

Effect of dexmedetomidine as an adjuvant to ropivacaine for wound infiltration in patients undergoing open gastrectomy

A prospective randomized controlled trial

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Abstract

Objectives: The primary objective of this study was to investigate whether dexmedetomidine could potentiate the analgesic efficacy of ropivacaine, when added to ropivacaine for wound infiltration in patients undergoing open gastrectomy.

Methods: Fifty patients scheduled for open gastrectomy were divided into 2 equal groups that were received wound infiltration using 20 mL 0.3% ropivacaine plus 2 mL normal saline (group R) or 20 mL 0.3% ropivacaine plus 2 mL 1.0 µg/kg dexmedetomidine (group DR). Visual analogue scale (VAS) pain score, patient-controlled analgesia (PCA) pump press number, sufentanil consumption, postoperative nausea and vomiting (PONV), and wound healing score were recorded.

Results: The VAS pain score were comparable between the 2 groups at the observation time points ($P > .05$), PCA pump press number and sufentanil consumption were higher in group R than that in group DR at 0 to 2, 2 to 4, 4 to 6 time intervals ($P < .05$) except for 6 to 8, 8 to 10, 10 to 12 time intervals ($P > .05$), meanwhile, the 24 hours total sufentanil consumption was also higher in group R than that in group DR (90.4 ± 20.5 vs 79.2 ± 9.4) ($P < .05$), there were no significant differences in PONV and wound healing score between the 2 groups ($P > .05$).

Conclusions: Dexmedetomidine as an adjuvant to ropivacaine for wound infiltration promoted the analgesic efficacy of ropivacaine, reduced sufentanil consumption, and had no effect on wound healing; it could be as an ideal adjuvant which could potentiate the analgesic efficacy of local anesthetics.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, DEX = dexmedetomidine, DR = dexmedetomidine with ropivacaine, PCA = patient-controlled analgesia, PCIA = patient-controlled intravenous analgesia, PONV = postoperative nausea and vomiting, R = ropivacaine, VAS = visual analogue scale.

Keywords: dexmedetomidine, pain, ropivacaine, wound infiltration

1. Introduction

Open gastrectomy is a frequent surgery performed due to the high morbidity of gastric diseases in our country. Inevitably, the incision made in the abdominal wall contributes to severe

postoperative pain which may cause decreased function of immune system, decreased healing, and painful suffering; these changes may probably negatively affect the postoperative recovery quality.^[1,2]

Successful postoperative analgesia facilitates faster recovery, improves patient satisfaction. Traditionally, the most frequently used analgesic method for abdominal surgery is patient-controlled intravenous analgesia (PCIA), the main drug used is opioids. However, opioid-induced side effects such as nausea or vomiting, pruritus (itching), urinary retention, sedation, and respiratory depression are very common.^[3,4] In order to reduce opioid-related adverse effects, a multimodal postoperative analgesia is recommended.

As a component of multimodal postoperative pain management, infiltration with local anesthetic around the surgical wound is an effective analgesic technique, which could decrease postoperative wound pain and analgesic usage.^[5] Unfortunately, the analgesia duration of local anesthetics is limited, peripheral nerve catheter is 1 method to provide prolonged or continuous analgesia for various peripheral regional anesthetic techniques. However, there are still some disadvantages of this method, such as dislocation of catheters^[6] or catheter infection.^[7] Thus an adjuvant which could extend the duration of single-shot peripheral nerve block is of particular interest. Undoubtedly, dexmedetomidine (DEX) is an ideal adjuvant in this context.

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DEX is a strong and highly selective α_2 -adrenoceptor agonist. It could enhance the analgesic efficacy of local anesthetics when added as an adjuvant for peripheral regional nerve block.^[8–10]

Therefore, we hypothesized that adding DEX to ropivacaine for wound infiltration could enhance the analgesic efficacy of ropivacaine. Therefore, we designed a prospective, double-blinded, randomized study to assess the effect of DEX as an adjuvant to ropivacaine for wound infiltration in patients undergoing open gastrectomy.

2. Materials and methods

2.1. Patients

The study was approved by the Hospital Ethics Committee of the Lianyungang clinical college of Nanjing medical university. After obtaining written information consent from patients, 50 patients aged 35 to 75 years with American Society of Anesthesiologists (ASA) grade I to III and underwent open gastrectomy in our hospital were enrolled. Patients were excluded if they had a history of allergy to any local anesthetics, body mass index $>30\text{ kg/m}^2$, opioids addiction or abuse, chronic pain, and psychiatric diseases which would affect postoperative assessments.

