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Effect of Dexmedetomidine Alone for Intravenous Patient-Controlled Analgesia After Gynecological Laparoscopic Surgery

A Consort-Prospective, Randomized, Controlled Trial

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Abstract: Gynecological laparoscopic surgery is minimally invasive compared with open surgical approaches, but postoperative pain is generally undermanaged. Pain management strategies related to the procedure-specific efficacy are needed. Many studies have shown that dexmedetomidine (DEX) has opioid-sparing properties. It is not clear whether DEX used alone for intravenous patient-controlled analgesia (PCA) could reduce postoperative pain after an invasive procedure. We hypothesized that DEX alone would reduce postoperative pain in women patients undergoing an elective gynecological laparoscopic procedure.

This CONSORT-prospective randomized controlled clinical study aimed to investigate the effects of DEX alone for intravenous PCA after gynecological laparoscopic operation. Forty women patients scheduled for elective gynecological laparoscopy were enrolled into the study at Shandong Cancer Hospital and Institute and randomly allocated into two groups (n = 20 each). In the DEX group (group D), the intravenous PCA protocol was DEX 0.25 μg/kg/h diluted to 100 mL in 0.9% saline. In the fentanyl group (group F), the PCA protocol was fentanyl 20 μg/kg diluted to 100 mL in 0.9% saline. The primary outcome was the mean pain score on a visual analogue scale (VAS) at 6 hours after the operation. The secondary outcomes included the Ramsay sedation score, the incidence of postoperative nausea and vomiting (PONV), satisfaction with pain control, and time to recovery of gastrointestinal function.

There were no significant differences in the patients' characteristics and intraoperative measurements ($P > 0.05$). No patients received rescue analgesic. The mean VAS scores at 6 hours post-operatively were not significantly different between the groups ($P > 0.05$). The incidence of PONV was less in group D than in group F ($P < 0.05$). The Ramsay sedation scores were not significantly between the groups ($P > 0.05$). Satisfaction with pain control was higher and time to recovery of gastrointestinal function was lower in group D ($P < 0.05$).

DEX alone is effective for intravenous patient-controlled analgesia after gynecological laparoscopic surgery without a change in sedation and with fewer side effects, and this effect was associated with better satisfaction with postoperative pain control and earlier recovery of gastrointestinal function.

(*Medicine* 95(19):e3639)

Abbreviations: α_2R = α_2-adrenoceptors, ASA = American Society of Anesthesiologists, BIS = bispectral index, BMI = body mass index, $ETCO_2$ = end-tidal carbon dioxide partial pressure, HR = heart rate, MAP = mean arterial pressure, PACU = postanesthesia care unit, PCA = patient-controlled analgesia, PTSS = pain treatment satisfaction scale, SpO_2 = peripheral oxygen saturation, TAP = transversus abdominis plane, VAS = visual analog scale, V_T = Tidal volume.

INTRODUCTION

Gynecological laparoscopic surgery is a widely performed procedure because of its advantages over laparotomy.[1,2] It is considered to be a minimally invasive procedure compared with open surgical approaches; however, high quality pain control after laparoscopy is still a challenge.[3] Undermanaged postoperative pain may exaggerate the surgical stress response and increase postoperative morbidity and mortality.[4] Although multimodal analgesia strategies have been recognized as a potential method to improve postoperative pain management,[5] unfortunately, inadequate pain control is still reported.[6] Studies about pain management in gynecological laparoscopy are sparse, and opioid-related adverse drug events are a matter of concern; innovative pain management regimens that minimize opioid use are necessary.[7]

Dexmedetomidine (DEX) is a highly selective α_2 adrenergic receptor agonist. Previous studies demonstrated that it has analgesic and opioid-spare effects.[8–10] But pain management in

