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ORIGINAL RESEARCH

Effect of Different Modes of Administration of Dexmedetomidine Combined with Nerve Block on Postoperative Analgesia in Total Knee Arthroplasty

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ABSTRACT

Introduction: Dexmedetomidine (DEX) as a nerve block adjuvant can significantly prolong analgesia. However, whether perineural or systemic administration of DEX is more beneficial in patients undergoing total knee arthroplasty (TKA) has not been thoroughly investigated. To this end, we evaluated the effects of perineural and systemic DEX administration on postoperative analgesia in patients undergoing TKA surgery.

Methods: We randomly assigned patients undergoing TKA under general anesthesia combined with femoral nerve block and sciatic nerve block to one of three groups: (1) ropivacaine plus perineural dexmedetomidine (DP): 0.25% ropivacaine 40 mL plus 0.5 μg/kg dexmedetomidine; (2) ropivacaine plus systemic dexmedetomidine (DS): 0.25% ropivacaine 40 mL plus systemic 0.5 μg/kg dexmedetomidine; (3) control group (C): 0.25% ropivacaine 40 mL.

Results: The average length of time until patients first experienced postoperative pain was significantly longer in the DP group (26.0 h [22.0–30.0 h]) than in the DS group (22.4 h [18–26.8 h]) and the control group (22.9 h [19.5–26.3 h], $P = 0.001$). For this result there was no significant difference between the DS and the control group. Compared with the DS and control groups, patients in the DP group had lower resting visual analogue scale (VAS) scores at 24, 48, and 72 h after surgery ($P < 0.05$). VAS activity scores at 12, 24, and 48 h after surgery in the DP group were lower than those in the DS and control groups, with a statistically significant difference ($P < 0.05$). Compared with the DS and control groups, the amount of postoperative opioids in the DP group was also significantly reduced, and the number of people needing postoperative rescue analgesia was significantly lower, with a statistical difference ($P < 0.05$). Meanwhile, the sleep satisfaction of patients in the DP group on the first night after surgery and the satisfaction with pain control at 72 h after surgery were both higher than those in the DS group and control group ($P < 0.05$).

Conclusions: Perineural administration of DEX can significantly prolong the interval until patients report pain for the first time after TKA,

Xiao-bin Jin, Rui Xiao and Wei Zhou contributed equally to this paper.

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relieve postoperative pain, reduce postoperative opioid dosage, and improve postoperative sleep quality and satisfaction with pain control.
Trial Registration: The trial was registered at the Chinese Clinical Trial Registry, identifier ChiCTR1900025808.

Keywords: Dexmedetomidine; Perineural administration; Systemic administration; Total knee arthroplasty; Postoperative pain

Key Summary Points

Why carry out this study?

Total knee arthroplasty is a very common surgery, with severe postoperative pain and long postoperative pain duration.

Dexmedetomidine, an adjuvant to nerve block, has been shown to prolong the analgesic duration of nerve block and improve postoperative pain in patients. Our study, however, is one of the first to compare the application of different methods of dexmedetomidine (DEX) administration combined with a lower concentration (0.25%) of ropivacaine in lower limb total knee arthroplasty (TKA) surgery.

We hypothesized that perineural dexmedetomidine administration would provide better analgesic effects than systemic dexmedetomidine administration in total knee arthroplasty surgery.

What was learned from the study?

Our study demonstrated that the perineural administration of 0.5 μg/kg DEX can significantly prolong the time until patients report pain for the first time after TKA, relieve postoperative pain, reduce postoperative opioid dosage, and improve postoperative sleep quality and satisfaction with pain control. However, systemic administration of the same dose of DEX does not provide the benefits associated with perineural administration.

INTRODUCTION

Dexmedetomidine (DEX), a highly selective alpha-2 receptor agonist, has sedative, analgesic, and anti-anxiety effects during anesthesia [1] via various mechanisms, including perineural [2, 3], intra-articular [4, 5], and systemic administration [6]. As a new adjuvant to nerve block, the perineural route for DEX can provide advantages in prolonged analgesia and inhibition of local inflammatory response [7, 8]. In addition, studies have shown that the systemic administration of DEX enhances analgesic effects and sleep quality [9, 10], dampens surgical stress and the inflammatory response [11, 12], reduces the incidence of postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) [13–15], and prolongs the duration of peripheral nerve block in patients with unilateral arthroscopic shoulder surgery [16]. However, the results of studies on the use of prolonged analgesia with systemic and perineural administration have been inconsistent. For example, Kathuria et al. [17] reported that there was no difference in the duration of block analgesia between systemic and perineural administration when DEX was used as a local anesthetic ropivacaine adjuvant for supraclavicular brachial plexus block. However, studies by Abdallah et al. [16] reported that DEX in both systemic and perineural administration prolonged the duration of shoulder arthroscopic analgesia in an outpatient setting, and was more effective when used around the nerves. These inconsistent results may be related to the dose and concentration of the drug, the type of surgery, and the severity of the trauma.

