomidine also reduced the 24-h cumulative morphine consumption to 63.9 mg (58.8 to 69.0 mg) and 66.2 mg (60.6 to 71.8 mg) for the Dex_P and Dex_{IV} groups, respectively, compared with 81.9 mg (75.0 to 88.9 mg) for the control group ($P < 0.001$). Dex_{IV} was noninferior to Dex_P for these outcomes. Both dexmedetomidine routes reduced the pain and opioid consumption up to 8 h postoperatively and did not prolong the duration of motor blockade.

Conclusion: Both perineural and IV dexmedetomidine can effectively prolong the ISB analgesic duration and reduce the opioid consumption without prolonging motor blockade. (**ANESTHESIOLOGY** 2016; 124:683-95)

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,[1–4] perineural,[5] intraarticular,[6] and possibly even IV.[7] Among these, the perineural route for dexmedetomidine has been the subject of increasing interest as the potential to significantly prolong the duration of analgesia after single-injection peripheral nerve blocks (PNBs) can have important wide-ranging benefits for patients and providers alike, especially within the setting of ambulatory surgery. Unfortunately, much of the existing literature relating to perineural dexmedetomidine is limited by small sample sizes, dosing inconsistencies, and unreliable block assessment protocols.[8–28] Moreover, of

What We Already Know about This Topic

- Dexmedetomidine has been suggested to prolong the duration of regional anesthesia when administered by either the IV or the perineural routes, but these have not been formally compared

What This Article Tells Us That Is New

- In 99 patients receiving interscalene block with 15 ml ropivacaine, 0.5%, with 0.5 μg/kg dexmedetomidine prolonged the blockade and reduced the 24-h opioid use compared with placebo control, and these effects were similar whether dexmedetomidine was administered intravenously or perineurally

the 21 studies published to date, 20 were conducted outside the auspices of a national investigational drug approval

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This article is featured in "This Month in Anesthesiology," page 1A. This article has a video abstract.

process[8–18,20–28] and 18 were performed in developing countries[8–18,20–22,24–26,28] and published either in nonanesthesia literature[10–12,14,17,20,22,23,28] or in very low–impact anesthesia journals.[8,13,15,18,21,24–27] Although the overall trend is encouraging, these studies have notably produced inconsistent results regarding the duration of postoperative analgesia afforded by the addition of perineural dexmedetomidine for PNB.[8–28]

Importantly, another α-2 adrenoceptor agonist and local anesthetic adjunct, clonidine, has been reported to prolong the duration of analgesia when administered intravenously in conjunction with local anesthetic–based PNB.[29] In view of the unwanted hemodynamic effects of IV clonidine,[30] investigators have recently examined the potential for IV dexmedetomidine to prolong the duration of postoperative analgesia after PNBs; however, to date, the results are inconsistent.[31,32] In addition, although the preliminary safety data for the perineural route of administration of dexmedetomidine may be encouraging,[33,34] only the IV route for dexmedetomidine is approved by the U.S. Food and Drug Administration (FDA)[35] and Health Canada.[36]

This randomized controlled trial aims to define and compare the efficacy of dexmedetomidine when administered perineurally or intravenously as a PNB adjunct to prolong the duration of analgesia after single-injection interscalene brachial plexus block (ISB). Specifically, we aimed to test the joint hypothesis that dexmedetomidine, added to the local anesthetic solution or infused intravenously, will prolong the duration of single-injection ISB analgesia and reduce the 24-h cumulative postoperative opioid consumption in outpatients undergoing major arthroscopic shoulder surgery and to successively examine whether the systemic route is as effective as the perineural route.

Materials and Methods

This study was approved by the Women's College Hospital Research Ethics Board (2011-0062-B), received a Health Canada (FDA equivalent) Non-Objection Letter (9427-D2692-22C), and was registered on www.clinicaltrials.gov (NCT02225054; principal investigator: R.B.; registration: August 21, 2014). The trial was conducted from May 2013 to March 2015 at the Women's College Hospital, an ambulatory center in Toronto, Ontario, Canada, affiliated with the University of Toronto. The authors prepared this study report in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[37]

Study Participants

After obtaining the written informed consent, adult patients (aged 18 to 65 yr) with American Society of Anesthesiologists physical status classification I to III scheduled for elective unilateral arthroscopic shoulder surgery using standardized general anesthesia (GA) and postoperative analgesic regimens inclusive of single-injection ISB were recruited to participate in this prospective, randomized, triple-masked,

parallel-arm, placebo-controlled, superiority clinical trial. Eligible surgical procedures included rotator cuff repair, bankart repair, superior labral tear from anterior to posterior repair, and acromioplasty. The individual surgeons' booking lists were reviewed in advance of the surgery date, and patients having arthroscopic surgical procedures were identified; subsequently, these patients were interviewed during their preadmission clinic visit before the day of surgery. Eligible patients were provided with an information leaflet describing the current study. Exclusion criteria included body mass index greater than $38\,kg/m^2$; pregnancy; failure to provide written informed consent; significant psychiatric or cognitive conditions interfering with consent or assessment; unstable coronary artery disease, congestive heart failure, or arrhythmias; preexisting neurological deficits or neuropathy affecting the brachial plexus; preexisting chronic pain or daily consumption greater than 30 mg oxycodone (or equivalent); baseline heart rate (HR) less than 60 beats/min or baseline systolic blood pressure less than 100 mmHg; significant renal or hepatic impairment; severe bronchopulmonary disease, including chronic obstructive pulmonary disease and obstructive sleep apnea; contraindications to PNB, including local skin infections, bleeding diathesis, and coagulopathy; allergies to local anesthetics, dexmedetomidine, or any component of multimodal analgesia; and concurrent distal clavicular resection.

