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Original Article

Perineuraxial dexmedetomidine decreases the minimum effective volume of ropivacaine for ultrasound-guided supraclavicular brachial plexus block

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Abstract: Dexmedetomidine is a selective α-2-adrenoceptor agonist which might be used as a local anesthetic (LA) adjuvant for peripheral nerve block. Previous study had showed that dexmedetomidine could suppress the peak amplitude of Na^+ current in neuronal cells. We designed this study to determine the minimum effective volume (MEV) of ropivacaine with or without dexmedetomidine for ultrasound-guided supraclavicular brachial plexus block (SBPB), to quantify the sparing effect of dexmedetomidine on the MEV of ropivacaine. Thirty-four adult patients scheduled for forearm and hand surgeries under supraclavicular brachial plexus block were randomized into two groups: Group R (0.75% ropivacaine) and Group RD (0.75% ropivacaine plus dexmedetomidine). A successful block was defined as complete loss of cold sensation at the sensory dermatomes of four main nerves within 45 min after completed LA injection. The MEV of ropivacaine with or without dexmedetomidine was determined by using up-and-down method introduced by Dixon and Massey. The MEV for 0.75% ropivacaine was 15.5 ml [confidence interval 95% (CI): 13.9-17.2 ml] in Group R vs. 14.0 ml (95% CI: 12.5-15.6 ml) in Group RD. Dexmedetomidine 30 μg decreased the MEV of ropivacaine by about 10%. Systolic arterial blood pressure and heart rate levels were lower in group RD than in group R, and sedation level was higher in group RD than in group R. There were no differences in the incidence of paraesthesia, nerve stimulation, vascular puncture, and bradycardia. Perineuraxial dexmedetomidine 30 μg produced a 10% reduction of MEV of ropivacaine for ultrasound-guided SBPB.

Keywords: Anesthetic techniques, regional, brachial plexus, anesthetics local, ropivacaine, equipment, ultrasound machines

Introduction

The supraclavicular brachial plexus block (SBPB) is commonly used to provide anesthesia for forearm and hand surgery. Large volumes of long-acting local anesthetic (LA) were usually chosen to improve the success rate and prolong the duration of brachial plexus block, which may resulted in increasing the risk of systemic toxicity. Ultrasound guidance was then invented to provide a successful peripheral nerve block by using a small volume of LA.

Dexmedetomidine, a selective α-2-adrenoceptor agonist, as a local anesthetic (LA) adjuvant has been shown to prolong the duration of analgesia in a series of preclinical and clinical studies [1-8]. One preclinical study showed that dexmedetomidine suppressed the peak amplitude of Na^+ current in neuronal cells [9]. For LAs suppress nerve excitability and exert clinical effects through the blockade of Na^+ channel [10], exposure to dexmedetomidine can produce inhibitory effects on Na^+ channel currents and may thus be potential mechanisms through which it may depress neuronal excitability [9]. This finding indicates that perineuraxial dexmedetomidine as an adjuvant might have a LA effect and decrease the LA requirement during brachial plexus block. However, this effect has not yet been investigated in clinical study.

The primary objective of the present study is to investigate whether perineuraxial dexmedetomidine as an adjuvant could decrease the minimum effective volume (MEV) of ropivacaine required for ultrasound-guided SBPB.

Methods

The present study was approved by the ethical committee of the Second Affiliated Hospital of Wenzhou Medical University and registered at Chinese Clinical Trials.gov (ChiCTR-OOC-1500-5869). After obtained written informed consent from all patients, thirty-four patients (ASA physical status I or II, aged from 18 to 65 years) scheduled for forearm and hand surgeries under SBPB were enrolled in this prospective, randomized, double-blinded study. Exclusion criteria were patients who receiving adrenoreceptor antagonist or agonist therapy, allergic to LAs, a current brachial plexus injury, infection at the puncture site, and unable to provide informed consent; those with a history of morbid obesity (body mass index >35 kg/m^2), hypertension, diabetes, chronic pain, and pregnant women.