Editor: Ashham Mansur.
Received: February 11, 2016; revised: April 6, 2016; accepted: April 15, 2016.
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XW and JY conceived and designed the trial; WL did the sample randomization; CZ and BW performed the experiment; FW prepared the postoperative analgesics; ZX and KW recorded the patients' data; JY, XW, FW analyzed the data and wrote the article. All the authors reviewed the manuscript.
This work was supported by funding from Shandong Medicine and Health Science Technology Development Foundation of China (2015WS0153), and Shandong Academy of Medical Sciences Foundation of China (2015–37). It was also supported by grants from the National Natural Science Foundation of China (Grant no. 81570241).
Trial Registration: chictr. org (ChiCTR-IPC-15006212).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003639

these studies was opioids combined with DEX. It is not clear whether DEX used alone for intravenous patient-controlled analgesia could reduce pain after gynecological laparoscopic surgery. Studies suggest conflicting results regarding its analgesic effects.[11,12] There are no prospective studies comparing DEX with other analgesics after gynecological laparoscopic operation.

Our study aimed to prospectively evaluate the effects of DEX alone on postoperative pain after gynecological laparoscopic surgery compared with fentanyl. We hypothesized that DEX alone would reduce postoperative pain in women patients undergoing elective gynecological laparoscopic operation. The primary outcome of this study was the pain intensity determined by the visual analogue scale pain score (VAS). The secondary outcomes included the incidence of nausea and vomiting postoperatively, the Ramsay sedation score, satisfaction with pain control, and time to recovery of gastrointestinal function.

METHODS

Study Protocol and Patient Data

This prospective randomized controlled clinical study was designed according to the CONSORT 2010 statement. The entire protocol (SDTHEC201504001) was approved by the Ethics Committee of Shandong Cancer Hospital and Institute, Jinan, Shandong Province, P.R. China (Chairperson Dr. Jinming Yu) on April 7, 2015. The name of the registry is www.chictr.org (Chinese clinical trial registry). The registration number is ChiCTR-IPC-15006212. Informed consent was obtained from all patients.

Women patients with newly diagnosed endometrial or cervical cancer, aged 20 to 70 years, ASA I-II, undergoing elective gynecological laparoscopies were enrolled into this study at our hospital between April 7 and December 31, 2015. A consent form was signed by all patients. Exclusion criteria included body mass index >30, cardiovascular, respiratory, or neurologic disease (particularly bradycardia with cardiac conduction or rhythm abnormalities), analgesic intake, history of substance abuse, any conversion to laparotomy, and refusal to participate in the follow-up assessment.

Randomization and Masking

Simple randomization was performed by independent research staff using 40 opaque sealed envelopes, 20 for each group, indicating the group assignment and describing the analgesic protocol for the DEX group (group D) and fentanyl group (group F). All the patients were blinded to the group assignment, and they were randomized immediately prior to entering the operating room. Two blinded attending anesthesiologists were responsible for anesthesia induction and maintenance. The postoperative patient-controlled intravenous anesthetic agents were prepared on the day of surgery by an independent research staff. The VAS score and Ramsay Sedation score postoperatively, the satisfaction with pain control, the incidence of postoperative nausea and vomiting (PONV) and dizziness, and time to first passage of flatus and bowel movement were assessed and recorded by our staff who were blinded to the group assignment.

