Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy

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Abstract. The present prospective, randomized, double-blinded, controlled study aimed to investigate the efficacy and safety of dexmedetomidine (DEX) combined with butorphanol for patient-controlled intravenous analgesia (PCIA) following total laparoscopic hysterectomy. A total of 88 patients undergoing total laparoscopic hysterectomy and receiving postoperative PCIA were divided into two groups following surgery. Patients received DEX 0.5 μg/kg intravenously in the DEX group or 0.9% normal saline in the control (CON) group following anesthesia induction. Postoperatively, the PCIA (10 mg butorphanol with 300 μg dexmedetomidine in the DEX group or without DEX in the CON group) was delivered as a 0.5 ml bolus (lockout interval of 15 min) with a continuous background infusion of 2 ml/h. Cardiovascular and respiratory variables, cumulative butorphanol consumption, pain scores, level of sedation, concerning adverse events and the degree of patient satisfaction were recorded for 24 h post-surgery. A total of 81 patients completed the study. Blood pressure and heart rate exhibited no significant difference between the two groups during surgery and for 24 h post-surgery. Compared with the CON group, patients in the DEX group required ~19% less butorphanol (P<0.05). During the first 24 h post-surgery, patients from the DEX group had a significantly lower visual analogue scale score at rest and movement states compared with the CON group (P<0.05). There was no significant difference in sedation score between the groups. The satisfaction scores were significantly higher in the DEX group compared with those in the CON group (P<0.05). Compared with the CON group, the DEX group exhibited a lower rate of postoperative nausea and vomiting (P<0.05). There was no occurrence of serious adverse events, including respiratory depression, hypotension, bradycardia and somnolence. In conclusion, following total laparoscopic hysterectomy, the loading dose of DEX (0.5 μg/kg) followed by a continuous infusion as an adjunct to butorphanol PCIA resulted in effective analgesia, significant butorphanol sparing and less butorphanol-induced nausea and vomiting without excessive sedation or adverse effects. The trial registration number was ChiCTR1800015675 at the Chinese Clinical Trial Registry (chictr.org.cn) and the date of registration was 4th April 2018.

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Introduction

Management of postoperative pain continues to be a challenging task. Opioid-based patient-controlled analgesia (PCA) is widely used in postoperative analgesia, which may cause a number of side effects, including postoperative nausea and vomiting (PONV), respiratory depression, pruritus and urinary retention (1). As a derivative of morphine, butorphanol has partial agonist/antagonist activity on μ-opioid receptors, agonist activity on κ-opioid receptors and no obvious activity on δ-opioid receptors (2). Butorphanol has been used for musculoskeletal pain, headaches and perioperative analgesia safety (3). Analgesia using butorphanol is five times greater than that using morphine (4). A previous study demonstrated that butorphanol exerted affective analgesia on patients following uvulopalatopharyngoplasty (5). Butorphanol PCA rarely leads to side effects, potential for abuse or systemic toxicity (6,7). The majority of patients (84%) undergoing general abdominal surgery and general anesthesia using butorphanol, a PCA, as the analgesic agent were able to obtain excellent postoperative pain relief (8). However, similarly to other opioids, butorphanol can lead to respiratory depression, excessive sedation, PONV and dizziness (9). Therefore, there has been a pursuit for combining currently available pharmacological agents to reduce the side effects. Using a combination of pharmacological agents that act on multiple pharmacologic sites is the optimal method for postoperative analgesia, which is defined as multimodal analgesia (10). This allows the use

of lower doses of opioids, which decreases the incidence of side effects. In order to decrease the side effects resulting from opioid-based, intravenous PCA (PCIA), the addition of various adjuncts has been broadly studied but their efficacy has not yet been confirmed (10).