No premedication was given before SBPB. All patients had an intravenous catheter inserted into the vein of nonoperated arm and Lactated Ringer's solution administered at 5 ml/kg/h. Pulse oximetry (SpO_2), electrocardiogram (ECG), and non-invasive arterial pressure (NIBP) were recorded before the block was performed. According to Gupta et al. [11], the Ultrasound-guided SBPB was carried out by a single operator who had considerable experience with this method. After sterile preparation of the probe and disinfection of the skin, a Sonosite M-Turbo (Sonosite, Inc., Bothell, WA, USA) with a 13-MHz linear probe was used to visualize the structures of the brachial plexus in the supraclavicular region. After a subcutaneous infiltration with 1% lidocaine, a 50-mm, 22-gauge needle (Stimuplex A, B.Braun, Havel's, Cincinnati, OH) was directed to the plexus under ultrasound guidance using in-plane technique. Before injection of LA, the needle tip position was identified by injecting 0.5 ml bolus of saline. After aspiration, the prepared LA injection containing 0.75% ropivacaine (AstraZeneca, Södertälje, Sweden) (Group R) or 0.75% ropivacaine with 0.3 ml (30 μg) dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang, China) (Group RD) was then deposited. Using six-injection technique, we ensure the upper, middle, and lower trunks of the plexus were surrounded with LA solution.

The patients were randomly allocated to one of the two groups by an anesthesiologist not involved in the study using sealed envelopes: Group R (0.75% ropivacaine, n = 17) and Group RD (0.75% ropivacaine plus dexmedetomidine, n = 17). The LA injections were prepared and then covered with nontransparent stickers by the same anesthesiologist not involved in the study. The volume of LA injection for consecutive patients was determined according to the block effect of the previous patient. Based on our experience, the initial volume of ropivacaine was 21 ml in Group R and 18 ml in Group RD was expected to be sufficient for most patients. The increment or decrement was set as 1.5 ml for both groups. A successful or a failed block determined, respectively, a 1.5 ml volume reduction or increase for the next patient.

An investigator blinded for the block conduction and the injected volume assessed each block. Using cold sensation test, the efficacy of the block was assessed at 5-min intervals for up to 45 min. The endpoint of a success or a failure of the block was defined according to Gupta et al [11]. A successful block was defined as complete loss of cold sensation at the sensory dermatomes of the ulnar, median, radial, and musculocutaneous nerves within 45 min after completed LA injection. Failure to achieve complete loss of cold sensation at any of the four sensory dermatomes after 45 min after completed LA injection was considered a failed block. The block was also deemed a failed block if the patient complained of pain during surgery, despite the complete loss of cold sensation. For patients with failed block, a supplemental peripheral nerve blocks, intravenous fentanyl intraoperatively or general anesthesia was administrated as appropriate to achieve surgical analgesia.

Systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), heart rate (HR), and SpO_2 were recorded at baseline, 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 90 min, and 120 min. Adverse events comprised hypotension (defined as a 30% decrease in relation to the baseline), bradycardia (defined as HR < 50 beats per minute), respiratory depression (defined as SpO_2 < 90%), or nausea and vomiting. We also recorded the paraesthesia, nerve stimulation, vascular puncture, and systemic

