

# The Effect of Opioid-Free Anesthesia on the Quality of Recovery After Gynecological Laparoscopy: A Prospective Randomized Controlled Trial

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**Purpose:** Opioid-free anesthesia (OFA) is an emerging technique that eliminates intraoperative use of opioids and is associated with lower postoperative opioid consumption and reduced adverse postoperative events. The present study investigated the effect of OFA on the quality of recovery in patients undergoing gynecological laparoscopy.

**Patients and Methods:** Seventy-five adult patients undergoing elective gynecological laparoscopy were randomly assigned to the OFA group with dexmedetomidine and lidocaine or the remifentanyl-based anesthesia (RA) group with remifentanyl. Patients, surgeons, and medical staff members providing postoperative care and assessing outcomes were blinded to group allocation. The anesthesiologist performing general anesthesia could not be blinded due to the different drug administration protocols by groups. The primary outcome was the quality of recovery measured using the Quality of Recovery-40 (QoR-40) questionnaire. Secondary outcomes were postoperative pain score, intraoperative and postoperative adverse events, and stress hormones levels.

**Results:** The patients in both groups had comparable baseline characteristics. The QoR-40 score on postoperative day 1 was significantly higher in the OFA group than in the RA group ( $155.9 \pm 21.2$  in the RA group vs  $166.9 \pm 17.8$  in the OFA group; mean difference:  $-11.0$ , 95% confidence interval:  $-20.0, -2.0$ ;  $p = 0.018$ ). The visual analog scale score at 30 min after surgery was significantly lower in the OFA group than in the RA group ( $6.3 \pm 2.3$  in the RA group vs  $4.1 \pm 2.1$  in the OFA group;  $p < 0.001$ ). The incidences of nausea and shivering in the post-anesthetic care unit were also significantly lower in the OFA group ( $p = 0.014$  and  $0.025$ ; respectively). Epinephrine levels were significantly lower in the OFA group ( $p = 0.002$ ).

**Conclusion:** OFA significantly improved the quality of recovery in patients undergoing gynecological laparoscopy.

**Keywords:** opioid-free anesthesia, quality of recovery, laparoscopy, gynecology, opioids

## Introduction

Opioids are commonly used for analgesia and supplementary sedation during general anesthesia and are the most widely used agents for the treatment of acute pain in the immediate postoperative period. Opioids provide effective analgesia and stable intraoperative hemodynamics, which are valuable during the perioperative period. However, the use of opioids during the perioperative period is risky. Opioids have many potential adverse effects, including respiratory depression, postoperative nausea and vomiting (PONV), and opioid-induced hyperalgesia (OIH).<sup>1</sup> These complications are associated with delayed patient recovery, prolonged stay in the post-anesthetic care unit (PACU), delayed hospital discharge, and unexpected hospitalization, all contributing to an increased burden on patients and resources.<sup>2</sup> Furthermore, the “opioid crisis” is already a serious problem in North America; fentanyl overdose is now the leading cause of death in Americans

aged 18–45.<sup>3</sup> The role of perioperative opioids is important in this regard, considering that 27.0% of chronic opioids start after surgery.<sup>4</sup>

Efforts have been made to minimize the use of opioids in light of the known adverse effects of opioids in the perioperative period.<sup>5</sup> Opioid-free anesthesia (OFA) is an extreme form of this movement in which multimodal non-opioid analgesic techniques are used to eliminate the intraoperative use of opioids.<sup>6</sup> OFA controls intraoperative hemodynamic stability and antinociception traditionally obtained by opioids using multimodal non-opioid agents such as  $\alpha$ -2 agonists, local anesthetics, and N-methyl-d-aspartate (NMDA) receptor antagonists.<sup>7</sup> OFA has demonstrated feasibility in various types of surgeries and patients.<sup>8</sup> In two meta-analyses, patients receiving OFA had a lower incidence of PONV than those receiving opioid-based anesthesia but had similar postoperative pain scores.<sup>9,10</sup> In another meta-analysis, OFA significantly reduced adverse postoperative events with significantly lower postoperative opioid consumption.<sup>11</sup> However, the literature on OFA is still controversial because some studies that have not shown benefits<sup>12,13</sup> or worse outcomes.<sup>14</sup> Now, the question is which patients and types of surgery benefit the most from the application of OFA.

Gynecological laparoscopy may be a suitable type of surgery that can maximize the benefits of OFA. The degree of pain during gynecologic surgery is considered moderate, which requires IV opioids in the perioperative period.<sup>15</sup> However, tolerance to pain can develop with intraoperative opioids, requiring more opioids during the acute postoperative period.<sup>16</sup> Even with increased interest in postoperative pain control, many patients experience moderate to extreme pain during the immediate postoperative period, which continues after discharge.<sup>17</sup> Furthermore, PONV, the most common adverse effect of opioids, makes the use of IV opioids more difficult. Two non-modifiable risk factors for PONV exist in this patient population: female sex and gynecological laparoscopy.<sup>2</sup> Therefore, alternative approaches to intraoperative opioids, such as OFA, may have a beneficial effect on the quality of recovery.

Therefore, this study aimed to determine the effects of OFA using dexmedetomidine and lidocaine on the quality of recovery in patients undergoing gynecological laparoscopy. We hypothesized that patients receiving OFA would result in a better quality of recovery than those receiving conventional remifentanyl-based anesthesia (RA). Furthermore, we assessed the feasibility of OFA for gynecological laparoscopy.