Total knee arthroplasty (TKA) is a traumatic surgery, with severe postoperative pain and long postoperative pain duration. Studies have shown that even with postoperative analgesia, 45–52% of patients still experience acute postoperative pain (1–3 days) after TKA, 52% experienced subacute pain (day 30), and 10–34% experienced chronic postsurgical pain (3 months and later) [18]. Postoperative pain reduces the quality of life, prolongs hospital stay, increases cost, increases POCD and POD,

and is not conducive to rapid postoperative recovery [19, 20]. Therefore, the development of strategies to prolong postoperative analgesia time and increase the analgesic effect after TKA is critical. Intraspinal anesthesia and analgesia is still one of the preferred analgesia methods for TKA patients [21], but for elderly patients who may have difficulties in spinal puncture or who are receiving anticoagulant therapy, spinal anesthesia may not be suitable. Spinal anesthesia can also reduce sympathetic nerve tension and cause significant hemodynamic disorders, especially in elderly patients or patients with a variety of basic diseases, which can increase perioperative risks [22]. Furthermore, anesthesia and analgesia in the spinal canal is likely to cause postoperative urinary retention, which increases the probability of retaining the catheter after surgery [23, 24]. With the increasing application of ultrasound in the regional block, peripheral nerve block is widely used in intraoperative and postoperative analgesia for TKA as a simple and efficient analgesic technique. To date, few reports have been published on the effects of DEX TKA postoperative analgesia methods. Therefore, the purpose of this study was to observe whether systemic or perineural administration of DEX had varying effects on the effectiveness of analgesia time and first report of pain at the surgical site after TKA surgery. In addition, we observed indicators including the severity of postoperative analgesia, postoperative analgesic drug use, incidence of POD and postoperative sleep, and other adverse reactions, in order to provide the optimal administration of DEX in TKA surgery.

METHODS

Study Participants

The trial was registered at the Chinese Clinical Trial Registry (ChiCTR1900025808; principal investigator: Xiao-bin Jin; date of registration: September 9, 2019). Ethical approval for this study (PJ2020-03-06) was provided by the Ethical Committee of the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui province, China, in February 2020. The trial was conducted from March 2020 to September 2020 at the First Affiliated Hospital of Anhui Medical University in accordance with the Declaration of Helsinki. After written informed consent was obtained, 110 patients with American Society of Anesthesiologists (ASA) physical status classification I to III scheduled for TKA surgery using standardized general anesthesia (GA) and combination of single-injection femoral nerve block (FNB) and sciatic nerve block (SNB) before surgery were recruited to participate in this prospective, randomized clinical trial. In total, 91 patients completed the study. Exclusion criteria were contraindications to a femoral-sciatic nerve block (e.g., coagulopathy) and infection at the puncture site; contraindication to dexmedetomidine (e.g., allergic to dexmedetomidine), pathological sinus node syndrome, and a basal heart rate of less than 50 beats per minute; mental or language barrier; or noncompliance.

Randomization and Blinding

Consenting study participants were randomized using a computer-generated list of random numbers. The allocation results were sealed in opaque envelopes that were kept with the research coordinator. On the day of surgery, the research coordinator handed one envelope per patient to the anesthesia assistant in the block procedure room, who prepared all the study solutions using an aseptic technique. DEX (100 μg/mL DEX hydrochloride; Jiangsu Pharmaceutical Co., Ltd, China) was used for this study. The anesthesia assistant was not involved in the latter procedure; patients, anesthesiologists performing FNB and SNB, and the research observers collecting outcome data were blinded to the allocation results. All study patients received either perineural or systemic administration of study solutions according to their group allocation as follows: (1) perineural DEX group (DP, $n = 30$), 0.25% ropivacaine 40 mL plus 0.5 μg/kg DEX perineurally, and 10 mL saline intravenously (i.v.); (2) systemic DEX group (DS, $n = 31$), 0.25% ropivacaine 40 mL and 1 mL saline and i.v .0.5 μg/kg DEX; (3) control group (*C*, n = 30), 0.25% ropivacaine

40 mL and 1 mL saline and i.v. 10 mL saline. All intravenous solutions were infused 15 min before the start of the operation.

Intraoperative and Postoperative Management

Demographic information was collected before surgery for each patient. Once the patients arrived in the operating room, noninvasive blood pressure monitoring, electrocardiogram, and pulse oximetry were applied, and intravenous access was secured on the patient's nonoperative side. Then 5 mL/kg sodium lactate ringer solution was administered intravenously and oxygen was inhaled by mask at 4 L/min. The BIS [Bispectral Index] VISTA Monitoring System (Aspect Medical Systems, Inc., USA) was used to monitor the depth of anesthesia for all of the patients. Before block performance, all patients received 1–2 mg systemic midazolam and 5–10 μg systemic sufentanil for anxiolysis and analgesia, respectively, as needed.

