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Perineural Dexmedetomidine Reduces the Median Effective Concentration of Ropivacaine for Adductor Canal Block

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Chunguang Wang**

AEF 2 **Zhiqiang Zhang**

BCE 3 **Wenhai Ma**

BC 1 **Rui Liu**

BC 1 **Qinghui Li**

B 3 **YanJun Li**

1 Department of Anesthesiology, The First Central Hospital of Bao Ding, Baoding, Hebei, P.R. China

2 Department of Cardio-Thoracic Surgery, The First Central Hospital of Bao Ding, Baoding, Hebei, P.R. China

3 Department of Orthopedics, The First Center Hospital of Bao Ding, Baoding, Hebei, P.R. China

Corresponding Authors:

Chun-guang Wang, e-mail: wangchunguang@163.com, Zhi-qiang Zhang, e-mail: zhiqiangzhangbds@yeah.net

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Background:

Multimodal analgesic regimens are well known as the best option for total knee arthroplasty. They include the adductor canal block, combined with local infiltration analgesia and a block of the interspace between the popliteal artery and the capsule of the posterior knee. However, these analgesic techniques all require a large amount of local anesthetics. In this study, we explored whether the quantity of local anesthetics could be decreased by using dexmedetomidine for the adductor canal block.

Material/Methods:

Fifty-four patients scheduled for unilateral, primary total knee arthroplasty were allocated into 2 groups: the ropivacaine group (group R) and the dexmedetomidine group (group RD). Ropivacaine 0.5% was chosen as the initial concentration, and the concentration was decreased or increased according to the response of the previous participant. Based on Dixon's up-and-down method, the median effective concentration was calculated.

Results:

The quadriceps strength was similar between the 2 groups, both at 30 min after adductor canal block and during recovery from general anesthesia in the Postanesthesia Care Unit. None of the patients in this study exhibited bradycardia or hypotension. The median effective concentration of ropivacaine for adductor canal block was 0.29% (95% confidence interval [CI], 0.28-0.31%) in group RD, which was lower than that in group R (0.38% [95% CI, 0.36-0.41%]).

Conclusions:

This study found perineural dexmedetomidine 1 µg/kg could reduce the median effective concentration of ropivacaine for the adductor canal block.

Keywords:

Anesthesia, Local • Anesthetics, Local • Dexmedetomidine

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Background

With the rapid increase in the aging population, surgical treatment is becoming more common among elderly people, especially those with degenerative knee disease. Total knee arthroplasty is the most effective treatment for restoring the function of the knee joint for patients with end-stage knee osteoarthritis. Unfortunately, the management of moderate to severe pain among these patients during the postoperative period remains a considerable challenge for the anesthesiologist [1]. Multimodal analgesic regimens are well known to be the best option for total knee arthroplasty. Such regimens can include adductor canal block, combined with local infiltration analgesia and a block of the interspace between the popliteal artery and the capsule of the posterior knee [2-6]. However, these analgesic techniques require a large amount of local anesthetics. Furthermore, most of the patients undergoing total knee arthroplasty are elderly. Compared with younger patients, the elderly are more sensitive to local anesthetics and metabolize them more slowly, which may lead to accumulation of these agents and even toxicity. To achieve effective analgesia, it is essential to reduce the consumption of local anesthetics during the perioperative period. Perineural adjuvant of local anesthetics is a useful technique to address this problem [7]. Previous studies found that dexmedetomidine can improve the potency of local anesthetics, while sparing nerve injury [8-10]. However, whether the quantity of local anesthetic for adductor canal block can be reduced by dexmedetomidine has not been reported. We speculated that the quantity of local anesthetics could be decreased by perineural administration of dexmedetomidine. Hence, we investigated the effect of perineural dexmedetomidine on the median effective concentration (EC50) of ropivacaine for adductor canal block.

Material and Methods

Subject Selection

The study complied with the Declaration of Helsinki. After approval by the Ethics Committee of our institution (no. [2018] 038) and obtaining written informed consent, we enrolled patients undergoing selective, unilateral primary total knee arthroplasty in our study. Patients with a contraindication for nerve block administration, diabetes, allergy to local anesthetics or dexmedetomidine, bradycardia, long-term administration of analgesics, renal or hepatic dysfunction, or an inability to complete assessments were excluded. According to a computer-generated randomization sequence, stored in sealed opaque envelopes, all subjects were randomly assigned to an experimental group: the ropivacaine group (group R) or the dexmedetomidine group (group RD). In group R, only ropivacaine was used for adductor canal block. In group RD, a mixture of dexmedetomidine 1 µg/

kg and ropivacaine was used for adductor canal block. The computer-generated randomization sequence and study medication were prepared by 2 of us (ZZ, RL). A senior anesthesiologist implemented adductor canal block, and another anesthesiologist performed the assessment on nerve block. Both anesthesiologists were blinded to the randomization of group allocation, type of medicine, and the concentration of ropivacaine. A nurse who did not participate in assessment was in charge of preparing the medication based on the assessment result.