Dexmedetomidine (DEX), a novel selective α_2-adrenergic receptor agonist, has been used for sedation or analgesia in intensive care and during surgery (11). DEX has analgesic, sedative and sympatholytic effects but does not cause respiratory depression (12). Due to its multiple effects, perioperative administration of DEX is applicable as a sedative and analgesic pharmacological agent (13). DEX also has analgesia and opioid-sparing effects when used as an adjuvant for postoperative analgesia (14,15). The results of one meta-analysis indicated opioid (morphine, fentanyl or sufentanyl)-DEX combination PCIA optimized analgesia, spared opioid consumption, deduced side effects and increased patient satisfaction when compared with PCIA opioid alone (16). Furthermore, postoperative administration of DEX may serve an important role in multimodal analgesia (16). However, the conclusion of this review was significantly confounded by the studies performed with differences in DEX dose, administration time and surgery (13-15). Furthermore, DEX is only licensed for patient sedation under intensive care and few studies have observed the effects of DEX in patients using butorphanol-based PCIA.

Based on the aforementioned results, it was hypothesized that DEX may improve the analgesic effect of butorphanol-based PCIA and reduce adverse effects in patients undergoing total hysterectomy. The aim of the present prospective, randomized, double-blinded, controlled study was to evaluate whether intraoperative and postoperative infusion of DEX added to butorphanol PCIA could enhance the analgesic effect in patients 24 h post-total laparoscopic hysterectomy. Simultaneously, the adverse effects associated with the DEX-butorphanol combination PCIA were also investigated.

Materials and methods

Study protocol. The present trial was retrospectively registered at the clinical trial (http://www.chictr.org.cn/index.aspx, registration number: ChiCTR1800015675). The present study was approved by the Institutional Human Investigations Committee of Yantai Yuhuangding Hospital (Yantai, China) and written informed consent was obtained from all patients prior to 88 patients undergoing total laparoscopic hysterectomy with general anesthesia being recruited.

Patients. The inclusion criteria were as follows: Aged between 38 and 65 years and an American Society of Anesthesiologists (ASA) grade of I or II. The exclusion criteria were as follows: ASA grade of ≥III, obesity [body mass index (BMI), >30], opioid addiction, treatment with sedative-hypnotic drug(s), uncontrolled hypertension, severe heart disease, conduction abnormality, neuropsychiatric diseases, alcohol abuse and allergy to either butorphanol or DEX. Prior to surgery, all patients were taught the operation of PCA and visual analogue scale (VAS) pain score (pain intensity on a 10-point VAS; 0, no pain and 10, the worst pain imaginable). Patients were instructed to push the PCA button when they experienced pain.

Randomization and blinding. A computer-generated randomization table was used to divide the patients randomly into control (CON) or DEX groups by an independent anesthetist prior to surgery. Another anesthetist, who was not involved in the present study, prepared the drugs according to the group. Anesthetists, surgeons, patients and nurses were blinded to the proposal during the study.

Anesthesia and PCIA. Following arrival at the operating room, electrocardiography, blood pressure (BP), pulse oxygen saturation (SPO_2), end-tidal CO_2 ($pETCO_2$) and the bi-spectral index (BIS) were monitored by an automated patient monitor (Philips IntelliVue MP60; Philips Medical Systems, Inc., Bothell, WA, USA). All patients were administered intravenously (i.v.) with midazolam (0.05 mg/kg), fentanyl (2-3 μg/kg; Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China), propofol (1.5-2 mg/kg; Fresenius Kabi Asia-Pacific, Ltd., Wanchai, Hong Kong) and cisatracurium (0.2 mg/kg; Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China) for induction. Following intubation with a laryngeal mask, patients were ventilated with a $PetCO_2$ at 35-40 mmHg. Fentanyl (2-3 μg/kg) was administered prior to skin incision. Anesthesia was maintained with sevoflurane (end-tidal concentration of 1.5-2.5%) and a continuous infusion of remifentanil (0.1-0.2 μg/kg/min; Yichang Humanwell Pharmaceutical Co., Ltd.). Cisatracurium (0.05 mg/kg) was administered during surgery until 1 h prior to the end of surgery. Titration of anesthetics was adjusted to maintain a BIS value of 40-60. Patients in the two groups received 4-6 ml/kg/h of Ringer's solution on the basis of fluid deficit, maintenance dose and intraoperative losses. Either hydroxyethyl starch (130/0.4) or ephedrine (6 mg i.v.) was administered to treat hypotension [mean BP (MBP), <60 mmHg]. Atropine (0.2 mg i.v.) was administered to treat bradycardia (HR, <50 bpm). A total of 0.5 μg/kg DEX (Jiangsu Hengrui Medicine Co., Ltd.) or the equivalent volume of 0.9% normal saline was infused i.v. for ≥10 min in the DEX and CON group following induction, respectively. A total of 30 min prior to the end of surgery, the two groups received 1 mg butorphanol (Jiangsu Hengrui Medicine Co., Ltd.) and 0.25 mg palonosetron. Following surgery, 1 mg neostigmine and 0.5 mg atropine were administered. The patients following extubation were delivered to the post-anesthesia care unit (PACU), where they were intensively cared for and administered with O_2.