The preoperative FNB and SNB were performed using ultrasound-guided (USG) monitoring with a 5 cm, 10 MHz linear probe and a 2–5 MHz curved array probe (M-Turbo, FUJIFILM SonoSite Inc., USA) and nerve stimulator (Stimuplex HNS12, B. Braun Medical Inc., Germany) with an electrically isolated 12 cm 22 G needle (Stimuplex D, B. Braun Medical Inc., Germany), under sterile conditions, by a staff regional anesthesiologist or by a directly supervised regional anesthesia fellow with experience in at least ten ultrasound-guided nerve-stimulator–assisted FNBs and SNBs. At the beginning of the procedure, the stimulator was adjusted to 1.0 mA, 2 Hz, 0.1 ms, and the stimulus intensity was gradually reduced to 0.4 mA when a response was obtained.

As described in a previous study, the femoral nerve is located 1 cm laterally to the femoral artery and under the ileorectal fascia; thus we chose 1 cm distal to the probe at the level of the inguinal crease with a 30° cephalad angle to the patient's skin as the puncture point [25, 26]. We kept the needle tip visualized under ultrasound during insertion, and when we induced the contraction of the quadriceps muscle with the movement of the patella, 20 mL of local anesthesia solution was administered by USG monitoring.

The sciatic nerve is located on the fascia plane between the medial adductor of the femur and the gluteal muscle at the proximal thigh. The curved array probe was first placed perpendicular to the groin crease about 8 cm away from the skin, and the position was then scanned by sliding and tilting the probe until a clear lateral image of the hyperechoic sciatic nerve was obtained, located at the posterior and medial side of the trochanter [26, 27]. The sciatic nerve was consistent with the plantar flexor or dorsiflexor. While observing the motor response, the current intensity gradually decreased to the target 0.4 mA, and then 20 mL of the solution was administered under direct ultrasound visualization. We defined block success as loss of sensation to light touch within 20 min of the last drop of solution injection. For patients whose block was unsuccessful after 30 min, the block failure was recorded and the case was eliminated.

After 5 min of preoxygenation, all patients received standardized GA administered by an anesthesiologist blinded to group allocation, including intravenous propofol (1.0–2.5 mg/kg), intravenous sufentanil (0.2–0.5 μg/kg), and intravenous cisatracurium (0.15–0.3 mg/kg), followed by insertion of a laryngeal mask. GA was maintained with intravenous propofol to the target BIS range (40–60) or adding sufentanil, according to the stress response after surgery. We regulated respiratory rate and tidal volume to 35–45 mmHg as an end-tidal arterial CO_2 partial pressure ($P_{ET}CO_2$). Intraoperative hypertension was defined as an increase in systolic blood pressure > 20% from preoperative values and/or systolic blood pressure > 160 mmHg, and intraoperative hypotension was defined as a decrease in systolic blood pressure > 20% from preoperative values and/or systolic blood pressure < 90 mmHg. Patients with intraoperative hypertension were treated first with 5–10 μg sufentanil and propofol dosage to the target BIS, then given nicardipine 0.1–0.2 mg in a single static push (2 mg/20 mL) as needed. Patients

with intraoperative hypotension were treated with increased infusion and immediately with infusion of phenylephrine by bolus. When a patient's heart rate (HR) was < 50 bpm, 0.2–0.5 mg atropine/intravenous bolus was given and repeated if necessary. For multimodal analgesia, all patients were given 100 mg flurbiprofen 30 min before surgery, and 10 mg azasetron was administered intravenously for postoperative nausea and vomiting (PONV). Surgery was performed for all patients by the same group of doctors and using the same surgical method.

At the end of the surgery, all of the patients were transferred to a post-anesthesia unit (PACU) for recovery until they achieved a Steward score of at least 4, assessing consciousness, airway, and movement [28]. All patients were given 100 mg celecoxib orally twice daily in the postoperative ward. Postoperative pain was calculated based on a visual analog scale (VAS; 10-cm scale, where 0 = no pain and 10 = the worst pain); those with a pain severity score of 4 or higher or patients requesting analgesics were given rescue analgesia (5–10 μg sufentanil administered intravenously in the PACU, and 100 mg intramuscular injection of flurbiprofen and repeated if necessary in the ward). PONV was treated sequentially with 5–10 mg tropisetron administered intravenously, followed by 10 mg intravenous metoclopramide, as needed.

Follow-up

All patients were followed up postoperatively by a research coordinator blinded to group allocation to document the time when they first experienced pain at the surgical site; when they first got out of bed for early rehabilitation training; pain severity scores; evaluation of POD; sleep quality; analgesic consumption; postoperative complications (e.g., deep venous thrombosis, paralysis of the common peroneal nerve); opioid-related side effects (e.g., PONV); and satisfaction with analgesia.

Outcome Measures

The primary major outcome was the postoperative analgesia time associated with the nerve block (specified in hours) to report the first pain at the surgical site after surgery. The secondary outcomes included cumulative consumption of analgesics (converted to oral morphine equivalent [29]) in the ward 24, 48, and 72 h after surgery; pain severity at rest and during movement at 6, 12, 24, 48, and 72 h postoperatively by a VAS (0–10 cm); number of patients needing rescue analgesia at 24, 48, and 72 h after surgery; and time (in hours) until patients first got out of bed for early rehabilitation training after their operation. Incidence of POD in the ward was assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) at 1, 2, and 3 days after surgery. The evaluation of subjective sleep quality (1 day postoperatively) and patient satisfaction at 72 h was assessed using a Likert scale [30].