Randomization and Blinding

Consented study participants were randomized by using a computer-generated list of random numbers in varying block sizes on a 1:1:1 ratio with no restrictions to any of the three study groups. Randomization was performed by an investigator with no further study involvement using the Random Allocation Software 2.0® (Isfahan University of Medical Sciences, Iran). The allocation results were sealed in opaque envelopes that were kept with the research coordinator. On the day of surgery, the research coordinator handed one envelope per patient to the anesthesia assistant in the block procedure room who prepared all the study solutions using an aseptic technique. Only preservative-free dexmedetomidine (100 µg/ml dexmedetomidine hydrochloride; Precedex, Hospira Inc., Canada) was used for the purposes of this study. The anesthesia assistant had no further role in the study; patients, anesthesiologists performing ISB, and the research coordinator collecting outcome data were blinded to the allocation results. All study participants received both perineural and IV study solutions according to their group allocation as follows: (1) perineural dexmedetomidine group (Dex$_p$), 0.5 µg/kg dexmedetomidine perineurally added to the local anesthetic solution plus 50 ml saline, 0.9%, IV infusion; (2) IV dexmedetomidine group (Dex$_{IV}$), 1 ml saline, 0.9%, perineurally added to the local anesthetic solution plus 0.5 µg/kg dexmedetomidine added to 50 ml saline, 0.9%, IV infusion; and (3) control group, 1 ml saline, 0.9%, perineurally added to the local anesthetic

solution plus 50 ml saline, 0.9%, IV infusion. The perineural study solution was mixed with 15 ml ropivacaine, 0.5%, with epinephrine 1:200,000 for a total of 16 ml administered in the single-injection ISB. The IV study solution was delivered over 30 min immediately after the induction of GA in the operating room. The timing of administration of the IV study solution was selected to ensure that patients were awake and cooperative to verify the block success (see Materials and Methods, Block Assessment, second sentence) and for the mandatory surgical safety checklist[38] performed in the operating room, before induction of GA, as per institutional standard of care.

Preoperative Procedures

All patients were premedicated with 1,000 mg oral acetaminophen and 400 mg celecoxib 1 h before the scheduled procedure, unless contraindicated. Noninvasive blood pressure, electrocardiogram, and pulse oximetry were applied and IV access secured on the patient's nonoperative side upon arrival to the block procedure room. Before block performance, all patients received 1 to 4 mg IV midazolam and/or 25 µg IV fentanyl for anxiolysis and analgesia, respectively, as needed.

ISB Technique

The preoperative ISB was performed using ultrasound guidance, under sterile conditions, by a staff regional anesthesiologist or by a directly supervised regional anesthesia fellow with experience in at least 10 ultrasound-guided ISBs. After sterile skin preparation with chlorhexidine and skin infiltration with 1% lidocaine, a high-frequency linear array transducer (6 to 13 MHz; SonoSite M-Turbo, USA) probe protected by a sterile dressing (3M Tegaderm®, USA) was placed in the transverse plane over the interscalene groove to visualize the carotid artery and the C5 and C6 nerve roots of the brachial plexus between the anterior and middle scalene muscles.[39] A 5-cm 22-gauge insulated needle (B. Braun Medical Inc., USA) was then inserted in plane with the ultrasound probe in a lateral-to-medial approach until the needle tip was adjacent to the C5 and C6 roots. After negative aspiration for blood, the 16 ml perineural study solution was injected in 5 ml aliquots to achieve spread around the C5 and C6 nerve roots.[40]

Block Assessment

All study participants were assessed for evidence of sensory blockade in the corresponding C5 and C6 dermatomes over the deltoid muscle before being transferred from the block procedure room to the operating room.[41] Testing was performed using loss of sensation to pinprick (25-gauge needle) every 5 min for a total of 30 min by comparing to the nonoperative extremity. The extent of sensory loss was graded on a three-point score where a score of 2 indicated normal sensation; 1, loss of sensation to pinprick, and 0, loss of sensation to light touch. Block success was defined as complete loss of sensation (sensory score = 0) over the deltoid area within

30 min of the end of local anesthetic injection. For patients in whom block success was not achieved after 30 min, block failure was documented, and the data were analyzed using an intention-to-treat approach.

Intraoperative Care

Standard intraoperative monitoring including electrocardiogram, pulse oximetry, noninvasive blood pressure, and temperature was used in all study participants. All patients received a standardized GA administered by an anesthesiologist blinded to group allocation, including 1 to 3 µg/kg IV fentanyl, 2 to 4 mg/kg IV propofol, and 0.6 mg/kg IV rocuronium and followed by tracheal intubation. GA was maintained with 5 to 7% desflurane in a 40:60 oxygen:air mixture. Ventilation rate and tidal volume were selected to attain a 30 to 40 mmHg as an end-tidal arterial CO_2 partial pressure (PCO_2). For analgesia, 1 to 2 µg/kg IV fentanyl and/or 0.05 to 0.1 mg/kg IV morphine were titrated to effect, as needed, if HR and/or mean arterial pressure (MAP) increased by 20% above the measured baseline. The IV study solution infusion was started immediately after induction and completed over 30 min. Hypotension or bradycardia encountered intraoperatively or in the recovery room was treated according to the following algorithm: bradycardia (HR decrease by 20% from baseline), 0.3 to 0.5 mg IV atropine; hypotension (MAP decrease by 20% from baseline), 0.1 mg IV phenylephrine; bradycardia and hypotension, 5 to 10 mg IV ephedrine. Four milligram IV ondansetron dose was administered for postoperative nausea and vomiting (PONV) prophylaxis 30 min before end of case; anesthesiologists were instructed to avoid using dexamethasone for PONV prophylaxis because of its potential confounding effect in prolonging the duration of analgesia.[42] Residual muscle relaxation was reversed with 50 µg/kg IV neostigmine and 5 to 10 µg/kg IV glycopyrrolate administered at the end of surgery. All patients underwent the standard surgical procedure as determined by the surgeons; participation in this study did not alter surgical management in any way.

Postoperative Management

All patients were transferred to PACU at the end of surgery, where they stayed until they met the hospital discharge criteria.[43] Postoperative pain in the PACU, defined as visual analog scale (VAS; 10 cm-scale where 0 = no pain and 10 = worst pain) pain severity score of 4 or greater or patient request for additional analgesics, was treated with rescue analgesia as needed, starting with 25 to 50 µg IV fentanyl every 5 min up to a total of 200 µg, followed by 2 to 4 mg IV morphine to a maximum of 20 mg or 0.2 to 0.4 mg IV hydromorphone to a maximum of 3 mg, administered by a blinded PACU nursing staff. Once oral intake was allowed, patients were able receive oral analgesics, either 30 mg codeine/300 mg acetaminophen/15 mg caffeine combination (Tylenol #3®; Janssen-Ortho, Canada) or 5 mg oxycodone hydrochloride/325 mg acetaminophen

combination (Percocet®; Bristol-Myers Squibb, Canada) if allergic to codeine, as needed. Discharged patients received a prescription for Tylenol #3® or Percocet® if intolerant to codeine to use for pain control, as needed. PONV in the PACU was treated sequentially with 2 to 4 mg IV ondansetron, followed by 12.5 to 25 mg IV dimenhydrinate and then 10 mg IV metoclopramide, as needed.

