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Adding Dexmedetomidine to Bupivacaine in Ultrasound-guided Thoracic Paravertebral Block for Pain Management after Upper Abdominal Surgery: A Double-blind Randomized Controlled Trial

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Abstract

Background: Paravertebral blocks are one of the possible postoperative pain management modalities after laparotomy. Adjuvants to local anesthetics, including alpha agonists, have been shown to lead to better pain relief and increased duration of analgesia.
Objectives: The aim of this study is to examine the effect of adding dexmedetomidine to bupivacaine for ultrasound-guided paravertebral blocks in laparotomy.
Methods: In this double-blind, randomized controlled trial (RCT), we enrolled 42 patients scheduled for T6 to T8 thoracic paravertebral block (TPVB) for analgesia after laparotomy. The patients were randomly assigned into two groups of BD (bupivacaine 2.5 mg/mL 20 mL plus dexmedetomidine 100 μg) and B (bupivacaine 20 mL alone). Following surgery, intravenous fentanyl patient-controlled analgesia was initiated. The numerical rating scale (NRS) for pain, sedation score, total analgesic consumption, time to first analgesic requirement, side effects (such as nausea and vomiting), respiratory depression, and patients' satisfaction during the first 48 hours of evaluation were compared in the two groups.
Results: Pain scores and mean total analgesic consumption at the first 48 hours in the BD group were significantly lower than Group B ($P = 0.03$ and $P < 0.001$, respectively). The time of first analgesic request was significantly longer in BD group ($P < 0.001$). Sedation scores and side effects did not differ significantly between the two groups.
Conclusions: Adding dexmedetomidine to bupivacaine for TPVB after laparotomy yielded better postoperative pain management without significant complications.

Keywords: Dexmedetomidine, Upper Abdominal Surgery, Ultrasound Guided, Thoracic Paravertebral Block, Postoperative Pain

1. Background

Various methods have been used for postoperative pain relief, such as oral and intravenous opioid and non-opioid analgesics, as well as peripheral nerve blocks and neuraxial analgesia (1-4). Although opioids are the most common pain killers used to control pain after surgery, there is always concern about their risk, such as dependence and complications (5, 6). Epidural and paravertebral blocks for peri-operative pain management for thoracic and abdominal surgeries are commonly used regional anesthetic techniques (7-9). To provide a longer duration of analgesia, a number of adjuvants, such as opioids, non-steroidal anti-inflammatory drugs, and alpha 2-agonists have been used in conjunction with local anesthetics for peripheral and neuraxial blocks, including paravertebral blockade (10-14).

The use of dexmedetomidine as an alpha-2 agonist has recently become more widespread (15). Dexmedetomidine is a selective alpha 2-adrenoceptor agonist with centrally mediated sympatholytic, sedative and analgesic effects (16). It acts on pain by reducing the activity of neurons in the brainstem, locus coeruleus, and increasing the inhibitory activity of γ-aminobutyric acid (GABA) neurons in the ventrolateral nucleus preopticus (17). Although dexmedetomidine has been approved only for sedation less than 24 hours, it is commonly administered for

a longer duration (18, 19). It provides pain relief without respiratory depression (20). The addition of dexmedetomidine to local anesthetics in peripheral nerve block has been shown to lead to a longer duration of the block with a reduction in analgesic requirements (21). Compared to opioids, it causes less nausea, vomiting, and constipation (22).

2. Objectives

The aim of this study is to examine the efficacy and side effects of adding dexmedetomidine to bupivacaine for ultrasound-guided thoracic paravertebral block (TPVB) after upper abdominal surgery.

3. Methods

In this double-blind, randomized controlled trial (RCT), we included 42 patients after approval of the Ethics Committee of Iran University of Medical Sciences (Ref. 933389/105) and obtained written informed consent from all patients. The inclusion criteria were patients of both sex, aged 20 - 65 years, meeting the criteria by the American Society of Anesthesiologists (ASA) physical status I/II, undergoing elective laparotomy, and receiving an ultrasound-guided TPVB after the surgery. Exclusion criteria were addiction, complicated surgical procedure, reduced level of consciousness after the operation, need for postoperative mechanical ventilation, local or systemic infection, and patient's unwillingness to participate in the study. This clinical trial was registered at the Iranian Registry of Clinical Trials on 12/27/2015 (IRCT2015121212642N23).

Using the power equation with a power of 90% and a risk of Type-I error of 0.05, an appropriate sample size was determined to be 21 subjects for each group:

$$2N = \frac{4\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \sigma^2}{\delta^2} \quad (1)$$

Using a randomization table, patients were assigned into two equal groups (n = 21 in each group). The first group (BD) received bupivacaine plus dexmedetomidine, and the second group (B) received only bupivacaine for TPVB. Both TPVB and data collection were performed by investigators who were blinded to group allocations.