2.2. Randomization and study design

Randomization into 1 of the 2 groups was based on computer random number generation. The randomization sequence was generated by a statistician who was not involved in the study. The details of the series were unknown to both the investigators and the patients, and the group assignments were kept in sealed envelopes. After the patient entering into the operation room and just before the induction of anesthesia, the numbered envelope was opened and the card inside determined into which group the patient would be placed.

Patients were randomized to receive ropivacaine wound infiltration (group R) or ropivacaine with DEX (group RD). In group R, wound infiltration initiated with 20 mL 0.3% ropivacaine (batch 14111736; Hengrui Medicine, Jiangsu, China) plus 2 mL normal saline. In group RD, wound infiltration initiated with 20 mL 0.3% ropivacaine plus 2 mL 1.0 $\mu\text{g/kg}$ DEX (batch 13070534; Hengrui Medicine) dissolved in normal saline.

The patients, the surgeon, the anesthesiologists, and the staff who collect the data were all blinded to the study drugs or the patient's group assignment.

2.3. Procedure of anesthesia and wound infiltration

After arriving at the operation room, all the patients received standard examinations including electrocardiogram, pulse oxygen saturation (SpO_2), invasive blood pressure, and bispectral index (BIS) monitoring. All patients in both groups received the same anesthetic protocol. Patients received propofol 2 mg/kg, sufentanil 0.5 $\mu\text{g/kg}$, and cisatracurium 0.15 mg/kg for induction. After tracheal intubation, mechanical ventilation was conducted with a tidal volume of 6 to 8 mL/kg and $\text{P}_{\text{ET}}\text{-CO}_2$ of 35 to 45 mm Hg. Anesthesia was maintained with sevoflurane/ O_2 /air mixture to keep BIS values between 40 and 60, cisatracurium was injected intravenously for muscle relaxation. Before the incision was sutured, ropivacaine or ropivacaine with DEX were infiltrated into the tissues around the incision, including the peritoneum, muscles, and subcutaneous tissue. All the surgical interventions were performed by the same surgical team.

2.4. Postoperative pain management

After operation, patients in both groups received a sufentanil-based intravenous patient-controlled analgesia (PCA) pump (total 2 $\mu\text{g/kg}$ sufentanil in 100 mL saline with 1 pump press delivering a 1.5 mL bolus and a continuous background infusion of 0.04 $\mu\text{g/kg/h}$ sufentanil). If the visual analogue scale (VAS) pain score assessed was >4 , 3 μg sufentanil as rescue analgesia was injected intravenously. Considering the strong analgesic efficacy of sufentanil, other analgesics were not administered.

2.5. Studied variables

Patient demographic information including age, weight, sex, ASA class, surgical approach, and time of operation were recorded.

VAS (0–10) pain score (VAS; 0, no pain, to 10, worst possible pain) was measured at 2, 4, 6, 8, 10, 12, and 24 hours time points after the end of surgery.

PCA press number and sufentanil consumption (PCA infused plus rescued sufentanil) were recorded at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, and 10 to 12 hours time intervals, and the total amount of 24 hours sufentanil consumption was also recorded in both groups.

Incidence of postoperative nausea and vomiting (PONV) for the first 24 hours after the end of surgery, and wound healing score (1, no effusion, 2, effusion, 3, infection) for the first 72 hours after the end of surgery were also analyzed.

Primary outcome measure in this study was the 24 hours sufentanil consumption. The secondary outcome measures included VAS pain score, PCA pump press number, incidence of PONV, and wound healing score.

2.6. Statistical analysis

According to our pilot study, a power analysis was performed using the 24 hours total sufentanil consumption. We projected a mean 24 hours sufentanil consumption of 92.1 ± 20.9 in 10 patients who received wound infiltration with ropivacaine. We calculate that 20 patients were required for each group to detect significant between-group differences of 20%, with an $\alpha = 0.05$, 2-tailed and $\beta = 0.2$. Taking into account potential dropouts in both groups, we decided to enroll 50 patients.