Upon discharge from the hospital, all patients were provided with a postoperative home diary to document the time when they first experienced pain at the surgical site; when they regained normal or presurgical strength in their arm; pain severity scores; analgesic consumption; block-related side effects (residual numbness, persistent tingling or weakness in the shoulder, arm, or forearm, and pain or bruising at the ISB site in the neck); opioid-related side effects (nausea and vomiting); and satisfaction with pain relief received. The diary was returned to the investigators using a prestamped, self-addressed envelope.

Follow-up

All study participants received a scripted phone call from the research coordinator on postoperative day 1 as well as at 7 and 14 days postoperatively to remind them to complete and return their home diary. A further phone call at 3 months was dedicated to inquiring about any block-related postoperative neurologic symptoms (persistent numbness or paresthesia, weakness, or nonsurgical pain in the operative extremity). Any complications that were potentially block related were followed until resolution.

Outcome Measures

Our staged joint hypothesis testing entailed sequential evaluation[44] of two primary outcomes, followed by comparison of the two dexmedetomidine administration routes. The first primary outcome was the duration of postoperative analgesia associated with ISB, designated as the time in hours to the first report of postoperative pain at the surgical site. The second primary outcome was the cumulative 24-h analgesic consumption (converted to oral morphine equivalent) at home.[45]

Secondary outcomes included (1) duration of motor blockade, designated as time (hour) to return to normal or presurgical strength in the arm[19]; (2) incidence of bradycardia (HR decrease by 20% from baseline) in hospital; (3) incidence of hypotension (MAP decrease by 20% from baseline) in hospital; and (4) incidence of postoperative neurologic symptoms (persistent numbness or paresthesia, weakness, or nonsurgical pain in the operative extremity) at 7 and 14 days as well as at 3 months postoperatively.

Analgesic outcomes assessed included (1) intraoperative fentanyl requirements (microgram); (2) time (hour) to PACU discharge (combined time for PACU phase I and II)[22]; (3) pain severity (at rest) VAS scores (centimeter) at PACU admission, 30, 60, and 90 min, at 8 and 24 h, and at 7 and 14 days postoperatively; (4) interval postoperative analgesic consumption during the PACU stay, at 8 and

24 h, and at 7 and 14 days (converted to oral morphine equivalent)[45]; (5) incidence of PONV during the PACU stay and the first 24 h postoperatively; and (6) patient satisfaction with analgesia measured on a VAS (10-cm scale where 0 = least satisfied and 10 = most satisfied) at 8 and 24 h postoperatively.

A research coordinator blinded to group allocation collected all of the outcome data.

Statistical Analysis

We aimed to test the joint hypothesis[46] that dexmedetomidine, regardless of the route of administration, prolongs the duration of ISB analgesia and reduces the cumulative 24-h postoperative analgesic consumption after shoulder surgery compared with intermediate-acting local anesthetic alone (control group) and to successively examine whether that the IV route is as effective as the perineural route. To control for type I error, we resorted to sequential hypothesis testing using the tree gatekeeping approach.[44] Consequently, we started by comparing the duration of analgesia; then, only after detecting a statistically significant difference in the first outcome (duration of analgesia) did we proceed to examine the second outcome (cumulative analgesic consumption). The IV route of administration (Dex_{IV}) was subsequently tested for noninferiority to the perineural route (Dex_P) using the duration of analgesia and analgesic consumption outcomes, in this order, using prespecified noninferiority margins; we only checked for superiority if noninferiority was demonstrated.[47]

Our preliminary pilot data from patients undergoing shoulder surgery under ISB with 15 ml ropivacaine, 0.5%, mixed with 0.5 µg/kg dexmedetomidine suggested that dexmedetomidine prolonged the duration of postoperative analgesia by at least 33%. This difference is considered clinically important and it corresponds to a size effect of 0.84. Matching treatment size effects have been reported by other trials evaluating the prolongation of block duration attributed to perineural dexmedetomidine.[9,48]

Assuming that using dexmedetomidine as an adjunct prolongs the analgesic duration of ISB after shoulder surgery by a size effect of 0.84 compared with ropivacaine alone and with a type I error estimate (α) of 0.05 and 80% power, we estimated that 84 patients, or 28 per group, would be needed to detect a statistically significant difference between the study groups. To account for attrition resulting from incomplete follow-up or patient dropout, we inflated the sample size by 15% and recruited 33 patients per group or 99 patients in total. With a minimum clinically important difference of 33%, a 25% difference in the duration of analgesia was prespecified as the noninferiority margin. Willing to accept an α = 0.05, the above calculated sample size (99 patients) provided 80% power for a one-sided test of the noninferiority hypothesis of IV dexmedetomidine for the duration of analgesia.

The above calculated sample size (99 patients) allows an 85% power at α = 0.05 to detect a size effect estimate of 0.84 in postoperative opioid consumption, which, based on our

preliminary data, corresponds to a 15 mg absolute difference in the first 24-h cumulative oral morphine equivalent consumption. With a minimum clinically important difference of 15 mg, a 10-mg difference was prespecified as the noninferiority margin. Willing to accept an α = 0.05, the above calculated sample size (99 patients) provided 80% power for a one-sided test of the noninferiority of IV dexmedetomidine for the 24-h cumulative opioid consumption.

