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

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Abstract

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

Methods: We enrolled ninety ASA I-III patients undergoing open abdominal cytoreductive surgery in this study. Patients were randomized assigned into three groups (TAP-R, TAP-DR, and CON, n=30 in each). All patients received standardized general anesthesia and postoperative Bd-TAP blocks were performed. The TAP-R, TAP-DR and CON group received Bd-TAP blocks with 0.3% ropivacaine, 0.3% ropivacaine and dexmedetomidine 0.5 μ g/kg, and 0.9% normal saline, respectively. All patients received patient-controlled intravenous analgesia (PCIA). The first request time for PCIA bolus, the VAS scores at 0, 6, 12, 24, and 48 hours after operation, the cumulative sufentanil consumption in 24 and 48 hours were compared. Pulmonary function was evaluated pre-operation and 24h after operation. The use of rescue drugs, early recovery quality was recorded.

Results: Median values of the first request time for PCIA in the TAP-DR was 13.5 (11.0-16.0) hours, which was significantly longer than those in the TAP-R and CON groups [7.0 (6.0-9.0) and 3.0 (1.0-4.5)]. The VAS scores at rest and on coughing of TAP-DR group at all time points after operation were significantly lower than those of CON group ($P < 0.05$). Cumulative sufentanil consumption in TAP-DR group were the least at 48h after surgery. Postoperative FEV₁ and FEV₁/FVC in TAP-DR group was significantly higher than group CON. Less rescue analgesics was needed by the patients in TAP-DR group ($P < 0.05$). There was no significantly difference in the early recovery quality between TAP-DR and CON group ($P > 0.05$).

Conclusion: Dexmedetomidine combined with ropivacaine for Bd-TAP blocks prolonged the first bolus time of PCIA for ovarian cancer surgery and decreased sufentanil consumption. The procedure provided better postoperative analgesia and improved postoperative pulmonary function without excessive sedation.

Keywords: Dexmedetomidine; Transversus abdominis plane blocks; Cytoreductive surgery; Ropivacaine

Introduction

As the malignant tumor of female reproductive system with the third highest morbidity, ovarian cancer also has the highest mortality rate among all gynecological cancers. Most patients were diagnosed with ovarian cancer with stage III and IV by the International Federation of Gynecology and Obstetrics (FIGO) staging [1].

Cytoreductive surgery which resect all the macroscopic tumor in combination with chemotherapy is the most effective treatment for ovarian cancer [2-4]. Cytoreductive surgery is one kind of extensive surgical procedures in abdomen, which requires combined resection of multiple organs and tissues and always leads to serious postoperative pain, that directly affects the quality of postoperative recovery and delay the time to chemotherapy [5, 6].

Transversus abdominis plane (TAP) block is to inject local anesthetics into the surface of transversus abdominis to produce analgesic effect. However, due to the different position of needle insertion and injection, there are differences in the diffusion and analgesic effect on local anesthetics [7]. The incision of cytoreductive surgery for ovarian cancer is almost up to xiphoid process and down to pubic symphysis, straddling the multiple nerve levels of whole abdomen. Over the past decades, there are different views on the effect of TAP block on gynecologic oncology [8, 9]. Some scholars have suggested that TAP block was safe and feasible in patient with morbid obesity, while Griffiths et al. [9] reported that TAP block conferred no benefit in women undergoing major gynecological cancer surgery. With the assistance of MRI and anatomical studies, Børglum et al. [10] found that the upper TAP compartments had no communicate with the lateral, 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 bilateral dual-transversus abdominis plane (Bd-TAP) blocks were firstly reported by Børglum et al. [11]. The range of Bd-TAP blocks can reach Th6-Th12, which can relieve postoperative pain of anterior abdominal wall. There were many studies on the efficacy of TAP in colorectal surgery, benign gynecologic surgery and prostatectomy. However, there are few studies on the evaluation of the effect of Bd-TAP blocks in cytoreductive surgery on ovarian cancer. Therefore, this study was to

evaluate the postoperative control of pain and recovery in patients with ovarian cancer underwent cytoreductive surgery by adding dexmedetomidine to ropivacaine in Bd-TAP blocks.