PCIA was commenced immediately following surgery. In the CON group, the PCA regimen consisted of 10 mg butorphanol. In the DEX group, the PCA regimen consisted of 10 mg butorphanol and 300 μg DEX. The PCA volume was made up to 100 ml with 0.9% normal saline. The PCA was infused with a 0.5 ml bolus on-demand, with a 15 min lockout interval and a 2 ml/h background rate. Therefore, a background infusion of DEX in the DEX group was 0.1 μg/kg/h.

Outcome measures. HR, MAP and SpO_2 were recorded as follows: Arrival at the operating room (baseline, T0); induction (T1); intubation (T2); 30 min following intubation (T3); 60 min following intubation (T4); extubation (T5); and 1, 2, 6, 12 and 24 h post-surgery (T6-T10). The pump-press number and consumption of butorphanol were recorded at T10. Pain scores at rest and movement were recorded at T6-T10. At the same

time points, the sedation level was scored using a 5-point scale (0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or a simple verbal command; 3, asleep, arousable only by strong physical stimulation; and 4, unarousable). The level of satisfaction (0, very satisfied; 1, satisfied; 2, less satisfied; 3, not satisfied) was assessed at T10. Bradycardia (HR, <50 bpm), hypotension (SBP, <90 mmHg), somnolence (sedation score, ≥3), and respiratory depression (respiration rate, <8 bpm over 5 min) were regarded as severe adverse events and were treated immediately. Other adverse events (PONV, itching and dizziness) were also recorded.

Statistical analysis. A difference of 20% in butorphanol PCIA consumption was expected. For a study power of 80% (α=0.05, β=0.2), the required sample size in each group was 38. To allow for a possible 15% drop-out rate, 44 patients were included in each group. Statistical analysis was performed using SPSS for Windows Version 16.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed data are expressed as the mean ± standard deviation. Patient characteristics, including age, weight, BMI, surgery time, anesthesia time, PACU stay time, pump-press number and butorphanol consumption were compared between the 2 groups using unpaired Student's t-tests. HR and MBP at different time points were compared between the two groups using two-way analysis of variance, followed by Bonferroni's post hoc test. The incidence of adverse events and the degree of satisfaction were analyzed using the χ^2 test. Pain and sedation scores were analyzed using the Mann-Whitney U-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic data and surgery/anesthesia-associated information. As indicated in Fig. 1, the CONSORT flow diagram of patient recruitment was demonstrated. A total of 88 patients were enrolled in the present study; 4 patients were excluded due to not meeting the inclusion criteria or declining to participate; 1 patient in the CON group withdrew due to their surgery being canceled and 2 patients (1 from the CON group and 1 from the DEX group) were excluded following surgery as PCA was discontinued. Finally, 81 patients completed the study (40 in the CON group and 41 in the DEX group). Basic demographic data and surgery/anesthesia-associated information in the 2 groups were compared (Table I). There were no significant differences in age, body weight, BMI, anesthesia time, surgery time and recovery time at PACU.