## Materials and Methods

### Study Design

This was a prospective, parallel-group, single-blind randomized controlled trial (RCT). The study protocol was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital, the Catholic University of Korea (approval number: KC20MNSI0130) on April 7, 2020. The study was conducted following the Declaration of Helsinki and registered on ClinicalTrials.gov (NCT04409964) on May 28, 2020. Full details of the study protocol have been published previously.<sup>18</sup> Written informed consent was obtained from all participating patients before inclusion in the study. The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement and the CONSORT Patient-Reported Outcomes (CONSORT PRO) Extension.<sup>19</sup>

### Study Participants

Patients aged 20–65 years who were scheduled for elective gynecological laparoscopy, including hysterectomy, oophorectomy, salpingectomy, cystectomy, cyst enucleation, and uterus myomectomy at Seoul St. Mary's Hospital, the Catholic University of Korea, were considered eligible. Exclusion criteria were emergency surgery, cancer surgery, chronic pain requiring medication, history of psychiatric disease, hypotension, bradycardia, atrioventricular block, intraventricular or sinoatrial block, body mass index  $>35$  kg/m<sup>2</sup>, known allergies, or history of adverse events to any of the drugs used for anesthesia, pregnancy, or lactation.

### Randomization and Blinding

The enrolled patients were randomized in a 1:1 ratio to the study (OFA group) or the control (RA group). A research nurse generated a block randomization scheme using stratified block randomization with a fixed block size using a web-based

random number generator ([www.random.org](http://www.random.org)). Once a patient has been enrolled, the medical staff opened an opaque, sequentially numbered envelope containing the group allocation.

Patients and surgeons were blinded to group allocation throughout the study period. The medical staff members providing postoperative care and assessing outcomes in the PACU and the ward were also unaware of the group allocation. The anesthesiologist performing general anesthesia could not be blinded due to the different drug administration protocols by groups. However, they did not participate in postoperative care or assessment of postoperative outcomes.

## Intervention

The previously published trial protocol involved the standardization of anesthesia induction and maintenance according to the clinical practice guidelines of the Enhanced Recovery After Surgery Society recommendations.<sup>20</sup> Before starting the study, the patients were instructed on how to assess their pain intensity using a visual analog scale (VAS; 0 cm, no pain and 10 cm, the worst pain imaginable) and how to use IV patient-controlled analgesia (PCA). To improve adherence to the protocol, they were asked to request analgesia without hesitation if the VAS pain score was >4.

None of the patients received premedication. Electrocardiography, noninvasive blood pressure measurements, pulse oximetry, neuromuscular monitoring using train-of-four (TOF) stimulation, bispectral index (BIS; A-2000TM SP, Aspect Medical Systems, Norwood, MA, USA) monitoring of anesthesia depth, and Surgical Pleth Index (SPI; General Electric Healthcare, Helsinki, Finland) measurements of nociception were performed in the operating room.

The OFA group received a loading dose of IV dexmedetomidine 0.7 µg/kg for 10 min before the induction of general anesthesia, followed by a continuous infusion of 0.5 µg/kg/h, which was adjusted in steps of 0.1 µg/kg/h to maintain SBP within ± 20% of baseline. Immediately after induction of anesthesia, a bolus dose of IV lidocaine 1.5 mg/kg was administered, followed by a continuous dose of 1.5 mg/kg/h. Dexmedetomidine and lidocaine infusions were stopped at the beginning of skin suturing.

The RA group received a continuous infusion of IV remifentanyl targeting an effector site concentration of 3.5 ng/mL using a target-controlled infusion (Orchestra Base Primea, Fresenius Vial, Brezins, France) before the induction of general anesthesia. After induction of anesthesia, the remifentanyl infusion was adjusted in increments of 0.5 ng/mL to maintain the SBP within ± 20% of the baseline. Remifentanyl infusion was stopped at the end of the skin suturing.

Based on ideal body weight, all patients received a bolus dose of IV propofol 1.5–2 mg/kg for the induction of general anesthesia. After confirmation of unconsciousness (BIS value <60), absence of an eyelash reflex, and no response to verbal stimulation, a bolus dose of IV rocuronium 0.8 mg/kg was administered, and after zero TOF twitches were achieved, orotracheal intubation was performed using a direct laryngoscope. Ventilation was controlled mechanically and then adjusted to maintain an end-tidal carbon dioxide value between 25 and 40 mmHg throughout the surgery. Additional rocuronium was administered as needed. Anesthesia was maintained with 4–6% desflurane (expired concentration) in 40% air/oxygen (total flow, 4 L/min) to maintain a BIS value between 30 and 60. A bolus dose of IV ephedrine 4 mg was administered in cases with systolic blood pressure (SBP) <80 mmHg or mean arterial pressure (MAP) <60 mmHg. If the heart rate (HR) decreased below 45 bpm, a bolus dose of IV atropine 0.25 mg was administered.

Laparoscopy was performed under video guidance, with three punctures in the abdomen. Intraperitoneal pressure was maintained at approximately 12 mmHg. To prevent PONV, all patients received IV dexamethasone 5 mg at the beginning of surgery and IV palonosetron 75 µg at the end of surgery. For postoperative pain control, multimodal analgesia, consisting of IV acetaminophen 1g and IV ketorolac 30 mg, was administered 30 min before the end of surgery. These non-opioid analgesics continued throughout the hospital stay in the ward. After confirming self-respiration, the patients were extubated and transferred to the PACU. If the patient complained of pain (VAS score >4) in the PACU, IV fentanyl 0.5–1 µg/kg was administered immediately. Once the acute pain was under control, IV PCA (fentanyl 15 µg/kg in normal saline 100 mL; basal rate 0 mL/h; bolus 1 mL; lock-out time 10 min) was applied to all patients and no loading dose was administered. If the patient complained of nausea and/or vomiting, IV metoclopramide 10 mg was administered. The patients were discharged to the ward when their Aldrete score was ≥9.

