

Original Article

Dexmedetomidine can extend the duration of analgesia of levobupivacaine in transversus abdominis plane block: a prospective randomized controlled trial

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Abstract: Background: Local analgesia technique has important advantages to manage postoperative pain; however, the duration of pain relief is relatively short due to the pharmacological characteristic of local anesthetics. Hence, in the current study, we planned to explore the hypothesis that adding dexmedetomidine to levobupivacaine in transversus abdominis plane (TAP) block prolongs the duration of analgesia. Methods: Sixty patients scheduled for elective abdominal hysterectomy were divided into two groups by a randomized and double-blinded method. Patients in the Control group ($n = 30$) received TAP block, using 40 mL of 0.25% levobupivacaine, and patients in the Dexmedetomidine group (Dex group) received the same volume and concentration of levobupivacaine but with additional 0.5 $\mu\text{g}/\text{kg}$ of dexmedetomidine for TAP block. Time for initial requirement of postoperative analgesic, total requirement of sufentanil for postoperative analgesia, Visual Analogue Scale (VAS) at different endpoints, and side effects were recorded. Results: The duration of analgesia was significantly longer in the Dex group than in the Control group (905.0 ± 114.2 min vs. 741.4 ± 105.3 min, $P < 0.001$), and the consumption of the rescue sufentanil in the first 24 hours postoperatively was less in the Dex group than in the Control group (29.4 ± 1.2 μg vs. 47.4 ± 2.0 μg , $P < 0.001$). The VAS point at rest was significantly lower in the Dex group than in the Control group at 8 and 12 hours ($P < 0.05$). The patient satisfaction with postoperative analgesia in the Dex group was better than in the Control group ($P = 0.006$). Side effects in the two groups were similar ($P > 0.05$). Conclusions: The addition of dexmedetomidine to levobupivacaine in TAP block can prolong the duration of analgesia and reduce postoperative analgesic requirements without additional side effects.

Keywords: Dexmedetomidine, levobupivacaine, transversus abdominis plane block

Introduction

Peripheral nerve blocks can present superior benefits compared to systemic analgesia for postoperative pain relief [1]. However, the major limitation of the regional anesthesia techniques is the relatively short duration of pain management. Despite the fact that catheter techniques are better than systematic opioid use for analgesia, they nevertheless have some complications such as catheter displacement and catheter-relevant infection risk, which could be avoided in selected settings by adding some medications prolonging blockade duration in single-shot regional anesthesia techniques [2]. Dexmedetomidine, an α_2 receptor agonist, with α_2/α_1 selectivity 8 times that of

clonidine, has the potential to enhance the quality of central and peripheral anesthesia when added to local anesthetics as an adjuvant [3, 4]. To our knowledge, there are few studies on the effect of adding dexmedetomidine to levobupivacaine in TAP block. Therefore, in the current study, we aimed to explore the hypothesis that adding dexmedetomidine to levobupivacaine in transversus abdominis plane (TAP) block would prolong the duration of analgesia.

Methods

Study subjects and grouping

Following Institutional Ethics Committee approval and written informed consent from all pati-

ents, 60 patients with the status of American Society of Anesthesiologists' physical class I or II, scheduled for elective abdominal hysterectomy through Pfannenstiel incision, were enrolled in this study. Exclusion criteria were as follows: body mass index (BMI) greater than 30 kg/m²; chronic hypertension; coagulation abnormality; platelet count less than 75×10⁹/L; local infection or sepsis; and patients with a history of cardiac, respiratory, renal, or hepatic failure. By using a computer-generated grouping by number sheets using Microsoft Excel, the patients were randomly assigned to one of two groups (*n* = 30). In the Control group, patients received 40 mL of 0.25% levobupivacaine for bilateral TAP block; patients in the Dexmedetomidine group (Dex group) received 40 mL of 0.25% levobupivacaine combined with 0.5 µg/kg of dexmedetomidine for bilateral TAP block.

Induction and maintenance of general anesthesia

All patients received no premedication. After arriving in the operating theater, each patient had an intravenous cannula inserted into a peripheral arm vein and received an infusion of 500 mL 37°C Ringer's solution before the induction of anesthesia. Standard monitoring included noninvasive blood pressure (NIBP), pulse oximetry (SpO₂), and electrocardiogram (ECG), and all patients were also monitored with the Bispectral Index (BIS) and train-of-four stimulation (TOF) (TCI-III-B, Weili Fangzhou Guangzhou, China).

