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Original Article

Which is the better adjuvant to ropivacaine in brachial plexus block: dexmedetomidine or morphine? A prospective, randomized, double-blinded, comparative study

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Abstract: Objectives: Dexmedetomidine has been utilized as an adjuvant to prolong single local anaesthetic injection technique in brachial plexus block despite of adverse effects and cost-effectiveness. Morphine, a classic opioid, is also used as an adjuvant in neuraxial and perineural nerve blocks. In this study, we compared the effects of these two different adjuvants to ropivacaine in interscalene brachial plexus blockade. The onset and duration of motor and sensory blocks are mainly focused in the study. Methods: A total of 92 patients scheduled for distal arm or forearm surgeries were divided into 3 groups in a randomized, double-blind mode. Under the direction of a nerve stimulator, an interscalene brachial plexus block was performed by a single injection of one of the following local anesthetics: 24 mL (120 mg) of 0.5% ropivacaine plus 1 mL saline in Group R; 24 mL (120 mg) of 0.5% ropivacaine plus 1 mL dexmedetomidine 0.75 μg/kg in Group RD; and 24 mL (120 mg) of 0.5% ropivacaine plus 1 mL (2 mg) morphine in Group RM. Onset time and durations of sensory and motor blocks, cardiovascular parameters, peripheral oxygen saturation (SpO_2), and adverse reactions were recorded and compared. Results: The onset time in the Group RD was significantly less than that in the Group RM ($P<0.05$), while the duration in the Group RD was longer than that in the Group RM ($P<0.05$). Both the onset time and the duration of blocks were not critically different in the Group RM and the Group R. For the side effects, more patients in the Group RD suffered from bradycardia ($P<0.05$). However, more patients in the Group RM had nausea and vomiting ($P<0.05$). Conclusions: Compared with morphine, dexmedetomidine can provide superior analgesia for interscalene brachial plexus block in adjunct to ropivacaine at 0.5%. As an adjuvant, morphine may have few significant benefits in peripheral nerve block.

Keywords: Dexmedetomidine, morphine, brachial plexus, nerve block

Introduction

Brachial plexus block is an important peripheral nerve block providing ideal analgesia in upper-extremity surgeries. Compared with general anesthesia, brachial plexus block can reduce opioid consumption, improve postoperative analgesia, shorten stay in the post-anaesthesia care unit, and accelerate postoperative rehabilitation [1]. Nevertheless, these advantages could be limited due to short analgesic duration of the most single-injection of local anaesthetics [2]. The limitation can be avoided by peripheral nerve catheters which provide continuously local anesthetic delivering and have been proven as an excellent method for postoperative analgesia [3]. However, peripheral nerve catheters are skillful and costly, and could increase workloads of postoperative management [4].

An adjuvant agent to local anesthetics in order to improve the quality and duration of anesthesia is the other choice to delete deficiencies of the single local anesthetics injection in peripheral nerve block. Numerous agents such as

clonidine [5], dexmedetomidine [6], tramadol [7], dexamethasone [8], midazolam [9], and hyaluronidase [10] were reported as potential adjuvants to some extent. Recently, a series of clinical trials [1, 6, 11, 12] used dexmedetomidine (an α_2 adrenoreceptor agonist) as an adjuvant to local anaesthetics and found that dexmedetomidine can improve the quality and the duration of peripheral nerve block. However, adverse effects relating to dexmedetomidine [6] have also been reported, such as postoperative sedation, hypotension, and bradycardia and so on. In addition, due to its expensive price, its cost-effectiveness ratio is higher than other potential adjuncts.

As a classic opioid, morphine has been widely used for treatments to moderate to severe pains. Intrathecal morphine had even been approved to manage refractory chronic pain by the U.S. Food and Drug Administration (FDA) [13]. Additionally, a combination of morphine and a local anaesthetic for epidural anesthesia provides superior analgesia than local anaesthetics alone [14, 15]. Moreover, several studies suggested peripheral nerve blocks in addition to morphine could enhance analgesia duration [16, 17].

Up to date, few studies are focused on comparing onset time, duration, and adverse effects of those two adjuvant agents (dexmedetomidine and morphine) in interscalene brachial plexus block with ropivacaine. This study compared the effects of these two adjuvants to ropivacaine in interscalene brachial plexus block.