Protocol

Participants received oxygen by nasal cannula and were placed in a supine position with the lower extremity externally rotated. Standard monitors were utilized and no premedication was used in the operation room. With a short-axis view, an ultrasound probe (liner transducer, 6-13 MHz, M-Turbo, Sonosite, USA) was placed on the anteromedial part of the thigh at the level of the midpoint, between the greater trochanter of the femur and the proximal edge of patella. The structure of the adductor canal, surrounded by the sartorius muscle, the vastus medialis muscle, and the adductor longus muscle, was identified clearly. After aseptic precaution, lidocaine 1% was injected into skin and subcutaneously. Then, an 80-mm short-beveled needle (PAJUNK®, PAJUNK GmbH Medizintechnologie, Germany), guided by ultrasound, was inserted through the sartorius muscle into the region between femoral artery and saphenous nerve. Local anesthetics were subsequently injected for adductor canal block.

Cutaneous sensation innervated by the saphenous nerve (the anteromedial aspect of the knee, shin area) was assessed 30 min after injection. The absence of acupuncture sensation in the area innervated by the saphenous nerve was defined as a complete sensory block. The scoring for sensory evaluation was as follows: 0 (totally absence of sensation), 1 (loss of acupuncture sensation but not touch sensation), and 2 (no loss of sensation, similar to contralateral side) [11]. The muscle strength was evaluated immediately after sensory assessment and recovery from general anesthesia in the Postanesthesia Care Unit. The scoring for the evaluation of muscle strength was as follows: 0 (no contraction), 1 (contraction, but patient cannot move joint), 2 (patient can move joint, but cannot resist gravity), 3 (patient can resist gravity), 4 (patient can counter resistance), and 5 (patient can counter full resistance) [12]. Adverse effects, such as bradycardia (heart rate <50 beats/min) and hypotension (the decrease of mean arterial pressure >20% baseline value), were recorded from the time of injection of local anesthetics to the induction of general anesthesia.

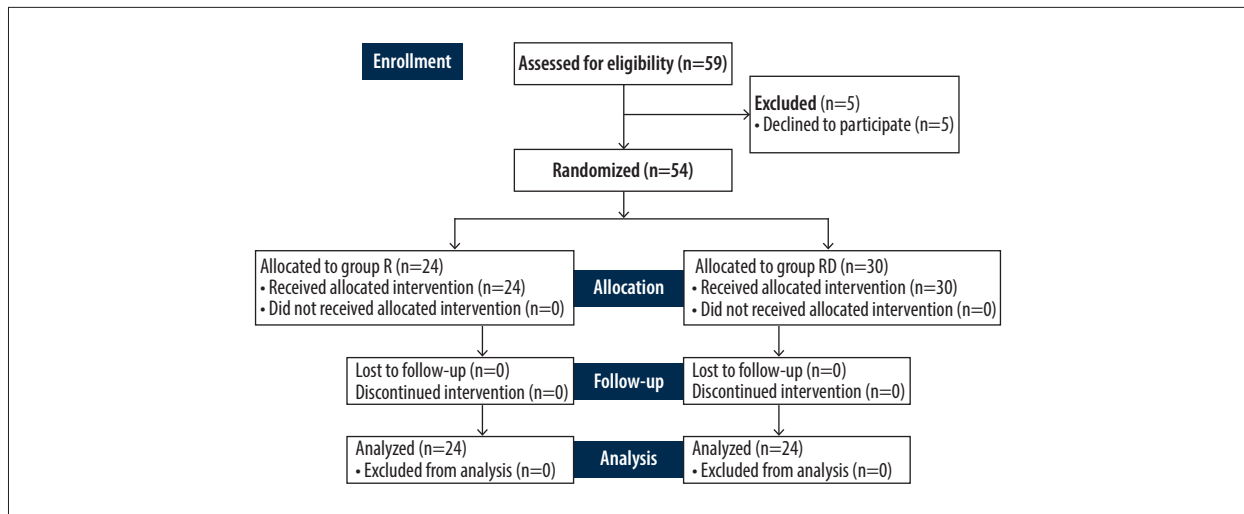


Figure 1. Study flow diagram. R – ropivacaine only; RD – ropivacaine mixed with dexmedetomidine.

Table 1. Characteristics of study participants*.