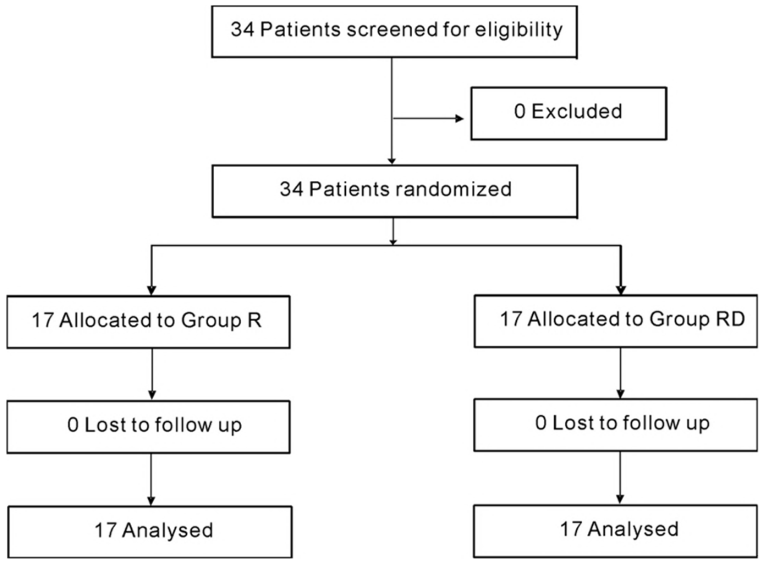

Figure 1. The flow chart for patient recruitment.

toxicity to LA during the block procedure. Sedation was evaluated by a 4-point scale (1 = awake and nervous, 2 = awake and calm, 3 = sleepy and easily arousal, 4 = sleepy and difficultly to rouse).

Statistics and power analysis

Using the formula by Dixon and Massey [12], sample size (N) was calculated as follows: Briefly, $N = 2(SD/SEM)^2$ where SD represents standard deviation and SEM the standard error of the mean. A sample size of 15 subjects in each group is needed for the study, assuming a 4 ml SD and 1.5 ml SEM. We assigned 17 patients to each of the two groups, anticipating a dropout rate of 10%.

The MEV of ropivacaine was estimated using up-and-down method introduced by Dixon and Massey [11]. Statistical analysis was performed with SPSS 16.0 for windows (SPSS Inc., Chicago, IL). Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Normality distributed data are presented as mean (SD). Categorical data are presented as n or n (%). Normally distributed data between two groups were analyzed using independent 2-sample *t* test. Repeat measured ANOVA was used for measurement with multiple time points.

Categorical data were analyzed using the method of χ^2 test or Fisher exact test. A value of $P < 0.05$ was considered as statistically significant.

Results

The patients were recruited from May 2015 to Oct 2015. A total of 34 subjects completed the study and were included in the final analysis (**Figure 1**). Characteristics and surgical data were similar between the two groups (**Table 1**). The sequence of successful and failed blocks is shown in **Figure 2**. The MEV for 0.75% ropivacaine was calculated using Dixon's formula to be 15.5 ml [confidence interval 95% (CI): 13.9-17.2 ml]. The MEV for 0.75% ropivacaine with dexmedetomidine 30 μg was calculated using Dixon's formula to be 14.0 ml (95% CI: 12.5-15.6 ml). Dexmedetomidine 30 μg decreased the MEV of ropivacaine by about 10%.

In group R, out of 6 failed blocks, 2 of these 6 patients required supplemental peripheral nerve block and 4 patients received intravenous fentanyl intraoperatively. In group RD, out of 7 failed blocks, 3 of these 7 patients required supplemental peripheral nerve block and 4 patients received intravenous fentanyl intraoperatively. The amounts of fentanyl used were similar between the two groups. None of these patients received general anesthesia.

Adverse events are listed in **Table 2**. No significant differences between the two groups were reported regarding the incidence of paraesthesia, nerve stimulation, vascular puncture, and bradycardia. More patients were sleepy but easily arousable in group RD than in group R ($P = 0.001$). No adverse events including systemic toxicity to LA, hypotension, respiratory depression, nausea, and vomiting were observed in either group. SAP levels in group RD at 30 and 45 minutes were significantly lower than those in group R ($P < 0.05$; **Figure 3**). DAP levels were similar between the two groups. HR level in group RD at 30 minute was significantly lower than that in group R ($P < 0.05$; **Figure 4**).