Materials and methods

Study design

This study was a prospective, randomized, controlled, double-blinded study, performed at the Department of Anesthesiology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) between January 2016 and May 2016. The study was reviewed and approved by the Hospital Ethics Committee of the Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, chaired by Professor Xueqiong Zhu (No. 2016-02). This study was registered with chictr.org.cn with a study number of ChiCTR-IPR-16007688. A written consent was signed by each patient prior to participation.

Patients

Patient inclusion criteria were as follows: 1) American Society of Anesthesiologists (ASA) classification of I-II; 2) scheduled for elective distal arm or forearm surgery; 3) aged 18 to 65 years; and 4) Body Mass Index (BMI) between 18 and 26 kg/m^2. Exclusion criteria were: 1) allergies to dexmedetomidine, morphine, or ropivacaine; 2) sinus bradycardia and other arrhythmia; 3) complicated with heart, liver or kidney dysfunction; 4) complicated with coagulation dysfunction; 5) female patients with pregnancy.

Intervention and process

The patients were randomly divided into three parallel groups, ropivacaine plus placebo group (Group R), ropivacaine plus dexmedetomidine group (Group RD) and ropivacaine plus morphine group (Group RM), with the random number generated by a commercially available statistical software package (SPSS for Windows version 13.0; SPSS Inc, Chicago, IL, USA). An independent supervisor nurse who was blinded to this study prepared the study medications according to the random number sequence.

Oxygen with the rate of 3 L/min deliver through Venturi mask when patients entered in operating room and lying on the operating table following with continuously non-invasive monitoring items including blood pressure (NIBP), electrocardiograph (ECG), peripheral oxygen saturation (SPO_2) and respiratory rate by monitors (the IntelliVue MP50; Philips, Shanghai, China), and those monitoring items were recorded every three minutes. The measurements of these vital signs at the 10th minutes after patients lying on the operating table were defined as the baselines. A peripheral vein access on the hand opposite to the surgical side was established with an 18-gauge intravenous cannula by the same supervisor nurse.

Patients received 24 mL (120 mg) of 0.5% ropivacaine (Naropina, AstraZeneca AB, Sweden) plus 1 mL saline (Group R), or 24 mL (120 mg) of 0.5% ropivacaine plus 1 mL dexmedetomidine (Aibeining, Jiang Su Hengrui Medicine Co., China) at 0.75 μg/kg (Group RD), or 24 mL (120 mg) of 0.5% ropivacaine plus 1 mL morphine (Northeast Pharmaceutical Group, China) at 2 mg (Group RM) by a single injection for intersca-

Table 1. Patient demographic characteristics

	Group R (n=27)	Group RD (n=31)	Group RM (n=34)
Gender (female/male)	9/18	8/23	6/28
Age (years)	39±10	37±10	42±8
Weight (kg)	65±10	61±5	58±11
ASA physical status (I/II)	22/5	27/4	25/9
Surgical duration (min)	71±16	74±17	69±15

Values are expressed as the mean ± SD or absolute numbers. ASA means American Society of Anesthesiologists; Group R means ropivacaine group; Group RD means ropivacaine plus dexmedetomidine group, Group RM means ropivacaine plus morphine group.

lene brachial plexus block. All brachial blocks were performed under nerve stimulation techniques by the same senior anesthetist. Skin landmarks including the cricoid cartilage, the two heads of the sternocleidomastoid muscle and the interscalene groove were marked. A horizontal line was drawn at the level of the cricoid cartilage to intersect the interscalene groove laterally, defining the needle insertion point. An 18 gauge, 35 mm, short-bevel stimulating needle (Biometer, Melsungen, Germany) was connected to a nerve stimulator (Stimuplex, Braun, Germany) and was initially set up to deliver 1.0 mA intensity current (2 Hz, 0.2 ms). After skin infiltration with 2 mL lidocaine at 1% (v/v %), the needle was inserted through the skin at a 45° angle and moved caudally towards brachial plexus until a deltoid motor response was elicited. The position of the needle was adjusted to maintain the proper twitch, while the intensity of stimulation was progressively reduced to 0.3 mA current. If the adequate motor response was observed and no blood or cerebrospinal fluid was found in a syringe withdraw, local anesthetics were injected gradually.

