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Effects of opioid-sparing general anesthesia on postoperative nausea and vomiting in laparoscopic gynecological surgery

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Background: In this study, we aimed to investigate whether opioid-sparing anesthesia (OSA) reduces postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic gynecological surgery.

Methods: Adult patients undergoing elective laparoscopic gynecological surgery were randomly assigned to either the opioid-using anesthesia (OUA) or the OSA groups. In the OUA group, remifentanyl was administered as an opioid during general anesthesia. In the OSA group, apart from a single dose of 5 µg/kg of alfentanil for tracheal intubation, no other opioids were used. In both groups, a multimodal intravenous non-opioid analgesic regimen was used preferentially in the post-anesthesia care unit (PACU). The primary outcome was the incidence of PONV, assessed by symptoms until the postoperative day 1.

Results: A total of 120 patients were included in this study. The incidence of nausea in the PACU was significantly lower in the OSA group compared to in the OUA group (31.7% in the OSA group vs. 51.7% in the OUA group, $P = 0.026$). Pain scores and the incidence of opioid analgesic administration were lower in the OSA group during PACU stay, resulting in a significantly lower number of patients requiring rescue opioid analgesics (3.3% vs. 18.3%, $P = 0.008$). There were no significant differences in intraoperative vital signs, hemodynamic interventions, or duration of PACU and hospital stay between the two groups.

Conclusions: OSA significantly reduced postoperative nausea, pain scores, and the need for rescue analgesics in the PACU without increasing hemodynamic instability in patients undergoing laparoscopic gynecological surgery.

Keywords: Analgesia; Anesthesia; Gynecologic surgical procedures; Opioid; Opioid analgesics; Postoperative nausea and vomiting; Postoperative pain.

Introduction

Postoperative nausea and vomiting (PONV) not only causes patient dissatisfaction but also increases medical costs due to delayed recovery and unexpected admissions [1-4]. Major risk factors for PONV include female sex, nonsmoking status, postoperative opioid use, and a history of PONV or motion sickness [5]. Additionally, younger age, use of inhaled anesthetics, prolonged surgery time, and certain types of surgery (laparoscopic, gynecological, and gallbladder surgery) are known to increase the incidence of PONV [6,7]. Thus, patients undergoing laparoscopic gynecological surgery have a high risk of PONV due to both surgical and patient characteristics.

Traditionally, opioids have been considered essential components of balanced anesthesia. However, concerns have arisen regarding their adverse effects, such as PONV, delayed recovery, respiratory depression, ileus, urinary retention, hyperalgesia, opioid dependence, and addiction. As a result, opioid-sparing strategies using multimodal analgesic measures such as non-steroidal anti-inflammatory drugs (NSAIDs), α_2 -agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, local anesthetics, corticosteroids, and regional anesthesia or analgesia have become key elements of enhanced recovery after surgery [8].

Recent developments in opioid-sparing strategies have suggested the possibility of opioid-free anesthesia, prompting active research regarding its benefits and feasibility [9,10]. Previous studies have reported the benefits of opioid-free anesthesia in reducing PONV, postoperative pain, opioid consumption, and recovery time; however, the evidence remains inconclusive, with substantial heterogeneity in protocols [11]. Specifically, the effects of opioid-free anesthesia on PONV and postoperative pain have shown mixed results in laparoscopic gynecological surgery [12,13].

Given the practical clinical environment, we permitted minimal opioid for tracheal intubation while restricting additional intraoperative opioids. We also aimed to reserve opioids as a last resort for postoperative pain management. Therefore, in this study, we investigated whether opioid-sparing anesthesia (OSA) reduces PONV while providing adequate pain control and hemodynamic stability in patients undergoing laparoscopic gynecological surgery.

Materials and Methods

Ethics

This prospective, randomized controlled study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-2006-619-004) and registered at Clinicaltrials.gov. (NCT04700761). This study complied with the ethical standards of the Helsinki Declaration-2013. All participants provided written informed consent.

Study population

Adult patients scheduled for elective laparoscopic gynecological surgery between February 2021 and May 2022 were included. Exclusion criteria were American Society of Anesthesiologists physical status ≥ 3 , uncontrolled hypertension, untreated intracranial aneurysm, pregnancy, severe hepatic or renal dysfunction, hypersensitivity to medications used in the study, refusal to use a pa-

tient-controlled analgesia (PCA) device after surgery, contraindications for the PCA regimen composed of NSAIDs, or inability/refusal to provide informed consent.