Discussion

In this prospective, triple-blinded, randomized, and up-down sequential allocation trial, we

Table 1. Patient characteristics and surgical data

	Group R	Group RD	*T*	χ^2	*P*-value
Age, mean (SD), years	38.7 (10.3)	35.8 (10.0)	0.842		0.406
Gender (male/female), n	10/7	12/5		0.515	0.473
Height, mean (SD), cm	167.8 (8.1)	169.9 (6.7)	0.834		0.410
Weight, mean (SD), kg	62.8 (8.7)	61.8 (10.6)	0.301		0.765
ASA physical status (I/II), n	13/4	15/2			0.656
Surgery duration, mean (SD), min	85.3 (50.3)	89.7 (38.4)	0.288		0.776
Type of surgery					1.000
Finger/wrist arthroplasty, n	2/1	3/2			
Finger/wrist ORIF, n	10/2	9/1			
Radius/ulnar ORIF, n	1/1	2/0			

Continuous variables are expressed as mean (SD). Continuous variables were analyzed using independent 2-sample *t* test. Categorical variables are expressed as counts. Categorical data were analyzed using the method of χ^2 test (gender) or Fisher exact test (other categorical variables). SD, standard deviation; ASA, American Society of Anesthesiologists; ORIF, open reduction-internal fixation.

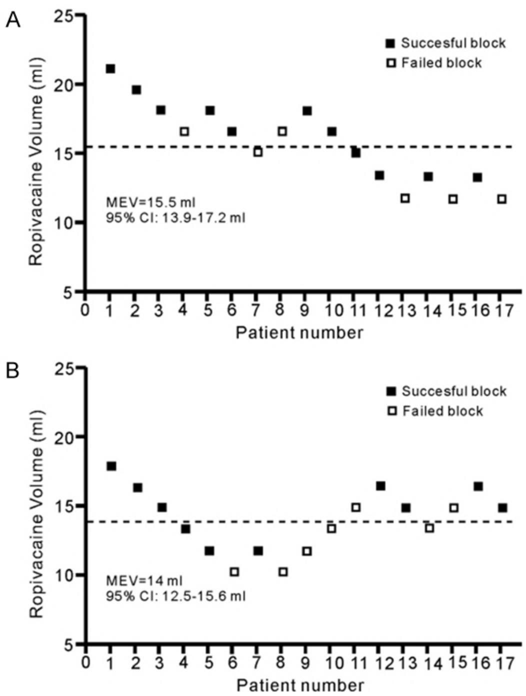

Figure 2. A. The minimum effective volume (MEV) of 0.75% ropivacaine required for ultrasound-guided supraclavicular brachial plexus block (SBPB) is 15.5 ml [confidence interval 95% (CI): 13.9-17.2 ml] using the formula of Dixon and Massey. The testing interval is 1.5 ml. The horizontal dashed line represents the MEV of 0.75% ropivacaine, 15.5 ml. B. The MEV for 0.75% ropivacaine with dexmedetomidine 30 μg is 14.0 ml (95% CI: 12.5-15.6 ml) using the formula of Dixon and Massey. The testing interval is 1.5 ml. The horizontal dashed line represents the MEV of 0.75% ropivacaine, 14.0 ml.

found the MEV of 0.75% ropivacaine required for ultrasound-guided SBPB using Dixon's formula to be 15.5 ml (95% CI: 13.9-17.2 ml), whereas the MEV of 0.75% ropivacaine with dexmedetomidine 30 μg using the same formula was 14.0 ml (95% CI: 12.5-15.6 ml). Perineuraxial dexmedetomidine 30 μg decreased the MEV of ropivacaine for ultrasound-guided SBPB by about 10%.

Several trials using LA coadministered with dexmedetomidine have been reported, of which the dose of dexmedetomidine rangered from 20 to 150 μg [1-4]. Esmaoglu et al [4]. have found that perineuraxial dexmedetomidine 100 μg may lead to bradycardia, whereas dexmedetomidine 20 μg have not [3]. We used dexmedetomidine 30 μg for the present study and the assumption that bradycardia will not occur with this dose.

Several preclinical studies showed that dexmedetomidine as an adjuvant added to LAs could enhance sensory blockade for peripheral nerve block [5-8]. In addition, several off-label clinical trials also found that dexmedetomidine as an adjuvant to LA could prolongs peripheral nerve block [1-4]. Previous studies, however, did not investigate whether pe-rineuraxial dexmedetomidine has a LA effect and quantify the sparing effect of dexmedetomidine on LA requirement during brachial plexus block. In our present study, we found that dexmedetomidine 30 μg as an adjuvant decreased the MEV of ropivacaine for ultrasound-guided SBPB by about 10%, which suggests that dexmedetomidine as an adjuvant might has a LA effect.

