Dexmedetomidine added to ropivacaine for transversus abdominis plane block inhibits stress response in laparoscopic surgery: a randomized controlled trial

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Abstract

Background: Intravenous dexmedetomidine is known to attenuate stress response in patients undergoing laparoscopic surgery. We investigated whether the addition of the highly selective alpha-2 adrenergic agonist dexmedetomidine into ropivacaine for ultrasound-guided transversus abdominis plane block could inhibit stress response during laparoscopic surgery, and determined the optimal dose of dexmedetomidine in it. Methods: One hundred and twenty-five patients undergoing laparoscopic gynecological surgery were included in this prospective and randomized double-blind study. Patients received general anesthesia with or without a total of 60 ml of 0.2% ropivacaine in combination with low (0.25 µg/kg), medium (0.50 µg/kg) or high dose (1.0 µg/kg) of dexmedetomidine for the four-quadrant transversus abdominis plane block (n = 25). The primary outcomes were stress marker levels during the operation. Results: One hundred and twenty patients completed the study protocol. Dexmedetomidine added to ropivacaine for transversus abdominis plane block significantly reduced serum levels of cortisol, norepinephrine, epinephrine, interleukin-6, blood glucose, mean arterial pressure and heart rate in a dose-dependent manner (P < 0.05), accompanied with decreased anesthetic and opioid consumption during the operation (P < 0.05), but the high dose of dexmedetomidine induced higher incidences of bradycardia than low or medium dose of dexmedetomidine (P < 0.05). Conclusion: The addition of dexmedetomidine at the dose of 0.5 µg/kg into ropivacaine for ultrasound-guided transversus abdominis plane block is the optimal dose to inhibit stress response in patients undergoing laparoscopic gynecological surgery.

Background

Laparoscopic surgery becomes more and more popular in gynecological patients due to a few benefits, including less tissue damage, smaller surgical incision, faster recovery and shorter hospital stay with consequent reduction in health care cost[1]. Although laparoscopic surgery is considered to be minimally invasive, this approach may induce a moderate stress response[2,3]. In addition, haemodynamic changes and local immune function impairment may lead to strong stress response during pneumoperitoneum with CO2[4-6]. It may cause cardiovascular complications and internal environment imbalance, which would be harmful to enhance recovery after surgery. Traditionally, this stress response can be alleviated by enhancing the depth of anesthesia and the intensity of analgesia. It has been shown that cortisol response to surgical stimulus can be significantly suppressed by increased blood concentration of remifentanil during laparoscopic cholecystectomy[7], but more adverse events as bradycardia and postoperative nausea and vomiting would happen. Compound anesthesia such as general anesthesia combined with epidural nerve block is an effective way to decrease the surgical stress[8]. However, potential neurological complications limit application of the technique.

The alpha-2 adrenergic agonist compounds like clonidine were used to provide sedation and analgesia in laparoscopic surgery[9]. Dexmedetomidine (DEX) shows a high ratio of specificity (α2/α1 1620:1) making it a highly selective alpha-2 agonist[10]. When administrated as an adjuvant, DEX inhibits stress response related to anesthesia and surgery, with less effect on the haemodynamic stability and respiratory function[11]. Bhardwaj et al found that DEX plus ropivacaine for the surgical wound infiltration
significantly alleviated postoperative pain and decreased the dose of rescue analgesic in patients undergoing lower segment cesarean section[12]. It is also shown that DEX added to ropivacaine extends the duration of brachial plexus blocks and improves postoperative pain[13]. When DEX is intravenously administrated during laparoscopic surgery, it significantly blunts stress response related to surgery and maintains haemodynamic stability[5]. Wu et al found that DEX intravenously administrated during thoracoscopic surgery significantly alleviates one-lung ventilation-related inflammatory and injurious responses by reducing neutrophil recruitment[14].

As a multimodal strategy to administrate postoperative pain, transversus abdominis plane (TAP) block can effectively relieve postoperative pain and decrease opioid consumption after laparoscopic surgery[15]. However, it is still unclear whether TAP block with DEX as an adjuvant to local anesthetics can reduce the stress response during the laparoscopic surgery.

In this prospective, randomized, double-blind study, we investigated whether single-injection bilateral TAP block using ropivacaine combined with DEX as an adjuvant inhibits the stress response in patients undergoing gynecological laparoscopic surgery, and determined the optimal dose of dexmedetomidine in it. The primary outcome investigated was the changing of stress marker levels during the operation. Second outcomes included hemodynamic change, general anesthetic and opioid consumption, postoperative pain scores, and adverse events.