Measurements

Onset times and durations of motor and sensory blocks in brachial plexus blocks are mainly measured in this study. Used assessments to sensory and motor blocks were reported as previously described [6] and briefly as follows. Sensory blocks were assessed by the pinprick sensation loss to a 22 gauge needle and the Visual Analog Scale (0-painless and 10-unbearable pain). Motor blocks were evaluated by thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and flexion at the elbow (musculocutaneous nerve) on a 3-point scale for motor functions (0-normal motor function, 1-reduced motor strength but able to move fingers, and 2-complete motor block). Both sensory and motor blocks were assessed every 3 minutes until 30 minutes after a local anesthetic injection before a surgery, and then once every 30 minutes after a surgery until they resolved.

The onset time was defined as the interval from administering of total local anesthetics to reaching complete sensory blocks (VAS score ≤3). Complete sensory blocks were defined by anesthesia blocks on all nerve territories. The duration of sensory blocks was defined as the interval from administering local anesthetics to all nerves completely resolving from anesthesia. Complete motor blocks were defined as the absence of voluntary movement on hand and forearm (score 0). The duration of motor block was defined as the interval from administering total local anesthetics to completely recovering of motor functions of hands and forearms.

Heart rate (HR), and mean arterial pressure (MAP) were recorded at 0, 5, 10, 15, 30, 45, 60, 90, and 120 minutes after administering anesthetics. Adverse events such as hypotension (a 20% decrease in relation to the baseline value), bradycardia (HR<50 beats per minute [bpm]), hypoxemia (SpO_2<90%), excessive sedation, Horner syndrome, nausea and vomiting episodes were also recorded, if occurred.

Power and statistical analysis

Based on preliminary experiments, a study including 78 patients (n=26) would have a power (90%) to detect significant differences in onset time of sensory blocks between the Group R and the Group RD/the Group RM. Extra 6 patients (n=2) were added in order to prevent error from loss to follow up.

Quantitative data were expressed as the mean ± standard deviation (mean ± SD). Single factor analysis of variance was used to compare in onset time and duration of sensory and motor blocks were compared among the groups. Data of HRs and MAPs at different time points were analyzed by variance analysis of repeated measures. One-way analysis of variance (ANOVA) was employed to analyze data of nonrepetitive measurements among more than two groups.

Table 2. Onset time and durations of sensory and motor blocks in three groups

Outcomes	Group R (n=27)	Group RD (n=31)	Group RM (n=34)
Onset time of sensory block(minutes)	12.00±2.23	6.8±1.75*,#	10.6±1.71
Onset time of motor block(minutes)	16.50±1.53	10.50±1.53*,#	15.80±1.35
Duration of sensory block(minutes)	281.29±24.97	403.53±41.77*,#	279.95±20.03
Duration of motor block(minutes)	160.65±11.81	235.39±23.85*,#	172.67±27.04

Values are expressed as the mean ± SD. Group R means ropivacaine group; Group RD means ropivacaine plus dexmedetomidine group; Group RM means ropivacaine plus morphine group; *: $P<0.05$ compared to The Group RM; #: $P<0.05$ compared to the Group R.

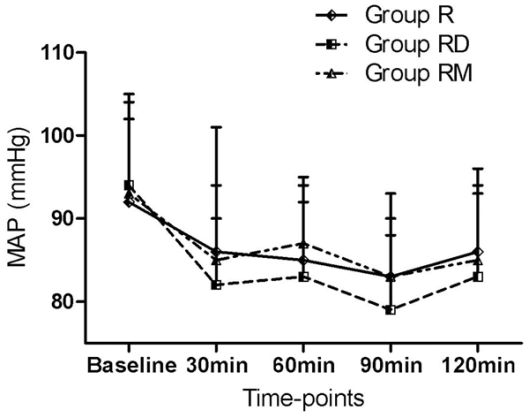

Figure 1. MAPs at 5 different time points in the three groups. Data are presented as the mean ± SD, n=27 in the Group R, n=31 in the Group RD, and n=34 in the Group RM. Group R means the ropivacaine group, Group RD means the ropivacaine plus dexmedetomidine group, Group RM means the ropivacaine plus morphine group.