The mechanism by which dexmedetomidine has a LA effect is not elucidated. LAs exert cli-

Table 2. Adverse events

	Group R	Group RD	χ^2	*P*-value
Paraesthesia, n (%)	4 (23.5)	3 (17.6)		1.000
Nerve stimulation, n (%)	2 (11.8)	2 (11.8)		1.000
Vascular puncture, n (%)	1 (5.9)	0 (0)		1.000
Bradycardia, n (%)	0 (0)	1 (5.9)		1.000
Max sedation level 1-2-3-4 (n)*	12-5-0-0	1-7-9-0	15.07	0.001

Categorical variables are expressed as counts (percentage) except maximum sedation level which are number of patients. Categorical data were analyzed using the method of χ^2 test (max sedation level) or Fisher exact test (other categorical variables). *χ^2 $P = 0.001$. SD, standard deviation.

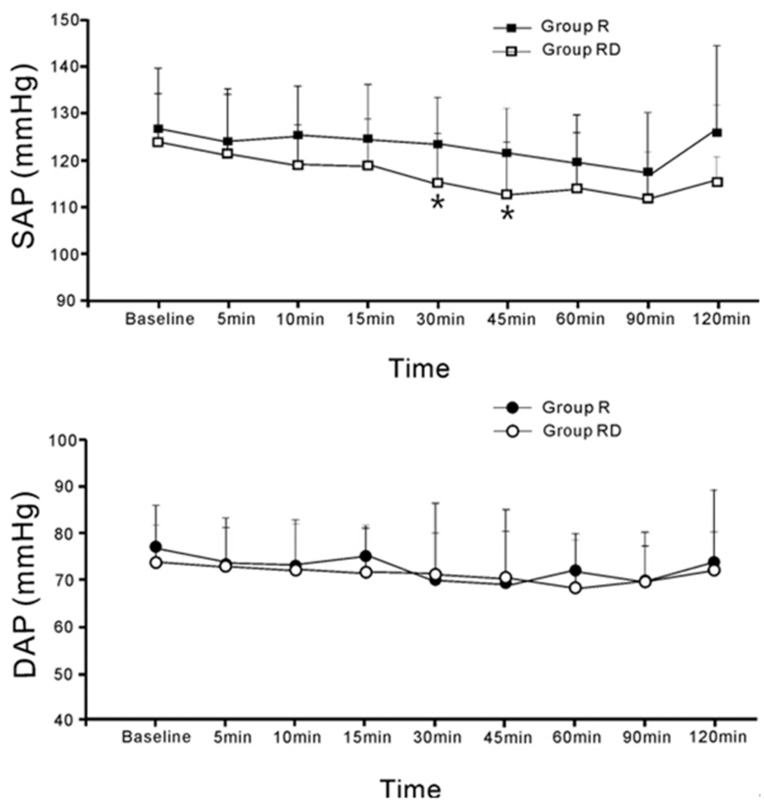

Figure 3. Systolic and diastolic arterial pressure time course. Asterisks indicate individual time points in which SAP levels in group RD were significantly lower than those in group R ($P < 0.05$). R, ropivacaine; RD, ropivacaine plus dexmedetomidine; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure.

nical effects through the blockade of voltage-dependent Na^+ channels. LAs block nerve impulse and conduction by preventing the influx of sodium ions [10]. Voltage-dependent Na^+ channels are Na^+ selective pores through the membranes of neuron cells and are critical to action-potential initiation and propagation. Membrane depolarization induces Na^+ channels opening, resulting in Na^+ ions influx through the channels and Na^+ current [13, 14]. Chen and colleagues found that dexmedetomidine significantly depressed Na^+ currents in cultured cerebellar neurons, which indicated that dexmedetomidine might affect neuronal activity in vivo [9].