Statistical analyses were performed using SPSS 16.0 for windows (SPSS 16, Chicago, IL). Continuous numerical data were expressed as median and interquartile range or mean and standard deviation. Categorical data were expressed as frequencies and percentages. Normally distributed numerical data between groups were analyzed using the Student *t* test. Skewed data between groups were analyzed by the Mann–Whitney *U* test. Categorical variables were compared using the Fisher exact test or the Pearson Chi-square test as applicable. All tests were 2 tailed. $P < .05$ was considered statistically significant.

3. Results

Fifty patients were enrolled in this study. Four patients were excluded: 3 patients refused to participate in the study and 1 patient was converted to laparoscopic surgery. Of the remaining 46 patients, 23 patients were randomized in each group in this study (Fig. 1).

3.1. Demographic characteristics

Patients in both groups had comparable demographic characteristic data and surgical approach as well as operation time ($P > .05$) (Table 1).

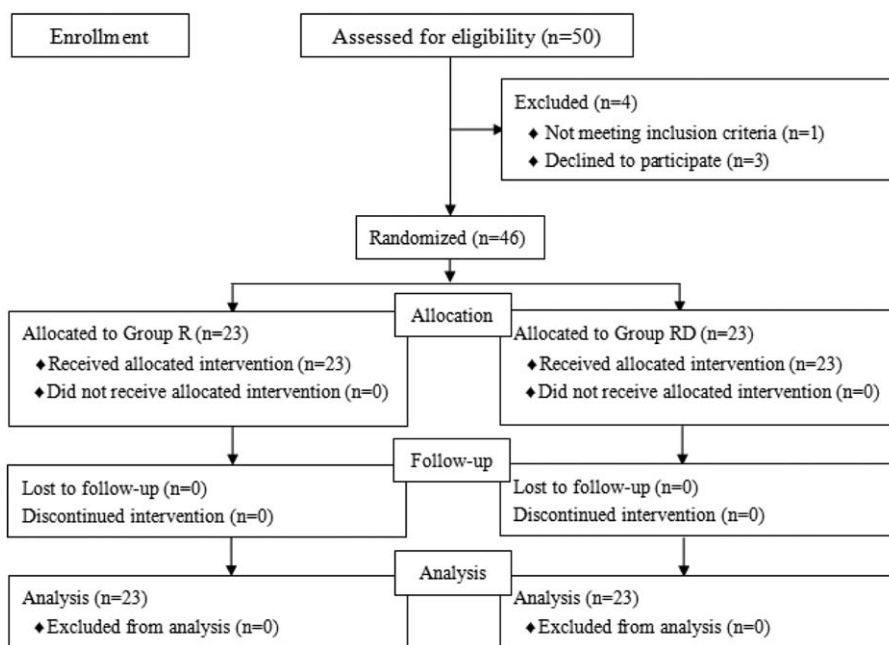


Figure 1. CONSORT diagram.

3.2. VAS pain score

The postoperative VAS pain score decreased gradually over time in both groups. However, there was no significant difference between the 2 groups during the observation time points ($P > .05$) (Table 2).

3.3. Sufentanil consumption and PCA press number at different time intervals

The PCA pump press number in group R was higher than that in group RD at 0 to 2, 2 to 4, 4 to 6-hour time intervals except 6 to 8, 8 to 10, and 10 to 12-hour time intervals. Along with the change of the PCA pump press number, the sufentanil consumption in group R was also higher than that in group RD at the same time intervals ($P < .05$) (Table 3).

3.4. Postoperative parameters

Compared with group RD, the total 24 hours sufentanil consumption was higher than that in group R ($P < .05$). The

incidence of PONV for the first 24 hours after the end of surgery in group R was higher than that in group RD; however, there was no significant difference between the 2 groups, the wound healing scores for the first 72 hours after the end of surgery in the 2 groups were comparable ($P > .05$) (Table 4).

4. Discussion

In this prospective study of patients who underwent open gastrectomy, the results indicated that 1.0 μg/kg DEX, as an adjuvant to 0.3% ropivacaine for wound infiltration, enhanced the analgesic effect of ropivacaine, as shown by lower requirement for postoperative sufentanil consumption and fewer PCA pump press number. Meanwhile, adding DEX to ropivacaine did not affect the wound healing.

Patients who underwent open gastrectomy usually complain of severe pain during the postoperative period, which may result in severe postoperative complications, prolong hospital stays, and develop to chronic pain.^[11]

Successful management of postoperative pain facilitates faster postoperative recovery, improves patient’s satisfaction, and may shorten hospitalization. Traditionally, PCIA is frequently used as

Table 1
Comparison of demographics, surgical approach, and operation time between the 2 groups.

