

# Dexmedetomidine-remifentanil vs propofol-remifentanil for monitored anesthesia care during hysteroscopy

## Randomized, single-blind, controlled trial

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### Abstract

**Background:** Although dexmedetomidine has been used as either the anesthetic agent for light sedation or as an adjunct to other sedatives, no study has investigated the usefulness of dexmedetomidine as the main sedative agent for invasive and painful procedures. The purpose of this study was to compare the safety of dexmedetomidine-remifentanil and propofol-remifentanil during monitored anesthesia care (MAC) for hysteroscopy.

**Methods:** Female patients undergoing hysteroscopy were randomly assigned to either the dexmedetomidine (group D) or the propofol group (group P). The study drug (0.6 ml/kg; dexmedetomidine 2 µg/ml or propofol 4 mg/ml) was loaded for 10 minutes followed by 0.1 to 0.5 ml/kg/hour to maintain a bispectral index of 60 to 80 during the procedure. In both groups, remifentanil was infused using a target-controlled-infusion system with a target concentration of 2 ng/ml and titrated during the procedure. The incidence rates of intraoperative respiratory depression in both groups were compared. Postoperative pain and patients satisfaction were also compared.

**Results:** A total of 69 female patients were included in this study. Dexmedetomidine significantly decrease the incidence of respiratory depression compared with propofol (15/34 [44.1%] vs 5/35 [14.3%],  $P=.006$ , group P and D, respectively). Postoperative pain and patients satisfaction score did not differ between the groups.

**Conclusion:** The combination of dexmedetomidine-remifentanil can reduce the incidence of respiratory depression without increasing hemodynamic complications compared with propofol-remifentanil for MAC during hysteroscopy.

**Abbreviations:** ASA = American society of anesthesiologists, BIS = Bispectral index, BMI = body-mass index, EEG = electroencephalography, HR = heart rate, ICU = intensive care unit, IQR = interquartile range, IUD = intrauterine device, MAC = monitored anesthesia care, MBP = mean blood pressure, NNT = need to treat, OAA/S = Observer's Assessment of Alertness and Sedation, PACU = post-anesthesia care unit, PONV = postoperative nausea and vomiting, SBP = systolic blood pressure, VAS = visual analogue scale.

**Keywords:** conscious sedation, dexmedetomidine, hysteroscopy, propofol

## 1. Introduction

Hysteroscopy is widely used for the diagnosis and treatment of endometrial and other intrauterine diseases.<sup>[1]</sup> Despite the short duration of the procedure, dilation of the cervix by Hegar dilators and extraction of intrauterine tissue can cause severe pain and

significant anxiety.<sup>[2]</sup> Various anesthetic methods, such as paracervical block,<sup>[3,4]</sup> topical anesthesia,<sup>[4]</sup> or general anesthesia,<sup>[5,6]</sup> have been used in conjunction with hysteroscopy. In recent years, monitored anesthesia care (MAC) has drawn attention for the anesthetic method of hysteroscopy owing to new

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sedatives and analgesics providing adequate analgesia and anxietyolysis during the procedure.<sup>[7,8]</sup>

The most common sedative agent for MAC is propofol. Propofol has a rapid onset and offset, easy titratability, and good anxiolytic activity<sup>[9]</sup>; however, it can also cause respiratory depression, which can be more severe when combined with opioid analgesics.<sup>[10]</sup> The above study group compared the safety and efficacy of remifentanyl-propofol and fentanyl-propofol for MAC during hysteroscopy, and demonstrated that remifentanyl prevents respiratory depression better than fentanyl.<sup>[7]</sup>

In contrast, dexmedetomidine, a highly selective  $\alpha_2$ -receptor agonist, is known to produce sedation and analgesia without causing significant respiratory depression. Although dexmedetomidine has been used as either the anesthetic agent for light sedation<sup>[11,12]</sup> or as an adjunct to other sedatives,<sup>[13]</sup> no study has investigated the usefulness of dexmedetomidine as the main anesthetic agent for invasive and painful procedures such as hysteroscopy.

The aim of this study was to test the hypothesis that dexmedetomidine-remifentanyl causes less respiratory depression and results in safer sedation as compared with propofol-remifentanyl for MAC during hysteroscopy.