**Methods**

**Research design**

This was a prospective randomized controlled study conducted in the Department of anesthesiology, the People's Hospital of China Three Gorges University, Yichang City, China. The study protocol was approved by the institutional review board of the People's Hospital of China Three Gorges University (20161103). The study was registered at www.chictr.org.cn with the identifier ChiCTR-IOR-16009753 on November 6, 2016. All participants provided written informed consent. Patients were recruited from December, 2016 to January, 2018.

**Participants**

Inclusion criteria consisted of women, ranging in age from 18 to 60 years, American Society of Anesthesiologists (ASA) physical status of I or II, gynecological laparoscopic surgery under general anesthesia, and less than 3 hours’ operation duration. Included procedures were myomectomy, ovarian cystectomy and diagnostic procedures. Subjects were excluded if they had malignant tumors, hypertension, diabetes, heart disease, adrenal gland disease, severe renal or hepatic disease, a history of chronic pain, bradycardia, pregnant, a long history of systemic corticosteroid, analgesic and adrenergic receptor agonist and antagonist, or dependent on alcohol, nicotine or opioid. Subjects were also excluded if they were allergic to local anesthetic, the body mass index exceeded 35 kg/m2, converted to open surgery for laparoscopic failure, or TAP block failed.
Study protocol

Following informed consent, subjects scheduled for gynecological laparoscopic surgery were randomized to the following groups: Control group (without TAP block); Ropivacaine group (only receiving 0.2% ropivacaine with total volume of 60 ml perineurally for TAP block); Low, Medium, High DEX + ropivacaine groups (receiving 0.2% ropivacaine combined with 0.25 µg/kg, 0.5 µg/kg, 1.0 µg/kg DEX with total volume of 60 ml perineurally for TAP block, respectively). The randomization was performed by the pharmacy department using a schedule provided by a statistics staff and was blinded to the anesthesia team, surgery team, patient and clinical investigators. The medicine was prepared by the pharmacist, labeled with study subject number, and physically delivered by pharmacy staff to the anesthesiologist performing the TAP block.

Subjects were taken to the operating room, and electrocardiography, heart rate (HR), pulse oxygen saturation and blood pressure were monitored. A peripheral intravenous catheter was inserted under local anesthesia. Midazolam (0.04 mg/kg) and sufentanil (0.1 µg/kg) were administered intravenously in patients. After sterile preparation and draping of the injection area, a four-quadrant ultrasound-guided (Mindray M9 13 mHz liner probe; Mindray Co. Ltd, Shenzhen, China) TAP block was performed using an in-plane technique by the same anesthesiologist using a 22 gauge plexus needle. The four-quadrant TAP block includes performing single-shot bilateral subcostal as well as posterior TAP blocks[16]. A total of 60 ml study solution containing ropivacaine and different concentration DEX was used for the four-quadrant TAP blocks with each site 15 ml. After block placement, sensory function was examined every 5 minutes during the next 20 minutes. Sensory function was assessed using a 3-point scale to pinprick with a toothpick (pinprick to abdominal wall: 0, normal sensation, sharp to pinprick; 1, pinprick felt but not sharp; 2, no sensation, pinprick not felt). The score of 2 indicates a successful TAP block.

After successful TAP block was confirmed, general anesthesia was induced with intravenous propofol (2-3 mg/kg), sufentanil (0.2-0.4 µg/kg), rocuronium (0.6 mg/kg), and lidocaine (1.5 mg/kg). After an endotracheal tube was placed, anesthesia was maintained with intravenous propofol at infusion rate of ranging from 4-6 mg/kg/h, remifentanil at infusion rate ranging from 0.1-0.4 µg/kg/min, and cisatracurium (0.05 mg/kg) intermittently for maintenance of neuromuscular blockade. Bispectral index was maintained between 40-60 during the operation. Once tube position was confirmed, positive pressure ventilation was started with tidal volume 6-8 ml/kg, and the respiratory rate was titrated to maintain the end-tidal CO2 between 35 and 45 mmHg. Intravenous flurbiprofen 1 mg/kg, sufentanil 0.1 µg/kg and tropisetron 4 mg were administered to the subjects at the end of surgery. The same surgeon performed all the procedures with the same laparoscopic surgical technique by using a pneumoperitoneum pressure of 12 mmHg (carbon-dioxide flow rate of 1.2 L/min). After operation, subjects received regular paracetamol 1 g every 6 h and intravenous dezocine (rescue analgesic) 0.1 mg/kg was administered when needed until the patient’s rest pain score was 3 or less. In addition, subjects received regular ondansetron 4 mg every 8 h as an enhanced recovery protocol.