Demographics	Group R (n=23)	Group RD (n=23)	P
Age, yr	63.7 ± 6.7	64.5 ± 6.4	.706
Sex (M/F) (n/n)	13/10	12/11	.767
Height, cm	166.3 ± 5.8	168.0 ± 6.6	.346
Weight, kg	62.6 ± 9.2	61.8 ± 6.6	.742
ASA (I/II/III) (n/n/n)	4/15/4	6/12/5	.656
Surgical approach	15/8	12/11	.807
Subtotal/total (n/n)			
Operation time, min	114.0 ± 10.1	116.4 ± 12.0	.475

Data are expressed as mean ± SD or number of patient.
ASA = American Society of Anesthesiologists, R = ropivacaine, RD = ropivacaine with dexmedetomidine.

Table 2
Comparison of VAS between the 2 groups.

VAS, h	Group R (n=23)	Group RD (n=23)	P
2	3 (2–4)	3 (2–4)	.808
4	3 (2–3)	3 (2–3)	.613
6	3 (2–3)	2 (2–3)	.526
8	2 (2–3)	2 (2–3)	.616
10	2 (1–3)	2 (1–3)	.851
12	2 (1–2)	2 (1–2)	.830
24	1 (1–2)	1 (1–2)	.683

Data are expressed as median [interquartile range (IQR)].
R = ropivacaine, RD = ropivacaine with dexmedetomidine, VAS = visual analogue scale.

Table 3**Comparison of PCA pump press number and sufentanil consumption between the 2 groups at different time intervals.**

Time intervals	PCA pump press number			Sufentanil consumption		
	Group R (n=23)	Group RD (n=23)	P	Group R (n=23)	Group RD (n=23)	P
0–2	4 (3–5)	3 (2–3)*	.007	12.5±4.4	9.8±2.1*	.01
2–4	4 (3–5)	2 (2–3)*	<.001	12.6±4.1	9.1±1.8*	.001
4–6	4 (2–4)	2 (2–3)*	<.001	11.6±3.5	8.4±1.4*	<.001
6–8	2 (1–2)	2 (2–2)	.677	8.9±2.6	8.7±1.3	.720
8–10	1 (1–2)	1 (1–2)	.226	7.7±2.2	7.1±1.4	.209
10–12	1 (0–1)	1 (0–1)	.385	7.0±1.9	6.5±1.4	.312

Data are expressed as median (IQR) or mean ± SD.

PCA = patient-controlled analgesia, R = ropivacaine, RD = ropivacaine with dexmedetomidine.

* $P < .05$.

the main component of postoperative pain management after major abdominal surgery. However, the use of opioids in PCIA is often associated with adverse effects, such as PONV, respiratory depression, urine retention, intestinal obstruction, and other side effects.^[12] EA could also provide better analgesia than PCIA, but it may be limited in daily clinical application due to contraindications, technical failure, or disastrous complications.^[13]

Wound infiltration with local anesthetics could be used as an effective supplement component of multimodal postoperative analgesia. Lee et al^[5] reported that local anesthesia infiltration at wound site decreased postoperative wound pain and analgesic usage in patient who underwent single-incision laparoscopic colectomy. Kong et al^[14] suggested that ropivacaine wound infiltration reduced the opioid analgesic requirement and incidence of PONV, while provided a good analgesia. This technique is beneficial but cannot offer long-term pain control; thus, how to prolong the effect of one single-shot administration of local anesthetics should be under consideration.

DEX is a highly selective and strong α_2 -adrenoceptor agonist which has sedative, analgesic, and sympatholytic properties. It has gained widespread clinical applications as an adjuvant to local anesthetics for peripheral regional anesthetic techniques.^[8–10] However, there are a few clinical studies regarding DEX added to local anesthetics for wound infiltration. In a recent study, Mandal et al^[8] suggested that DEX added to 2% lignocaine with adrenaline for local infiltration at the trauma site not only reduced bleeding but also decreased perioperative fentanyl consumption, and provided better surgeon's satisfaction score and lesser side effects. In another study, Kim and Kang^[15] reported that adding DEX to ropivacaine for perianal injection may have an additive effect in reducing postoperative pain and fentanyl consumption in patient who underwent hemorrhoidectomy.