Methods

Subjects

From June 2020 and December 2020, patients aged 18–75 years, with ASA grade I–III and body mass index (BMI) of 18.5–30 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, previous alcohol and opioid dependence, and infection at injection site.

This study was approved by the Ethics Committee of Anhui Provincial Hospital of China and the written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (no: ChiCTR2000003221).

Anesthesia protocol

All the patients received standardized protocol of premedication and intraoperative anesthesia. Anesthesia was induced by 0.5-1.5 mg midazolam, 0.3-0.5 µg/kg sufentanil and 0.3 mg/kg etomidate, while 0.9-1.2 mg/kg rocuronium was given when consciousness disappeared. Anesthesia was maintained by target controlled infusion (TCI) of propofol and remifentanil, intermittent infusion of 0.1 mg/kg cisatracurium, 5~10 µg sufentanil, inhalation of 1-2% sevoflurane to keep the bispectral index (BIS) between 45 and 60. Intraoperative fluid management was following goal-directed therapy. Blood transfusion was given when hemoglobin below 80 g/L. Oxycodone 0.1 mg/kg was given when the abdomen was closed. Ondansetron 16 mg and dexamethasone 5 mg were administered intravenously for postoperative nausea/vomiting (PONV).

Bd-TAP blocks

Patients were randomly assigned into three groups by using a computer-generated random number table. The three groups received injections as follows: TAP-R group (0.3% ropivacaine), TAP-DR group (0.3% ropivacaine and dexmedetomidine 0.5 µg/kg), and CON group (0.9% normal saline).

Drugs was mixed with normal saline to 60ml, 15ml for each point. The cytoreductive surgery has a wide incision (Fig. 1A). After sterilization of the injection site, Bd-TAP blocks were performed by the Sonosite ultrasound with a linear 6-13 MHz transducer. A 24 G 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. 2ml saline was injected to confirm the position of the needle, and then the drug was injected. The upper intercostal TAP blocks were showed in Fig. 1B. The classic lateral TAP blocks showed in Fig. 1C.

PCIA pump

At the end of TAP blocks, the patient was sent to the post-anesthesia care unit (PACU). The PCIA pump was connected after the tracheal tube was pulled out. Formula: sufentanil 100 µg and ondansetron 16mg dilute with normal saline to 100 ml, continuous dose 0.03 µg/kg/h sufentanil, bolus dose 0.03 µg/kg sufentanil, lock time 15 min. When VAS score was more than 4, flurbiprofen axetil 50 mg was given intravenously, no more than 300 mg within 24 hours.

Data collection

All the data collection were completed by two independent investigators who were blind to the group assignment. Pain was measured using VAS (0, no pain; 10, worst imaginable). Pulmonary function were measured by portable pulmonary function detector pre- and 24 hours postoperative. The postoperative complications including nausea, vomiting, puncture site infection, hemorrhage at the puncture site, drowsiness were recorded.

Statistical analysis

According to the results of previous study [12] and our pre-experimental observations in 6 patients, we considered that a clinically important reduction of the first request time for PCIA was 3 hours. Sample size was estimated at 28 patients in each group, which was calculated with α of 5% and 80% power. Taking into account for dropouts, 90 patients were estimated.

Statistical analysis was performed using SPSS 21.0. Normally distributed variables were presented as mean (standard deviation). Data not conforming to normally distribution were presented as median (inter-quartile range). Meanwhile, one-way ANOVA was used to compare the means of the normally distributed variables, and Kruskal-Wallis test was used to compare variables not normally distributed. Significance levels were set to $P<0.05$.