## 2. Materials and methods

This randomized and single-blind study was approved by the Institutional Review Board of Seoul National University Bundang Hospital and registered with the Clinical Research Information Service (CRiS), under the registration number KCT0000616. Written informed consent was obtained from all participating patients. The female patients aged 18 to 70 years with ASA classification I–II who were undergoing elective hysteroscopy under MAC were enrolled. Exclusion criteria were

1. any upper airway abnormality that may cause difficulty in airway management such as limited mouth opening, Mallampati classification,  $\geq 3$ <sup>[14]</sup> and cervical immobility,
2. history of respiratory insufficiency or sleep apnea,
3. second or third degree atrioventricular block,
4. chronic use of analgesics,
5. history of drug abuse,
6. history of psychological disorders or psychotropic medication
7. allergy to study drugs, and
8. patients refusal to participate.

Subjects were randomly divided into the propofol group (group P) and the dexmedetomidine group (group D) by an independent anesthesiologist who was involved only in randomization, using a computer-generated random number table (Random Allocation Software ver. 1.0, Isfahan University of Medical Sciences, Isfahan, Iran) before arriving to the operating theater. Subjects were premedicated with 0.03 mg/kg of midazolam in the reception area. In the operating room, electrocardiogram, non-invasive arterial pressure, pulse oximetry, and Bispectral index (BIS) were monitored. 5 l/minute of oxygen was supplied via a non-rebreathing oxygen mask. Thereafter, the study drug, consisting of either 4 mg/ml of propofol in Group P or 2  $\mu$ g/ml of Dexmedetomidine in Group D, was administered. In both groups, 0.5 ml/kg of the study drug was infused intravenously over 10 minutes, after which 0.1 to 0.6 ml/kg/hour was infused continuously in order to maintain a BIS score of 60 to 80. The infusion rate was decreased by 3 ml/hour if the BIS decreased below 60 and was increased by 3 ml/hour when the BIS rose

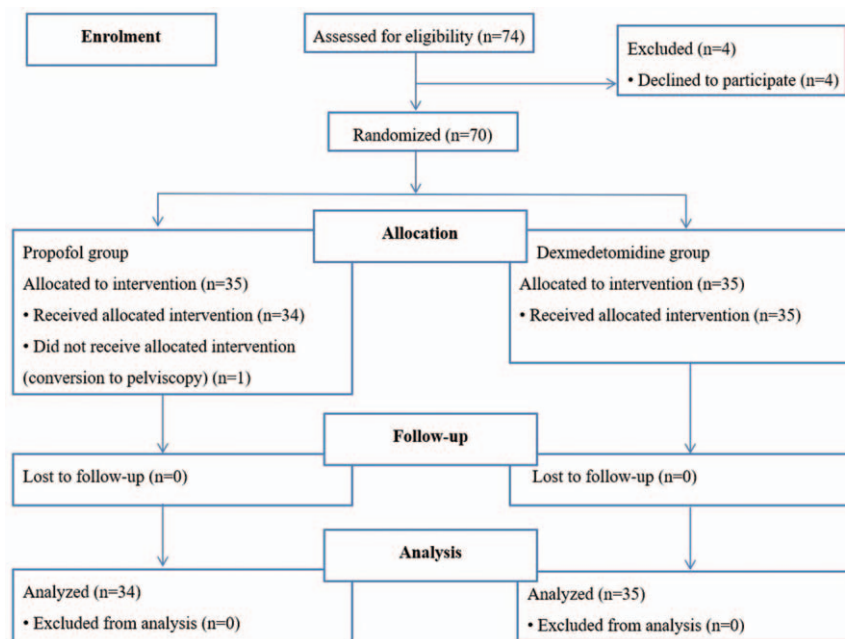
above 80. When the BIS reached above 80, regardless of the maximum maintenance dose of the study drugs (0.6 ml/kg/hour), midazolam 0.2 mg/kg was injected intravenously and countered as the patient need to treat (NNT). Remifentanyl was infused continuously using a target-controlled infusion pump (Master TCI, Fresenius Vial SA, Brezins, France) in both groups. The effect-site concentration was initially set at 1 ng/ml and was increased to 2 ng/ml just prior to cervical dilation with a Hegar dilator. Remifentanyl was increased by 0.5 ng/ml if any signs of insufficient analgesia were present, such as facial grimacing, movements, complaints of discomfort or pain, systolic blood pressure (SBP) >140 mm Hg or tachycardia (heart rate [HR] > 100 beats/minute or sudden increase of 30 beats/minute over baseline). Adverse hemodynamic events were defined as hypertension (SBP >150 mm Hg), hypotension (SBP <90 mm Hg), tachycardia (heart rate >110 beats/minute) or bradycardia (heart rate <50 beats/minute). Respiratory depression was defined as SpO<sub>2</sub> of 90% or lower or a respiratory rate of less than 8 breaths/minute for longer than 1 minute.<sup>[7,15]</sup> Tachycardia and hypertension were treated by titrating the opioid infusion; bradycardia and hypotension were treated with atropine or ephedrine, respectively. In case of respiratory depression, jaw-thrust, or assisted ventilation was applied as necessary.