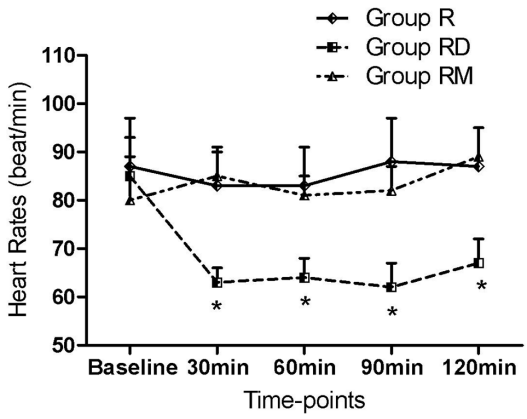

Figure 2. Heart rates at 5 different time points in the three groups. Data are presented as the mean ± SD, n=27 in the Group R, n=31 in the Group RD, and n=34 in the Group RM. Group R means the ropivacaine group, Group RD means the ropivacaine plus dexmedetomidine group, Group RM means the ropivacaine plus morphine group. *$P<0.05$ in comparison of the Group RD and the Group RM.

Categorical variables were evaluated with the χ^2 test, applying the Yates correction. All data were analyzed using a commercially available statistical software package (SPSS for Windows version 13.0; SPSS Inc., Chicago, IL, USA). A statistical significance was set up at P<0.05.

Results

A total of 105 patients were enrolled, with 13 dropouts, 92 patients were recruited (Group R: n=27, Group RD: n=31, Group RM: n=34), received the study interventions, and analyzed finally. All patients completed surgeries under a single-injection interscalene brachial plexus block, no other analgesics or general anesthesia were performed. None of the patients had severe complications. Demographic characteristics of the patients are presented in the **Table 1**. For these parameters including the proportion of genders, the mean age, weight, ASA physical status and surgical duration, no difference was found among the three groups (all *P values* are more than 0.05).

Compared to the Group RM, the onset time of sensory and motor blocks in the Group RD was less by 47.5% ($P<0.05$) and 50.5% ($P<0.05$), respectively. The durations of sensory and motor blocks in the Group RD were more by 49.1% ($P<0.05$) and 54.9% ($P<0.05$) than those in the Group RM. The onset time and durations of sensory and motor blocks were No difference was found in the onset time and durations of sensory and motor blocks between the Group RM and the Group R (all $P>0.05$), presented in the **Table 2**.

No significant difference in MAP levels was detected among three groups at all time-points (all *P values are more than* 0.05), presented as **Figure 1**. HRs in the Group RD were significantly lower than those in the Group R and Group RM (all $P<0.05$), presented as **Figure 2**).

Table 3. Adverse events in the three test groups

	Group R (n=27)	Group RD (n=31)	Group RM (n=34)
Hypotension (a 20% decrease in relation to the baseline value)	5	8	6
Bradycardia (HR<50 beats per minute [bpm])	4	14*	7
Hypoxemia (SpO_2<90%)	0	0	0
Excessive sedation (can not be awakened)	0	2	0
Horner syndrome	2	4	3
Nausea and vomiting episodes	0	0	4#

Values are expressed as the mean ± SD or absolute numbers. ASA means American Society of Anesthesiologists; Group R means ropivacaine group; Group RD means ropivacaine plus dexmedetomidine group, Group RM means ropivacaine plus morphine group; *P<0.05 compared to The Group RM, #P<0.05 compared to the Group RD.

Data of adverse events of the three groups are showed in the **Table 3**. More patients in the Group RD suffered from bradycardia than those in the Group RM (P<0.05). However, more patients in the Group RM had nausea and vomiting than in those in the Group RD (P< 0.05).

Discussion

This study aims to compare dexmedetomidine and morphine in their effects as adjuvants to local anaesthetic ropivacaine in the interscalene brachial plexus block. Results showed that ropivacaine combined with dexmedetomidine provides superior analgesia in interscalene brachial plexus blocks with the single-injection technique, compared to morphine and placebo. As an adjuvant, morphine did not show any benefit in the peripheral nerve block.

Dexmedetomidine, an α2-adrenergic receptor agonist has a higher ratio of α1/α2 activity (1300-1620:1) than clonidine (220:1). It has been widely used as a sedative or analgesic in the ICU and clinical anesthesia [18] and was also firstly proposed as an adjuvant therapy to lidocaine in the IV regional anesthesia resulting in prolonged durations of sensory and motor blocks [19]. A series of relevant clinical trials have demonstrated dexmedetomidine as an adjuvant could shorten onset time and prolong duration of sensory and motor blocks [6, 20], although some controversial conclusions were reported [21, 22]. Our study found onset time of sensory and motor blocks was shortened and duration of sensory and motor blocks was significantly prolongedin the interscalene brachial plexus blocks using an adjuvant of dexmedetomidine. The results are consistent with most similar studies [6, 19, 20]. In addition, Kanazi and colleagues have added dexmedetomidine to bupivacaine during a spinal block and foundthis combination was safe and more effective [23]. Mechanisms of dexmedetomidine producing superior anesthetic effects in peripheral nerve blocks remain unclear. However, some reports have indicated that multiple factors are involved [24] such as vasoconstriction, central analgesia, anti-inflammatory properties, and synergic effects with local anesthetics.