Outcome measurements
A total of 5 ml whole vein blood sample was collected to detect the levels of serum cortisol (Cor), norepinephrine (NE), epinephrine (E), interleukin (IL) -6 and blood glucose (Glu) at predetermined time intervals including prior to induction (T0, baseline), prior to pneumoperitoneum (T1), prior to the end of pneumoperitoneum (T2), and at the end of surgery (T3), respectively. Blood samples were stored in capped vacutainer tubes at -80°C for determining stress hormone. Serum Cor, NE, E and IL-6 were measured by the corresponding enzyme linked immunosorbent assay kit from the Siemens Company. Consumption of propofol and remifentanil were recorded at the end of operation. The duration from the completion of anesthesia to awareness of patient was also recorded. At the same timepoints, mean arterial pressure (MAP) and HR were recorded, respectively. Adverse events during the procedure were defined as follows: bradycardia: HR < 55 bpm; tachycardia: HR > 30% above baseline value; hypotension: systolic blood pressure (SBP) < 90 mmHg; hypertension: SBP > 140 mmHg.

Patients were followed up at 1 (H1), 6 (H6), 12 (H12), and 24 (H24) hours after surgery. During the assessment, patients were asked to rate their pain at rest and with movement on a 0 to 10 numeric rating scale (0, no pain; 10, pain as bad as you can imagine), respectively. The total consumption of dezocines within 24 hours after surgery were recorded.

Sample size calculation

We anticipated a difference of 30% in the intraoperative stress marker levels between the control and treated groups as being clinically meaningful. A sample size of 22 subjects per group was estimated necessary to detect such a difference with a power of 80% at an alpha level of 0.05 based on the results of our pilot study, which was calculated using PASS software version 15.0 (NSCC, USA). We planned to include 25 patients each group to account for the potential dropouts.

Statistical analysis

Kolmogorov-Smirnov test was used to examine the normality of distribution of continuous outcomes. Normally distributed continuous variables, such as serum Cor, NE, E, IL-6, and Glu changes, MAP and HR over time, and postoperative pain scores at rest and with movement, were expressed as mean ± standard deviation (SD) and were compared using repeated-measures analysis of variance. Whereas comparisons to baseline were analyzed by a post hoc Dunnett multiple-comparisons test, and intergroup comparisons were analyzed by Tukey multiple-comparisons test, as indicated. The demographic characteristics, consumption of propofol and opioid during the operation and rescue analgesics after surgery, and anesthesia recovery time were compared using repeated-measure analysis of variance, whereas a post hoc Tukey multiple-comparisons test compared values between the 5 groups. Categorical data (including the ASA status and the incidence of bradycardia) were described as frequencies and proportions, and were analyzed by using Chi-square test. Data analysis was performed using IBM SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp), and 2-tailed P < 0.05 was considered statistically significant.

Results
Demographic, physiology and surgical characteristic

Figure 1 shows the CONSORT diagram of inclusion. A total 301 of patients were screened for potential inclusion, of which 125 patients were recruited and randomized. Three patients were withdrawn for converting to open surgical procedure, and two patients failed in TAP block were excluded. Thus, the final numbers of participants were 120. TAP Block success rate was 98.4%. The patient characteristics were similar among the five groups (Table 1).

Primary outcomes

The intraoperative levels of serum Cor, NE, E, IL-6 and Glu were lower from prior to pneumoperitoneum (T1) to the end of surgery (T3) in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups than in Control group ($P < 0.05$). However, they were still higher from prior to pneumoperitoneum (T1) to the end of surgery (T3) than the corresponding baseline value (T0) in Control, Ropivacaine, and Low DEX + ropivacaine groups ($P < 0.05$). On the contrary, they were decreased from prior to pneumoperitoneum (T1) to the end of surgery (T3) compared to the baseline value (T0) in High DEX + ropivacaine group ($P < 0.05$). There were no significant differences in all these parameters at any timepoints in Medium DEX + ropivacaine group ($P > 0.05$, Table 2).