## Outcomes

### Primary Outcome

The primary outcome was the quality of recovery on postoperative day (POD) 1 measured using the Quality of Recovery-40 (QoR-40) questionnaire scores. The QoR-40 questionnaire includes five dimensions of recovery: physical comfort (12 items), emotional state (9 items), physical independence (5 items), psychological support (7 items), and pain (7 items). Each item is scored on a 5-point Likert scale (none of the time, some of the time, usually, most of the time, and all of the time). The total score on QoR-40 ranges from 40 (poorest possible recovery) to 200 (best possible recovery), and a difference of 6.3 is deemed minimal clinically important.<sup>21</sup> The QoR-40 interviews were conducted in person by a blinded investigator trained on the QoR-40 questionnaire, visiting all patients in the ward. All patients completed the questionnaire the day before surgery and POD 1.

### Secondary outcomes

To determine whether OFA had the same effects as RA, such as hemodynamic stability and sedation, we obtained intraoperative hemodynamic data (SBP, MAP, and HR), anesthetic depth (BIS), and nociception severity (SPI) data, at baseline, before intubation (at the time of unconsciousness), immediately after intubation, at the time of the incision, at the end of the surgery, and immediately after tracheal extubation. Furthermore, to assess intraoperative complications, episodes of bradycardia (<45 bpm) in association with the administration of atropine, and hypotension (SBP <80 mmHg or MAP <60 mmHg) were recorded.

Pain severity was assessed using the VAS score upon arrival at the PACU and every 15 min thereafter. Additionally, the level of sedation (awake/sedated and responsive to verbal stimuli/sedated and unresponsive to verbal stimuli), the incidence of PONV and shivering, the need for analgesics and antiemetics, and the duration of stay in the PACU were assessed. These outcomes were evaluated again 24 h after surgery. In addition, the time to the first flatus or defecation was recorded.

To assess the effect of OFA on attenuating stress response, an ancillary stress hormone study was performed on 50 enrolled patients (25 in each group). Two stress hormones (epinephrine and norepinephrine) were measured at baseline, immediately after tracheal intubation, at the time of incision, immediately after tracheal extubation, and 24 h after surgery. All blood samples were placed in tubes and centrifuged within 1 h, and plasma was separated and stored at  $-70^{\circ}\text{C}$  until analysis.

## Sample Size

The primary outcome was the QoR-40 score on POD 1. Based on a previous study that reported a 13-point difference in QoR-40 scores between different anesthetic techniques,<sup>22</sup> a sample size of 34 was calculated to be necessary to achieve a power of 80% with a type I error of 0.05. An additional 15% of the participants were included to account for possible loss to follow-up. Therefore, the final sample size was 78 participants (39 in each group).