Results

Basic characteristics

A total of 90 patients were enrolled in this study. There were 30 patients in each group. One patient in CON group was excluded due to changes in surgical method. One patient in TAP-R group was excluded due to transfer to ICU after surgery. Therefore, 88 patients were included in the final analysis. The study flow is shown in Fig. 2.

The age was 57(32-73) years old, 56(38-70) years old and 56(38-70) years old in CON group, TAP-R group and TAP-DR group, respectively. There were no significant differences of height, weight, BMI, ASA physical status among the three groups ($P>0.05$). (Table 1)

Pain control

The first bolus time of TAP-R group was significantly prolonged compared to CON group [median (IQR): 7.3(6.5-8.0) hours vs. 3.0(2.3-3.5) hours] ($P<0.001$), while TAP-DR group has the longest bolus time among the three groups [median (IQR): 13.5(12.4-14.5) hours] ($P<0.001$). There was less sufentanil consumption delivered by PCIA in TAP-DR group at 24h ($P=0.01$), 48h ($P=0.04$) after surgery compared with that in CON

group (Table 2). It showed a trend that fewer patients in group TAP-R needed rescue analgesia compared with CON group also not significant ($P>0.05$). The rescue analgesia of TAP-DR was significantly reduced compared to CON group ($P<0.05$).

Postoperative recovery

There were no significant differences of time to stand, time to walk, time to return of bowel function and time to readiness for discharge among the 3 groups ($P>0.05$). The VAS scores at rest and on coughing of TAP-R group in the first 12h were significantly lower than that of CON group ($P<0.05$). The VAS scores at rest and on coughing of TAP-DR group was significantly reduced at each time point compared with that of CON group ($P<0.05$) (Fig. 3). Pulmonary function tests showed that TAP-DR group had better FEV₁ and FEV₁/FVC than CON group at 24h after operation (Fig. 4).

Adverse events

No adverse events such as puncture site infection, bleeding, paresthesia, local anesthetics toxicity and drowsiness were observed in all patients. The incidence of nausea and vomiting was 6/30 in TAP-DR group and 7/29 in CON group respectively. There were 9 patients (3 patients in CON group, 4 patients in TAP-R group, 2 patients in TAP-DR group) who used antiemetics.

Discussion

This is the first prospective randomized study evaluating the analgesic effects and recovery quality of Bd-TAP in patients with ovarian cancer underwent cytoreductive surgery. We found that Bd-TAP could provide effective incision analgesia for patients underwent cytoreductive surgery. An enormous amount of studies have confirmed that subcostal TAP can provide better coverage of T7-T10 dermatomes [13, 14]. Sondekoppam et al. [15] found that the spread of ultrasound-guided subcostal and lateral TAP injections in embalmed cadavers ranged from T7/8-L1 dermatomes in majority of the hemi-abdomens, but the lateral cutaneous branches of the segmental nerves was 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, the median abdominal incision avoids this very well [15]. However, a single injection of TAP block provides with limited action time. The addition of adjuvant should prolong the action time of local anesthetic [16]. A meta-analysis showed that dexmedetomidine significantly reduced postoperative pain scores at 8 hours [17]. 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. [18] reported that the numbness from the TAP block lasted approximately 6 days in a case of combination of dexamethasone and dexmetosine in bilateral TAP blocks for abdominal hysterectomy. Although this is 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. We found that the VAS score at rest and on coughing of the group TAP-DR was lower than that of the CON group at 48h after operation. In our study, addition of dexmedetomidine increase the time to first request for PCIA by almost 6.5h when compared with TAP-R group, reduce the need for rescue analgesia at 48h. Dexmedetomidine as an adjuvant carries a favorable effect on chronic postoperative pain reported by Abd-Elshafy et al. [19], which was in accordance with our results.