Hemodynamic changes from the baseline to 24 h post-surgery were presented (Fig. 2). With respect to the baseline MBP and HR, there was a decrease induced by anesthesia induction and an increase evoked by intubation. There was a trend of a lower HR and MBP in the DEX group following infusion with the loading dose of DEX but none of the patients required their doses to be corrected. Furthermore, there was no significant difference between the two groups during surgery and 24 h after surgery with regards to MAP and HR.

PCIA evaluation. PCIA was commenced immediately following surgery. Patients in the CON group exhibited a significantly higher pump-press number and significantly increased butorphanol consumption compared with those in the DEX group (P<0.05). Patients in the DEX group consumed 19% less butorphanol during 0-24 h post-surgery compared with the CON group (Fig. 3). At the same time, patients in the DEX group exhibited a significantly lower VAS score at rest and movement states compared with the CON group (P<0.05; Fig. 4). There were no significant differences in the sedation score between the groups. None of the patients had a sedation score ≥3 (Fig. 5). Furthermore, results indicated that the satisfaction scores were significantly greater in the DEX group compared with those in the CON group (P<0.05; Table II).

Post-operative adverse effects. Compared with the CON group, the DEX group exhibited a significantly lower incidence of nausea and vomiting (P<0.05). However, the incidence of itching and dizziness was similar in the two groups. Changes in the respiratory rate were not significantly different between the groups. Notably, there was no instance of serious adverse events (respiratory depression, hypotension, bradycardia or somnolence; Table III).

Discussion

The results of the present trial indicated that the combination treatment of DEX and butorphanol strengthened the analgesic effect of butorphanol, and reduced butorphanol consumption and the butorphanol-induced PONV, without severe adverse events.

PCIA has been studied extensively for postoperative analgesia. The use of opioids for postoperative analgesia typically results in nausea, vomiting and other adverse events. In multimodal analgesia, adding an adjunct to an opioid in PCIA for pain control is popular (17). An important aspect of multimodal analgesia is that the PCIA must have superior analgesic effects with minimal side effects. Compared with clonidine, DEX has a more favorable pharmacokinetic profile, including a higher α_2:α_1 specificity ratio, 1,600:1 vs. 200:1; a shorter plasmatic half-life T1/2, 2-2.5 vs. 9-12 h; and a higher protein binding, 94 vs. 50%. The advantages of DEX for postoperative analgesia, either as an opioid-sparing effect or reducing pain scores, have been verified in numerous studies (18,19). Notably, adding DEX to opioids may improve postoperative analgesia. A number of studies have applied this method but the DEX doses have been different and the conclusion remains unclear (16).

When butorphanol is infused at a background rate, it may produce potential analgesia and a certain degree of sedation (6). Butorphanol being infused continuously can maintain stable plasma concentrations, resulting in extended analgesia (7). Patients who underwent abdominal surgery expressed satisfaction with the butorphanol PCIA (7). Reedy *et al* (20) indicated that the respiratory rate and sedation status of patients who received butorphanol or morphine were similar. Patients received effective analgesia and minimal sedation.

The recommended loading dose of DEX is 0.5-1 μg/kg in adults (12). A previous study demonstrated that a loading dose 0.5 μg/kg DEX alleviated labor pain (21). A larger loading dose of DEX may delay anesthetic recovery. The