Patients were randomly assigned to the OSA or opioid-using anesthesia (OUA) groups using computer-generated randomization codes and the block randomization method (Random Allocation SoftwareTM, ver. 1.0; Informer Technologies), stored in sealed envelopes. Patients, gynecological surgeons, caregiving nurses, and investigators assessing postoperative outcomes were blinded to the group assignments.

Anesthesia protocol

Upon arrival in the operating room, noninvasive blood pressure, electrocardiogram, pulse oximetry, and bispectral index (BIS) were monitored.

In the OSA group, anesthesia was induced using thiopental sodium (5 mg/kg), sevoflurane (6 vol%), and rocuronium (6 mg/kg). A single dose of 5 μ g/kg alfentanil was administered to alleviate the stimulus of endotracheal intubation. After rocuronium injection, 50 mg/kg magnesium sulfate was loaded over 10 min and infused continuously at a rate of 15 mg/kg/h until the end of surgery. Anesthesia was maintained with sevoflurane under BIS monitoring, targeting a range between 40 and 60. To maintain the systolic blood pressure and pulse rate within 20% of baseline, the concentration of sevoflurane was controlled to a maximum of 8 vol% and a temporary decrease in BIS was allowed. However, the minimum concentration of sevoflurane was regulated to maintain a BIS < 60.

In the OUA group, anesthesia was induced with thiopental sodium (5 mg/kg), sevoflurane (6 vol%), and target-controlled infusion (TCI) using the Minto model, targeting remifentanyl at 3 ng/ml and rocuronium (6 mg/kg). After the rocuronium injection, magnesium sulfate was administered in the same manner as in the OSA group. Anesthesia was maintained by targeting a BIS between 40 and 60 with sevoflurane. The TCI of remifentanyl was controlled in the range of 0–6 ng/ml to maintain the systolic blood pressure and pulse rate within 20% of ward measurements.

For both groups, when adequate hemodynamic control was not achieved by dose adjustment of anesthetic agents, inotropics (e.g., ephedrine, dopamine, dobutamine, etc.), vasopressors (e.g., phenylephrine, norepinephrine, etc.), short-acting β -blocker (e.g., esmolol), or calcium channel blocker (e.g., nicardipine) were administered based on the attending anesthesiologist's judgment. At the end of surgery, a combination of neostigmine and glycopyrrolate was administered based on train-of-four monitoring results.

Intravenous PCA consisted of a mixture of ketorolac (180 mg)

and normal saline in a total volume of 50 ml. The infusion rate, bolus dose, and lockout interval were set to 1 ml/h, 1 ml, and 15 min, respectively. All patients were given dexamethasone (5 mg) and palonosetron (0.075 mg) for PONV prophylaxis when intravenous PCA infusion began at the end of the surgery.

Postoperative protocol

The same postoperative analgesic protocol was applied in both groups. Postoperative pain was measured using an 11-point (0–10) numerical rating scale (NRS).

In the post-anesthesia care unit (PACU), an intravenous non-opioid analgesic regimen consisting of nefopam (20 mg) and propacetamol (1 g) was applied to patients with NRS score ≥ 3 . Opioids were administered as the final rescue drug only when adequate pain control was not achieved with the non-opioid regimen. Fentanyl (25 μ g or 50 μ g) was administered for pain presenting with an NRS score of 3–5 or ≥ 6 , respectively.

Intravenous ibuprofen was administered as a rescue analgesic. When patients reported pain with an NRS score ≥ 4 , ibuprofen (400 mg) was given intravenously, and pain was re-evaluated 30 min later. If the NRS score remained ≥ 4 , 100 mg of tramadol was administered intravenously as a rescue. Ibuprofen was administered up to four times a day.

For PONV, intravenous metoclopramide (10 mg) was administered. If PONV symptoms persisted, ramosetron (0.3 mg) was administered as a secondary rescue antiemetic.

Outcome variables

The primary outcome measure was the incidence of PONV. Secondary outcomes included the administration of rescue antiemetic, postoperative NRS for pain, and the administration of rescue pain medication. The outcomes, along with PONV, postoperative pain, and the administration of rescue medications, were assessed in the PACU and at 6 h and 1 day postoperatively.

Perioperative arterial pressure and pulse rate were measured at baseline before anesthesia induction, before and after endotracheal intubation, during surgery (mean value from start to end), after extubation, and during the PACU stay (mean value during the stay). Anesthetic drug dosages and hemodynamic interventions during surgery were documented. The concentration of administered sevoflurane was recorded every 5 min. The area under the curve for sevoflurane concentration was calculated using integral calculus and divided by total anesthesia time to determine the mean sevoflurane dose administered to each patient.