It is considered that extensive abdominal surgery is associated with pulmonary function decline and respiratory complications. However, there is lack of effective analgesic methods without affecting respiratory function. Despite the completion of bilateral TAP block, dysfunction of the diaphragm was detected on M-mode sonography at rest [20]. Our study found that postoperative FEV₁/FVC decreased to about 66%. The postoperative measured FEV₁ was significantly higher in TAP-DR group than that in CON group. Considering the lesion scope and the type of surgery were consistent among the groups, TAP-DR group showed better FEV₁/FVC at 24h after operative. Therefore, the addition of dexmedetomidine showed improvement on postoperative pulmonary function, which was in accordance with previous study [19].

However, we did not observe significant differences of the early recovery quality among groups, which was contrary to previous findings [19, 21]. We speculated that multi-factors might affect our results, including a wide age range, differences in surgical scope and surgical trauma. All the subjects were given a PCIA in the study, and sufentanil was formulations for PCIA. Oxycodone was given when the abdomen was closed and non-steroidal anti-inflammatory drug was used as rescue drugs. Oxycodone as a peripheral κ-opioid agonist provides effective visceral analgesia by activating receptors expressed on afferent nerves within the gut [22]. We observed a definite analgesic effect in TAP-DR group, due to the potential risks, the use and dosage of the drugs need to be quantified.

There were also some limitations in this study. First, cytoreductive surgery for ovarian cancer brings long incision and damaged 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 use 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 the adverse reactions related to block, vigilant for systemic toxicity should always be maintained. Finally, during the follow-up, we found that many patients had long-term postoperative pain. Researches on the mechanism and the solution of long-term pain may also be needed.

In conclusion, addition of dexmedetomidine to ropivacaine for Bd-TAP blocks prolonged the first bolus time of PCIA in cytoreductive surgery and decreased sufentanil consumption. The procedure provided better postoperative analgesia and improved postoperative pulmonary function without excessive sedation. Our results indicated that dexmedetomidine as adjuvant of Bd-TAP can provide effective pain relief at 48h.

Abbreviations: PCIA:patient-controlled intravenous analgesia; FIGO:Federation Internationale de Gynecologie et d'Obstetrique Classification; Bd-TAP: Bilateral dual-transversus abdominis plane; BMI:body mass index;TCI:TargetControlledInfusion;PONV:postoperativenausea/vomiting;

PACU:post-anesthesia care unit

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: ChiCTR2000003221, Principal investigator: Jian-ping Zhang, Date of registration:24/04/2020)

Consent for publication: Not applicable

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

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

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Authors' Note: Jian-ping Zhang, MD, and Na Zhang, MD, Co-first authors.

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Figure legends

Figure 1 Bd-TAP blocks in cytoreductive surgery **A.** Typical operation scar of cytoreductive surgery for ovarian cancer; **B.** The upper intercostal TAP blocks; **C.** The classic lateral TAP blocks. The arrow points to the injection site. TA, transversus abdominis; RA, rectus abdominis; PC, peritoneal cavity; EO, external oblique muscle; IO, internal oblique.

Figure 2 CONSORT flow diagram. TAP-R, transversus abdominis plane with ropivacaine; TAP-DR, transversus abdominis plane with ropivacaine and dexmedetomidine; ICU, intensive care unit.

Figure 3 VAS evaluation. **A.** VAS at rest during the first 48 postoperative hours; **B.** VAS on coughing during the first 48 postoperative hours, * $P<0.05$ vs group CON. VAS, visual analog scale.

Figure 4 Pre- and postoperative FVC, FEV₁ and FEV₁/FVC of three groups. * $P<0.05$ vs group CON. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1s.