Anesthesia was induced at the effect site with 4.0 µg/mL of propofol and 4.0 ng/mL of remifentanyl by a target-controlled infusion (TCI) (TCI-III-B, Weili Fangzhou Guangzhou, China) with the pharmacokinetic and pharmacodynamic (PK-PD) model introduced by Schnider and colleagues [5] for propofol and Minto and colleagues [6] for remifentanyl. After a BIS value below 60, 0.6 mg/kg rocuronium was administered to facilitate tracheal intubation. Anesthesia was also maintained with propofol and remifentanyl. The concentration of propofol was adjusted in steps of 0.5 µg/mL according to the value of BIS, which was maintained between 40 and 60, but the concentration of propofol shouldn't less than 2.0 µg/mL to avoid intraoperative awareness. Similarly, the concentration of remifentanyl was adjusted in steps of 0.5 ng/mL based on the variation of blood pressure

and heart rate, which was kept within 10 percent of the former record of blood pressure or heart rate. Hypotension was defined as systolic blood pressure (SBP) less than 90 mmHg or a 20% decrease from the baseline level. Baseline blood pressure of the patient was recorded in the preoperative room as the average of three readings taken 1 min apart. Ephedrine 5 mg was given intravenously if necessary. Bradycardia was defined as heart rate less than 60 beats per minute. Atropine 0.5 mg was intravenously administered when bradycardia occurred.

TAP block and postoperative pain management

After induction of anesthesia, TAP blocks were performed by an attending anesthetist, who was blinded to the patient's grouping, under dynamic ultrasound guidance (Nano Maxx TM, Sono Site, USA). A broadband linear array ultrasound probe was placed in the axial plane across the mid-axillary line midway between the costal margin and the iliac crest. After ensuring the three layers of the abdominal wall by a fixed radiographer, a block needle was inserted in the plane until its tip was located between the internal oblique and transverses abdominis muscles. After careful aspiration, 20 mL of the study medication was injected, and the hypoechoic layer was detected on ultrasound. The same steps were repeated on the contralateral side. Postoperative pain was addressed by patient-controlled intravenous analgesia (PCIA). The PCIA was set with a bolus of 3 µg sufentanil and 10 min of locking time, without a background dose.

Data collecting

Patients' demographic data, including age, body weight, height, and duration of surgery were recorded. The duration of analgesia was defined as the period from the time of TAP block to the first requirement of bolus of 3 µg sufentanil postoperatively by PCIA. The total requirements of rescue sufentanil for postoperative pain management were also recorded. Blood pressure and heart rate were recorded at 10 min intervals during surgery (after induction of anesthesia) and at 30 min intervals after surgery. Postoperative pain (at rest) was assessed using a 10-cm Visual Analogue Scale (VAS), where 0 cm represented no pain and 10 cm