Anesthesia and Surgery

In both groups, general anesthesia was induced with propofol (2 mg/kg), fentanyl (2 μg/kg). Tracheal intubation was facilitated with rocuronium (0.8 mg/kg). Anesthesia was maintained with propofol (5–8 mg/kg/h) and sevoflurane (inspiratory concentration 0.82%). Rocuronium was administered every 40 minutes. Analgesia was provided with fentanyl (1–2 μg/kg) as required, and the last administration was at least 0.5 hours before the end of the surgical suturing. The tidal volume (V_T) was 6 to 8 mL/kg, and the respiratory rate was 14 to 17 per minute. Anesthesia monitoring included electrocardiography and pulse oximetry, arterial blood pressure was measured via a radial artery catheter in all patients. Analysis of arterial blood gases was conducted to make sure that the P_H was 7.35 to 7.45 and the end-tidal carbon dioxide partial pressure ($ETCO_2$) was 35 to 45 mm Hg. The V_T and respiratory rate were adjusted accordingly. Patients were also monitored with a bispectral index monitor (BIS) (Aspect Medical System Inc., Norwood, MA), which was maintained between 40 and 60. A central venous line was inserted in all patients. All patients received standardized fluid management, which consisted of 10 mL/kg lactated Ringer solution preoperatively followed by 6 mL/kg/h perioperatively. The procedures performed included radical hysterectomy and pelvic and para-aortic lymphadenectomy. Administration of fentanyl and rocuronium was discontinued approximately 30 minutes before the completion of surgery. Propofol and sevoflurane were also stopped 10 minutes prior to the end of surgery. IV neostigmine 0.04 to 0.07 mg/kg and atropine were administrated for neuromuscular-blocked reversal at the end of the procedure. Patients were extubated after meeting extubation criteria. Extubation criteria included adequate oxygenation as indicated by SpO_2 >92% on room air, spontaneous respiratory rate >7 breaths/min, and <30 breaths/min, adequate ventilation as indicated by tidal volume >5 mL/kg, $ETCO_2$ <50 mm Hg. Patients could follow verbal commands and intact cough or gag reflex, sustained 5 seconds head lift or hand grasp and hemodynamically stable. We did not inject the abdominal trocar sites with local anesthetics during the study period in any of ours cases. All surgical procedures were performed by the same surgical team. The operations were performed under a CO_2 pneumoperitoneum (12 mm Hg). Laparoscopy port placement consisted of a periumbilical 10-mm port, 5-mm ports in both the right and left lower quadrants, and a 10-mm suprapubic port. For incisions longer than 5 mm, fascia closure was performed using the laparoscopic closure device, and the skin layer was closed in a subcuticular manner.

Postoperative Analgesia Management

Before surgery, the patients were instructed to use the PCA pump, and they also received instructions using a 10-cm VAS (0–3 mild pain; 4–6 moderate pain; 7–10 severe pain). Additionally, we also used the same device for assessing the Ramsay sedation score. After the operation, the patients were transferred to the postoperative care unit (PACU), and the PCA infuser was immediately prepared for use.

The PCA protocol in group D consisted of DEX 0.25 μg/kg/h diluted to 100 mL. The PCA protocol in group F was fentanyl 20 μg/kg diluted to 100 mL. The PCA protocol in both of groups included a 2-mL/h background infusion and a 1-mL bolus dose followed by 15 minutes of lockout time. After extubation, we encouraged the patients to press the analgesic-demand button if they experienced pain (VAS >4). If the pain control was not sufficient, then rescue analgesia (30 mg pethidine by intramuscular injection) was used, and administration was repeated if needed until the VAS score was <4. Nausea and vomiting were treated with ondansetron 4 mg IV according to the patient's request. Hypotension (mean arterial pressure ≤60 mm Hg) was treated with either ephedrine 5 mg IV or phenylephrine 100 μg IV, and bradycardia (<40 bpm without hypotension) was treated with atropine 0.2 mg.

MEASUREMENTS

The patients' age and body mass index (BMI; calculated as weight (kg)/[height (m)]^2), the description of the procedure performed, and operative time were collected from the patient charts. Monitoring during the operation consisted of electrocardiography, peripheral oxygen saturation (SpO_2), BIS, invasive blood pressure, and capnography. Heart rate (HR) and mean arterial pressure (MAP) were recorded at the following time points: arrival at the operating room (T_0); on intubation (T_1); 30 minutes after incision (T_2); on extubation (T_3); on arrival at the PACU (T_5); 4 hours post-surgery (T_4); 8 hours post-surgery (T_6); and 24 hours post-surgery (T_7). Time of first passage of flatus and bowel movement were retrieved from the nursing flow sheet. The total intraoperative dose of fentanyl, propofol, and sevoflurane was calculated. As oral pain medications are rarely used while patients have access to PCA, we did not include their use. The Ramsay sedation scale was applied to assess the sedation state: 1 = anxious, agitated, or restless; 2 = cooperative, oriented, and tranquil; 3 = responds to command; 4 = brisk response to a light glabellar tap or loud auditory stimulus; 5 = sluggish response to a light glabellar tap or loud auditory stimulus; and 6 = no response to the stimuli. The VAS score and Ramsay sedation score at 4, 6, 8, 24, and 48 hours postoperatively and the incidence of PONV and dizziness were assessed and recorded in the general ward. The satisfaction with pain control was assessed using the pain treatment satisfaction scale (PTSS, 0 = no satisfaction to 10 = complete satisfaction) at 48 hours after the PCA pump was removed.[13]