The SPSS for Windows statistical package (Version 22; IBM, USA) was used in our calculations. We performed our analysis under the assumptions that (1) the three groups studied are independent, (2) the source populations of our data are normally distributed, and (3) the variances within each group are equal. We used the Shapiro–Wilk test to confirm the normality of data distribution. All of our analyses were performed using an intention-to-treat approach.
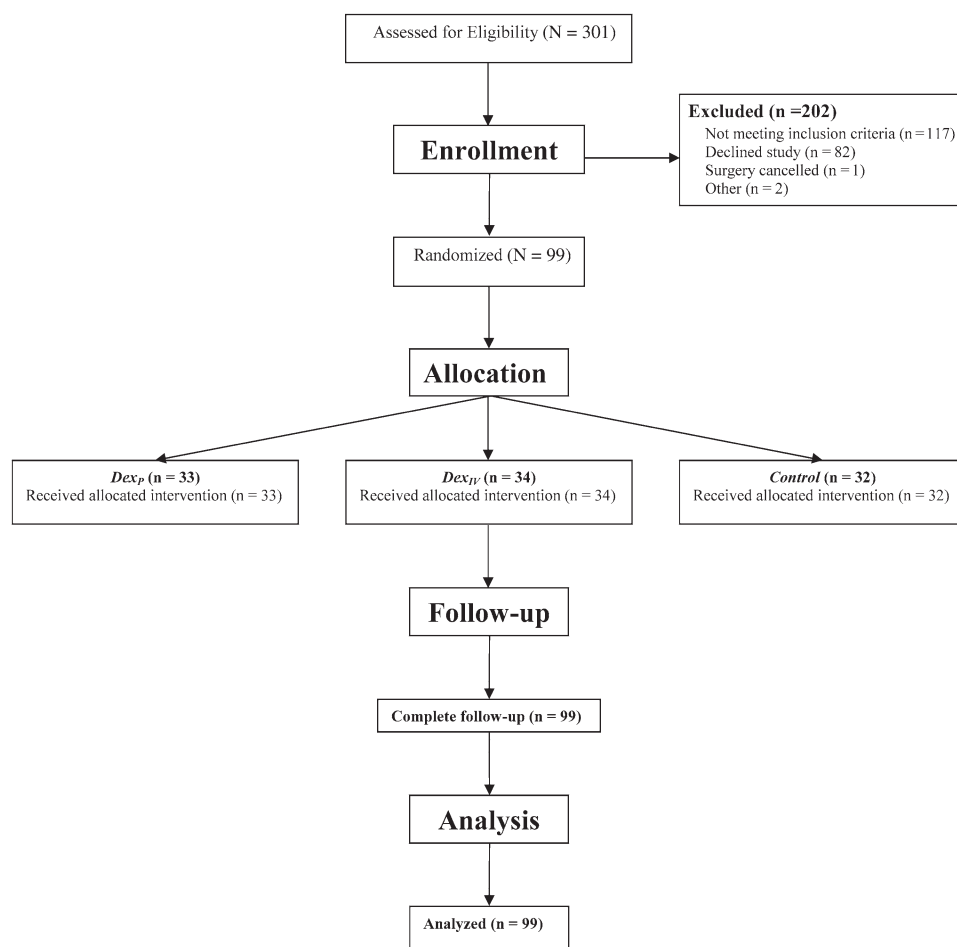
We presented continuous data as mean (SD) or mean (95% CI); we presented categorical data as numbers or percentages. A one-way ANOVA combined with the t test for *post hoc* testing was used in analyzing the continuous data. The chi-square or Fisher exact test combined with the Mann–Whitney U test for *post hoc* testing was used in

analyzing the categorical data. The Kruskal–Wallis test combined with the Mann–Whitney–Wilcoxon U test for *post hoc* testing was used in analyzing the ordinal data. The Kaplan–Meier survival analysis combined with the log-rank test with adjustment for multiple comparisons was used in analyzing the time-to-event outcomes. Noninferiority testing was done by comparing the 95% CI of the difference between groups ($Dex_{IV} - Dex_P$) to the predetermined noninferiority margin.

We set the threshold of statistical significance of the two-tailed P value for the log-rank test and the one-way ANOVA comparison among groups at 0.017 according to the Bonferroni correction. For repeated outcome measurements, the P values were corrected using the Bonferroni–Holm step-down adjustment.[49]

Results

A total of 301 patients were assessed for eligibility; of these, 202 were excluded (117 did not meet exclusion criteria, 82 declined, 1 had their surgery cancelled, and 2 had a change in the surgical procedure). The CONSORT[37] flow diagram showing patient progress through the study phases is depicted in figure 1. A total of 99 patients were randomized,

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                    │  Assessed for Eligibility (N = 301)  │
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               ┌───────────────┐                            │ Excluded (n =202)                    │
               │  Enrollment   │ ─────────────────────────▶ │   Not meeting inclusion criteria (n=117) │
               └───────────────┘                            │   Declined study (n = 82)            │
                                     │                       │   Surgery cancelled (n = 1)          │
                                     ▼                       │   Other (n = 2)                      │
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                            │  Allocation   │
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Dex$_P$ (n = 33)	*Dex$_{IV}$* (n = 34)	*Control* (n = 32)
Received allocated intervention (n = 33)	Received allocated intervention (n = 34)	Received allocated intervention (n = 32)

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Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing patient progress through the study phases. Dex$_{IV}$ = IV dexmedetomidine; Dex$_P$ = perineural dexmedetomidine.

all of whom (Dex$_P$: n = 33, Dex$_{IV}$: n = 34, and control group: n = 32) received the study interventions, completed the study protocol, and had their data analyzed. All study participants received the oral premedication with acetaminophen and celecoxib. Results data for the primary outcomes were available from all recruited patients, and the missing data for the secondary outcomes were minimal. Block success was confirmed in all patients within 30 min of ISB completion. The demographic characteristics of the study participants were similar with no statistically significant or clinically meaningful differences between the three groups (table 1). The time interval between block completion and initiation of the IV study solution infusion was 41.9 min (40.8 to 43.0 min), 41.7 min (40.9 to 42.5 min), and 42.5 min (41.5 to 43.5 min) in the Dex$_P$, Dex$_{IV}$, and control groups, respectively ($P = 0.49$).

The duration of analgesia after ISB was significantly longer in patients who received dexmedetomidine, regardless of the route of administration, specifically, 10.9 h (10.0 to 11.8 h) and 9.8 h (9.0 to 10.6 h) for the Dex$_P$ and Dex$_{IV}$ groups, respectively, compared with 6.7 h (5.6 to 7.8 h) for the control group ($P < 0.001$) (table 2). The duration of analgesia was statistically similar for the Dex$_P$ and Dex$_{IV}$ groups ($P = 0.07$). The Kaplan–Meier survival analysis plot for the duration of analgesia for the three groups is depicted in figure 2. The difference in the duration of analgesia (Dex$_{IV}$ – Dex$_P$) was –1.1 h (–2.3 to 0.14 h), with the lower limit of the CI not crossing the prespecified noninferiority margin ($P = 0.03$), suggesting a noninferiority of IV dexmedetomidine for duration of analgesia.

Correspondingly, postoperative cumulative 24-h oral morphine equivalent consumption was significantly less in patients who received dexmedetomidine, regardless of the route of administration, specifically, 63.9 mg (58.8 to 69.0 mg) and 66.2 mg (60.6 to 71.8 mg) for the Dex$_P$ and Dex$_{IV}$ groups, respectively, compared with 81.9 mg (75.0 to 88.9 mg) for the control group ($P < 0.001$). We were not able to detect a statistically significant difference in cumulative oral morphine equivalent consumption at 24 h between the Dex$_P$ and Dex$_{IV}$ groups ($P = 0.54$) (table 2). The difference in the cumulative opioid consumption (Dex$_{IV}$ – Dex$_P$) was 2.3 mg (–5.3 to 9.9 mg), with the upper limit of the CI not crossing the prespecified noninferiority margin ($P = 0.04$), suggesting noninferiority of IV dexmedetomidine for opioid consumption.