Statistical analysis

Based on a pilot study at our institution, the incidence of PONV in patients undergoing laparoscopic gynecological surgery with inhaled anesthetics was estimated at 33%. To detect a one-third reduction (from 33% to 11%), a sample size of 65 patients per group was calculated, considering a type 1 error rate of 5%, power of 80%, and a dropout rate of 15%.

Data were analyzed by the per-protocol principle to confirm the effect of OSA on PONV under optimal conditions. To avoid postoperative opioids as confounding variables in PONV development, patients who did not receive any postoperative opioids were analyzed as subgroups. Data normality was assessed using the Shapiro–Wilk test. Continuous variables, expressed as mean $\pm$ standard deviation (SD), were analyzed using Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables, presented as frequencies (percentages), were analyzed using the Chi-square test or Fisher's exact test. Blood pressure and heart rate comparisons utilized repeated-measures ANOVA. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.) and R package 3.6.1 (R Foundation for Statistical Computing). Standardized mean difference (SMD), absolute risk difference (ARD) with 95% CIs, and number needed to treat (NNT) were reported where appropriate, and *P* < 0.05 considered statistically significant.

Results

A total of 130 patients were enrolled in this study and 10 were excluded for the following reasons: one patient whose surgery was converted to an open procedure, eight patients in whom the study protocol was violated, and one patient who withdrew informed consent. Therefore, 120 patients were included in the final analysis, with 60 in each group (Fig. 1).

Patients' characteristics, anesthesia, and surgery were not significantly different between the two groups (Table 1). The mean sevoflurane dose was higher in the OSA group than in the OUA group (2.9 ± 0.4 vs. 2.7 ± 0.4 vol%, respectively; SMD = 0.480).

Table 2 shows the incidence of PONV and the rescue antiemetic administration during each period. When analyzing the incidence by symptom and period, the difference was significant only for the incidence of nausea in the PACU (31.7% in the OSA group vs. 51.7% in the OUA group, *P* = 0.026; ARD = 20% [95% CI, 2.4%, 36%]; NNT = 5). The administration of ramosetron showed no statistically significant difference between the two groups.

The postoperative maximum (6.7 ± 1.7 vs. 7.5 ± 1.6 ; *P* =

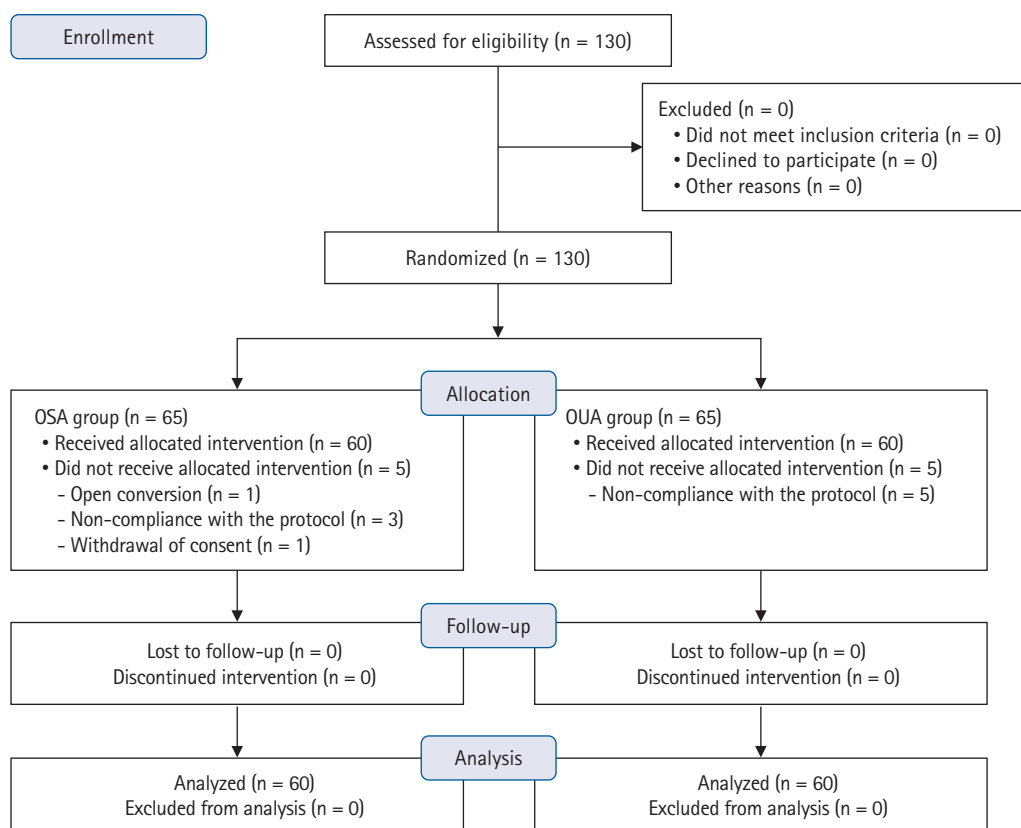


Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart. OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia.