Administering dexmedetomidine as an adjuvant in brachial plexus blocks is an off-label use. Concerns are still left on the safety of dexmedetomidine's off-label use. Although a couple of studies [1, 6, 19, 21-24] have demonstrated the dexmedetomidine's off-label use is safe and effective, adverse events are also noted in our study. MAP and HR levels were affected negatively using dexmeditomidine as an adjuvant in brachial plexus blocks, compared to the baseline. Fourteen patients in the Group RD suffered from bradycardia, although all of them were reversed by intravenously administering 0.5 mg of atropine. No significant hypotension, excessive sedation, or other adverse events were observed in this off-label use. Recently, Han and colleagues [25] found that rat axillary brachial plexus with a mildly curvilinear incision exposed to high-dose (40 μg/kg) dexmedetomidine did not show significant apoptosis and degeneration. Although further studies are still required to confirm the results, few current studies indicate that the safety of this off-label use of dexmedetomidine is in doubt.

Morphine induces analgesic effects via μ-opioid receptors. It has been employed as a first-line medication for postoperative analgesia in hos-

pitals [26, 27]. As early as thirty years ago, Lanz and colleagues [28] added various doses of morphine (1-5 mg) to 0.75% bupivacaine in epidural anesthesia and found that analgesia duration was prolonged in all experimental groups with morphine when compared with controls without morphine. Due to opioid-associated side effects such as respiratory depression, nausea, vomiting, and pruritus, a high-dose of morphine is not recommended in postoperative analgesia. However, this study did not detect any difference in onset time and durations of motor or sensory blocks in the interscalene brachial plexus block with ropivacaine between with and without morphine. This finding is inconsistent with the expectations of our preliminary studies and also with those similar studies in other literatures [16, 17]. Two potential reasons are discussed as follows. (i) morphine dosages were different. In previous studies, higher doses of morphine (75 μg/kg [16] or 100 μg/kg [17]) were administered. In this study, 2 mg of morphine (an equivalent to about 30 μg/kg in a person with a body weight of 65 kg) was given. (ii) In peripheral nerve blocks, morphine at a high dose may enhaces analgesic effects via a relative high plasma concentration. In this study, a low dose of morphine can only induce analgesic effect by local diffusion. In consideration of its adverse effects, such as nausea and vomiting, morphine as an adjuvant in this peripheral nerve block has no apparent advantage.

Some limitations exist in this study. Firstly, all data of this study were obtained from one single medical center and the study sample was small. Secondly, plasma concentrations of dexmedetomidine and morphine were not monitored in the study. dexmedetomidine and morphine were administered via a single injection in interscalene brachial plexus blocks. No data on pharmacokinetics and pharmacodynamics are analyzed in this study. Finally, an optimal dose of dexmedetomidine in brachial plexus blocks was not detected and will be confirmed in our further studies.

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Disclosure of conflict of interest

None.

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References

[1] Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 2013; 110: 915-925.

[2] Grant SA, Nielsen KC, Greengrass RA, Steele SM, Klein SM. Continuous peripheral nerve block for ambulatory surgery. Reg Anesth Pain Med 2001; 26: 209-214.

[3] De Oliveira GS Jr, Castro Alves LJ, Nader A, Kendall MC, Rahangdale R, McCarthy RJ. Perineural dexamethasone to improve postoperative analgesia with peripheral nerve blocks: a meta-analysis of randomized controlled trials. Pain Res Treat 2014; 2014: 179029.

[4] Choquet O, Capdevila X. Case report: three-dimensional high-resolution ultrasound-guided nerve blocks: a new panoramic vision of local anesthetic spread and perineural catheter tip location. Anesth Analg 2013; 116: 1176-1181.

[5] Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. Anesthesiology 2009; 111: 406-415.

[6] Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg 2010; 111: 1548-1551.

[7] Kapral S, Gollmann G, Waltl B, Likar R, Sladen RN, Weinstabl C, Lehofer F. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anesth Analg 1999; 88: 853-856.