Statistical Analysis

The sample size was calculated based on the assumption that perineural administration of DEX would prolong the analgesia longer than systemic administration. We determined the following preliminary experimental results of analgesia time: DS 21.6 ± 4.8 h; C 21.0 ± 3.4 h; DP 25.3 ± 4.6 h. Therefore, each group required 28 patients to achieve a power of 0.90 at a level of significance of 0.05. Allowing for a drop-out rate of 15%, each group ultimately required 33 patients.

SPSS version 13.0 software (SPSS, IBM) was used for statistical analysis. Numerical variables are expressed as means and standard deviation (SD). The data that were normally distributed were analyzed by one-way ANOVA and post hoc tests. The data with skewed distribution were analyzed by the Kruskal–Wallis test and pairwise multiple comparisons. The P value for the overall H test and Fisher's exact test was set at 0.05. Frequency data were analyzed using the Chi-square comparison method, and further analyses for pairwise comparisons between groups were conducted using an R×C

contingency table. $P < a = 0.05/3 = 0.017$ was considered to indicate a statistically significant difference.

RESULTS

We assessed the eligibility of a total of 110 patients from March 2020 to September 2020. We excluded 27 patients who did not meet the inclusion criteria, and our final enrollment included 91 patients. We randomly assigned the patients to one of the three groups (Fig. 1). Demographic and clinical data were similar across groups (Table 1). Intraoperative medication, operating time, anesthesia time, and PACU residence time were similar across groups (Table 2).

Patients who received perineural DEX in the DP group had longer analgesic time to first reported pain after TKA than the DS and control groups (DP, 26.0 h [22.0–30.0 h]; DS, 22.4 h [18–26.8 h]; and control group, 22.9 h [19.5–26.3 h]; $P = 0.001$). Only 6 patients (20%) in the DP group required rescue analgesics in the first 24 h postoperatively, while 19 patients (61%) in the DS and 19 patients (63%) in the control group required rescue analgesics in the first 24 h postoperatively ($P = 0.001$, Table 3). The DP group patients had the lowest need for oral opioids ($P = 0.001$) at 24, 48, and 72 h postoperatively compared with the DS and the control group (Table 3). The time that patients first got out of bed for exercise was similar among the three groups ($P = 0.447$). At 24, 48, and 72 h postoperatively, the DP group had lower VAS scores than the DS and control groups ($P < 0.001$) (Fig. 2). The DP VAS scores with activity at 12, 24, and 48 h postoperatively were also lower compared with the DS and control groups ($P < 0.001$) (Fig. 3). Patients in the DP group had the highest quality of sleep on the first night after surgery and the highest satisfaction with postoperative pain control at 72 h after surgery compared to the DS and C groups ($P < 0.001$).

Incidence of intraoperative bradycardia, hypertension, and PONV were similar among