Statistical Analysis

The sample size calculation was based on an initial pilot study measuring the VAS scores 6 hours postoperatively in 10 patients where the standard deviation in each group was to be approximately 2.02. We considered a difference of 2 in the pain scores at 6 hours after the operation to be clinically relevant given the lack of prior comparative data. To have 80% power at an $\alpha = 0.05$ level to detect a two-tailed difference of at least 2.0 VAS points, we required 16 patients in each arm. Based on a 20% estimated loss to follow-up rate, we enrolled 20 patients in each group. For sample size estimation and power computation, we used G*Power software, version 3.1.0, available at http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3.
Statistical analyses were performed using SPSS for Windows 11.5 (SPSS Inc., Chicago, IL). Continuous data were described as medians with ranges or means with the standard deviation; categorical data were expressed as percentages. The means of continuous measures were compared between the study groups using one-way analysis of variance (ANOVA), and the medians were compared using a Mann–Whitney test. The proportions of categorical variables were compared between the study groups using a Pearson χ^2 test. We used Kolmogorov–Smirnov and normal-quantile plots to determine whether continuous variables were normally distributed. Age, body mass index, duration of surgery, fluids, estimated blood loss, urine output, total intraoperative dose consumption of fentanyl, sevoflurane, and propofol, mean VAS score, satisfaction with pain control, and time of first flatus and bowel movement were analyzed by one-way ANOVA. MAP and HR were analyzed by repeated measures ANOVA. The chi-square test was used to compare the categorical data including, the incidence of PONV and dizziness. The ASA status (I to II) and procedure completed were analyzed by Pearson χ^2 test. The Mann–Whitney test was used to compare the Ramsay sedation scale between groups. P-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics and Intraoperative Outcomes

Forty patients were recruited, but 4 patients were excluded because of an intraoperative conversion to laparotomy (2 patients) and loss to follow-up (2 patients) in group F. Thirty-six patients were included in the statistical analysis, 20 in group D and 16 in group F (Figure 1). No patients received rescue analgesic. The baseline characteristics and duration of surgery, total fluids during the operation, estimated blood loss, urine output, and total dose of intraoperative fentanyl, sevoflurane, and propofol were not significantly different between the two groups (Table 1). The procedures performed were similar (Table 1). The HR and MAP were not significantly different between the two treatment groups (Figure 2).

Postoperative Efficacy Outcomes

The VAS scores and Ramsay sedation scale after 4, 6, 8, 24, and 48 hours were not significantly different between the groups (Figures 3 and 4, respectively).

Postoperative Tolerance Outcomes

The incidence of PONV was less in group D than in group F ($P < 0.05$, Table 2). The incidence of dizziness was not significantly different between the two groups ($P > 0.05$). The times to the first passage of flatus and bowel movement were earlier in group D than in group F, and the satisfaction with pain control was significantly higher in group D than in group F ($P < 0.05$, Table 3).

DISCUSSION

The results of the present study indicated that with a procedure-specific, opioid-free postoperative pain management regimen, patients reported the same postoperative pain after 6 hours with either DEX or fentanyl for postoperative analgesia following gynecological laparoscopic surgery.