At the end of hysteroscopy, the amounts of remifentanyl used during the procedure were checked and the patients were transferred to the post-anesthesia care unit (PACU). The mean blood pressure (MBP) and HR were recorded every 5 minutes until the patients were ready for discharge from the PACU. During the stay in the PACU, a nurse blind to the study groups recorded levels of postoperative pain using a visual analogue scale (VAS; with 0: no pain to 100: intractable pain), and the incidence of nausea and vomiting. If the pain score exceeded 50, rescue analgesics (ketorolac 30 mg) was injected intravenously as needed. If nausea or vomiting was present, antiemetics (ramosetron 0.3 mg) were injected intravenously. Patients were discharged from the PACU when the modified Aldrete score was over 8. At discharge from the PACU, the patients were asked to rate their overall satisfaction with sedation using a 100-point rating scale (0: not satisfied to 100: extremely satisfied).

The primary outcome of this study was the incidence of intraoperative respiratory depression. In a pilot study using a combination of propofol and remifentanyl during hysteroscopy, the incidence of respiratory depression (SpO<sub>2</sub> <90%) was 40%. Based on this result, the decreases in the incidence of respiratory depression to 10% using dexmedetomidine was considered clinically significant. A sample size of 35 participants per group was calculated with a significance level of 0.05 ( $\alpha=0.05$ ) and a power of 80% ( $\beta=0.20$ ) considering a 10% drop-out rate. Data were analyzed using Students *t* test (demographic data, hemodynamic variables), Fishers exact test (frequencies of intraoperative respiratory depression, postoperative nausea and vomiting [PONV]), and the Wilcoxon rank sum test (patients satisfaction scores). A *P* value <.05 was considered to indicate statistical significance.

## 3. Results

Seventy four patients were screened for this study, 4 of whom refused enrolment, leaving 70 patients to be randomized into groups. One patient from group P was excluded due to conversion to general anesthesia (conversion to pelviscopy), leaving the data of 69 patients for analysis (Fig. 1). Demographic



**Figure 1.** CONSORT flow diagram. Seventy patients were randomized; 1 patient from group P was excluded due to conversion to general anesthesia.

and surgical characteristics, including the amount of remifentanyl administered and the PACU time did not differ significantly between the 2 groups (Table 1).

The incidence of respiratory depression was markedly lower in group D than in group P (15/34 [44.1%] vs 5/35 [14.3%]; groups P and D, respectively,  $P=.006$ ), all of which occurred intraoperatively (Table 2). The respiratory depression was normalized in all patients uneventfully within 1 minute by manipulating the airway patency, assisted ventilation and dose adjustments.

The intraoperative adverse events differed between the 2 groups (Table 2). There were 10/34 (29.4%) and 3/35 (8.6%) cases of intraoperative hypotension (SBP < 90 mm Hg) in the group P and group D, respectively ( $P=.027$ ). In P group,

hypertension (SBP > 140 mm Hg) occurred in 1 patient (2.9%), while no patients in D group became hypertensive ( $P=.493$ ). However, the mean arterial pressures (MBP) were not significantly different between the 2 group except at the time before the start of the operation ( $67 \pm 17$  vs  $86 \pm 17$ , groups P and D respectively;  $P < .001$  and at the time of 1 minute after the start of the operation ( $72 \pm 15$  vs  $81 \pm 16$ , groups P and D respectively;  $P < .013$ ) (Fig. 2). The intraoperative heart rate was significantly lower in group D than in group P (Fig. 2). Tachycardia occurred in only 2 patients (5.9%) of group P ( $P=.239$ ). Bradycardia occurred in the 6 (17.6%) patients of group P and 19 (54.3%) of group D ( $P=.002$ ). The NNT were 1 in group P and 3 in group D ( $P=.614$ , Table 2).