Some studies reported that perineuraxial dexmedetomidine could decrease blood pressure and heart rate [2, 4, 15]. We used 30 μg perineuraxial dexmedetomidine and also found that SAP levels at 30 and 45 minutes were significantly lower in dexmedetomidine group when compared with the ropivacaine group. HR level at 30 minutes was significantly lower in dexmedetomidine group than that in ropivacaine group. However, we did not found that perineuraxial dexmedetomidine increased the incidence of hypotension and bradycardia. We think that dexmedetomidine-induced adverse effects such as hypotension and bradycardia are likely to be dependent on the total dose. Esmaoglu et al [4] found that perineuraxial dexmedetomidine 100 μg added to levobupivacaine for axillary brachial plexus block may lead to bradycardia. Fritsch et al [2] used perineuraxial dexmedetomidine 150 μg added to ropivacaine for interscalene block and also found that bradycardia was more frequent in dexmedetomidine group. However, peri-neuraxial dexmedetomidine 20 μg was not result in significant bradycardia [3].

One previous study had showed that neuraxial dexmedetomidine could cause sedation [16]. Another study reported that peri-neuraxial dexmedetomidine-associated sedation increased in a dose-dependent manner [17]. Our results also indicated that more patients were sleepy

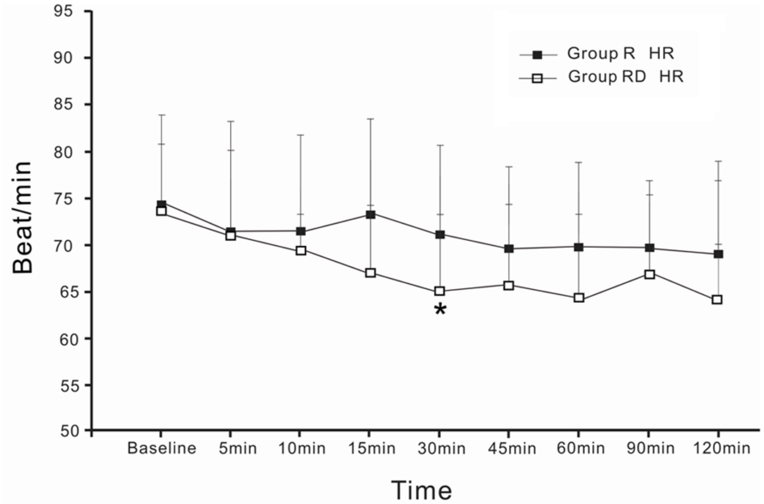

Figure 4. Heart rate time course. Asterisks indicate individual time point in which HR level in group RD was significantly lower than that in group R (*P* < 0.05). R, ropivacaine; RD, ropivacaine plus dexmedetomidine; HR, heart rate.

but easily arousable in dexmedetomidine group than in ropivacaine group. Systemic uptake of dexmedetomidine may result in sedation by activating α-2-adrenoceptors in the locus coeruleus [3]. The sedation resulted from intravenous dexmedetomidine has been known as "cooperative sedation," which may indicate that sedation from perineural administration may be of benefit to patients [7, 18].

Although many studies did not show that perineural dexmedetomidine has neurotoxicity [2, 5, 6] and perineural dexmedetomidine might attenuate the LA-induced acute perineural inflammation [5], the use of perineural dexmedetomidine for clinical nerve blocks is not approved by the US Food and Drug Administration. Further studies are needed to determine whether dexmedetomidine can be safety for perineural use in humans.

There were some limitations to the present study. Firstly, we did not record the onset and duration of sensory block because our primary aim was to investigate the MEV of ropivacaine with or without dexmedetomidine and there were numerous studies had compared the differences between the two groups. Secondly, we did not determine the effects of different doses of perineural dexmedetomidine on the MEV of ropivacaine and the side effects. Further studies are needed to explore the optimal dose of dexmedetomidine. Finally, we did not observe postoperative neurological symptoms consistently, but no one complained any neurological sequelae at any time postoperatively. Further studies are required to investigate the effects of perineural dexmedetomidine on brachial plexus nerve structures.