Many studies have reported the opioid-sparing effects of DEX, either in combination with opioids for postoperative analgesia or as a continuous infusion intraoperatively. However, no studies have concentrated on the analgesic effects of DEX alone for minimally invasive procedures. This is the first study to evaluate its inherent action for analgesia following gynecological laparoscopic surgery. Dexmedetomidine exerts its effects through α_2-adrenoceptors (α_2R) and has a powerful affinity for this receptor (almost 8 times greater than clonidine). Studies suggest that DEX activates α_2R in the locus coeruleus of the brain and spinal cord and then cause the activation of potassium channel, facilitating K^+ efflux, and inhibition of voltage-gated Ca^{2+} channels, which is the main mechanism by which it exerts its anesthetic effects.[14,15]

There are several strategies for postoperative analgesia management for abdominal laparoscopic surgery, each with its own advantages and disadvantages. Transversus abdominis plane (TAP) block is increasingly considered for analgesic regimens due to its high efficacy, particularly when guided by ultrasound.[16,17] Epidural analgesia is suggested for routine use in open upper abdominal surgery, but it is not recommended for laparoscopic procedures because the risks of epidural

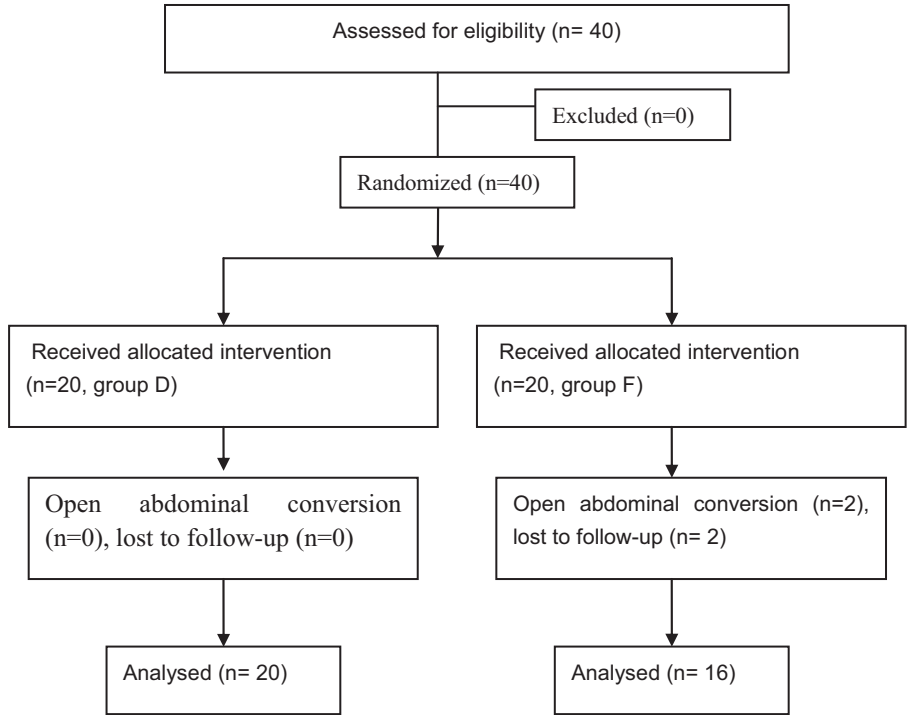

FIGURE 1. Flow chart of patients enrolled in the study.

placement are thought to outweigh the potential benefits.[18] Surgical site infiltration is preferred in some clinical centers because it is easily performed; however, most of the time, the sensation of pain occurs not only around the incision site but also on the shoulder and upper abdomen.[19,20] Therefore, it is not always effective to use a local anesthetic. Given that intravenous PCA has few contraindications and its effect in pain management can be maintained continuously with a stable therapeutic concentration.