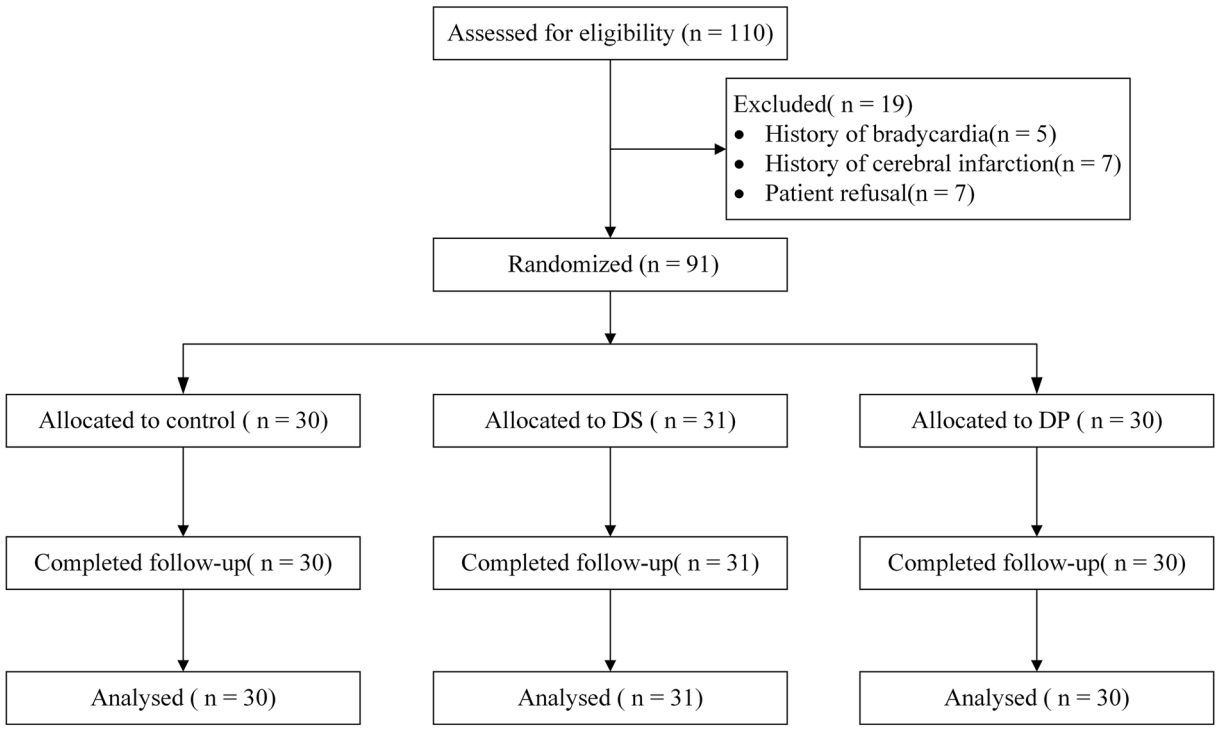

Fig. 1 Consolidated standards of reporting trials flow diagram showing patient progress through the study phases. *DS* systemic dexmedetomidine, *DP* perineural dexmedetomidine

Table 1 Patient demographic characteristics

Parameter	C (n = 30)	DS (n = 31)	DP (n = 30)	P value
Age (years)	65.7 (5.0)	65.7 (6.7)	63.7 (7.7)	0.408
Sex (female/male)	24/6	21/10	24/6	0.443
BMI	24.2 (3.3)	24.8 (4.0)	26.1 (2.8)	0.104
ASA status (I/II/III)	2/28/0	2/29/0	2/28/0	0.999
Surgical side (left/right)	13/17	12/19	16/14	0.504

Values are expressed as the mean (SD) or absolute numbers
BMI body mass index, *ASA* American Society of Anesthesiologists, *DP* perineural dexmedetomidine group, *DS* systemic dexmedetomidine group, *C* control group

Table 2 Intraoperative medication and recovery indicators

Parameter	C (n = 30)	DS (n = 31)	DP (n = 30)	P value
Propofol (mg)	441 (72.7)	440.6 (125.0)	424.0 (111.4)	0.772
Sufentanil (μg)	18.5 (2.9)	19.5 (3.1)	20.0 (2.3)	0.134
Duration of operation (min)	84.3 (18.1)	82.2 (24.2)	83.5 (21.5)	0.637
Duration of anesthesia (min)	117.3 (16.9)	119.5 (25.0)	117.5 (26.8)	0.921
Time of extubation (min)	16.7 (5.9)	16.7 (8.1)	16.2 (7.4)	0.958
Time in PACU (min)	35.4 (5.3)	36.1 (10.0)	35.4 (6.0)	0.639

Continuous values are represented by mean (SD)
PACU post-anesthesia care unit, *Time of extubation* time from end of surgery until extubation, *DP* perineural dexmedetomidine group, *DS* systemic dexmedetomidine group, *C* control group

the three groups after surgery ($P > 0.05$). None of the three groups reported the occurrence of POD, deep vein thrombosis, or fall after getting out of bed. There were two people in the DP group, one person in the DS group, and two people in the control group who reported distal limb numbness during postoperative follow-up, but all recovered within 48 h.

DISCUSSION

This randomized trial demonstrated that perineural DEX (0.5 μg/kg) prolonged the analgesic time to first reported pain following ropivacaine FNB and SNB analgesia. This finding is clinically important because 80% of patients treated with perineural DEX did not require emergency analgesia within 24 h of surgery. In addition, other clinical parameters including postoperative pain score, satisfaction with pain relief, postoperative accumulation of opioids, and first-night sleep quality were improved in patients receiving perineural DEX, and the number of patients requiring rescue analgesics in the postoperative 72 h was diminished in the DP group. However, we did not observe an equivalent benefit in the DS and control groups. These results showed that systemic use of 0.5 μg/kg DEX was not superior to that of the control group. The time until first getting out of bed and exercise, and the incidence of adverse complications did not differ among the three groups.

During the refractory period of the action potential, hyperpolarization-activated cation

Table 3 Intraoperative adverse events and postoperative data

Outcomes	C (n = 30)	DS (n = 31)	DP (n = 30)	Overall P	P value for DS vs. DP
Duration of analgesia: time to first report pain (h)	22.9 (3.4)	22.4 (4.4)	26.0 (4.0)	0.001	0.001
Number of patients requiring analgesics at first postoperative 24 h	19	19	6	0.001	0.001
Cumulative oral morphine equivalent consumption (mg) at first postoperative 24 h	30 (19–30)	30 (15–30)	14 (10–15)	0.000	0.000
Number of patients requiring analgesics at second postoperative 24 h	16	14	12	0.579	
Cumulative oral morphine equivalent consumption (mg) at second postoperative 24 h	30 (20–30)	30 (25–30)	20 (14–30)	0.001	0.001
Number of patients requiring analgesics at third postoperative 24 h	6	4	4	0.465	
Cumulative oral morphine equivalent consumption (mg) at third postoperative 24 h	30 (20–30)	30 (25–30)	20 (15–20)	0.000	0.001
Time until first getting out of bed to exercise (h)	47.6 (5.0)	48.5 (9.9)	45.4 (9.4)	0.447	
Incidence of intraoperative bradycardia	5	6	5	0.950	
Incidence of intraoperative hypotension	5	3	3	0.697	
PONV at 72 h	3	2	3	0.881	
Quality of sleep on the first night	3 (2–4)	2 (2–4)	4 (3–4)	0.001	0.002
Patient satisfaction with pain relief at 72 h	3 (2–3)	2 (2–3)	4 (3–4)	0.000	0.000
POD	0	0	0	1.000	
Length of hospital stay (days)	6.4 (1.1)	6.3 (1.3)	6.2 (1.4)	0.598	