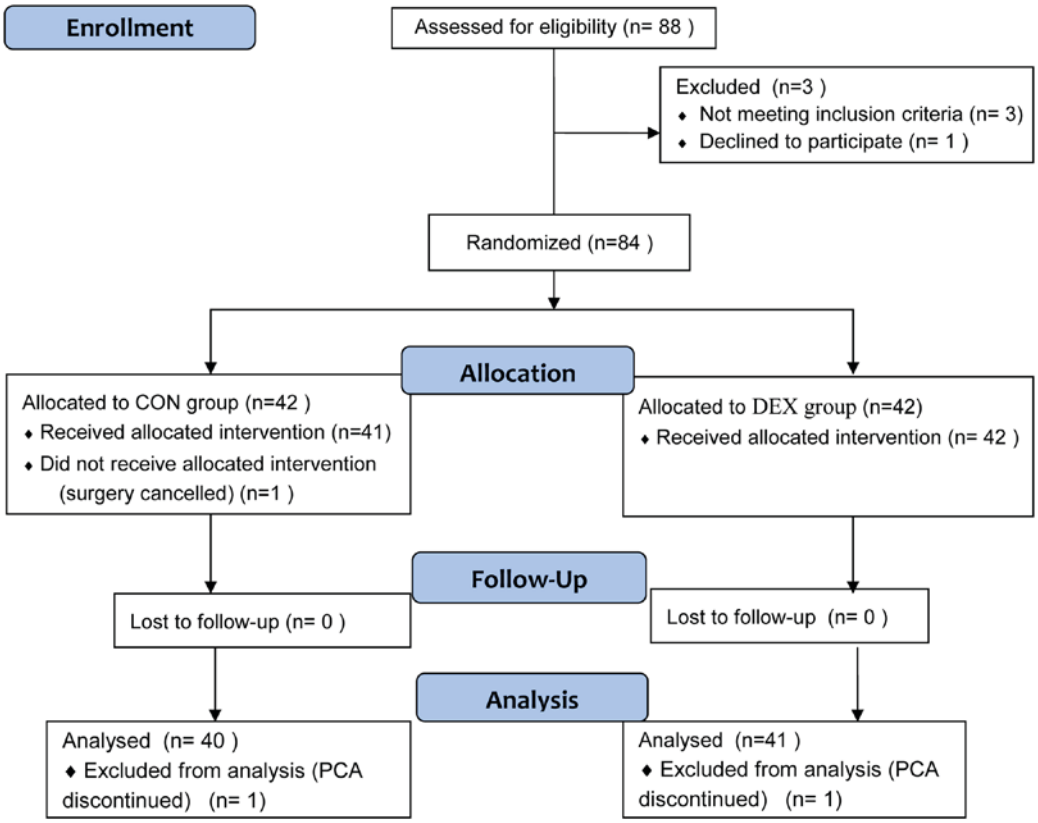

Figure 1. CONSORT flow diagram.

onset time, distribution half-life and elimination half-life of DEX are ~15 min, 6 min and 2 h respectively (12,22). The duration of total laparoscopic hysterectomy is relatively short (~80 min), so a loading dose of 0.5 μg/kg was administered.

In the present study, a significant reduction in the pain score and butorphanol consumption was observed in the DEX groups, suggesting an analgesic effect of DEX. The opioid-sparing effects of DEX in the present study were similar to those observed in other studies (14,15,19). Possible mechanisms underlying DEX that were suggested included the following: Inhibition of nociceptive neurotransmission via activating peripheral, spinal and supraspinal α_2-adreno receptors; attenuation of the stress response and the affective-motivational components of pain; and alleviation of hyperalgesia resulting from opioid administration or surgical inflammation (22,23).

A specific level of sedation following surgery is necessary for patients to reduce worry and anxiety. Moderate sedation during the early post-operative period is regarded as a clinical method to maintain hemodynamic stability and to provide comfort and analgesia without interfering with the evaluation of the conscious state (7). Furthermore, sedation can prevent aimless movement from inadequate analgesia and promote recovery (7). Given the sedative properties of butorphanol, butorphanol infused at the background dose resulted in a low level of sedation. The use of DEX, recognized as a sedative and analgesic drug, combined with butorphanol following surgery may arouse concerns of unnecessary or excessive sedation. However, no excessive sedation following DEX was observed during postoperative PCIA in the present study. Such moderate sedation ensures that patients adequately remain orientated and calm, cooperative, breathing and coughing. This observation may be due to: i) The doses of DEX used in the present study being lower than the recommended maintenance infusion for sedation and ii) the reduced consumption of butorphanol serving a vital role in mitigating sedation.