Although not designed for this purpose, previous studies showed a trend that DEX reduced postoperative pain whether used intraoperatively or postoperatively.[8,21,22] Frolich et al[23] reported that intravenous infusion of DEX reduced pain ratings for cold and ischemic pain. Another study also indicated that DEX was intravenously infused at a dose below the clinical dose inhibited conditioned pain modulation in humans.[24] In our study, we demonstrated a similar pain perception within the first postoperative 48 hours in the DEX and fentanyl groups. In

TABLE 1. Demographic and Perioperative Data

	Group D (n = 20)	Group F (n = 16)	*P*
Age, y	44.9 ± 8.4	49.7 ± 9.8	0.199
BMI, kg/m^2	24.1 ± 3.2	26.4 ± 7.0	0.190
ASA, I to II (n)	6/14	4/12	1.000
Operating time, min	221.3 ± 80.9	211.3 ± 56.3	0.678
Procedures completed (n%)			0.675
Radical hysterectomy	4 (20%)	3 (19%)	
Radical hysterectomy + PLND	6 (30%)	7 (43%)	
Radical hysterectomy + PALND	10 (50%)	6 (38%)	
Estimated blood loss, mL	655.0 ± 158.9	728.1 ± 144.9	0.163
Fluids, mL	297.5 ± 521.3	334.4 ± 551.6	0.838
Urine output, mL	480.0 ± 195.6	596.9 ± 321.7	0.187
Fentanyl dose, mg	0.40 ± 0.10	0.42 ± 0.12	0.421
Propofol dose, mg	501.5 ± 61.2	508.1 ± 64.8	0.755
Sevoflurane dose, MAC	1.0 ± 0.1	1.0 ± 0.1	0.793

Variables presented as mean ± SD or number of patients n.

ASA = American Society of Anesthesiology, BMI = body mass index, Group D = dexmedetomidine group, Group F = fentanyl group, PALND = para-aortic lymphadenectomy, PLND = pelvic lymphadenectomy.

None showed any statistical significance ($P > .05$).

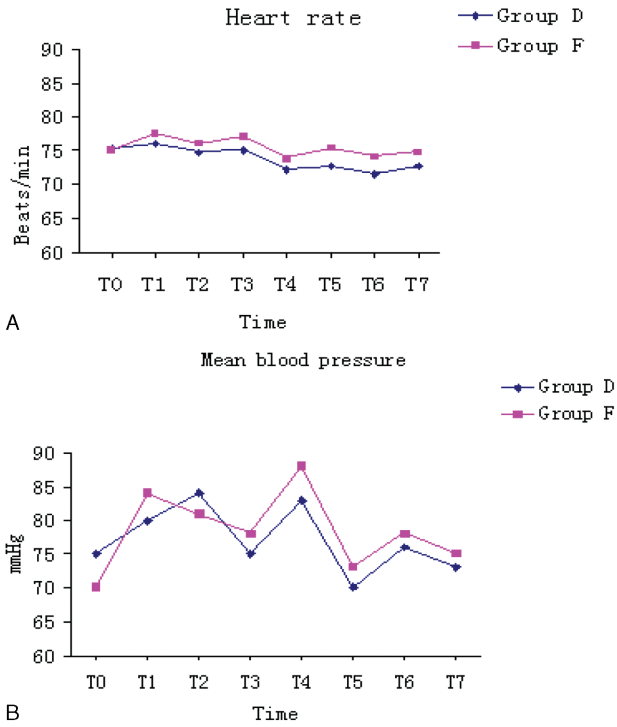

FIGURE 2. Comparison of heart rate (HR) (beats/min) and mean blood pressure (MBP) (mm Hg) $P > 0.05$. (A) Heart rate at different time points, (B) mean blood pressure at different time points.

addition, we observed a reduced incidence of PONV and higher satisfaction with pain control and faster recovery of bowel function following DEX-based postoperative analgesia regimen.