Group	Age, y	M/F, n	Height, cm	Weight, kg	Length of surgery, min
R	63.21±4.37	13/11	168.83±5.43	63.71±5.63	86.88±4.08
RD	62.67±5.31	16/14	167.63±4.90	65.37±4.72	86.90±5.06

F – Female; M – Male; R – ropivacaine only; RD – ropivacaine plus dexmedetomidine. * Data are expressed as number or mean±standard deviation.

Measurements

Based on previous research, 0.5% ropivacaine 15 mL was chosen as the initial concentration [13,14]. The interval of concentration was set at a ratio of 1: 1.2. According to the response of the previous subject (complete block or incomplete block), the concentration was decreased or increased. The 2 groups were run in parallel. According to Dixon's up-and-down method, the ending rule requires 6 consecutive up-and-down sequences [15]. In the current study, the primary outcome was the EC50 of ropivacaine for adductor canal block, and the value of EC50 was determined by the Dixon and Massey method. Eight consecutive up-and-down sequences, considered sufficient to study the EC50 of ropivacaine, were achieved with 24 patients in group R and 30 patients in group RD.

Statistical Analysis

Statistical analysis was conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data are shown as mean±standard deviation, median (interquartile range), or number. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were tested using *t* tests. Nonnormally distributed continuous variables were tested by the Mann-Whitney *U* tests. Discrete variables were tested using the χ^2 test. *P*<0.05 was considered statistically significant.

Table 2. Quadriceps strength evaluation*.

Group	Quadriceps strength	
	30 min after ACB	In PACU
R	5 (5-5)	5 (5-5)
RD	5 (5-5)	5 (5-5)

ACB – adductor canal block; PACU – Postanesthesia Care Unit; R – ropivacaine only; RD – ropivacaine plus dexmedetomidine. * Data are expressed as median (interquartile range).

Results

Fifty-nine subjects were recruited for this study. Five declined to participate, and 54 participants completed the study (Figure 1). The 2 experimental groups were similar in terms of age, sex, height, weight, and the length of surgery (Table 1; *P*>0.05). Quadriceps strength was similar between the 2 groups, both at 30 min after adductor canal block and during recovery from general anesthesia in the Postanesthesia Care Unit (Table 2; *P*>0.05). None of the participants exhibited bradycardia or hypotension. The sequences of positive and negative responses are presented in Figure 2. According to the up-and-down method, the median effective concentration of ropivacaine for adductor canal block was 0.29% (95% confidence interval [CI], 0.28-0.31%) in group RD, which was lower than that in group R (0.38% [95% CI, 0.36-0.41%]; *P*<0.05).

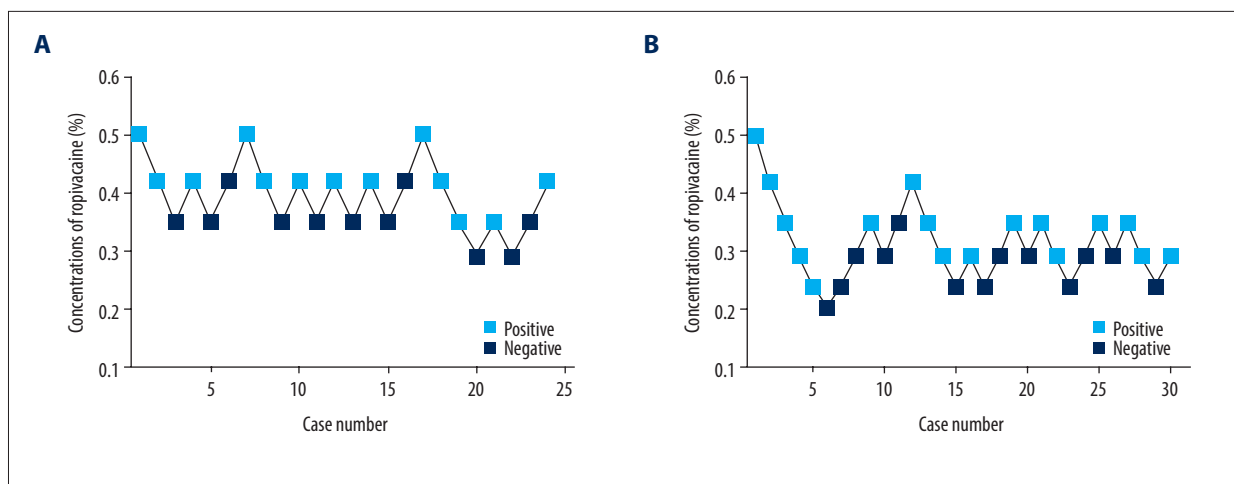


Figure 2. Sequential responses to up-and-down concentrations of ropivacaine for adductor canal block. (A) The sequential responses to up-and-down concentrations of ropivacaine in Group R. (B) The sequential responses to up-and-down concentrations of ropivacaine in Group RD. Empty squares indicate a positive response (ie, complete sensory block), and black squares indicate a negative response (ie, incomplete sensory block).