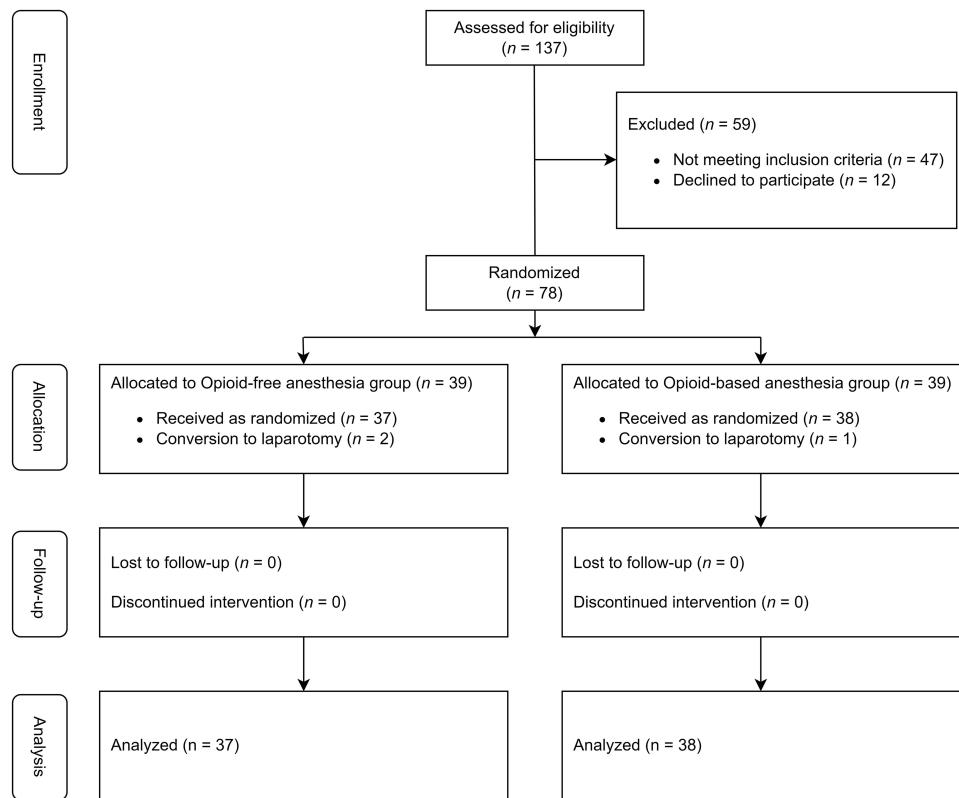
## Statistical Analysis

A researcher blinded to the group allocation performed the statistical analysis of all randomized patients (intention-to-treat analysis). The Kolmogorov–Smirnov test was used to check the normality of the distribution of the quantitative variables. Independent-sample *t*-test or Mann–Whitney *U*-test was used to analyze the quantitative variables, including the primary outcome (QoR-40). Chi-square or Fisher's exact test was used to analyze the qualitative variables. Continuous endpoints repeatedly measured during the study period were analyzed using repeated-measures two-way analysis of variance. As a sensitivity analysis, analysis of covariance (ANCOVA) was performed after controlling for preoperative QoR-40 scores. Values are expressed as mean  $\pm$  standard deviation, median (IQR), or number of patients (percentage). Statistical significance was set at  $p < 0.05$ . Statistical analyses were performed with SPSS (version 18.0; IBM SPSS Inc., Chicago, IL, USA).

## Results

### Patients

Of the 137 patients screened from June 2020 to September 2021, 78 patients underwent randomization, and three patients (one in the RA group and two in the OFA group) did not receive the allocated intervention due to conversion to laparotomy during surgery. Therefore, a total of 75 patients (38 in the RA group and 37 in the OFA group) were included in the analysis (Figure 1).



**Figure 1** Consolidated standards of reporting trials (CONSORT) flowchart of the study.

The baseline characteristics of the patients are shown in [Table 1](#). The incidence of risk factors for PONV according to the Apfel simplified risk score was similar between the two groups (non-smoking: 89.5% in the RA group vs 94.6% in the OFA group,  $p = 0.674$ ; history of PONV or motion sickness: 52.6% in the RA group vs 43.2% in the OFA group,  $p = 0.560$ ). There was no difference between the two groups in the type of surgery the patients received ( $p = 0.325$ ).

**Table 1** Characteristics of the Patients at Baseline

Variable	RA Group (n = 38)	OFA Group (n = 37)	ASD
Age, years	44 ± 10	41 ± 10	0.300
Height, cm	159.8 ± 4.4	160.4 ± 4.8	0.130
Weight, kg	58.7 ± 11.1	57.3 ± 6.5	0.154
ASA physical status, I/II	23/15	32/5	0.616
Non-smoking status	34 (89.5%)	35 (94.6%)	0.189
History of PONV or motion sickness	20 (52.6%)	16 (43.2%)	0.310
History of abdominal surgery	18 (47.4%)	12 (32.4%)	0.310
Hypertension	2 (5.4%)	1 (2.7%)	0.137
Diabetes mellitus	0 (0.0%)	1 (2.7%)	0.236
Thyroid disease	4 (10.5%)	2 (5.4%)	0.189
Type of surgery			0.257
Hysterectomy <sup>a</sup>	19 (50.0%)	17 (46.0%)	
Myomectomy <sup>b</sup>	6 (15.8%)	7 (18.9%)	
Adnexectomy only	5 (13.2%)	1 (2.7%)	
Cystectomy/cyst enucleation only	8 (21.1%)	12 (32.4%)	

**Notes:** Values are expressed as mean ± standard deviation, or number of patients (percentage). <sup>a</sup>With or without adnexectomy. <sup>b</sup>With or without cystectomy/cyst enucleation.

**Abbreviations:** RA, remifentanyl-based anesthesia; OFA, opioid-free anesthesia; ASD, absolute standardized difference; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

## Primary Outcome

All patients completed the QoR-40 questionnaire without difficulty. The baseline QoR-40 score was not different between the two groups ( $180.6 \pm 15.6$  in the RA group vs  $182.6 \pm 14.8$  in the OFA group; mean difference:  $-2.0$ , 95% confidence interval [CI]:  $-9.0, 5.0$ ;  $p = 0.573$ ; Table 2). However, the primary outcome of the study, the QoR-40 score on POD 1, was significantly higher in the OFA group than in the RA group ( $155.9 \pm 21.2$  in the RA group vs  $166.9 \pm 17.8$  in the OFA group; mean difference:  $-11.0$ , 95% CI:  $-20.0, -2.0$ ;  $p = 0.018$ ). Comparison of the five domains of the QoR-40 questionnaire on POD 1 showed that the OFA group scored higher in physical comfort ( $45.8 \pm 7.1$  in the RA group vs  $49.6 \pm 5.4$  in the OFA group; mean difference:  $-3.8$ , 95% CI:  $-6.7, -0.9$ ;  $p = 0.011$ ) and pain ( $31.2 \pm 3.5$  in the RA group vs  $33.2 \pm 2.0$  in the OFA group; mean difference:  $-2.0$ , 95% CI:  $-3.3, -0.7$ ;  $p = 0.004$ ) compared to the RA group (Table 2).

## Secondary Outcomes

### Anesthesia and Recovery Characteristics

A comparison of anesthesia and recovery characteristics between the two groups is presented in Table 3. The duration of anesthesia ( $154.0 \pm 55.6$  min in the RA group vs  $138.4 \pm 33.4$  min in the OFA group,  $p = 0.145$ ), time to eye-opening ( $5.1 \pm 1.8$  min in the RA group versus  $5.4 \pm 1.7$  min in the OFA group,  $p = 0.485$ ), and extubation ( $5.8 \pm 2.1$  min in the RA group vs  $5.7 \pm 1.7$  min in the OFA group,  $p = 0.763$ ) were similar in the two groups. Intraoperative hemodynamics (SBP, MAP, and HR), BIS and SPI values were maintained within the intended range (Figure 2). The level of sedation in the PACU did not differ between the two groups ( $p = 0.392$ ), and the duration of stay in the PACU was significantly shorter in the OFA group ( $39.6 \pm 5.6$  min in the RA group vs  $33.9 \pm 5.6$  min in the OFA group,  $p < 0.001$ ).