The use of dexmedetomidine was not associated with a prolongation in the duration of motor blockade, regardless of the route of administration ($P = 0.3$) (table 2). The Kaplan–Meier survival analysis plot for the duration of motor blockade in the three groups is depicted in figure 3.

Each of the three groups had similar intraoperative opioid consumption ($P = 0.57$) and duration of PACU stay ($P = 0.5$). Patients receiving dexmedetomidine, regardless of the route of administration, reported less pain (VAS) at 8 h postoperatively, specifically, 0.9 cm (0.4 to 1.4 cm) and 1.3 cm (0.7 to 1.9 cm) in the Dex$_P$ and Dex$_{IV}$ groups, respectively, compared with 2.6 cm (1.5 to 3.7 cm) for the control group ($P = 0.006$). There was no difference in pain at 8 h between the Dex$_P$ and Dex$_{IV}$ groups. Pain severity (VAS) was similar among all three groups at all other times measured (table 2).

There were no differences in postoperative opioid consumption between the three study groups during their PACU stay. The proportions of patients requiring analgesics during their PACU stay were also similar (table 2). During the first postoperative 8 h interval at home, analgesic consumption was lower in the two groups that received dexmedetomidine, specifically, 13.9 mg (9.4 to 18.4 mg) and 14.1 mg (9.8 to 18.4 mg) of morphine required by patients in the Dex$_P$ and Dex$_{IV}$ groups, respectively, compared with 23.3 mg (17.7 to 28.9 mg) for the control group ($P = 0.008$). There was no difference in morphine consumption during their first 8 h at

Table 1. Patient Demographic Characteristics

Parameter	Dex$_P$ (n = 33)	Dex$_{IV}$ (n = 34)	Control (n = 32)
Age (yr)	42.0 (37.8–46.2)	36.1 (31.7–40.5)	38.0 (33.2–42.8)
Sex (female/male)	7/26	9/25	7/25
Height (cm)	175.8 (172.7–178.9)	173.6 (169.7–177.5)	176.7 (173.2–180.2)
Weight (kg)	82.3 (78.6–87.8)	83.3 (76.3–90.3)	83.7 (78.6–88.8)
ASA status (I/II/III)	18/15/0	19/14/1	17/15/0
Surgical side (left/male)	16/17	13/21	15/17
Duration of surgery (min)	154.0 (144.4–163.6)	150.0 (138.4–163.6)	156.0 (145.2–166.8)
Surgical procedure			
Arthroscopy + acromioplasty	9	7	8
Arthroscopy + acromioplasty + rotator cuff repair	14	12	9
Arthroscopy + bankart repair	6	8	9
Arthroscopy + SLAP repair	2	3	3
Other	2	4	3

Values are expressed as the mean (95% CI) or absolute numbers.

ASA = American Society of Anesthesiologists; Dex$_{IV}$ = IV dexmedetomidine; Dex$_P$ = perineural dexmedetomidine; SLAP = superior labral tear from anterior to posterior.

Table 2. Results

Outcomes	Dex$_P$ (n = 33)	Dex$_{IV}$ (n = 34)	Control (n = 32)	P Value for Overall Group Effect*	P Value for Dex$_P$ vs. Dex$_{IV}$†
Duration of analgesia: time to first pain (h)‡	10.9 (10.0 to 11.8)	9.8 (9.0 to 10.6)	6.7 (5.6 to 7.8)	< 0.001	0.07
Postoperative cumulative 24-h oral morphine equivalent consumption (mg)‡	63.9 (58.8 to 69.0)	66.2 (60.6 to 71.8)	81.9 (75.0 to 88.9)	< 0.001	0.54
Duration of motor blockade: time to return to baseline motor strength (h)	16.4 (13.5 to 19.3)	16.1 (11.8 to 20.4)	15.4 (11.4 to 19.4)	0.3	0.6
Intraoperative IV fentanyl consumption (μg)	158.0 (138.9 to 177.2)	170.0 (154.0 to 186.1)	158.0 (136.4 to 179.6)	0.57	0.33
Time to PACU discharge (h)	3.2 (2.9 to 3.4)	3.0 (2.8 to 3.2)	3.2 (2.9 to 3.4)	0.5	0.53
Number of patients requiring analgesics in PACU	5 (15.2)	8 (23.5)	7 (22)	0.67	0.4
Rest pain severity VAS score at PACU admission (cm)§	0.2 (−0.1 to 0.5)	0.2 (−0.04 to 0.4)	0.5 (0.0 to 1.0)	0.308	1.0
At 30 min	0.3 (−0.1 to 0.7)	1.1 (0.4 to 1.8)	1.3 (0.5 to 2.1)	0.058	0.04
At 60 min	0.5 (0.1 to 0.9)	0.7 (0 to 1.4)	0.8 (0.1 to 1.5)	0.77	0.61
At 90 min	0.4 (0.0 to 0.8)	0.1 (−0.1 to 0.3)	0.5 (−0.1 to 1.1)	0.38	0.15
At 8 h	0.9 (0.4 to 1.4)	1.3 (0.7 to 1.9)	2.6 (1.5 to 3.7)	0.006	0.31
At 24 h	5.5 (4.6 to 6.4)	5.3 (4.4 to 6.2)	5.6 (4.7 to 6.5)	0.87	0.75
At 7 days	2.9 (2.0 to 3.8)	3.0 (2.3 to 3.7)	2.7 (1.9 to 3.5)	0.88	0.85
At 14 days	2.1 (1.3 to 3.0)	1.9 (1.3 to 2.5)	2.0 (1.3 to 2.7)	0.89	0.69
Oral morphine equivalent consumption in PACU (mg)‖	3.9 (1.0 to 6.8)	8.0 (3.9 to 12.1)	10.8 (4.5 to 17.2)	0.1	0.1
At 8 h	13.9 (9.4 to 18.4)	14.1 (9.8 to 18.4)	23.3 (17.7 to 28.9)	0.008	0.85
At 24 h	49.9 (40.1 to 59.7)	51.0 (41.2 to 60.8)	58.9 (50.8 to 67.1)	0.326	0.87
At 7 days	17.2 (8.7 to 25.7)	18.6 (12.9 to 24.3)	17.7 (10.6 to 24.8)	0.96	0.78
At 14 days	11.4 (4.9 to 17.9)	12.8 (7.2 to 18.4)	11.3 (6.1 to 16.5)	0.92	0.74
Postoperative incidence of PONV in PACU	9 (27)	3 (9)	7 (22)	0.13	0.06
At 24 h	7 (21)	9 (27)	9 (28)	0.84	0.61
Incidence of intraoperative bradycardia (n/N) (≥ 20% decrease from baseline)	2 (6)	4 (12)	6 (19)	0.27	0.42
Incidence of intraoperative hypotension (n/N) (≥ 20% decrease from baseline)	16 (49)	22 (65)	22 (69)	0.22	0.18
Incidence of postoperative neurologic symptoms at 7 days (n/N) (numbness, paresthesia, weakness, and pain)	5 (15)	8 (24)	2 (6)	0.15	0.39
At 14 days (n/N)	4 (12)	5 (15)	2 (6)	0.62	0.76
At 3 months (n/N)	0 (0)	0 (0)	1 (3)	0.66	N/A
Patient satisfaction with pain relief at 8 h (VAS, in cm)	9.4 (8.6 to 10.2)	8.6 (7.8 to 9.4)	8.4 (7.4 to 9.4)	0.21	0.14
At 24 h (VAS, in cm)	7.0 (5.9 to 8.1)	6.7 (5.8 to 7.6)	6.2 (5.1 to 7.3)	0.54	0.67