The present study demonstrated that adding DEX to butorphanol PCIA decreased PONV compared with butorphanol alone. This may be due to the antiemetic properties of DEX since higher plasma concentrations of catecholamines is an important factor leading to PONV (24). Additionally, the butorphanol-sparing effect of DEX, which resulted in a reduction in PONV, has been demonstrated in gynecological patients (25). A meta-analysis demonstrated that DEX can reduce the occurrence of PONV, which is likely attributable to the reduced consumption of opioids (26). A decreased consumption of butorphanol in patients receiving DEX may explain the reduced incidence of PONV.

Owing to the lack of evidence for the off-label use of DEX in non-intensive care unit settings, the risk of respiratory depression from the combination of DEX and butorphanol requires consideration. Therefore, the basal rate was set at 0.1 μg/kg/h with a maximum limit of 0.2 μg/kg/h. This is far below the manufacturer's recommended dosage (0.2-0.7 μg/kg/h). No respiratory depression was observed in the present study, indicating that adding DEX to butorphanol PCA does not affect respiratory stability.

When DEX was administered in a large bolus dose, hemodynamic effects, including hypotension and

Table I. Basic demographic data and surgery/anesthesia-associated information.

Variables	CON group, n=40	DEX group, n=41
Age (years)	46.5±9.2	47.2±10.3
Weight (kg)	63.2±7.4	64.3±10.2
BMI (kg/m^2)	22.3±1.8	21.8±2.0
Operation time (min)	79.2±11.3	81.2±12.8
Anesthesia time (min)	95.6±12.1	96.1±10.6
PACU stay time (min)	35.8±7.9	36.6±8.2

Data were presented as mean ± standard deviation. BMI, body mass index, PACU, post-anesthesia care unit. CON, control; DEX, dexmedetomidine.

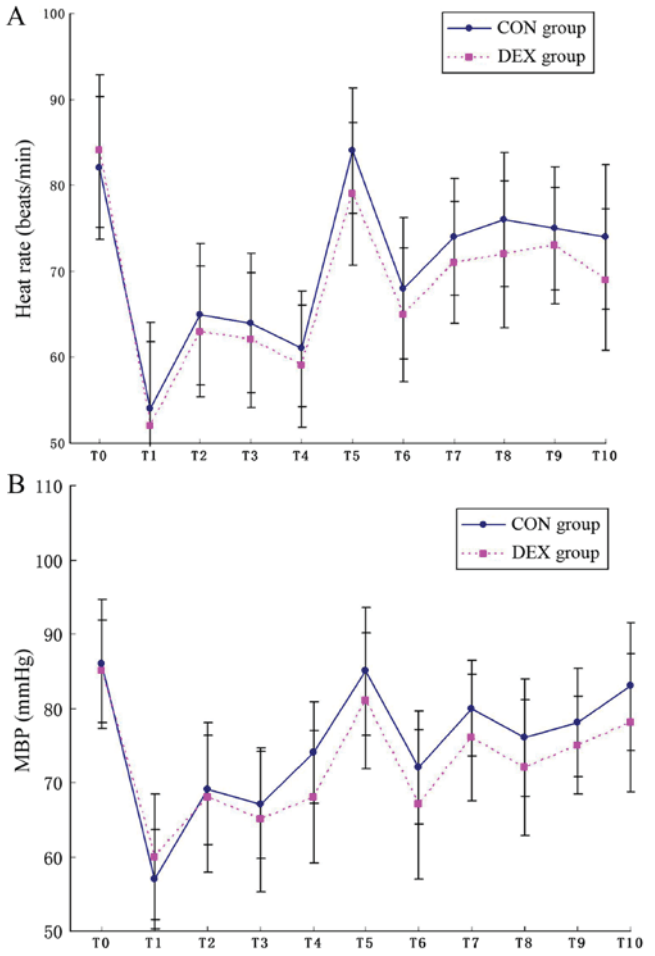

Figure 2. HR and MBP. (A) HRs at different time points. (B) MBP at different time points. T0, baseline; T1, induction; T2, intubation; T3, 30 min after intubation; T4, 60 min after intubation; T5, extubation; and T6-T10, 1, 2, 6, 12 and 24 h post-surgery. MBP, mean blood pressure; HR, heart rates; CON, control; DEX, dexmedetomidine.