### Adverse Events

A comparison of adverse events between the two groups is presented in Table 4. Regarding intraoperative complications, the incidence of hypotension was significantly lower in the OFA group than in the RA group (50.0% in the RA group vs 24.3% in the OFA group,  $p = 0.039$ ), but the incidence of bradycardia was similar in the two groups (15.8% in the RA group vs 2.7% in the OFA group,  $p = 0.108$ ). VAS score at 30 min after surgery was significantly lower in the OFA group ( $6.3 \pm 2.3$  in the RA group vs  $4.1 \pm 2.1$  in the OFA group,  $p < 0.001$ ), and the incidence of patients that requiring rescue analgesics in the PACU was significantly lower in the OFA group (73.7% in the RA group vs 21.6% in the OFA group,  $p < 0.001$ ). The incidences of nausea (23.7% in the RA group vs 2.7% in the OFA group,  $p = 0.014$ ) and shivering

**Table 2** Primary Outcome Analysis

Variables	RA Group (n = 38)	OFA Group (n = 37)	Mean Difference (95% CI)	p value
Preoperative QoR-40				
Total	$180.6 \pm 15.6$	$182.6 \pm 14.8$	$-2.0 (-9.0, 5.0)$	0.573
Physical comfort	$55.0 \pm 4.0$	$55.4 \pm 4.3$	$-0.4 (-2.3, 1.5)$	0.696
Emotional state	$39.9 \pm 4.2$	$40.5 \pm 4.1$	$-0.5 (-2.5, 1.4)$	0.579
Physical independence	$20.7 \pm 3.1$	$21.2 \pm 3.4$	$-0.5 (-2.0, 1.0)$	0.524
Psychological support	$32.4 \pm 3.5$	$32.9 \pm 2.9$	$-0.5 (-2.0, 1.0)$	0.528
Pain	$32.5 \pm 2.8$	$32.6 \pm 2.7$	$-0.1 (-1.4, 1.1)$	0.848
Postoperative QoR-40				
Total	$155.9 \pm 21.2$	$166.9 \pm 17.8$	$-11.0 (-20.0, -2.0)$	0.018
Physical comfort	$45.8 \pm 7.1$	$49.6 \pm 5.4$	$-3.8 (-6.7, -0.9)$	0.011
Emotional state	$33.3 \pm 5.4$	$35.2 \pm 5.2$	$-1.9 (-4.3, 0.5)$	0.125
Physical independence	$16.7 \pm 4.2$	$18.5 \pm 4.1$	$-1.9 (-3.8, 0.1)$	0.056
Psychological support	$28.9 \pm 5.0$	$30.3 \pm 4.8$	$-1.4 (-3.7, 0.9)$	0.217
Pain	$31.2 \pm 3.5$	$33.2 \pm 2.0$	$-2.0 (-3.3, -0.7)$	0.004

**Note:** Values are expressed as mean  $\pm$  standard deviation.

**Abbreviations:** RA, remifentanyl-based anesthesia; OFA, opioid-free anesthesia; QoR, quality of recovery.



**Table 3** Anesthesia and Recovery Characteristics

Variables	RA Group (n = 38)	OFA Group (n = 37)	p value
Duration of anesthesia, min	154.0 ± 55.6	138.4 ± 33.4	0.145
Time to eye-opening, min	5.1 ± 1.8	5.4 ± 1.7	0.485
Time to extubation, min	5.8 ± 2.1	5.7 ± 1.7	0.763
Remifentanyl dose, µg/kg/min	0.11 ± 0.04		
Dexmedetomidine dose, µg/kg/h		0.63 ± 0.28	
Level of sedation in PACU, I/II/III <sup>a</sup>	34/3/1	31/6/0	0.392
Duration in PACU, min	39.6 ± 5.6	33.9 ± 5.6	<0.001

**Notes:** Values are expressed as mean ± standard deviation, or number of patients. <sup>a</sup>I, awake; II, sedated and responsive to verbal stimuli; III, sedated and unresponsive to verbal stimuli.