**Table 1**  
**Demographic and surgical characteristics of the 2 groups.**

	Group P (n = 34)	Group D (n = 35)	P-value
Age (yr)	45.5 (39.8–53.5)	42.0 (39.0–51.0)	.479
Height (cm)	157.9 (154.1–162.3)	160.8 (155.7–165.0)	.073
Weight (kg)	56.7 (52.0–61.1)	56.0 (53.2–63.0)	.696
BMI	22.4 (20.5–24.7)	21.6 (20.0–25.2)	.479
ASA class (I/II)	29 (85) / 5 (15)	33 (94) / 2 (6)	.259
Types of the operations	Endometrial polypectomy (27) Leiomyoma removal (3) IUD removal (1) Lysis of intrauterine adhesion (1) Endometrial biopsy (1) Endometrial ablation (1)	Endometrial polypectomy (30) Leiomyoma removal (4) IUD removal (1)	
Remifentanyl dose (µg)	201.5 (136.0–267.3)	205.0 (161.5–247.8)	.944
Duration of operation (min)	25.0 (20.0–35.0)	30.0 (20.0–42.5)	.376
Duration of anesthesia (min)	50.0 (45.0–60.0)	45.0 (40.0–66.3)	.905
PACU time (min)	30.0 (30.0–35.0)	30.0 (30.00–40.0)	.812

Values are expressed as median (IQR) or number (%).

Demographic data and surgical characteristics were not different significantly between the 2 groups.

ASA = American society of anesthesiologists, BMI = body-mass index, IUD = intrauterine device, PACU = post-anaesthesia care unit.

**Table 2**  
The incidence of intraoperative adverse events.

	Group P (n=34)	Group D (n=35)	P value
Respiratory depression	15 (44.1%)	5 (14.3%)	.006
Hypertension (SBP > 140 mm Hg)	1 (2.9%)	0 (0%)	.493
Hypotension (SBP < 90 mm Hg)	10 (29.4%)	3 (8.6%)	.027
Tachycardia (HR > 100 bpm)	2 (5.9%)	0 (0%)	.239
Bradycardia (HR < 50 bpm)	6 (17.6%)	19 (54.3%)	.002
Need to treatment (NNT)	1 (2.9%)	3 (8.6%)	.614

Values are expressed number (%).

HR = heart rate, SBP = systolic blood pressure.

In the PACU, the MBP was generally lower in group D, but the heart rate was significantly lower in group D compared with group P throughout the PACU stay (Fig. 3). The postoperative pain scores (median: 7.5 [IQR: 0–42.5] vs median: 0 [IQR: 0–20.0], groups P and D, respectively,  $P = .116$ ) and the incidences of rescue analgesics use (8/34 [23.5%] vs 3/35 [8.6%], group P and D, respectively,  $P = .09$ , Table 3) did not show statistical difference between the 2 groups. The patients satisfaction scores were also not significantly different between the 2 groups (median: 90.0 [IQR: 70.0–100] vs median: 90.0 [IQR: 80.0–100],  $P = .234$ , groups P and D, respectively). The incidences of PONV were low regardless of group allocation, and there was no significant difference between the groups (3/34 [8.8%] vs 1/35 [2.9%],  $P = .356$ , groups P and D, respectively, Table 3).