Figures

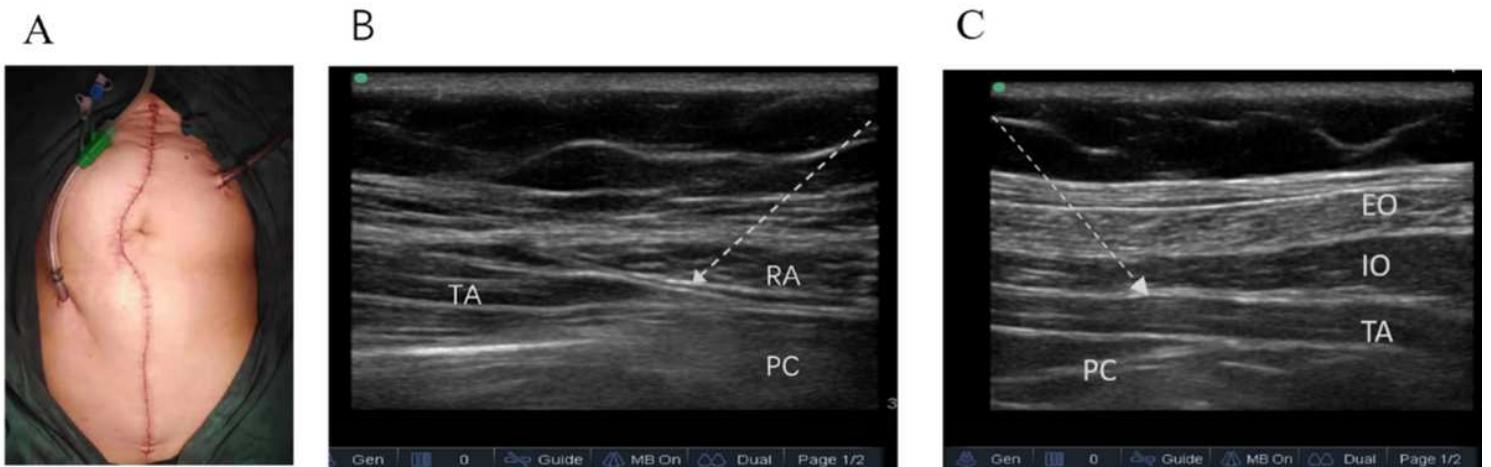


Figure 1

Bd-TAP blocks in cytoreductive surgery A. Typical operation scar of cytoreductive surgery for ovarian cancer; B. The upper intercostal TAP blocks; C. The classic lateral TAP blocks. The arrow points to the injection site. TA, transversus abdominis; RA, rectus abdominis; PC, peritoneal cavity; EO, external oblique muscle; IO, internal oblique.