All patients underwent general anesthesia with fentanyl and midazolam as premedication; induction and maintenance were performed using propofol, fentanyl, and cisatracurium. After completion of the surgical procedure, patients were extubated and transferred to recovery room. In the recovery room, patients were placed in the lateral decubitus position while they were conscious. Under aseptic condition and using local anesthesia, a linear ultrasound probe (high frequency 6 - 13 MHz; Sonosite, USA) was placed between the sixth to eighth thoracic spinous process. A 10-cm 22-G sonovisible needle (Pajunk, Germany) was inserted using in-plane technique and guided to the paravertebral space. After ascertaining that the tip of the needle was in the target site, anesthetic solution was administered. The injectate in the BD group consisted of 20 mL of bupivacaine 0.25% (Mylan, Cyprus) plus dexmedetomidine 100 μg with a volume of 1 mL (Precedex; Pfizer, USA); meanwhile, 20 mL of bupivacaine 0.25% was administered in group B. Patients were transferred to the ward with intravenous patient controlled analgesia (PCA) with the following settings: fentanyl 10 $\mu g.mL^{-1}$ with a 2 mL bolus dose and a 15-minute lockout time.

Patients were evaluated 2, 6, 12, 24, and 48 hours after the block. Pain was evaluated using the numerical rating scale (NRS) from zero (no pain) to 10 (maximum imaginable pain). Fentanyl consumption by PCA in the first 24 and 48 hours, as well as the time to first analgesic request were recorded. A satisfaction score was obtained [dissatisfied (1), neutral (2), satisfied (3), and very satisfied (4)]. Sedation was measured according to the Ramsay scale system. In case of more than one occurrence of nausea, intravenous (IV) ondansetron 4 mg was administered; the number of doses over the first 48 hours was recorded. Respiratory depression was defined as a respiratory rate less than 8 $breaths.min^{-1}$.

Statistical analysis was performed using the SPSS software version 21 (IBM, USA). Normal distribution of quantitative data was confirmed using the Kolmogorov-Smirnov test. To compare qualitative data, chi-square or Fisher's exact tests were used, and *t*-test was used to compare quantitative data for independent groups. Changes in quantitative data were examined using repeated measurements. The cutoff for a statistically significant difference was set at 0.05.

4. Results

The characteristics and baseline variables of patients, including the type of laparotomy and surgical time were not significantly different between the groups (Table 1).

According to the results of the repeated measurements test, pain scores (NRS) over time in the BD group were significantly lower than in the control group (P = 0.003). Also, sedation scores in the BD group were significantly lower than in the control group at 6th and 48th hours (Table 2).

Daily mean fentanyl consumption in the BD group showed a significant reduction compared to the B group (P < 0.001). The result of the *t*-test for independent groups showed that the mean total amount of fentanyl in BD

Table 1. Characteristics Data [a]

Variable	BD	B	P-Value
Age (y)	47 ± 12	49 ± 11	0.26
Gender (M:F)	7:14	11:10	0.42
Height (cm)	163 ± 9	168 ± 7	0.6
Weight (kg)	64 ± 7	66 ± 13	0.58
Kind of laparotomy			
Cholecystectomy	10	16	0.35
Splenectomy	7	3	0.31
Hydatid cyst	2	2	1.00
Pancreatic mass	2	0	0.49
Operation duration (min)	268 ± 68	267 ± 40	0.28

[a] Values are expresse as mean ± SD.

Table 2. Pain, Sedation Score, Fentanyl Consumption, and Time to First Analgesic Request [a]

Interval (h)	BD	B	P-Value
Pain score (NRS)			
0	5.6 ± 1	5.1 ± 0.7	0.13
2	2.9 ± 0.8	3.5 ± 0.7	0.02 [b]
6	2.1 ± 1.2	3.1 ± 0.7	0.47
12	1.5 ± 1.2	2.4 ± 0.6	0.09
24	1.4 ± 0.9	2.2 ± 0.5	0.001 [b]
48	1.4 ± 0.6	1.8 ± 0.3	0.13
Sedation score			
2	1.6 ± 0.4	1.4 ± 0.5	0.13
6	1.6 ± 0.6	1.3 ± 0.4	0.02 [b]
12	1.3 ± 0.4	1.6 ± 0.7	0.47
24	1.3 ± 0.6	1.6 ± 0.5	0.09
48	1.1 ± 0.3	1.5 ± 0.5	0.001 [b]
Fentanyl consumption (μg)			
1st day	410 ± 62	500 ± 66	> 0.001 [b]
2nd day	271 ± 83	350 ± 80	> 0.001 [b]
Total	641 ± 140	820 ± 102	> 0.001 [b]
First analgesic request time (h)	5.3 ± 1.3	3.1 ± 1	> 0.001 [b]

[a] Values are expressed as mean ± SD unless otherwise indicated.
[b] There are significant differences.

group was significantly lower (P = 0.01). The first analgesic request time in BD group was significantly longer than in the B group (P < 0.001) (Table 2).