Values are expressed as the mean (95% CI) or absolute numbers (%).

* The P value for the overall F test and the Fisher exact test is set at 0.05. † The Bonferroni-corrected P value for the Dex$_P$ vs. Dex$_{IV}$ comparison is set at 0.017. ‡ Primary outcome. § The Bonferroni–Holm-corrected P value for the repeated measurement of pain severity VAS scores is 0.00625. ‖ The Bonferroni–Holm-corrected P value for the repeated measurement of oral morphine equivalent consumption is 0.01.

Dex$_{IV}$ = IV dexmedetomidine; Dex$_P$ = perineural dexmedetomidine; N/A = not applicable; n/N = percentage; PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting; VAS = visual analog scale.

home between the Dex$_P$ and Dex$_{IV}$ groups (fig. 4). Beyond 8 h postoperatively, oral morphine equivalent consumption was similar between the three groups when evaluated at 24 h, 7 days, and 14 days.

We found similar incidences of PONV among all three groups both during their PACU stay (P = 0.13) and at 24 h

(P = 0.84). The incidences of bradycardia (P = 0.27) and hypotension (P = 0.22) on the day of surgery were similarly very low for all three groups. The incidence of postoperative neurological symptoms was similar in the three groups at 7 days (P = 0.15), 14 days (P = 0.62), and 3 months (P = 0.66) postoperatively (table 2). Only one patient in the

Duration of Analgesia Survival Plot
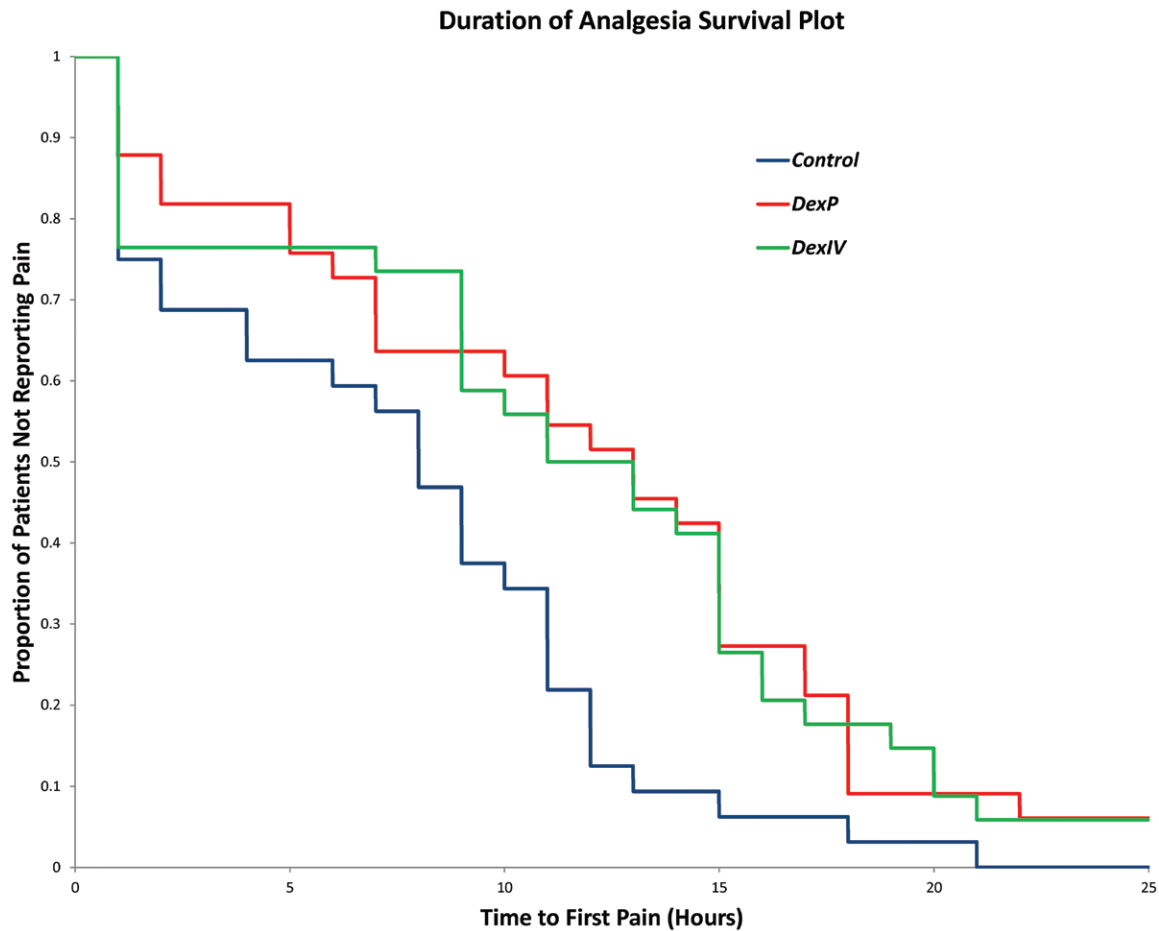
Fig. 2. Kaplan–Meier survival plot representing the duration of analgesia in the three study groups. Dex_{IV} = IV dexmedetomidine; Dex_P = perineural dexmedetomidine.

control group reported persistent paresthesia when assessed at 3 months, which resolved completely by 4 months.

Finally, all patients had similar satisfaction rating with their pain relief when evaluated at 8 h ($P = 0.21$) and 24 h ($P = 0.54$) postoperatively.