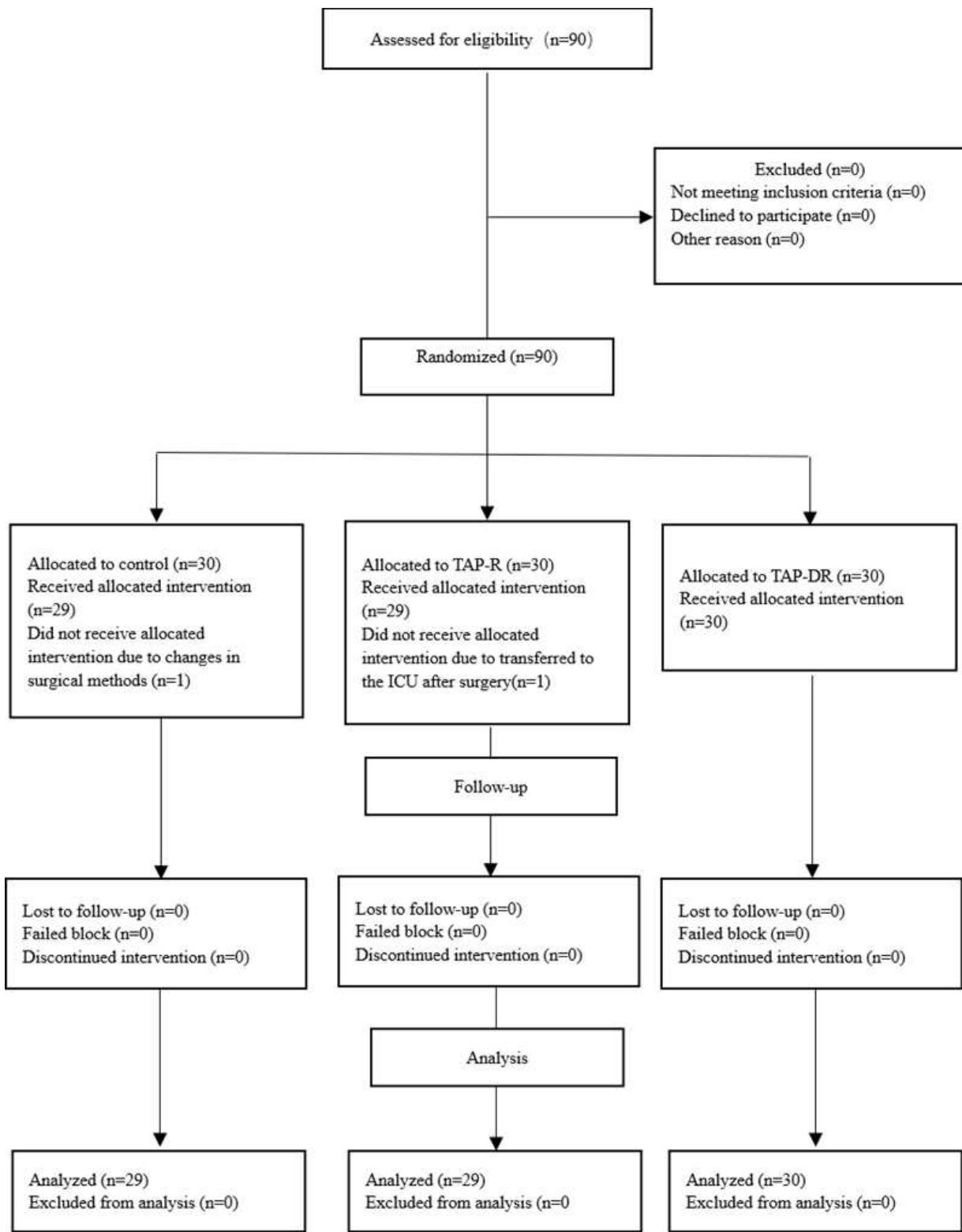


Figure 2

CONSORT flow diagram. TAP-R, transversus abdominis plane with ropivacaine; TAP-DR, transversus abdominis plane with ropivacaine and dexmedetomidine; ICU, intensive care unit.