Dex in TAP block

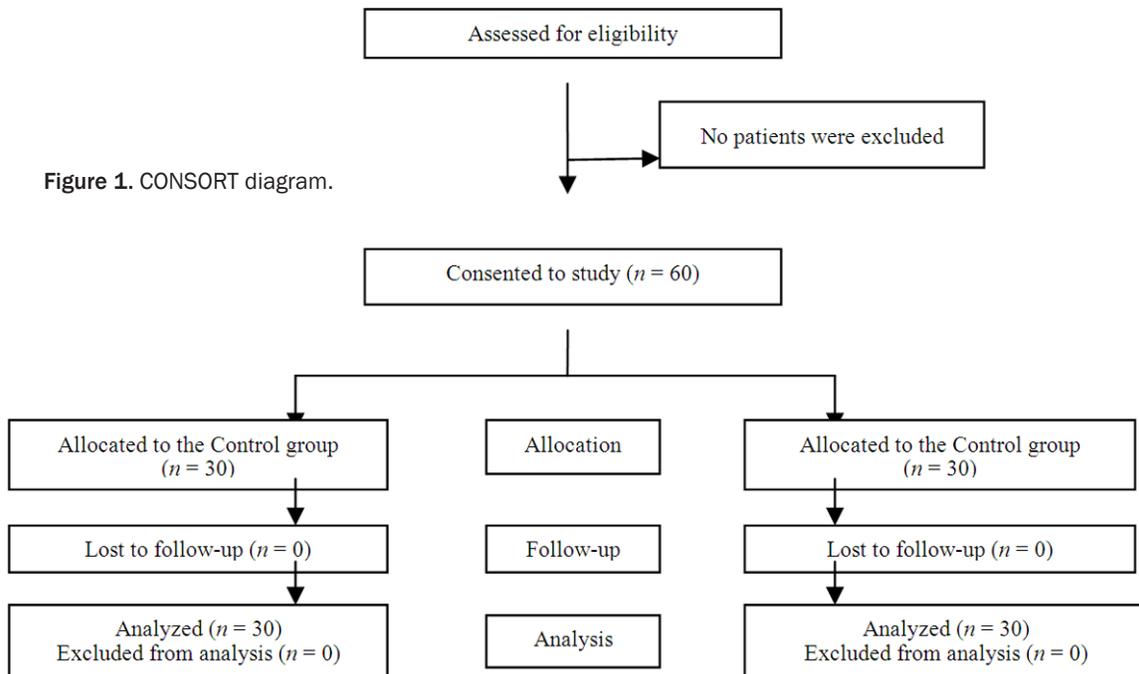


Figure 1. CONSORT diagram.

represented most severe pain, at the time points of 1, 4, 8, 12, and 24 h postoperatively. Side effects such as hypotension, bradycardia, respiratory depression, sedation, and nausea and vomiting were also recorded. Respiratory depression (defined as breath rate < 12 bpm or $SpO_2 < 90\%$) during surgery and the first 24 h postoperatively were also recorded by a fixed anesthesia assistant. Sedation was ranked as none = awake and alert, mild = awake but drowsy, moderate = asleep but can be awakened, severe = cannot be awakened. The satisfaction of postoperative analgesia was also studied in the first 24 h after surgery.

Statistical analysis

According to G* power software, to detect a difference of 160 min in mean pain-free duration with type I error of 0.05 and a test power of 90%, at least 18 patients needed to be included in each group. Demographic data were collected and are presented as count or mean \pm SD as appropriate. Nominal data were analyzed using the chi-square test, and continuous data were analyzed using Student's *t*-test for intergroup comparison. Duration of anesthesia was analyzed using Kaplan-Meier survival analysis. The total requirement of sufentanil between the two groups was compared with an unpaired *t*-test. The VAS at different time points was compared with Student's *t*-test between the two groups. Side effects and satisfaction of po-

stoperative analgesia between the two groups were compared with the chi-square test. Statistical analysis was performed with GraphPad Prism 5 (version 5.01). Statistical significance was defined as $P < 0.05$ (two-sided).

Results

Comparison of general conditions between two groups

The CONSORT diagram of the present study is shown in **Figure 1**. A total of 60 parturients were assessed for eligibility, and all of them were enrolled and randomly assigned to the Dex group ($n = 30$) or Control group ($n = 30$). There were no differences in age, weight, height, or duration of surgery between the two groups (all $P > 0.05$) (**Table 1**).

Comparison of issues of postoperative analgesia between two groups

The duration of analgesia was significantly longer in the Dex group than in the Control group (905.0 ± 114.2 min vs. 741.4 ± 105.3 min, $P < 0.001$) (**Figure 2**). The consumption of the rescue dose of sufentanil in the first 24 hours postoperatively was lower in the Dex group than in the Control group (29.4 ± 1.2 μ g vs. 47.4 ± 2.0 μ g, $P < 0.001$) (**Figure 3**). The VAS point at rest was significantly lower in the Dex

Table 1. Patients' demographic and surgical data

	Dex group (n = 30)	Control group (n = 30)	P-value*
Age (y)	48 ± 5	46 ± 4	0.19
Height (cm)	163 ± 3	163 ± 3	0.42
Weight (kg)	55 ± 5	55 ± 5	0.75
Duration of surgery (min)	81 ± 9	79 ± 10	0.41

Data are presented as mean ± SD. *Student t-test.

Comparison of side effects between two groups

The incidence of side effects, such as hypotension, bradycardia, nausea and vomiting, respiratory depression and severe sedation were similar between groups ($P > 0.05$) (Table 2).