The stress of the surgical procedure and CO_2 pneumoperitoneum are considered to be the causes of pain following gynecological laparoscopy. However, the mechanisms of postoperative pain are complex and involve many other factors such as gender, race, and psychological factors. Therefore, it is

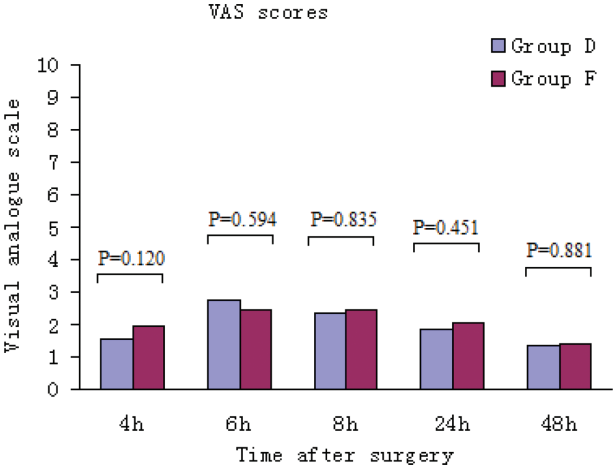

FIGURE 3. VAS scores at different times after surgery. Group D = dexmedetomidine, Group F = fentanyl, VAS = visual analogue scale.

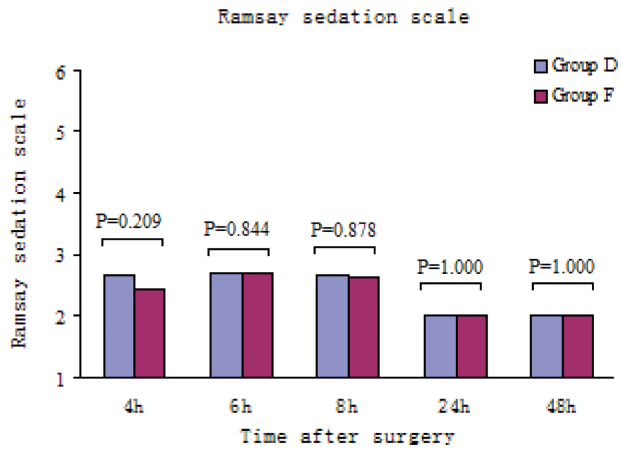

FIGURE 4. Ramsay sedation scale at different times after surgery. Group D = dexmedetomidine, Group F = fentanyl.

important to pursue pain management options in the context of what is known about their procedure-specific efficacy.[7] In the current investigation, DEX alone for intravenous patient-controlled analgesia reduced postoperative pain, and the mean VAS scores were 1.55 ± 0.60, 2.75 ± 1.71, 2.35 ± 1.26, and 1.85 ± 0.87 at 4, 6, 8, and 24 hours respectively, and the scores in the fentanyl group were 1.97 ± 0.85, 2.44 ± 1.75, 2.44 ± 1.21, and 2.06 ± 0.77 at the same time intervals, respectively. There were no statistically significant differences between the two groups. A previous study demonstrated that the postoperative pain of propofol-based anesthesia was decreased significantly at 0.5 and 1 hour in patients following gynecological laparoscopies.[25] In the present study, we evaluated the pain score 4 hours postoperatively. The anesthetic consumption during surgery, including fentanyl, propofol, and sevoflurane was not significantly different between the two groups. Hence, we thought that the analgesic effect of postoperative DEX was due to the direct action of DEX. A newly published study indicated that DEX showed superior efficacy for analgesia after spinal surgery, and the authors concluded that DEX might be a substitute for remifentanil as an adjuvant in total intravenous anesthesia.[26] Our results similarly implied that DEX alone used for intravenous PCA was a better choice for postoperative analgesia in patients after gynecological laparoscopy compared with fentanyl. The Ramsay sedation scores were similar between the two groups; the possible reason was that we used a lower dose of DEX, as the suggested dose was 0.2 to 0.7 μg/kg/h.[22]

TABLE 2. Side Effects

	Group D (n = 20)	Group F (n = 16)	*P*
Dizzy, n (%)	2 (10%)	2 (12.5%)	0.813
PONV, n (%) nausea	1 (5%)*	5 (31.3%)	0.020
Vomiting	0	0	

Variables presented as number of patients, n (%).
Group D = dexmedetomidine, Group F = fentanyl, PONV = postoperative nausea and vomiting.
*$P < 0.05$.