Discussion

Multimodal analgesic regimens with nerve block as the core have become the best option for total knee arthroplasty. These local anesthesia techniques allow reducing the use of opioids. However, for patients undergoing simultaneous bilateral total knee arthroplasty, the use of high-dose local anesthetics may increase the risk of toxicity. Adjunct medications, such as dexmedetomidine, clonidine, and dexamethasone, can enhance the analgesic effect of local anesthetics [7-11,16-18].

Dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, was demonstrated to strengthen the quality of peripheral nerve block both in experimental and clinical research [7-11]. Brummett et al [8] showed that dexmedetomidine could increase the action time and improve the potency of ropivacaine in rats. Andersen et al [10] found that dexmedetomidine could increase the action time of ulnar nerve block. Andersen et al [14] also reported that dexmedetomidine could extend the duration of nerve block. In our study, we found that the EC50 of ropivacaine for adductor canal block was 0.29% (95% CI, 0.28-0.31%), which could be reduced to 0.38% (95% CI, 0.36-0.41%) when combined with 1 µg/kg dexmedetomidine. Our results indicated that the quantity of local anesthetics could be decreased by about 24% through perineural administration of dexmedetomidine. Ye et al [19] found that retrobulbar dexmedetomidine enhanced the effect of retrobulbar block and decreased the minimum local anesthetic concentration of ropivacaine by about 22%, without any neurotoxic effects. Zhang and Li [20] reported that epidural dexmedetomidine for labor analgesia reduced the EC50 of ropivacaine by about 25%. These results were consistent with our results showing a decrease of 24% of EC50. Raof et al [21] found that the minimum local

anesthetic concentration decreased by about 35% with dexmedetomidine for ultrasound-guided transversus abdominis plane block. The differences in the types of local anesthetics and the dose of dexmedetomidine may explain the variation in results. Lu et al [9] reported that EC50 of ropivacaine was decreased by about 49% with dexmedetomidine for obturator nerve block. Those results exceeded our results, which showed a 24% decrease in EC50. The differences may be related to variations in the assistance modes of the nerve block (ultrasound vs nerve stimulator) and assessment methods (motor block vs sensory block).

The mechanism of dexmedetomidine in analgesia is still unclear. Previous studies suggested that a selective alpha-2 adrenergic receptor agonist could inhibit the release of substance P from the spinal dorsal horn neurons and activate the alpha-2 adrenergic receptors in locus ceruleus [22]. However, more research attention has been paid to the peripheral mechanism of dexmedetomidine rather than the central mechanism. Alpha-2 adrenergic receptor agonists could produce an effect similar to local anesthetics by inhibiting the release of norepinephrine and production of non-receptor-dependent action potentials in alpha and C fibers [23,24]. Brummett et al [8] found that hyperpolarization-activated cation currents could be blocked by peripheral dexmedetomidine, which extended the hyperpolarization of unmyelinated C fibers. Moreover, there are some mechanisms independent of alpha-2 adrenergic receptors by which the K⁺ current and Na⁺ current could be blocked by dexmedetomidine, leading to inhibition of neuronal activity [25].

Prior to perineural administration of dexmedetomidine, it is important to understand its adverse effects, including neurotoxicity, bradycardia, and hypotension. Most previous studies

have not found evidence of neurological toxicity of dexmedetomidine when it is used as an adjuvant to local anesthetics. Brummett et al [26] found that dexmedetomidine did not cause injury of axons or myelin sheaths, but it could improve bupivacaine-induced perineural inflammation. Kim et al [27] found that dexmedetomidine could reduce inflammation and nerve injury induced by ropivacaine after intraneural injection. Keplinger et al [28] found that perineural dexmedetomidine used at a clinical concentration did not cause long-term post-block paresthesia. Lu et al [9] reported that no painful paresthesia or nerve injury occurred after obturator nerve block with dexmedetomidine added to lidocaine. Bradycardia and hypotension can be caused by dexmedetomidine in a dose-dependent manner. Esmaglu et al [29] reported that dexmedetomidine caused a high incidence of bradycardia and hypotension from 5 to 90 min after injection. However, we did not observe bradycardia or hypotension in the current study. The differences may be explained by different experimental protocols and doses of dexmedetomidine.

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Conclusions

This study found that perineural dexmedetomidine 1 $\mu\text{g}/\text{kg}$ could reduce the EC50 of ropivacaine for adductor canal block.

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