Values are mean (SD) or median [IQR] or number. Likert scale where 1 = very dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, and 5 = very satisfied

POD postoperative delirium, *PONV* postoperative nausea and vomiting

The P value for the overall H test and Fisher's exact test is set at 0.05. The P value for the DS vs. DP pairwise comparison and Fisher's exact test using the permutation method for categorical variables and Tukey test using ranks for post hoc testing for continuous variables is set at 0.017

currents usually restore neurons to resting potential and normal functional activities. By blocking these currents, DEX can strengthen the inhibition of neuronal conduction and produce analgesic effects [31]. Promising evidence in both animal [32] and human [33] studies suggests that DEX can produce analgesic effects. There is a moderate level of evidence to suggest that DEX peripheral nerve administration can prolong the analgesic time of brachial plexus block from 7.5 to 11.9 h [34]. This result is consistent with the results of our study. Peripheral nerves use DEX to extend the analgesic time of TKA patients from 21.6 ± 4.8 h to 25.3 ± 4.6 h. Recent studies have shown that systemic administration of DEX can prolong the effects of the corresponding perineural injection of analgesic [16], and its effect may be mediated by the binding of α_2 receptors in the central nervous system, by inhibiting pain

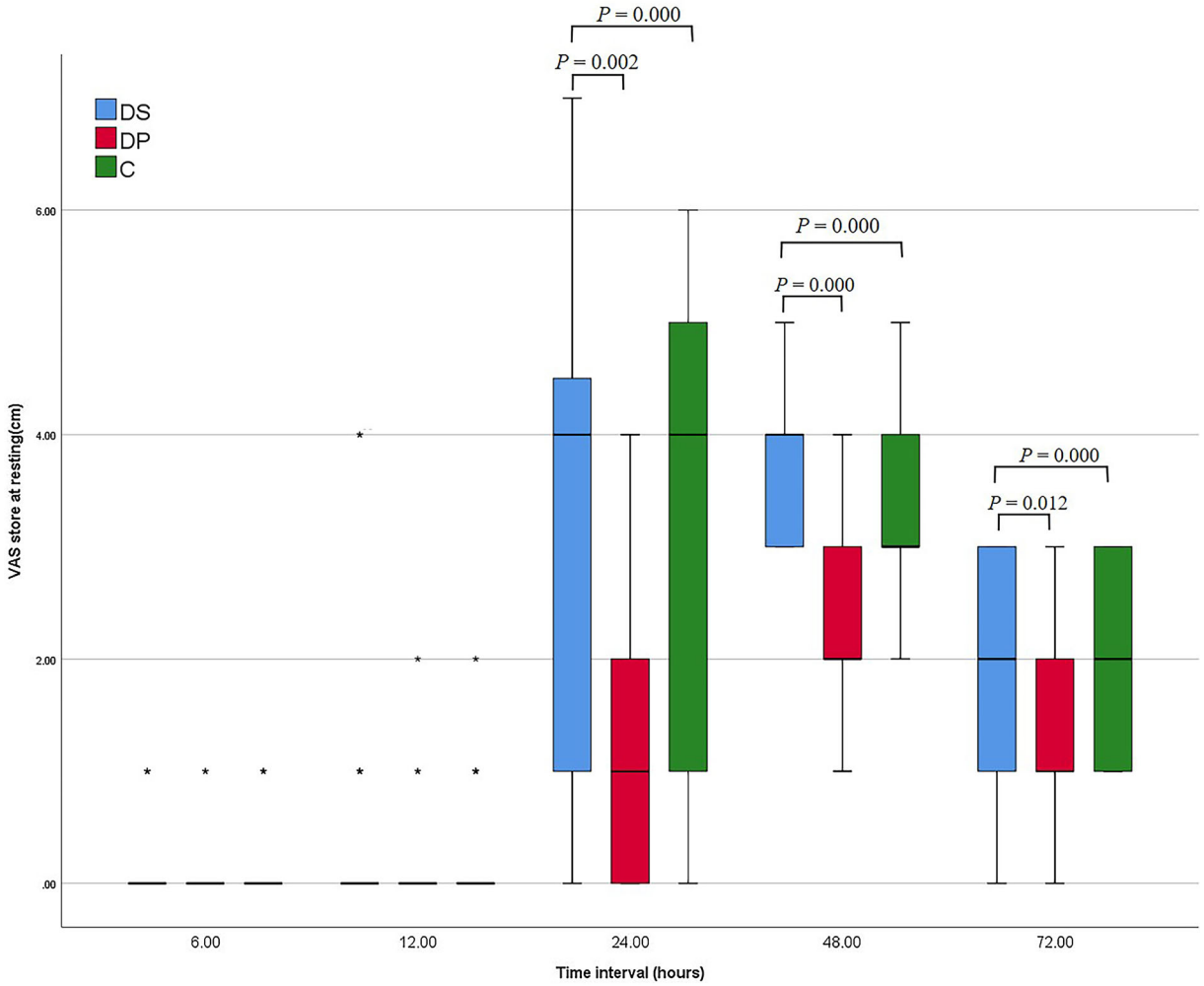

Fig. 2 Postoperative pain severity visual analogue scale resting pain score (cm) 6, 12, 24, 48, and 72 h postoperatively. Boxes represent the median with 25th/75th percentile. Whiskers represent the minimum/maximum values, excluding outliers. *DS* systemic dexmedetomidine 0.5 μg kg^{-1}, *DP* perineural dexmedetomidine 0.5 μg kg^{-1}, *C* control group. The adjusted *P* value above the box is the result of pairwise comparison between the two groups and with significance set at 0.05

transmitters to inhibit the transmission of pain [35]. In Abdallah et al.'s study [16], systemic administration of 0.5 μg/kg DEX was associated with analgesia, whereas systemic doses of 0.5 and 1.0 μg/kg DEX in Kang et al.'s previous studies [36] had no significant analgesic effect. Further, in a recent study, systemic DEX (2 μg/kg) did not prolong the analgesic duration of quadruple nerve block with ropivacaine 0.32% after TKA [37]. Our study showed that systemic injection of 0.5 μg/kg DEX did not prolong analgesia time. This difference may be due to the greater trauma and greater postoperative pain in our patients undergoing TKA compared to those in an outpatient setting undergoing major arthroscopic shoulder surgery in Abdallah et al.'s study. In addition, the difference in results may be related to the local anesthetic concentration used and the dose of DEX. Several other studies on the pharmacokinetics and pharmacodynamics of systemic DEX have reported that clinical analgesia is dose-independent [38] and not significant below a certain threshold [39, 40].