TABLE 3. Recovery of Bowel Function and Satisfaction for Pain Control

	Group D (n = 20)	Group F (n = 16)	*P*
Time to first passage of flatus, h	40.0 ± 9.5*	62.0 ± 8.7	0.000
Time to first bowel movement, h	58.6 ± 7.7*	79.2 ± 10.0	0.000
Satisfaction for pain control	8 ± 1.10*	6 ± 1.01	0.000

Variables presented as mean ± SD.
Group D = dexmedetomidine, Group F = fentanyl.
*$P < 0.01$.

Fentanyl is a common opioid for postoperative analgesia, but complications were also a concern, particularly PONV. Kim et al[27] reported that fentanyl 25 μg/kg for intravenous PCA resulted in at least a 30.3% incidence of PONV in patients undergoing laparoscopic-assisted hysterectomy. Similarly, Choi et al[28] demonstrated that intravenous PCA with fentanyl, with a lower background dose, resulted in a 23.2% incidence of PONV following colorectal cancer laparoscopic surgery. The dose of fentanyl in our study was between these two at 20 μg/kg with a background of 0.2 μg/kg. Consistent with these studies, we found that 31.2% of patients in the fentanyl group experienced PONV, while only 10% in DEX group experience PONV. Other studies, including a meta-analysis, also showed that DEX reduced the incidence of PONV.[8,29] At the same time, satisfaction with pain management was higher for patients who received DEX analgesia. No patient developed bradycardia or hypotension in the DEX group. The incidence of dizziness was similar between two groups, and no patient experienced respiratory depression.

Another finding of this study was the beneficial effect of DEX on bowel function recovery. The times to the first passage of flatus and bowel movement were 40.0 ± 9.5, 58.5 ± 7.7 hours, respectively, in the DEX group, while in the fentanyl group, these times were 62.0 ± 8.7, 79.2 ± 10.0 hours, respectively. It is well known that opioids slow the intestinal transit time, and an opioid receptor antagonist was showed to improve gastrointestinal recovery.[30] Although we do not know the exact mechanism of DEX for gut function recovery, one possible explanation might be that it is an opioid-free postoperative analgesia. Further study is still needed to confirm this possibility.

There are several limitations in the current study. First, we did not have a sham analgesic group. Because the delay between the requirement for analgesia and injection of the medication is an important concern, we used PCA to maintain a background drug infusion. We did not obtain a different dose level of DEX for postoperative analgesia due to the lack of personal resources. Another limitation is that our study population was women patients undergoing gynecological laparoscopic procedures, and we did not evaluate the baseline pain scores. However, because we used a random design, it is likely that differences in the baseline pain scores among the study groups were similar. We did not compare DEX with other analgesics and pain management methods, but we will investigate this in our future work. Further studies to investigate dose-dependent differences in pain scores with DEX in other study populations and for other surgical procedures are needed. It is true that DEX is a little expensive and that is the main barrier for widespread use of DEX. We did not compare the difference of ICU length of stay and length of hospital stay between two groups. But patients in group DEX had more satisfaction for postoperative pain control. Besides, the incidence of nausea and vomiting was decreased in group D when compared with group F. So, DEX infusion is a useful alternative to opioid analgesics, despite its high cost. It was also demonstrated by other studies.[31,32]

In conclusion, when used in a procedure-specific, opioid-free regimen for postoperative pain management, intravenous patient-controlled analgesia with DEX alone is an effective method of analgesia after gynecological laparoscopic surgery. Our findings suggest that intravenous infusion of DEX alone at 0.25 μg/kg/h postoperatively not only reduces postoperative pain, but also enhances satisfaction with pain control and improves the recovery of gastrointestinal function with a lower incidence of postoperative nausea and vomiting.

ACKNOWLEDGMENTS

The authors would like to thank all the staffs in gynecological ward.

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