Discussion

This study demonstrates that dexmedetomidine, whether applied perineurally or intravenously, is an effective local anesthetic adjunct capable of selectively prolonging the duration of ISB analgesia and reducing the cumulative analgesic consumption at 24 h without prolonging the duration of motor blockade. Although the available literature emphasizes direct perineural mechanisms,[34,50,51] our findings are the first to suggest that IV dexmedetomidine as an adjunct to PNB seems to be as effective as perineural dexmedetomidine for the purpose of postoperative analgesia. This, in addition to its sedative,[52] opioid-sparing,[53] and potential antiemetic effects,[54] may favor the choice of dexmedetomidine as a sedating agent for surgeries performed under regional anesthesia.

Although two previous studies[31,32] have signaled the potential for IV dexmedetomidine to prolong the duration

of sensory blockade after single-injection PNB, neither has definitively demonstrated the clinically important effect of adjunctive dexmedetomidine on the duration of analgesia. The first study was an observational trial in healthy volunteers in which Marhofer et al.[32] examined the effect of low-dose (20 μg) perineural and IV dexmedetomidine on the duration of sensory blockade after ulnar nerve block. Because no surgical procedures were ever performed in the volunteers, the analgesic effect cannot be discerned, and the findings are not readily generalizable to routine regional anesthesia practice.[55] The second was a study performed in end-stage renal disease patients undergoing construction of arteriovenous fistula in which Rutkowska et al.[31] compared the effects of a continuous infusion of IV midazolam or IV dexmedetomidine on the duration of sensory–motor blockade after supraclavicular block. Unfortunately, the time to complete resolution of sensory blockade was reported as a surrogate measure for postoperative analgesia, the validity and reliability of which is questionable. Additional shortcomings of this trial include the lack of generalizability to nonrenal patients and the potential for renal disease to differentially affect the metabolism of both midazolam[56] and dexmedetomidine,[57] insufficient blinding, and the absence of a perineural dexmedetomidine group.

Duration of Motor Block Survival Plot
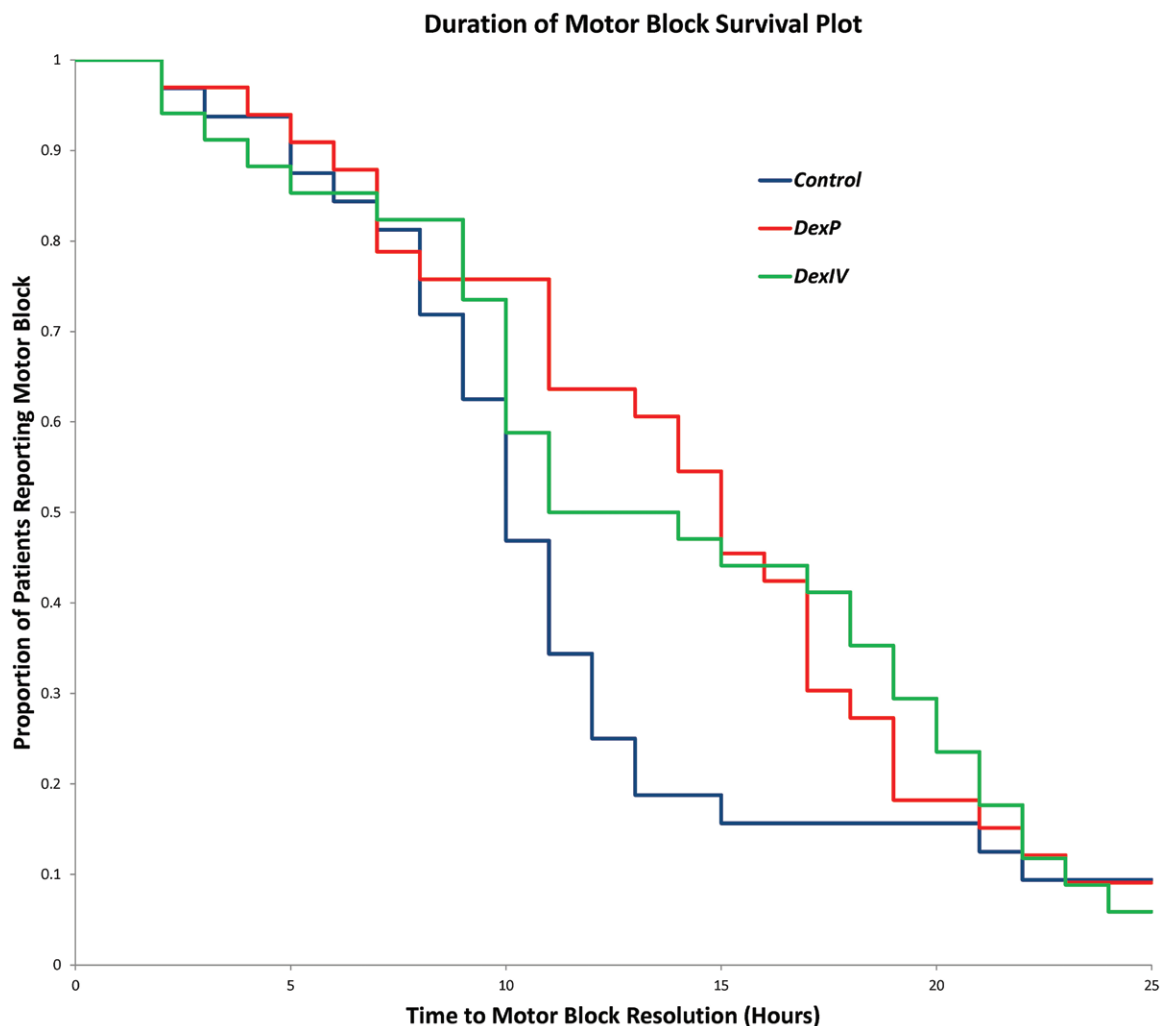
Fig. 3. Kaplan–Meier survival plot representing the duration of motor blockade in the three study groups. Dex_{IV} = IV dexmedetomidine; Dex_P = perineural dexmedetomidine.
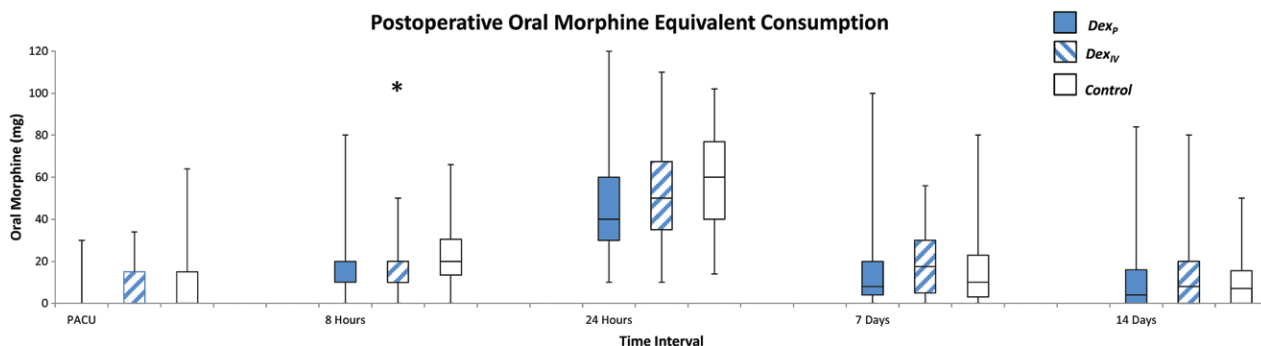
Fig. 4. Box plots of postoperative oral morphine equivalent consumption in the three study groups during the first 2 weeks. *Statistically significant difference between the three study groups (*F* test, Bonferroni–Holm correction). Dex_{IV} = IV dexmedetomidine; Dex_P = perineural dexmedetomidine.