MAP and HR from prior to pneumoperitoneum (T1) to the end of surgery (T3) in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups were significantly decreased as compared with that in Control group ($P < 0.05$). Further, the addition of 1.0 µg/kg DEX for TAP block (High DEX + ropivacaine group) significantly decreased MAP and HR levels at these same timepoints as compared with Ropivacaine, Low, and Medium DEX + ropivacaine groups ($P < 0.05$). There were no significant differences in MAP and HR at any timepoints in Medium DEX + ropivacaine group ($P > 0.05$, Table 3).

Secondary outcomes

The consumption of propofol and remifentanil during the operation were lower in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups than in Control group ($P < 0.05$), though there were no significant differences among the Ropivacaine, Low, Medium, and High DEX + ropivacaine groups ($P > 0.05$). There were no significant differences between the duration from the completion of anesthesia to awareness among these five groups ($P > 0.05$). The incidence of bradycardia was higher in High DEX + ropivacaine group than the other groups ($P < 0.05$, Table 4).

The pain scores at rest and with movement at 1 hour after surgery (H1) in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups were significantly decreased compared with Control group ($P < 0.05$). There were lower pain scores at rest and with movement between 6 (H6) and 12 (H12) hours after surgery in Medium and High DEX + ropivacaine groups than in Control, Ropivacaine, and Low DEX + ropivacaine groups ($P < 0.05$). There were no differences in pain scores at 24 hours after surgery (H24) among the five groups (Table 5). The total consumption of dezocine over 24 hours in Control group was more than in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups ($P < 0.05$). The consumption of
dezocines for the first 24 hours after surgery were lower in both Medium and High DEX + ropivacaine groups when compared to Control, Ropivacaine, and Low DEX + ropivacaine groups ($P < 0.05$, Table 4).

**Discussion**

In the present study, we investigated the effects of different doses of DEX in combination with ropivacaine for TAP block in patients undergoing laparoscopic surgery. The addition of DEX was found to significantly reduce serum Cor, NE, E, IL-6 and Glu levels in a dose-dependent manner, and decrease the anesthetic and opioid consumption during the operation, and also improve postoperative pain. However, it is noted that 1 µg/kg DEX in combination with 0.2% ropivacaine for TAP blockade produces a stronger inhibition of stress response with higher incidence of bradycardia. Therefore, the addition of 0.5 µg/kg DEX as an adjuvant for TAP blockade is the optimal dose to control the surgical stress.

Pneumoperitoneum induces CO2 peritoneal absorption resulting in hypercarbia, which enhances systemic vascular resistance, MAP, HR and the risk of arrhythmia by stimulating sympathetic nervous system [17]. Generally, opioid analgesic agents or general anesthetic agents are administered to blunt the systemic response. The α- or β-adrenergic antagonists such as esmolol are also used to control the stress response. However, there are many adverse effects following the administration such as postoperative nausea and vomiting, and delayed recovery from anesthesia. Our present study further provided evidences that pneumoperitoneum affects hemodynamic stability indicated by increased levels of MAP and HR during the surgery. The increased levels of stress markers such as serum Cor, NE, E, IL-6 and Glu during the operation in the control group indicates stronger stress response following laparoscopic surgery. Accordingly, the total dosage of propofol and remifentanil were also significantly increased in the control group.

Epidural or perineural DEX has been used in the range of 0.5~1 µg/kg without any incidence of neurological deficits[18-20]. Even a higher dose (150 µg) DEX was added to ropivacaine for interscalene brachial plexus blocks, there were no acute or delayed neurological sequelae, and no significant adverse events[13]. It is reported that the addition of 1 µg/kg DEX to bupivacaine for caudal block has less adverse effect on the cardiovascular system in pediatrics[21]. Based on the previous reports, three different doses(0.25, 0.5, 1.0 µg/kg) of DEX in the present study were selected for TAP block. DEX was found to significantly increase sedation and analgesia and decrease blood pressure and HR in a concentration-dependent manner in the healthy volunteers[22]. It also decreased catecholamines 45-76% and kept inhibition of catecholamine in subsequent infusions[22]. The excitability of sympathetic-adrenal medullary system increases when the body is in a state of stress, this results in sympathetic nerve stimulation and catecholamine hormone secretion including Cor, NE and E. Meanwhile, the level of blood glucose is generally increased, and cytokines such as IL-6, IL-10 are used to evaluate the systemic stress response to injury[23]. In the present study, we found that perineural DEX, like intravenous administration, significantly decreased the levels of stress indicators such as serum Cor, NE, E, IL-6 and Glu, at the dose of 0.5 µg/kg and 1 µg/kg, but not 0.25 µg/kg. However, perineural administration of DEX at the dose of 1.0 µg/kg increased cardiovascular adverse effects such as bradycardia. Therefore, the dose of 0.5 µg/kg
DEX is the optimal dose as an adjuvant to ropivacaine for TAP block during the gynecological laparoscopy surgery in terms of inhibition of stress response.