#### 4. Discussion

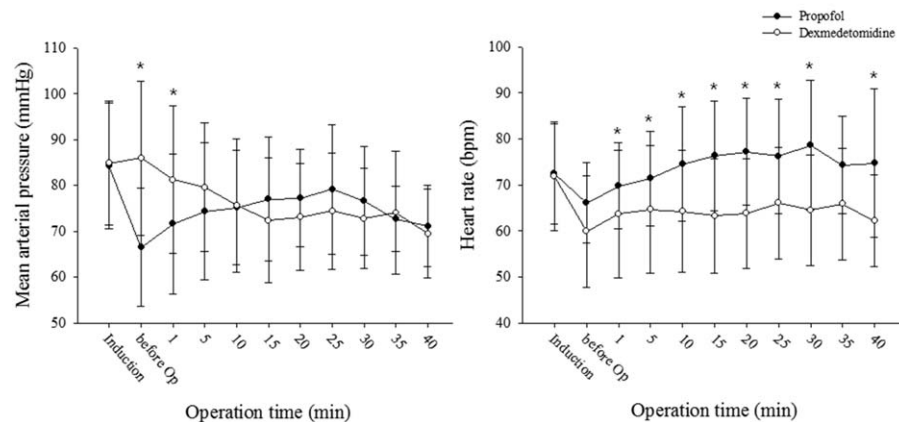
This randomized, single-blind, comparative study aimed to compare propofol-remifentanyl and dexmedetomidine-remifentanyl in terms of respiratory depression, hemodynamic stability, recovery time, patients satisfaction with anesthesia during hysteroscopy under MAC. The principal finding of this study was that the combination of dexmedetomidine and remifentanyl can reduce the incidence of respiratory depression leading to oxygen desaturation. Dexmedetomidine also resulted in lower heart rate and less hypertension compared with propofol. However, dexmedetomidine was not associated with a higher

pain score, lower patients satisfaction, and prolonged recovery time.

Sedation with dexmedetomidine is associated with minimal respiratory depression and a preservation of the ventilatory and occlusion pressure response to CO<sub>2</sub>.<sup>[16]</sup> In healthy volunteers, even a very high dose of dexmedetomidine could maintain the respiratory drive.<sup>[17]</sup> However, some studies reported that bolus administration of high doses of dexmedetomidine may result in obstructive sleep apnea.<sup>[17,18]</sup> This study showed dexmedetomidine combined with remifentanyl can provide adequate sedation and analgesia in the painful procedure such as hysteroscopy without causing severe complications.

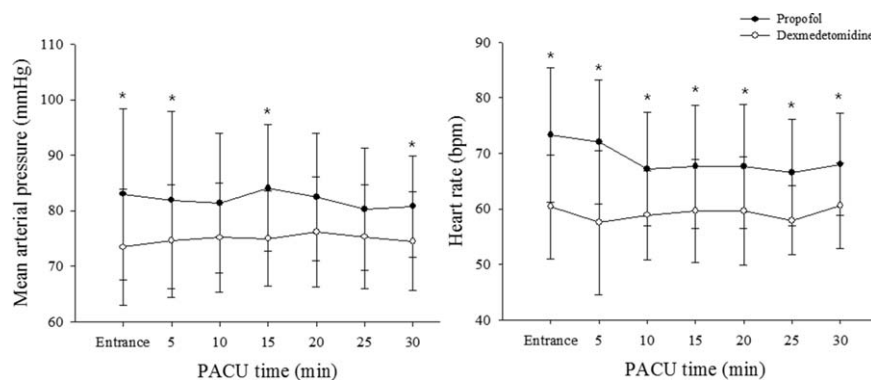
Dexmedetomidine has analgesia-sparing effects via central actions in the locus ceruleus and in the dorsal horn of the spinal cord.<sup>[19,20]</sup> In many studies, dexmedetomidine as an anesthetic adjunct during general anesthesia reduced the anesthetic requirement and postoperative opioid consumption. However, dexmedetomidine used alone yielded less effective pain control during colonoscopy<sup>[21]</sup> or endoscopic retrograde cholangiopancreatography<sup>[22]</sup> than did a benzodiazepine combined with an opioid. The result of this study is also consistent with previous studies. The amounts of remifentanyl used in this study were not significantly different between the 2 groups; the analgesic effect of dexmedetomidine does not seem to be enough to attenuate the nociception during hysteroscopy, such as cervical dilation or intrauterine tissue extraction, or to reduce intraoperative opioid consumption.

The anti-emetic effect of dexmedetomidine is related to the ability to reduce emetic sequelae by decreasing the need for the inhalation agent during the operation and opioid immediately after surgery.<sup>[23]</sup> Although the study population is a high-risk group of PONV, the incidence of PONV of this study is quite low. This phenomenon could result from the following reasons. The first reason is the difference in the type of anesthesia. In the previous report, the incidence of PONV after hysteroscopy under MAC is known as about 5% and the incidence was much higher under general anesthesia (11.3%–34%).<sup>[24,25]</sup> Second possible reason is midazolam premedication. In the meta-analysis, midazolam premedication resulted in decreasing the incidence and the severity of PONV.<sup>[26,27]</sup> In our study, intravenous midazolam of 0.03 mg/kg was used in every patient before



**Figure 2.** Intraoperative changes in the mean arterial pressure and heart rate. The mean arterial pressure before the start of the operation and immediately after the start of the operation was significantly higher in group D compared with group P. Also, the intraoperative heart rate was significantly lower in group D than in group P. BPM = beats per minute.