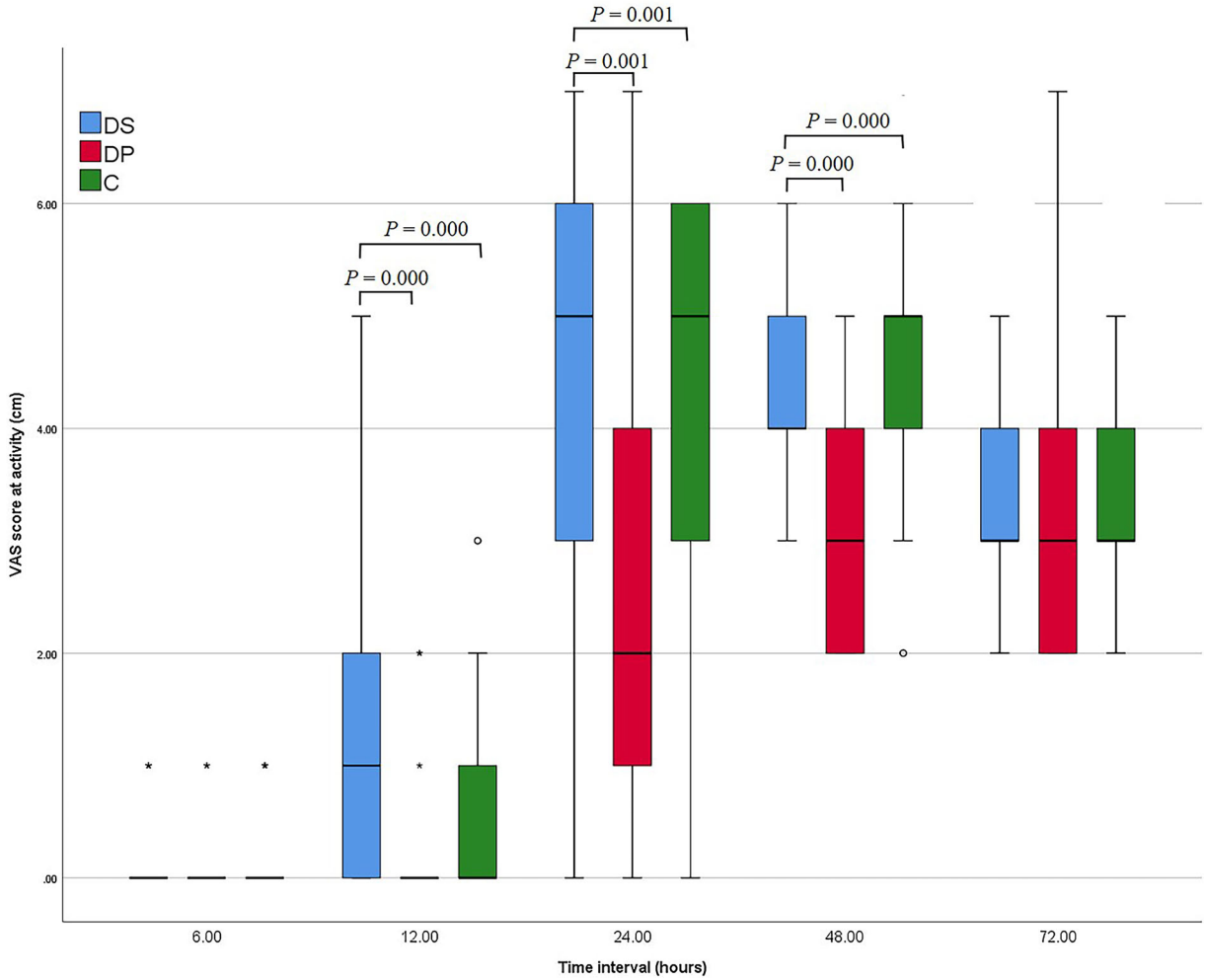

Fig. 3 Postoperative pain severity visual analogue scale pain score at activity (cm) 6, 12, 24, 48, and 72 h postoperatively. Boxes represent the median with 25th/75th percentile. Whiskers represent the minimum/maximum values, excluding outliers. *DS* systemic dexmedetomidine 0.5 μg kg^{-1}, *DP* perineural dexmedetomidine 0.5 μg kg^{-1}, *C* control group. The adjusted *P* value above the box is the result of pairwise comparison between the two groups and with significance set at 0.05

Moreover, prolonged motor block time of peripheral nerve block is usually an undesirable side effect, which can affect the patient's rapid recovery after surgery, especially for patients with joint replacement. It has been reported that the use of 0.5 μg/kg DEX for peripheral nerves can selectively extend the duration of the sensory block without prolonging motor block [16]. In our study, no significant use of DEX was observed to prolong motor block time, there was no difference in the time until getting out of bed for the first time across all groups, and we found no difference in the average postoperative hospital stay. This contradicts the previous data [7] showing that the use of DEX as an adjuvant drug for SNB also prolongs sensory and motor block time. The differing results may be related to the difference in local anesthetic concentration and dose of DEX. The reason that we did not observe prolongation of motor block may have been that the local anesthetic we chose was a low concentration (0.25%) of ropivacaine, and due to ropivacaine sensorimotor

dissociation [41]. In addition, each of our nerve blockades was only 0.25 μg/kg DEX.

Our study is, however, one of the first to compare the application of different administration methods for DEX combined with a lower concentration (0.25%) of ropivacaine in lower limb TKA surgery. The first example [2] of a similar study involved volunteers with an ulnar nerve block. Because the study participants did not undergo surgery and had no postoperative pain, its clinical reference value is limited. The second study [16] involved an outpatient-based shoulder arthroscopic surgery. The postoperative pain among patients was not as strong as that with surgery of the lower extremity, and their experimental results were mainly obtained through patient self-evaluation. The research results may not be applicable to TKA in hospitalized patients. Severe pain is common after TKA surgery. For the rapid-rehabilitative surgical protocol advocated by many, postoperative pain will undoubtedly affect the patient's recovery. Proper use of DEX in anesthesia for TKA patients can maximize the benefits for patients and is worthy of consideration by clinical anesthesiologists. In our study, the reduction in opioid consumption and the increase in sleep quality and patient satisfaction scores were other clinical benefits we observed.