Table 4**Comparison of 24 hours sufentanil consumption, wound healing score, and PONV between the 2 groups.**

Parameters	Group R (n=23)	Group RD (n=23)	P
24 h total sufentanil consumption, μg	90.4±20.5	79.2±9.4*	.022
Wound healing score	1 (0–1)	1 (0–1)	.572
Nausea	5 (21.7%)	3 (13.0%)	.699
Vomiting	2 (8.7%)	1 (4.3%)	—

Data are expressed as mean ± SD, median [interquartile range (IQR)], and number of patient.

PONV = postoperative nausea and vomiting, R = ropivacaine, RD = ropivacaine with dexmedetomidine.

* $P < .05$.

In our study, to reduce the patient's postoperative pain and improve the patient's analgesia, an additional 3 μg sufentanil was injected intravenously as long as the pain the patient complained was higher than a VAS pain score of 4; thus, no significant difference in VAS pain score was observed between the 2 groups. However, we still could come to the conclusion that adding DEX to ropivacaine for wound infiltration promoted the analgesic efficacy of ropivacaine from the decreased PCA pump press number and sufentanil consumption during the first 6 hours after surgery. The efficacy of wound infiltration decreased gradually as time extended, the PCA may play a relatively important role in postoperative analgesic care from 6 to 24 hours after surgery. Meanwhile, the pain the patient complained was also decreased, that might be the reasons no significant differences in PCA pump press number and sufentanil consumption were observed from 6 to 24 hours after surgery.

The exact mechanism of action of DEX is still unknown, but 2 possible theories have been clarified: The first one is vasoconstriction mediated by action of vascular α_2 adrenoceptors around the site of injection, which delays the absorption of local anesthetic and prolongs the efficacy of local anesthetic.^[16] Akimoto et al^[17] recently reported that DEX improved the tissue distribution and anesthetic action of lidocaine; this effect may be related to vasoconstriction caused by DEX. Masuki et al^[18] also reported that DEX could cause more α_2 -selective vasoconstriction than clonidine in the human forearm. The second one is a direct effect on peripheral nerve activity, which is mediated directly by blocking an activity-dependent cation current (the I_h current); the I_h current normally acts to reset the nerve from a hyperpolarized state back to the resting membrane potential.^[19] By keeping the nerve in a hyperpolarized state, the nerve is unable to generate a new action potential, especially in C-fibers and A δ fibers.^[20] Thus, the effect of DEX might be associated with vasoconstriction or peripheral nerve activity; however, further studies are still needed to explore the mechanism for the action in detail. In our study, it was possible that DEX interfered with the absorption of ropivacaine via vasoconstriction. Meanwhile, DEX inhibited the impulse conduction in primary afferents by blocking the I_h current, these effects may contribute to the result that DEX potentiate the analgesic efficacy of ropivacaine for wound infiltration.

The risk of delayed wound healing might be 1 reason that surgeons are hesitate to use the wound infiltration anesthesia technique. However, the result of our study showed that wound healing was not affected by this technique. In addition, the vasoconstriction around the wound mediated by DEX may reduce the effusion from the wound, which might be beneficial to the wound healing.

PONV are common complications concerning patients receiving opioids for PCA). Intensive research was performed to develop therapeutic strategies to prevent this complication. Many investigators have suggested that DEX could reduce the incidence of PONV. Song et al^[21] reported that adding DEX to a fentanyl-based PCA pump reduced the frequency and severity of nausea in patients with at least 3 risk factors for PONV. Mohta et al^[22] also reported that DEX added to bupivacaine for paravertebral block decreased the incidence of PONV in patients who underwent major breast cancer surgery. Although the incidence of PONV was decreased in group RD in this study, there was no significant difference between the 2 groups, the sample size was small might be the reason.

5. Limitations

There were still some limitations in this study. First, only 1 concentration of DEX and ropivacaine were evaluated in our study. Additional studies are needed to investigate more concentration of DEX and ropivacaine. Second, we recorded the VAS pain score every 2 hours during the first 12 hours after the surgery, some patients may fall asleep when we assessed the VAS pain score, and this may make the patients uncomfortable. Third, the plasma concentration of DEX was not detected in our study; further studies are needed to explore whether its action was related to systemic absorption.