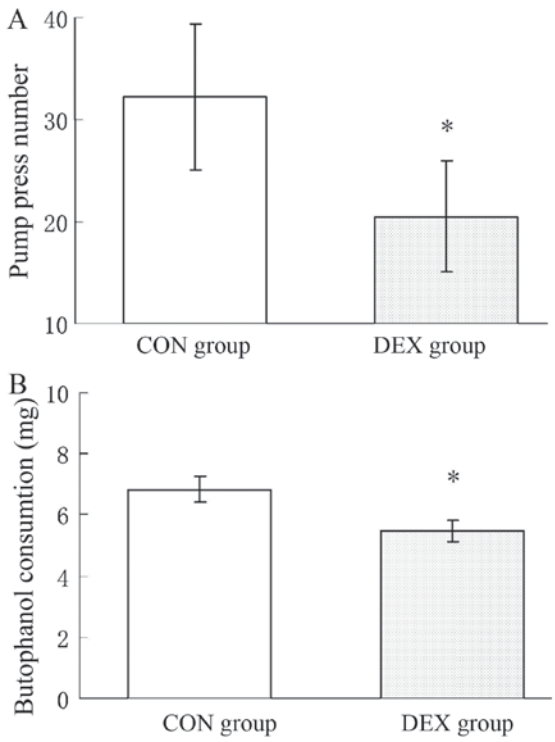

Figure 3. Pump-press number and butorphanol consumption 24 h post-surgery. (A) Pump-press number and (B) butorphanol consumption. *P<0.05. CON, control; DEX, dexmedetomidine; CON, control; DEX, dexmedetomidine.

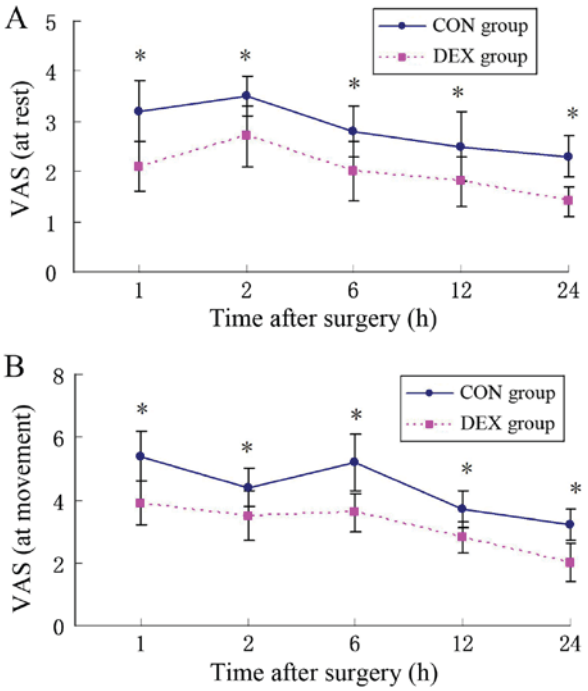

Figure 4. VAS pain score at different time points in the two groups. (A) VAS pain score at rest and (B) VAS pain score at movement. *P<0.05. VAS, visual analogue scale; CON, control; DEX, dexmedetomidine.

bradycardia, were the most frequent adverse events (27). A previous study reported that postoperative infusion of DEX with sufentanil without a bolus dose could avoid hemodynamic effects; however, anti-PONV effects of DEX were lessened in the first 4 h post-surgery. Additionally, a study involving healthy volunteers demonstrated that a 0.5 μg/kg loading dose can provide sufficient analgesia without clinically significant hypotension or

Table II. Comparison of patient satisfaction in two groups.