**Figure 3.** Postoperative changes in mean arterial pressure and heart rate. In the PACU, the mean arterial pressure and heart rate were significantly lower in group D compared with group P. BPM = beats per minute, PACU = post-anesthetic care unit.

entering the operation room, which might decrease the incidence of PONV in both groups.

Dexmedetomidine decreases BP by inhibiting sympathetic outflow and lowering circulating catecholamine level<sup>[17,28]</sup> and heart rate partly due to sympatholytic effects, but also due to a vagal mimetic effect.<sup>[29]</sup> In contrast to propofol, large doses of dexmedetomidine cause direct  $\alpha_2$ -mediated vasoconstriction by acting on the postsynaptic vascular smooth muscle. This biphasic cardiovascular response caused by dexmedetomidine bolus was observed in the current study. The increase in blood pressure before the operation was attributed to the direct effects of  $\alpha_2$ -adrenoreceptor stimulation of vascular smooth muscle. After the transient increase in blood pressure, a decrease in BP occurred, presumably due to an inhibition of sympathetic outflow that overrode the direct effects on the vasculature. Compared with propofol, dexmedetomidine decrease blood pressure, and heart rate at PACU. These cardiovascular effects of dexmedetomidine could be helpful in patients with increased cardiac morbidity by reducing perioperative tachycardia and hypertension, consequently, decreasing the chance of adverse cardiovascular events in the postoperative period.<sup>[30]</sup>

The present study has some limitations. First, dexmedetomidine was titrated to keep BIS score between 60 and 80. BIS is a non-invasive electroencephalography (EEG)-based method of monitoring the hypnotic state during anesthesia and sedation. Propofol is known to be well correlated with both the BIS scores and drug concentration, and BIS score from 60 to 80 means that the patient is moderately sedated.<sup>[31]</sup> Although there have been controversies, it is generally accepted that BIS can be used for the dexmedetomidine-induced sedation. When 0.7  $\mu\text{g}/\text{kg}/\text{hour}$  of dexmedetomidine was used for intraoperative sedation, BIS score was maintained between 60 and 80, and Observer’s Assessment of Alertness and Sedation (OAA/S) score was between 2 and 3.<sup>[32]</sup> Dexmedetomidine-induced moderate sedation was achieved in the ICU patients when the BIS

scores were maintained between 60 and 80.<sup>[33]</sup> Venn et al showed that the BIS score for maintaining Ramsay sedation scale at 5 were not different between propofol and dexmedetomidine groups.<sup>[34]</sup> In contrast, Kasuya showed that the BIS is significantly lower with dexmedetomidine than propofol using the OAA/S score.<sup>[35]</sup> Second, we used loading dose in both groups. Dexmedetomidine has a slower onset, loading dose is usually required for intraoperative sedation. Loading dose of propofol is not used generally. However, propofol loading was already used in the previous investigation.<sup>[32]</sup> and the loading dose of the propofol used in this study is less than that of the previous study. Further study administrating propofol by target-controlled infusion method may be needed.

In conclusion, the combination of dexmedetomidine-remifen-tanil can provide adequate and safe anesthesia, causing significantly less respiratory depression than propofol-remifen-tanil for MAC during hysteroscopy.

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**Table 3**

**The incidence of postoperative adverse events.**

	Group P (n = 34)	Group D (n = 36)	P value
Incidence of PONV	3 (8.8)	1 (2.9)	.356
Postoperative pain score (VAS)	7.5 (0 – 42.5)	0 (0 – 20.0)	.117
Rescue analgesics	8 (23.5)	3 (8.6)	.09
Patients’ satisfaction score	90.0 (70.0 – 100)	90.0 (80.0 – 100)	.234

Data are expressed as number (%) or median (IQR).

IQR = interquartile range, PONV = postoperative nausea and vomiting, VAS = visual analogue scale.

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