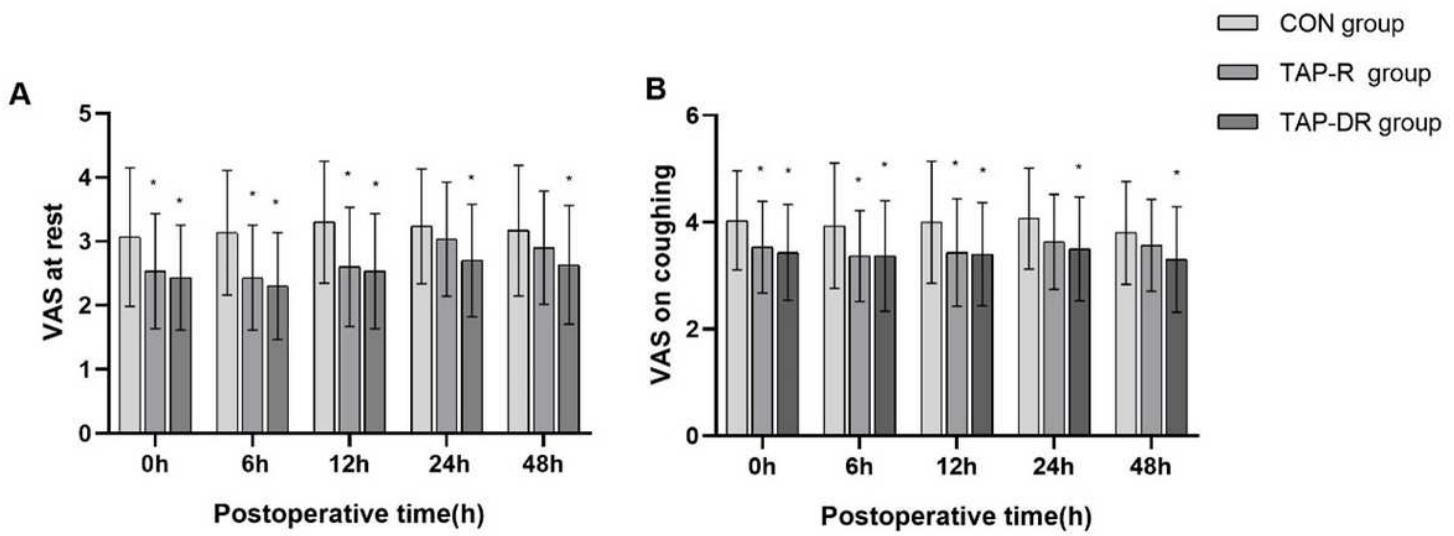


Figure 3

VAS evaluation. A. VAS at rest during the first 48 postoperative hours; B. VAS on coughing during the first 48 postoperative hours, *P<0.05 vs group CON. VAS, visual analog scale.

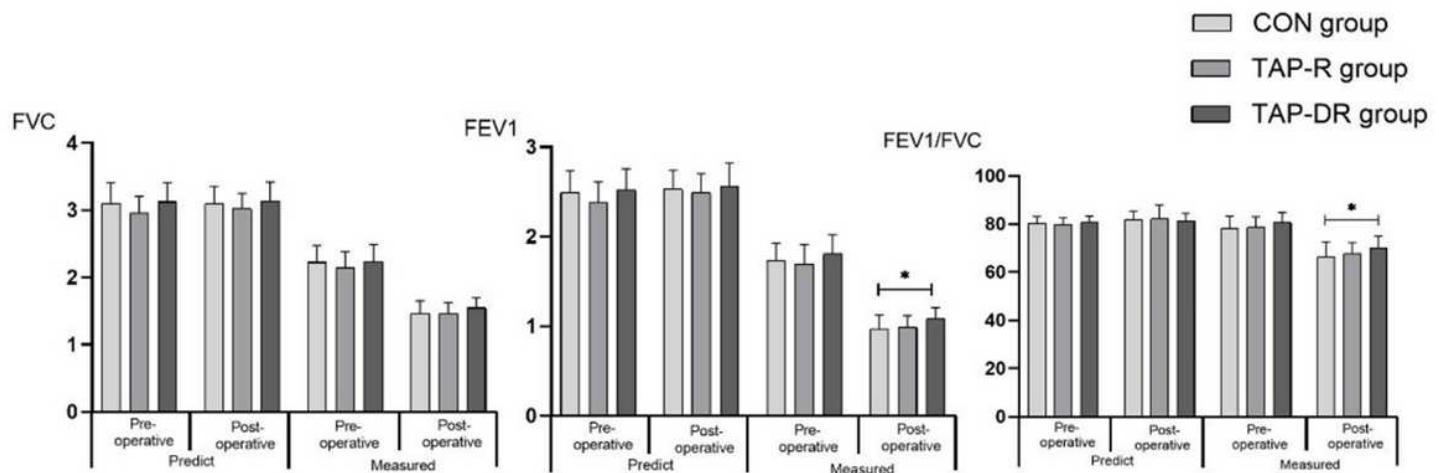


Figure 4

Pre- and postoperative FVC, FEV1 and FEV1/FVC of three groups. *P<0.05 vs group CON. FVC, forced vital capacity; FEV1, forced expiratory volume in 1s.