In conclusion, the addition of dexmedetomidine 30 μg decreased the MEV of ropivacaine for ultrasound-guided SBPB by about 10%, with a higher sedation level when compared with ropivacaine alone. Perineural dexmedetomidine 30 μg did not increase the incidence of hypotension and bradycardia. Our results encourage the use of perineural dexmedetomidine as an adjuvant for patients undergoing peripheral nerve block.

Disclosure of conflict of interest

None.

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References

[1] Keplinger M, Marhofer P, Kettner SC, Marhofer D, Kimberger O, Zeitlinger M. A pharmacodynamic evaluation of dexmedetomidine as an additive drug to ropivacaine for peripheral nerve blockade: a randomised, triple-blind, controlled study in volunteers. Eur J Anesthesiol 2015; 32: 790-6.

[2] Fritsch G, Danninger T, Allerberger K, Tsodikov A, Felder TK, Kapeller M, Gerner P, Brummett CM. Dexmedetomidine added to ropivacaine extends the duration of interscalene brachial plexus blocks for elective shoulder surgery when compared with ropivacaine alone: a single-center, prospective, triple-blind, randomized controlled trial. Reg Anesth Pain Med 2014; 39: 37-47.

[3] Marhofer D, Kettner SC, Marhofer P, Pils S, Weber M, Zeitlinger M. Dexmedetomidine as

an adjuvant to ropivacaine prolongs peripheral nerve block: a volunteer study. Br J Anesth 2013; 110: 438-42.
[4] Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg 2010; 111: 1548-51.
[5] Brummett CM, Norat MA, Palmisano JM, Lydic R. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. Anesthesiology 2008; 109: 502-11.
[6] Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. Anesthesiology 2009; 111: 1111-9.
[7] Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. Anesthesiology 2011; 115: 836-43.
[8] Brummett CM, Amodeo FS, Janda AM, Padda AK, Lydic R. Perineural dexmedetomidine provides an increased duration of analgesia to a thermal stimulus when compared with a systemic control in a rat sciatic nerve block. Reg Anesth Pain Med 2010; 35: 427-31.
[9] Chen BS, Peng H, Wu SN. Dexmedetomidine, an alpha2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current. Br J Anesth 2009; 103: 244-54.
[10] Strichartz G. Molecular mechanisms of nerve block by local anesthetics. Anesthesiology 1976; 45: 421-42.
[11] Gupta PK, Hopkins PM. Effect of concentration of local anesthetic solution on the ED_{50} of bupivacaine for supraclavicular brachial plexus block. Br J Anesth 2013; 111: 293-6.
[12] Dixon WJ, Massey FJ. Introduction to statistical analysis. 4th edition. New York: McGraw-Hill; 1983.
[13] Wagner LE, Eaton M, Sabnis SS, Gingrich KJ. Meperidine and lidocaine block of recombinant voltage-dependent Na^+ channels: evidence that meperidine is a local anesthetic. Anesthesiology 1999; 91: 1481-90.
[14] Hille B. Ionic Channels of Excitable Membranes. 2nd Edition. Sunderland, MA: Sinauer Associates; 1992.
[15] Mirkheshti A, Saadatniaki A, Salimi A, Manafi Rasi A, Memary E, Yahyaei H. Effects of dexmedetomidine versus ketorolac as local anesthetic adjuvants on the onset and duration of infraclavicular brachial plexus block. Anesth Pain Med 2014; 4: e17620.
[16] Saadawy I, Boker A, Elshahawy MA, Almazrooa A, Melibary S, Abdellatif AA, Afifi W. Effect of dexmedetomidine on the characteristics of bupivacaine in a caudal block in pediatrics. Acta Anesthesiol Scand 2009; 53: 251-6.
[17] Keplinger M, Marhofer P, Kettner SC, Marhofer D, Kimberger O, Zeitlinger M. A pharmacodynamic evaluation of dexmedetomidine as an additive drug to ropivacaine for peripheral nerve blockade: a randomised, triple-blind, controlled study in volunteers. Eur J Anesthesiol 2015; 32: 790-6.
[18] Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. Neurosurgery 2005; 57: 1-10.