Discussion

In the current study, we demonstrated that the addition of dexmedetomidine to levobupivacaine in TAP block can extend the duration of analgesia, reduce the requirement of postoperative sufentanil, and promote the satisfaction of analgesia of the patient. Almarakbi WA and his colleagues [7] also added dexmedetomidine to bupivacaine in TAP block and found it could prolong the duration of postoperative analgesia; the results were similar to our results. Moreover, Luan [8] compared using ropivacaine alone with using ropivacaine and dexmedetomidine in TAP block and concluded that ropivacaine, when combined with dexmedetomidine, can reduce postoperative sufentanil consumption and provide superior pain management, which is also consistent with our results. In the present study, our results reinforced that dexmedetomidine can play the role of an effective adjuvant for local anesthetics in TAP block again. Recently, dexmedetomidine has been used by anesthetists in both adults and children with neuraxial anesthesia or peripheral nerve block, and they suggested that dexmedetomidine could be an effective and safe adjuvant [7-9]. Clinical trials combining dexmedetomidine as an adjuvant with local anesthetics have been also conducted by some researchers in brachial plexus block, and the results showed that dexmedetomidine can extend the duration of analgesia of local anesthetics [10-15]. Hence, we could conclude that adding dexmedetomidine to local anesthetics could prolong the duration of analgesia and reduce the need for postoperative analgesics.

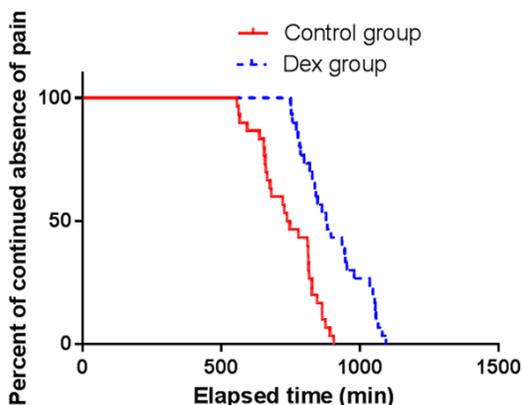


Figure 2. Cumulative percentages of continued absence of pain after TAP block in the Dex group (blue dotted line) and in the Control group (red solid line), analyzed by the Kaplan-Meier survival analysis. Log-rank differences between the two groups were significant ($P < 0.001$).

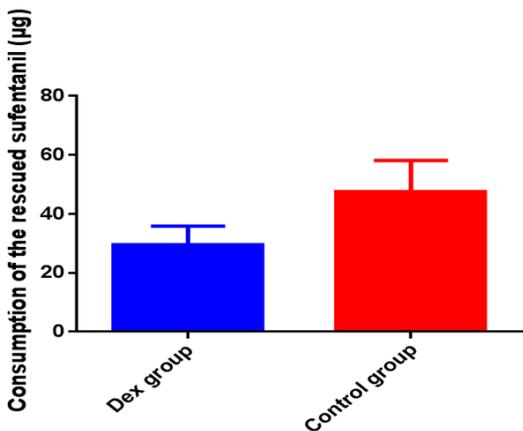


Figure 3. Consumption of rescue fentanyl in the first 24 hours postoperatively; significantly higher in Control group than in Dex group ($P < 0.05$).

group than in the Control group at 8 and 12 hours time point ($P < 0.05$) (Figure 4). The Dex group has higher rate of excellent satisfaction during postoperative period than that in the Control group (83% vs. 50%, $P = 0.006$) (Table 2).

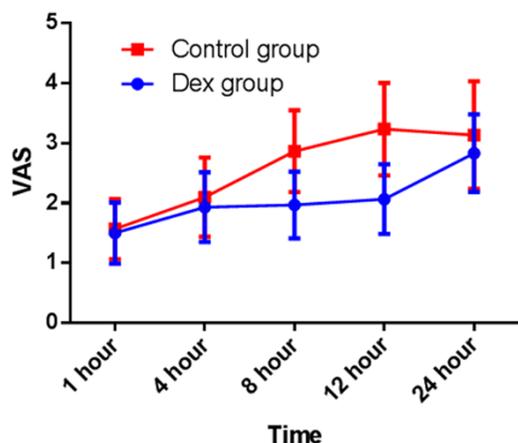


Figure 4. Comparison of postoperative VAS at rest between the two groups. The VAS scores were lower at 8 and 12 hours in the Dex group ($P < 0.05$).