Nausea and vomiting (P = 0.17) and antiemetic medication (P = 0.32) showed no significant difference between the groups. Respiratory depression (treated with oxygen by face mask 5 L.min^{-1}) was observed in three patients in group B, although there was no significant difference between the two groups in this regard (P = 0.23). Also, satisfaction scores were not significantly different between the two groups (P = 0.23).

5. Discussion

Our results showed that adding 100 μg dexmedetomidine as an adjuvant to bupivacaine for TPVB yielded lower pain scores and delayed the first analgesic request during the first 48 hours after surgery. The selection of local anesthetic, dose, concentration, and volume can affect onset, offset, quality, and duration of regional analgesia; hence, we chose bupivacaine, which is a widely-used long-acting local anesthetic.

Paravertebral block is one of the popular and easy-to-perform techniques, which provides analgesia equivalent to a thoracic epidural with less neurological side effects and a lower risk of hypotension. Performing thoracic and lumbar paravertebral blocks under ultrasound guidance reduces complications and increases accuracy and efficiency (23).

Following paravertebral block, the duration of anesthesia depends on the dose and volume of the local anesthetic. For post-surgical pain relief, it is not possible to easily increase the dose, concentration, and volume of these drugs. Although application of the continuous block may play a special role in these situations, there are some limitations to its common use (such as ambulatory and emergency circumstances, and lack of nursing care and equipment, etc.). Hence, many studies have been conducted to add various adjuvants to local anesthetics (10, 24).

As dexmedetomidine has been demonstrated to have both peripheral and neuraxial analgesic activity, it was hypothesized that it may be helpful for both analgesic and anesthetic purposes (24-26). In a published study, addition of dexmedetomidine to spinal anesthesia provided longer sensory and motor block during surgery, as well as an enhancement of postoperative analgesia (27). Similarly, other studies with the addition of dexmedetomidine to the supraclavicular and paravertebral blocks showed a longer duration of analgesia with lower pain scores, which agree with the results of our study (28, 29).

In another study by Mirkheshti, the effects of dexmedetomidine or ketorolac added to local anesthetic for infraclavicular blocks was evaluated, and the researchers found a prolonged sensory and motor block with dexmedetomidine; however, the time to first rescue analgesic was longer in the ketorolac group. One possible explanation for the difference with our results is that they performed their study using lidocaine, while we used bupivacaine (30).

Mohta et al. performed paravertebral blocks preoperatively in patients undergoing breast surgery and found lower analgesic requirements during and after surgery in the dexmedetomidine group (31). Paravertebral blocks using dexmedetomidine in patients undergoing kidney surgery showed an enhancement of analgesia in the dexmedetomidine group with lower ropivacaine consumption, which supports our findings as well (32). Most studies have shown that adding dexmedetomidine to local anesthetics can enhances the potency of central and peripheral nervous blocks (31-33).

High doses of dexmedetomidine may lead to sedation and changes in hemodynamics such as hypotension and bradycardia. Adding 1 $\mu g.kg^{-1}$ dexmedetomidine to lumbar plexus blocks has been shown to maintain a stable hemodynamic status postoperatively without excessive sedation. We had no respiratory depression in the BD group, which is in agreement with the results of this study (34). Although in our study, side effects including nausea, vomiting, and respiratory depression were not different between the groups, in some previous studies, these side effects were actually reduced in the dexmedetomidine group (32). We obtained higher satisfaction scores in the BD group, although it did not reach a statistical significance. The Ramsay sedation score was higher at the 6th hour in group BD, showing that dexmedetomidine can produce sedation as well.

Continuous administration of dexmedetomidine in paravertebral blocks have also been used and resulted in decreased intraoperative anesthetic drug requirement with lower analgesic requirements in the postoperative period (35).

This study had some limitations. First, we could not evaluate late neurologic complications caused by perineural injection of dexmedetomidine, even though no complications were noted during the first two days of monitoring. Second, it would also be interesting to investigate whether the superior pain control in the group that received dexmedetomidine translates into a lower risk of chronic pain after surgery. Third, we did not measure dexmedetomidine blood levels in the postoperative period.

In conclusion, our study showed that adding dexmedetomidine to bupivacaine in paravertebral block after laparotomy leads to a longer sensory blockade, reduced analgesic requirements, and a longer time to first analgesic request, without significant increase in side effects, which is in agreement with the findings of most previous studies (31, 36). Further studies are required to determine the optimal dose of dexmedetomidine and confirm its safety and efficacy with larger series of patients.

Footnotes

Authors' Contribution: Study concept and design: FI and MA; Acquisition of data: LB and SHRF; Drafting of the manuscript: PR, LB, and ACH; Critical revision of the manuscript for important intellectual content: FI and ACH; Study supervision: FI and MA.

Clinical Trial Registration Code: This clinical trial was registered at the Iranian Registry of Clinical Trials on 12/27/2015 (IRCT2015121212642N23).

Conflict of Interests: There are no conflicts of interest to report.

Ethical Approval: Ref. 933389/105.

Funding/Support: Only departmental funds were used.

Informed Consent: Written informed consent was obtained from all participants.

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