TAP block is a myofascial plane block that targets at the peripheral nerve level, which has been used as a multimodal protocol to optimize postoperative pain outcomes. Previous studies have showed that TAP blockade can produce effective analgesia and reduce the dosage of opioid for the abdominal surgery\[15, 24-25\]. As a selective \(\alpha_2\) adrenoceptor agonist, DEX is intravenously administered to patients as a sedative. Also, it is widely used as an adjuvant for the perineural nerve block. When DEX is combined with a local anesthetic agent, it can prolong the duration of block, which is possibly due to local vasoconstriction in peripheral nerves\[26\] or direct inhibition in peripheral nerve action\[27\]. DEX was found to dose-dependent enhance of the local anesthetic effect of lidocaine in rats\[28\] and in healthy volunteers\[29\].

Meta-analysis of randomized controlled trials showed that TAP block is an effective approach to attenuate postoperative pain and decrease the use of opioid after laparoscopic surgery\[15, 30\]. A cadaver study showed that the spread of local anesthetics is not restrained by pneumoperitoneum in midaxillary technique transversus abdominis plane block\[31\]. DEX was found to provide analgesic effects through supraspinal, ganglionic, spinal, and peripheral actions when it is intraveously administered\[22\], and to reduce the consumption of opioids during the surgery. This is consistent with our present study that the consumption of anesthetic agent propofol and analgesic remifentanil during the operation were significantly decreased when TAP block with DEX added to ropivacaine was performed, and postoperative pain was also significantly improved. In our study, the addition of DEX (less than 1.0 \(\mu g/kg\)) for TAP block was found to provide effective postoperative analgesia without adverse effect on awkeness of patient from general anesthesia.

**Limitations**

First, we only investigated the female subjects. Perhaps there is a gender bias. Second, it is difficult for patients to be totally blind to random allocation because there is a blank control group (no TAP block).

**Conclusion**

In conclusion, DEX as an adjuvant added to ropivacaine for TAP block at the dose of 0.5 \(\mu g/kg\) is the optimal dose to inhibit the stress response during the gynecological laparoscopic surgery, and improve postoperative pain. Future studies are needed to evaluate the efficacy of addition of DEX to peripheral nerve blockade for more involved and painful procedures such as open surgery or the other types of surgery.

**Declarations**

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

**Authors’ contributions:**

All authors (ZJQ, CYX, HBL, TTL, LYZ, ZYX, MZ and JPL) made substantial contributions to the study conception and design, were involved in revising this manuscript critically, approved the final manuscript and agreed to be accountable for all aspects of the work. CYX, HBL, TTL and MZ collected and analyzed the patient data, and ZJQ was a major contributor in writing the manuscript. LYZ, ZYX and JPL took part in the coordination of this project. ZJQ applied for funding.

**Ethics approval and consent to participate**

The study protocol was approved by the institutional review board of the People’s Hospital of China Three Gorges University in November 2016 (No. 20161103). Written informed consents were obtained either from the patients or legal representatives.

**Consent for publication**

All included patients or their family members signed the informed consent form to report individual patient data. All authors have confirmed the manuscript and approved the publication of the manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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Abbreviations

DEX: Dexmedetomidine; TAP: Transversus abdominis plane; ASA: American Society of Anesthesiologists; HR: Heart rate; Cor: Cortisol; NE: Norepinephrine; E: Epinephrine; IL-6: Interleukin-6; Glu: Glucose; MAP: Mean arterial pressure; SBP: Systolic blood pressure; SD: Standard deviation

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Tables

Due to technical limitations, the tables for this manuscript are only available as a download in the supplemental files section

Figures
CONSORT flow diagram. Control group: no transversus abdominis plane (TAP) block. Ropivacaine group: TAP block with perineural ropivacaine 0.2% only. Low, Medium and High dexmedetomidine (DEX) + ropivacaine group: TAP block with perineural ropivacaine 0.2% and DEX 0.25, 0.5, 1.0 μg/kg, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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