Table 2. Side effects and patient satisfaction with postoperative analgesia

	Dex group (n = 30)	Control group (n = 30)	P-value*
Hypotension	3 (10)	4 (13)	0.688
Bradycardia	6 (20)	2 (7)	0.129
Nausea and vomiting	2 (7)	2 (7)	1.0
Respiratory depression	0	0	1.0
Severe sedation	0	0	1.0
Patient Satisfaction			
Excellent	25 (83)	15 (50)	0.006
Good	5 (17)	15 (50)	0.006

Data are presented as number (%). *Chi-square test.

study. Firstly, some researchers believed that dexmedetomidine, by the action of α_2 -AR, induces vasoconstriction, which might contribute to prolong the period of analgesia [9, 18]. Secondly, Eledjam and his colleagues compared adding clonidine and epinephrine to local anesthetics and suggested that clonidine plays a role through α_2 -AR agonists rather than by the action of vasoconstriction [19]. Similar to clonidine, dexmedetomidine may take effect through α_2 -AR agonists. Later, in a pig study, the author also suggested that dexmedetomidine enhances local anesthetic action by the action of α_2 -AR [20]. In the current study, 0.5 $\mu\text{g}/\text{kg}$ of dexmedetomidine combined with levobupivacaine in TAP block resulted in a significant extension of analgesia, lower requirement of rescue-dose sufentanil, and higher

satisfaction of postoperative analgesia. Similar to our study, diverse clinical trials also demonstrated that adding dexmedetomidine to different local anesthetics in neuraxial and peripheral nerve blocks can prolong the time before the first rescue analgesic in postoperative pain management [13-21].

Concerns about the safety of the administration of perineural dexmedetomidine with local anesthetics in nerve block have been considered. A preclinical study that demonstrated adding dexmedetomidine to ropivacaine extends the duration of sensory blockade showed no neurotoxicity even at a high dose of 20 $\mu\text{g}/\text{kg}$ of dexmedetomidine administered when combined with ropivacaine in sciatic nerve blocks in rats [21]. In another animal study, conducted by Brummett and his colleagues, they found there was no neurotoxicity when rats were administered a high dose of dexmedetomidine to bupivacaine [22]. In clinical trials, there were no reports of neurological deficit when adding dexmedetomidine to central and peripheral nerve blocks [13-21], similar to the findings of the present study, in which we also did not find any obvious symptoms or signs of dysfunction in the nervous system, reinforcing the safety of using perineural dexmedetomidine. However, dexmedetomidine in clinical practice may be associated with some side effects such as respiratory depression, sedation, hypotension, and bradycardia [16, 23]. In this study, although side effects were similar between the two groups, 6 patients in the Dex group experienced bradycardia. Although the bradycardia was easily treated by 0.5 mg atropine, the incidence could reveal that when dexmedetomidine is used in anesthesia practice, attention should be paid to bradycardia as a side effect.

Limitations existed in the current study. First, there was no standard by which to evaluate the effectiveness of TAP block, because patients lost consciousness after the induction of general anesthesia. To solve this problem, a fixed radiographer was involved in our study to help us verify exact placement of the blocking needle guided by ultrasound, even though the three layers of the abdominal wall were easy for anesthetists to distinguish. Second, the safety of perineural dexmedetomidine could be argued because our study was small, and no specific assessments of safety were done. Hence, the

safety of perineural dexmedetomidine in a larger sample size and specific assessment variables should be carefully evaluated in both animals and humans. Third, dexmedetomidine in TAP block would be absorbed into the bloodstream, but we did not monitor the dose of propofol and remifentanyl used during surgery in this study. Because of the pharmacological characteristic of dexmedetomidine, it may reduce the requirement of propofol and remifentanyl [24-26].

In summary, the addition of 0.5 µg/kg dexmedetomidine to levobupivacaine in TAP block can help prolong the duration of postoperative analgesia and reduce postoperative analgesic requirements without additional serious side effects. Although we concluded that dexmedetomidine has the advantage of prolonging postoperative analgesia in the current study, no adjuvant has been approved by the Food and Drug Administration (FDA) and, thus, such additions should be used with careful consideration.

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Disclosure of conflict of interest

None.

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