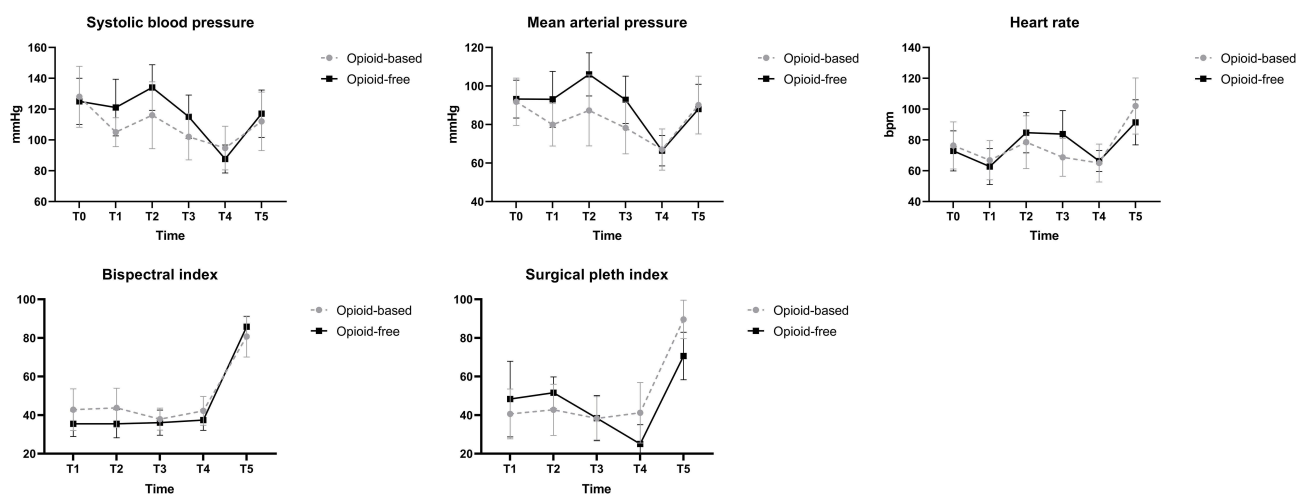
**Abbreviations:** RA, remifentanyl-based anesthesia; OFA, opioid-free anesthesia; PACU, post-anesthetic care unit.

(15.8% in the RA group vs 0% in the OFA group,  $p = 0.025$ ) in the PACU were also significantly lower in the OFA group.

However, some of the differences in secondary outcomes did not last beyond 24 h after surgery (Table 4). The VAS score at 24 h after surgery was similar in the two groups ( $3.4 \pm 1.9$  in the RA group vs  $3.4 \pm 1.8$  in the OFA group,  $p = 0.872$ ), and the incidence of patients who needed rescue analgesics was also similar (81.6% in the RA group vs 73.0% in the OFA group,  $p = 0.539$ ). The incidences of nausea and shivering were similar in the two groups. The time to first flatus or defecation was similar in the two groups ( $20.0 \pm 5.2$  h in the RA group vs  $22.7 \pm 6.8$  h in the OFA group,  $p = 0.058$ ).

### Ancillary Stress Hormone

The ancillary stress hormone study in 50 patients revealed that the levels of epinephrine were significantly lower in the OFA group than in the RA group ( $p = 0.002$ ; Figure 3). The pairwise comparison revealed that the level of epinephrine was significantly lower in the OFA group immediately after tracheal intubation ( $16.43 \pm 9.63$  pg/mL in the RA group vs  $8.60 \pm 3.09$  pg/mL in the OFA group;  $p = 0.001$ ), at the time of incision ( $15.61 \pm 8.29$  pg/mL in the RA group vs  $8.83 \pm 3.06$  pg/mL in the OFA group;  $p = 0.001$ ), and immediately after tracheal extubation ( $13.34 \pm 5.48$  pg/mL in the RA group vs  $7.49 \pm 3.03$  pg/mL in the OFA group;  $p < 0.001$ ). The levels of norepinephrine were similar between the two groups ( $p = 0.088$ ; Figure 3).

**Figure 2** Intraoperative hemodynamic data, anesthetic depth, and nociception severity.

**Abbreviations:** T0, baseline; T1, before intubation (at the time of unconsciousness); T2, immediately after intubation; T3, at the time of incision; T4, at end of surgery; T5, immediately after tracheal extubation.

**Table 4** Adverse Events

Variables	RA Group (n = 38)	OFA Group (n = 37)	p value
Intraoperative			
Hypotension	19 (50.0%)	9 (24.3%)	0.039
Bradycardia	6 (15.8%)	1 (2.7%)	0.108
30 min after surgery			
Visual analog scale	6.3 ± 2.3	4.1 ± 2.1	<0.001
PCA use, mL	2.0 ± 1.2	1.7 ± 1.2	0.219
Rescue analgesics	28 (73.7%)	8 (21.6%)	<0.001
Nausea	9 (23.7%)	1 (2.7%)	0.014
Vomiting	2 (5.3%)	0 (0.0%)	0.493
Rescue anti-emetics	9 (23.7%)	3 (8.1%)	0.127
Shivering	6 (15.8%)	0 (0.0%)	0.025
24 h after surgery			
Visual analog scale	3.4 ± 1.9	3.4 ± 1.8	0.872
PCA use, mL	14.6 ± 12.4	17.4 ± 11.5	0.312
Rescue analgesics	31 (81.6%)	27 (73.0%)	0.539
Nausea	18 (47.4%)	14 (37.8%)	0.548
Vomiting	5 (13.2%)	3 (8.1%)	0.711
Rescue antiemetics	5 (13.2%)	2 (5.4%)	0.430
Shivering	6 (15.8%)	6 (16.2%)	1.000
Pruritus	1 (2.6%)	0 (0.0%)	1.000
Time to first flatus, h	20.0 ± 5.2	22.7 ± 6.8	0.058
PCA stopped due to side effects	5 (13.2%)	2 (5.4%)	0.430