Satisfaction rating	CON group (%), n=40	DEX group (%), n=41
Very satisfied	7 (17.5)	19 (46.3)[a]
Satisfied	22 (55.0)	16 (39.0)[a]
Moderately satisfied	9 (22.5)	5 (12.2)[a]
Not satisfied	2 (5.0)	1 (2.4)

Data indicated the number and percentage of patients, n (%). [a]P<0.05 vs. CON group.

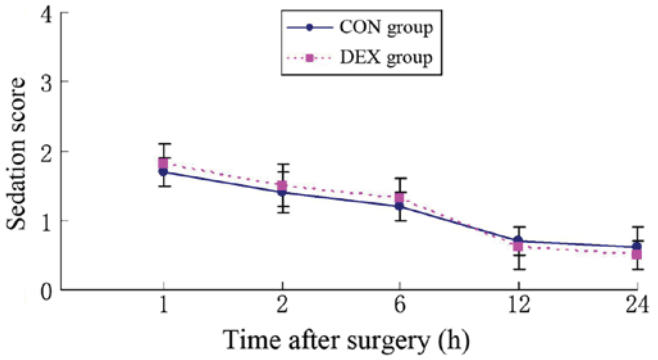

Figure 5. Sedation score 24 h post-surgery. CON, control; DEX, dexmedetomidine.

Table III. Postoperative side effects from patients in two groups.

Side effect	CON group (%), n=40	DEX group (%), n=41
Nausea	12 (30.0)	7 (17.1)[a]
Vomiting	7 (17.1)	2 (4.9)[a]
Itching	2 (5.0)	2 (4.9)
Respiratory depression	0 (0)	0 (0)
Dizziness	8 (20.0)	6 (14.6)
Bradycardia	0 (0)	0 (0)

Data indicated the number and percentage of patients, n (%). [a]P<0.05 vs. CON group.

bradycardia (28). Therefore, in order to minimize the adverse effects (e.g., hypotension, hypertension and bradycardia), a small bolus-loading dose of DEX (0.5 μg/kg) was selected instead of the manufacturer's recommended dose (1 μg/kg). Significant hypotension or bradycardia was not observed in the present study, which may be due to the low loading dose of intraoperative DEX and a relatively lower maintenance dose. However, hemodynamic deterioration associated with DEX has been reported (29). In the present study, there were not statistically significant differences in HR and MAP between the two groups; however, HR and MAP were lower in the DEX group. The hemodynamic effects associated with DEX being added to butorphanol PCA should be appreciated.

The present study has certain limitations. To begin with, different groups with different doses of DEX to examine whether lower or higher doses of DEX were more effective were not designed. This requires verification in future studies. Secondly, SBP <90 mmHg was defined as hypotension and HR <50 bpm was defined as bradycardia. However, others have defined MBP <60 mmHg or a 20% drop from the baseline as hypotension and HR <50 bpm or a 20% drop from the baseline as bradycardia (14,24). Finally, the present study was performed at one hospital. Further studies including more patients from different centers and undergoing different types of surgery may provide more definitive results.

In conclusion, compared with butorphanol PCIA alone, a small loading dose of DEX infusion (0.5 μg/kg) followed by a continuous infusion (0.1 μg/kg/h) as an adjunct to butorphanol PCIA can reduce butorphanol consumption, improve the analgesic effect and increase the patient satisfaction level. The present study suggested that DEX combined with butorphanol PCIA is a potential analgesia for patients following total laparoscopic hysterectomy. Post-operative DEX administration may serve a role in multimodal pain therapy. Further studies are required to establish the effect-dose balance between optimal postoperative analgesia and minimal side effects in DEX-butorphanol PCIA.

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Authors' contributions

JD and JL registered the clinical trial, recruited patients, collected data and wrote the manuscript. JJ and CS analyzed the data. JM designed the study and edited the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Human Investigations Committee of Yantai Yuhuangding Hospital of Qingdao University and written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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