[8] Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. Br J Anaesth 2014; 112: 427-439.

[9] Laiq N, Khan MN, Arif M, Khan S. Midazolam with bupivacaine for improving analgesia quality in brachial plexus block for upper limb sur-

geries. J Coll Physicians Surg Pak 2008; 18: 674-678.
[10] Koh WU, Min HG, Park HS, Karm MH, Lee KK, Yang HS, Ro YJ. Use of hyaluronidase as an adjuvant to ropivacaine to reduce axillary brachial plexus block onset time: a prospective, randomised controlled study. Anaesthesia 2015; 70: 282-289.
[11] Zhang Y, Wang CS, Shi JH, Sun B, Liu SJ, Li P, Li EY. Perineural administration of dexmedetomidine in combination with ropivacaine prolongs axillary brachial plexus block. Int J Clin Exp Med 2014; 17: 680-685.
[12] Abdallah FW, Dwyer T, Chan VW, Niazi AU, Ogilvie-Harris DJ, Oldfield S, Patel R, Oh J, Brull R. IV and perineural dexmedetomidine similarly prolong the duration of analgesia after interscalene brachial plexus block: a randomized, three-arm, triple-masked, placebo-controlled trial. Anesthesiology 2016; 124: 683-695.
[13] Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt W, Yaksh T, Mekhail N. Polyanalgesic consensus conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2012; 15: 436-464.
[14] Axelsson K, Johanzon E, Essving P, Weckström J, Ekbäck G. Postoperative extradural analgesia with morphine and ropivacaine. A double-blind comparison between placebo and ropivacaine 10 mg/h or 16 mg/h. Acta Anaesthesiol Scand 2005; 49: 1191-1199.
[15] Marcus RJ, Wong CA, Lehor A, McCarthy RJ, Yaghmour E, Yilmaz M. Postoperative epidural morphine for postpartum tubal ligation analgesia. Anesth Analg 2005; 101: 876-881.
[16] Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P. The addition of opioids to local anaesthetics in brachial plexus block: the comparative effects of morphine, buprenorphine and sufentanil. Anaesthesia 1997; 52: 858-862.
[17] Bourke DL, Furman WR. Improved postoperative analgesia with morphine added to axillary block solution. J Clin Anesth 1993; 5: 114-117.
[18] Gu H, Liu J, Wu C. Impact of dexmedetomidine versus propofol on cardiac function of children undergoing laparoscopic surgery. Int J Clin Exp Med 2014; 7: 5882-5885.
[19] Memiş D, Turan A, Karamanlioğlu B, Pamukçu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004; 98: 835-840.
[20] Song JH, Shim HY, Lee TJ, Jung JK, Cha YD, Lee DI, Kim GW, Han JU. Comparison of dexmedetomidine and epinephrine as an adjuvant to 1% mepivacaine in brachial plexus block. Korean J Anesthesiol 2014; 66: 283-289.
[21] Agarwal S, Aggarwal R, Gupta P. Dexmedetomidine prolongs the effect of bupivacaine in supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol 2014; 30: 36-40.
[22] Esmaoglu A, Mizrak A, Akin A, Turk Y, Boyaci A. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. Eur J Anaesthesiol 2005; 22: 447-451.
[23] Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006; 50: 222-227.
[24] Kaygusuz K, Kol IO, Duger C, Gursoy S, Ozturk H, Kayacan U, Aydin R, Mimaroglu C. Effects of adding dexmedetomidine to levobupivacaine in axillary brachial plexus block. Curr Ther Res Clin Exp 2012; 73: 103-111.
[25] Han JH, Kim DO, Yi JW, Parka SW, Kanga WJ, Choia YK, Kimc SH, Kod IG, Jind JJ, Kimd SE, Kimd CJ. Dexmedetomidine, α2-adrenoceptor agonist, does not induce apoptosis in the brachial plexus of rats. Animal Cells and Systems 2014; 18: 407-415.
[26] Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 2008; 107: 1384-1389.
[27] Gulur P, Koury K, Arnstein P, Lee H, McCarthy P, Coley C, Mort E. Morphine versus hydromorphone: does choice of opioid influence outcomes? Pain Res Treat 2015; 2015: 482081.
[28] Lanz E, Kehrberger E, Theiss D. Epidural morphine: a clinical double-blind study of dosage. Anesth Analg 1985; 64: 786-791.