**Note:** Values are expressed as mean ± standard deviation, or number of patients (percentage).

**Abbreviations:** RA, remifentanyl-based anesthesia; OFA, opioid-free anesthesia; PCA, patient-controlled analgesia.

## Sensitivity Analysis

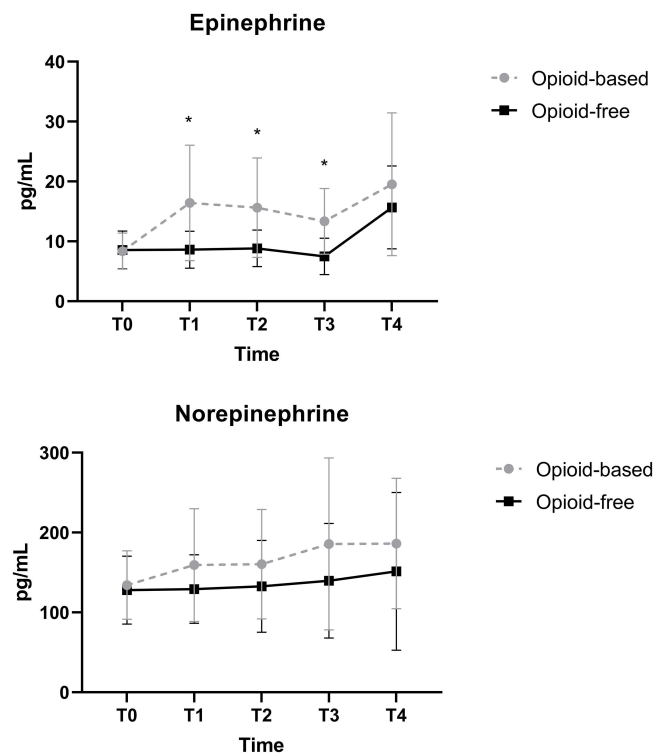
An ANCOVA was performed to determine the effect of OFA on POD 1 QoR-40 scores after controlling for the preoperative QoR-40 scores. After adjustment for preoperative QoR-40 scores, there was a statistically significant difference in QoR-40 scores on POD 1 between the two groups ( $p = 0.021$ ).

## Discussion

The present study aimed to evaluate the effect of OFA using dexmedetomidine and lidocaine on the quality of recovery in patients undergoing gynecological laparoscopy. Our findings suggest that patients who receive OFA have a better quality of recovery than those who receive opioid-based anesthesia with remifentanyl. Furthermore, fewer intraoperative hypotension, and well-maintained hemodynamics and anesthetic parameters confirm that OFA is a safe and feasible technique in gynecological laparoscopy. Patients receiving OFA experienced less pain, and fewer incidences of PONV and shivering than those receiving RA in the PACU. The duration of stay in the PACU was shorter in patients who received OFA. Furthermore, patients receiving OFA showed less stress response to surgery than those receiving RA.

Although OFA has been validated and considered feasible in various types of surgery, there is still controversy about the choice of agents.<sup>1</sup> In our study, IV dexmedetomidine and lidocaine were used as alternatives to remifentanyl. Dexmedetomidine is a potent  $\alpha$ -2 agonist with sedative, analgesic, anti-shivering, and anesthetic sparing effects. Lidocaine has been widely used intraoperatively due to its sympatholytic and analgesic effects. Generally, low-dose IV lidocaine does not cause adverse effects and is considered a safe component of intraoperative analgesia.<sup>23</sup> OFA with dexmedetomidine and lidocaine has been successfully used in gastric,<sup>24,25</sup> hepatobiliary,<sup>26–28</sup> breast,<sup>29</sup> cardiac,<sup>30</sup> thoracic,<sup>31,32</sup> orthopedic,<sup>33,34</sup> and spine surgery<sup>35,36</sup> with a reduction in postoperative pain intensity and opioid





**Figure 3** Stress hormones. \*Indicates  $p < 0.05$ .

**Abbreviations:** T0, baseline; T1, immediately after tracheal intubation; T2, at the time of incision; T3, immediately after tracheal extubation; T4, 24 h after surgery.

consumption, and a lower rate of postoperative complications. Considering these studies and our results, OFA with dexmedetomidine and lidocaine could benefit the general population.

However, in a recent multicenter RCT comparing opioid-based anesthesia and OFA with dexmedetomidine in patients undergoing major or intermediate surgery, OFA resulted in a greater incidence of postoperative serious adverse events than opioid-based anesthesia, and the study was terminated early due to five cases of severe bradycardia in the OFA group. Additionally, patients receiving OFA had more postoperative hypoxemia, delayed extubation, prolonged stay in the PACU, and intraoperative bradycardia. On the other hand, OFA was associated with less morphine consumption and a lower incidence of PONV, which was similar to the findings to our study.<sup>14</sup> The high incidence of serious adverse events may have been due to higher doses of dexmedetomidine (mean dose  $1.2 \pm 2 \mu\text{g}/\text{kg}/\text{h}$ ) than in our study (mean dose  $0.63 \pm 0.28 \mu\text{g}/\text{kg}/\text{h}$ ).

Previous reports on OFA in gynecological surgery have shown conflicting results due to heterogeneity in terms of the OFA protocol, patient selection, and outcome. In a prospective RCT in patients undergoing elective gynecological laparoscopy, OFA with dexmedetomidine and esketamine was compared with opioid-based anesthesia with sufentanil. Contrary to the findings of our study, the incidence and severity of PONV, pain scores, and morphine consumption were equivalent in both groups.<sup>12</sup> The reason may be due to different drug administration protocols using esketamine, and different patient populations, where the proportion of patients with risk factors for PONV was higher than in our study. In a retrospective study of patients undergoing laparoscopic hysterectomy, OFA with clonidine and ketamine was associated with less perioperative morphine equivalent use than opioid-based anesthesia with sufentanil, but with similar pain scores and incidence of PONV.<sup>37</sup> However, the definitions and anesthetic protocols used in this study were not standardized.