Our work is also the first to show that dexmedetomidine, regardless of the route of administration, produces a differential prolongation of PNB duration (sensory more than motor blockade). A similar phenomenon was detected in our earlier review.[7] This finding contradicts existing data, which suggest that using dexmedetomidine as a PNB adjunct similarly prolongs both sensory and motor blockade duration.[19,31,32] Such a discrepancy could be attributed to the fact that earlier studies evaluated healthy volunteers rather than surgical patients,[32] did not quantify the actual duration of

motor blockade,[19] and used bupivacaine,[31] which is known to prolong motor blockade duration compared with ropivacaine.[58] In addition, our study is the first to show that dexmedetomidine prolongs the duration of analgesia after ISB for shoulder surgery. A previous study conducted by Fritsch *et al.*[19] in the setting of ISB for shoulder surgery was unable to isolate the effect of dexmedetomidine on the duration of analgesia because patients were given postoperative analgesics for non–shoulder-related pain. The potential to prolong the duration of analgesia after single-injection ISB is especially important because the moderate–severe acute postoperative pain of arthroscopic shoulder surgery[59] frequently outlasts the duration of single-injection ISB,[60] the occurrence of rebound pain,[61] and the technical difficulties[62] and muted enthusiasm[63] associated with perineural catheters in this patient population.

Regional anesthesia researchers have been exploring the strategies to prolong the duration of PNB analgesia in patients undergoing ambulatory procedures.[64,65] Although ambulatory catheters are an effective option,[66] their practical utility is governed by a stringent patient selection criteria.[62] Liposomal bupivacaine is another effective alternative, but its use is limited by price, availability, lack of FDA approval, and the similar prolongation of both sensory and motor blockade duration it produces.[67] Adjuvants constitute another option, and numerous local anesthesia additives[65] have been explored in search of the ideal adjunct that satisfies the criteria of (1) effectively prolonging the duration of analgesia and (2) not being associated with a significant risk of neurotoxicity.[68–70] Among these adjuncts, dexamethasone has seemed most promising,[71–75] especially because we have demonstrated its efficacy when administered intravenously.[42] However, dexmedetomidine as a local anesthetic adjunct may ultimately prove superior to dexamethasone in terms of its differential prolongation of sensory–motor blockade.[42] The current study suggests that dexmedetomidine likely affects the Aδ and unmyelinated C fibers differently from motor neurons. This phenomenon has been observed before in the setting of neuraxial blockade[7]; however, the exact mechanism of action remains speculative and has been addressed elsewhere.[33,34,50,51,76–79]

Our results are subject to several important limitations related to the external validity, interventions selected, outcomes measured, potential bias and confounding effects, and power to detect differences. The benefits of dexmedetomidine observed herein are specific to the setting of analgesic ISB using ropivacaine in outpatient arthroscopic shoulder surgery; the generalizability to ISB for surgical anesthesia, other PNBs, different local anesthetics, and other surgical procedures requires further investigation. The dose of dexmedetomidine chosen for our study interventions was based on our own anecdotal experience. Dose-ranging data are wanting, and further research is needed,[5,7] especially with recent evidence suggesting that a 1 μg/kg dose of perineural dexmedetomidine produces a greater block prolongation than a 0.5 μg/kg

dose.[32] Next, our clinically meaningful outcome of interest was the duration of postoperative analgesia after a single-shot PNB accompanied by a single dose of dexmedetomidine as an adjunct. Our patients were discharged from hospital within 3 h of surgery and it was not pragmatically feasible for us to formally assess the duration of sensory or motor blockade while the patients were at home. Moreover, the duration of sensory blockade may not be a reliable and valid surrogate measure for duration of pain relief; indeed, the latter is a validated and widely used outcome to examine the effect of adjuncts on local anesthetic–based PNB.[42,80–83] We also did not evaluate the effect of dexmedetomidine on block onset or on the risk of experiencing rebound[61,84] or chronic pain.[85] Importantly, we recognize the possibility that the intrinsic analgesic effect of dexmedetomidine[86] may have contributed to our findings and that our use of epinephrine in the perineural solutions may have affected the duration of analgesia. Similarly, one may also argue that the difference in dexmedetomidine administration time between the perineural and IV groups may have contributed to the present results. Last, the possibility that patients may have been asleep at that time may have interfered with the measurement of our outcomes; however, the randomized nature of our trial would have at least partially accounted for time of day differences between groups.

It is noteworthy that our study was not powered to detect statistically significant but not clinically important differences between the two routes of dexmedetomidine administration for any of our measured primary outcomes. Likewise, we used relatively wide noninferiority margins to facilitate this initial comparison of dexmedetomidine administration routes[87]; further comparisons are needed to confirm our results and investigate equivalence. Although we found no differences in postoperative neurologic symptoms or the incidence of hemodynamic variations among the three study groups, compared with control group, our trial was not powered to detect the differences in potential dexmedetomidine-related adverse effects. Indeed, it seems likely that the lack of difference in the incidence of bradycardia and hypotension may be due to the slow infusion rate that we used.

In conclusion, our results suggest that adding dexmedetomidine to single-injection ISB with long-acting local anesthetic, whether perineural or IV, is as effective in prolonging the duration of analgesia without prolonging the duration of motor blockade.

Acknowledgments

Competing Interests

Reproducible Science

Full protocol available from Dr. Abdallah: abdallahf@smh.ca. Raw data available from Dr. Abdallah: abdallahf@smh.ca.

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