There are some limitations to our study. First, the dose and concentration of DEX and ropivacaine were determined based on our clinical work experience and previous studies [16]. Our study only showed that the use of 0.25% ropivacaine combined with 0.5 μg/kg DEX around the nerves was more beneficial than 0.25% ropivacaine combined with systemic 0.5 μg/kg DEX. However, our results cannot be extrapolated to different doses of DEX and ropivacaine, as it is difficult to predict the interaction between the two drugs. Therefore, further dose studies should be conducted. Second, we did not specifically evaluate the time of the motor block. We believe that it is more accurate to judge patients' motor function recovery by the time they first get out of bed for exercise. Finally, our study group is TKA patients, whose postoperative pain is obvious, elderly patients, and other special conditions, so our results may need to be confirmed in other patient populations, including those undergoing lower limb surgery.

CONCLUSION

Our study demonstrated that the perineural administration of 0.5 μg/kg DEX can significantly prolong the time until patients report pain for the first time after TKA, relieve postoperative pain, reduce postoperative opioid dosage, and improve postoperative sleep quality and satisfaction with pain control. However, systemic administration of the same dose of DEX does not provide the benefits associated with perineural administration.

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Compliance with Ethics Guidelines. The study was conducted at the First Affiliated Hospital of Anhui Medical University from March to September 2020 in accordance with the Declaration of Helsinki. The trial was registered at the Chinese Clinical Trial Registry (ChiCTR1900025808 Principal Investigator: Xiao-bin Jin, Date of registration: September 9, 2019). Ethical approval for this study (PJ2020-03-06) was provided by the Ethical Committee of the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui province, China, in February 2020. Written informed consent was obtained from the participants.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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