The primary outcome of our study was the quality of recovery assessed using the QoR-40 questionnaire. The QoR-40 questionnaire is a global measure of the quality of recovery that incorporates five dimensions of health: physical comfort, emotional state, physical independence, psychological support, and pain.<sup>38</sup> Generally, a 10-point difference equates to a 15% improvement in the quality of recovery.<sup>38</sup> The validity and reliability of QoR-40 have been confirmed in previous

studies, and it has been used to investigate recovery after various anesthetic and surgical techniques.<sup>39,40</sup> The QoR-40 questionnaire is recommended by the Standardized Endpoints in Perioperative Medicine initiative as a measure of patient comfort.<sup>41</sup> According to a study comparing OFA and opioid-based anesthesia in patients undergoing laparoscopic sleeve gastrectomy, patients receiving OFA scored higher QoR-40 scores than those receiving opioid-based anesthesia,<sup>24</sup> which was also demonstrated in our study. Given the evidence that OFA has been feasible in different types of surgery, it will be meaningful to test the effect of OFA on the quality of recovery in other types of surgery.

The two domains that showed significant differences in our study were pain and physical comfort. Short-acting opioids, such as remifentanyl, are associated with acute tolerance to opioids and/or OIH.<sup>16</sup> Remifentanyl has been reported to stimulate the overproduction of proinflammatory cytokines and reactive oxygen species, triggering the activation of neuronal NMDA receptors, which are important factors in the development of OIH.<sup>42–44</sup> Furthermore, remifentanyl induces excessive activity of matrix metalloproteinase-9, which in turn mediates extracellular matrix abnormalities, resulting in various neuropathological conditions, including OIH.<sup>45–47</sup> In a meta-analysis of 27 studies involving 1494 patients, patients treated with high intraoperative doses of opioids reported higher postoperative pain intensity and morphine use after 24 h than those treated with lower doses.<sup>48</sup> In our study, the presence of OIH after RA was demonstrated in the VAS score at 30 min after surgery and the incidence of patients who require rescue analgesics was higher in patients receiving RA than in those receiving OFA.

Differences in physical comfort are most likely due to PONV and shivering. Postoperative opioid use is one of the four risk factors for PONV in the Apfel simplified risk score,<sup>49</sup> and the use of intraoperative and/or postoperative opioids is associated with PONV in a dose-dependent manner.<sup>2</sup> Furthermore, since female patients undergoing gynecological laparoscopy constitute a large number of well-known risk factors for PONV, the incidence of PONV was expected to be high in the patients who participated in our study.<sup>2</sup> Postoperative shivering is proposed to be a sign of adrenergic activation associated with acute opioid withdrawal.<sup>50</sup> In our study, the OFA protocol may have contributed to a lower incidence of PONV and shivering due to the direct effect of eliminating intraoperative opioids, the reduction in postoperative opioid consumption, and the antiemetic effect of dexmedetomidine.<sup>50–52</sup>

Surgery elicits a systemic reaction encompassing a wide range of endocrinological, immunological, and hematological effects, namely, the stress response. Epinephrine and norepinephrine are classic markers of a stress response during anesthesia.<sup>53,54</sup> It is well-known that inhibition of the stress response to surgery can affect postoperative outcomes by beneficial effects on organ function.<sup>20,53</sup> Although the underlying mechanism is poorly understood, dexmedetomidine has been reported to reduce inflammatory and stress responses, possibly by attenuating cytokine production, inhibiting apoptosis, and central sympatholytic effects.<sup>54,55</sup> It not only reduces surgical stress similar to remifentanyl but also alleviates neuroinflammation. Similar to dexmedetomidine, lidocaine has been reported to decrease the levels of inflammatory cytokines.<sup>56</sup> In our study, the beneficial effect of OFA on stress response was demonstrated through reduced levels of epinephrine.

Our study has several limitations. First, this was a single-blind study in which the anesthesiologist participating in the intraoperative management of the patients was open to group allocation. The two groups had different infusion protocols, which made it impossible for the anesthesiologist to be blinded. However, all other personnel involved in the study, especially the outcome assessor, were blinded to the group allocation. Second, there has been a lack of validated depth of anesthesia and nociception monitors during OFA. In our study, the BIS values were measured to assess the depth of anesthesia, and the SPI values were measured to monitor the severity of nociception. The BIS value has been validated during sedation with dexmedetomidine.<sup>57</sup> The SPI value has been widely used for several years and has been reported to be more valid than other nociceptive monitors, such as the pupillary pain index and nociception level (NoL).<sup>58,59</sup> As expected, the BIS and SPI values of patients receiving OFA were within acceptable ranges. Third, the follow-up period was only until the first day after surgery. The QoR-40 scores on the day later than the first day after surgery may have been different, considering that pain-related outcomes and adverse effects were not different between the two groups at 24 h after surgery. Future research is needed to determine whether eliminating opioids in the postoperative period, that is, opioid-free analgesia can extend the beneficial effect of OFA beyond the immediate postoperative period.

## Conclusion

In conclusion, in patients undergoing gynecological laparoscopy, patients receiving OFA with dexmedetomidine and lidocaine had a better quality of recovery on POD 1 than those receiving opioid-based anesthesia with remifentanyl. Physical comfort and pain were the domains that scored higher in patients receiving OFA. In future clinical trials, the focus should be on finding the most effective OFA protocol in terms of efficacy and cost, and which patients and types of surgery OFA will benefit the most.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital, the Catholic University of Korea (approval number: KC20MNSI0130) on April 7, 2020. Written informed consent was obtained from all participants.

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## Disclosure

The authors report no conflicts of interest in this work.

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