6. Conclusions

Taken together, wound infiltration is an effective and safe postoperative analgesic technique, which could be as an effective component of multimodal postoperative analgesic regimen; adding 1.0 µg/kg DEX to 0.3% ropivacaine for wound infiltration prompted the analgesic properties of ropivacaine, reduced sufentanil consumption, and had no effect on wound healing; it could be as an ideal adjuvant which potentiates the analgesic efficacy of local anesthetics.

References

- [1] Cepeda MS, Africano JM, Polo R, et al. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003;105:151–7.
- [2] Carr DB, Goudas L. Acute pain. *Lancet* 1999;353:2051–8.
- [3] Dahl JB, Jeppesen IS, Jørgensen H, et al. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *Anesthesiology* 1999;91:1919–27.
- [4] Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 2009;64:643–51.
- [5] Lee KC, Lu CC, Lin SE, et al. Infiltration of local anesthesia at wound site after single-incision laparoscopic colectomy reduces postoperative pain and analgesic usage. *Hepatogastroenterology* 2015;62:811–6.
- [6] Marhofer D, Marhofer P, Triffterer L, et al. Dislocation rates of perineural catheters: a volunteer study. *Br J Anaesth* 2013;111:800–6.
- [7] Compere V, Legrand JF, Guitard PG, et al. Bacterial colonization after tunneling in 402 perineural catheters: a prospective study. *Anesth Analg* 2009;108:1326–30.
- [8] Mandal D, Das A, Chhauha S, et al. The effect of dexmedetomidine added to preemptive (2% lignocaine with adrenaline) infiltration on intraoperative hemodynamics and postoperative pain after ambulatory maxillofacial surgeries under general anesthesia. *Anesth Essays Res* 2016;10:324–31.
- [9] Bharti N, Sardana DK, Bala I. The analgesic efficacy of dexmedetomidine as an adjunct to local anesthetics in supraclavicular brachial plexus block: a randomized controlled trial. *Anesth Analg* 2015;121:1655–60.
- [10] Abdallah FW, Dwyer T, Chan VW, et al. 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;124:683–95.
- [11] Dajczman E, Gordon A, Kreisman H, et al. Long-term postthoracotomy pain. *Chest* 1991;99:270–4.
- [12] Kehlet H, Rung GW, Callesen T. Postoperative opioid analgesia: time for a reconsideration? *J Clin Anesth* 1996;8:441–5.
- [13] Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009;102:179–90.
- [14] Kong TW, Park H, Cheong JY, et al. Efficacy of continuous wound infiltration of local anesthetic for pain relief after gynecologic laparoscopy. *Int J Gynaecol Obstet* 2014;124:212–5.
- [15] Kim BG, Kang H. The effect of preemptive perianal ropivacaine and ropivacaine with dexmedetomidine on pain after hemorrhoidectomy: a prospective, randomized, double-blind, placebo-controlled study. *Indian J Surg* 2014;76:49–55.
- [16] Yoshitomi T, Kohjitani A, Maeda S, et al. Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. *Anesth Analg* 2008;107:96–101.
- [17] Akimoto T, Hashimoto S, Sunada K. Dexmedetomidine (12.5 (g/mL) improves tissue distribution, anesthetic action, and hemodynamic effects of lidocaine after palatal infiltration in rats. *Odontology* 2016;104:390–6.
- [18] Masuki S, Dinenna FA, Joyner MJ, et al. Selective alpha2-adrenergic properties of dexmedetomidine over clonidine in the human forearm. *J Appl Physiol* 1985;2005;99:587–92.
- [19] Brummett CM, Hong EK, Janda AM, et al. 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.
- [20] Kroin JS, Buvanendran A, Beck DR, et al. Clonidine prolongation of lidocaine analgesia after sciatic nerve block in rats is mediated via the hyperpolarization activated cation current, not by alpha-adrenoreceptors. *Anesthesiology* 2004;101:488–94.
- [21] Song Y, Shim JK, Song JW, et al. Dexmedetomidine added to an opioid-based analgesic regimen for the prevention of postoperative nausea and vomiting in highly susceptible patients: a randomised controlled trial. *Eur J Anaesthesiol* 2016;33:75–83.
- [22] Mohta M, Kalra B, Sethi AK, et al. Efficacy of dexmedetomidine as an adjuvant in paravertebral block in breast cancer surgery. *J Anesth* 2016;30:252–60.