0.007; ARD = 1.7% [95% CI, -4.5%, 8.9%]; NNT = 60) and mean NRS scores (4.6 ± 1.2 vs. 5.4 ± 1.4 ; $P = 0.001$; ARD = -3.3% [95% CI, -12.1%, 4.6%]; NNT = -30) for pain were different between the two groups only in the PACU (Table 3). At the same time, fewer patients in the OSA group required opioids than those in the OUA group (3.3% vs. 18.3%, respectively; $P = 0.008$; ARD = 15% [95% CI, 3.8%, 26.8%]; NNT = 7).

A subgroup analysis of patients who did not receive postoperative opioids showed that the incidence of nausea in the PACU was still significantly lower in the OSA group than in the OUA group (30.4% vs. 53.2%, $P = 0.019$; ARD = 22.8% [95% CI, 4.2%, 41.5%]; NNT = 4) (Table 4).

The vital signs during the intraoperative and immediate postoperative periods were not significantly different between the two groups at any time point (Fig. 2).

Discussion

In this study, we demonstrated that OSA reduces the nausea symptoms in the PACU following laparoscopic gynecological surgery. Additionally, we observed decreased postoperative pain and rescue analgesic requirements in the PACU immediately after ad-

ministering OSA.

While postoperative opioid use is a well-known major risk factor for PONV [5], the impact of intraoperative opioid use on PONV has not been well characterized. The 4th Consensus Guidelines for the Management of PONV recommend minimizing both intraoperative and postoperative opioids; however, the supporting literature primarily focuses on postoperative opioids [1]. Few studies have examined the restriction of intraoperative opioids alone, and these studies are often confounded by postoperative opioid use. Moreover, it remains controversial whether commonly used ultra-short-acting opioids, such as remifentanyl, significantly affect PONV [14,15].

For OSA, agents such as dexmedetomidine, ketamine, magnesium sulfate, lidocaine, and β -blockers are commonly used in combination to achieve intraoperative analgesia or hemodynamic stability [12,13,16,17]. Each drug has unique characteristics, and safety issues must be considered as the side effects of multimodal agents may outweigh their benefits [18,19]. In this study, the concentration of sevoflurane was adjusted for OSA using intraoperative magnesium sulfate that is an analgesic adjuvant less potent than opioids [20]. There was only a minimal increase (0.2 vol%) in the mean sevoflurane concentration with no serious side effects

Table 1. Characteristics of Patients, Anesthesia, and Surgery

Variable	OSA group (n = 60)	OUA group (n = 60)	SMD
Age (yr)	43.7 ± 11.5	43.1 ± 10.6	0.054
Height (cm)	159.7 ± 5.1	158.9 ± 5.8	0.146
Weight (kg)	62.1 ± 10.2	59.7 ± 9.4	0.246
ASA physical status			0.181
I	39 (65.0)	44 (73.3)	
II	21 (35.0)	16 (36.7)	
PONV risk factors			
Smoking	5 (8.3)	2 (3.3)	0.215
Motion sickness	31 (51.7)	36 (60.0)	0.168
History of PONV	7 (11.6)	4 (6.7)	0.174
Type of surgery			0.201
Surgery confined to adnexa	28 (46.7)	25 (41.7)	
Myomectomy	21 (35.0)	19 (31.7)	
Hysterectomy	11 (18.3)	16 (26.7)	
Mean sevoflurane dose (vol%)	2.9 ± 0.4	2.7 ± 0.4	0.480
Alfentanil dose (µg)	319.7 (60.7)	0.0 (0.0)	7.444
Remifentanil dose (µg)	0.0 (0.0)	306.2 ± 175.3	2.470
Rocuronium dose (mg)	43.1 ± 11.3	40.3 ± 8.8	0.276
Intraoperative input/output (ml)	178.0 ± 297.6	211.5 ± 322.6	0.108
Crystalloid (ml)	463.7 ± 228.6	529.8 ± 217.5	0.297
Colloid (ml)	47.5 ± 140.6	78.3 ± 203.2	0.176
Urine output (ml)	234.0 ± 242.8	219.9 ± 202.7	0.063
Hemodynamic interventions			
Inotropics	26 (43.3)	22 (36.7)	0.136
Vasopressors	24 (40.0)	18 (30.0)	0.211
Beta blockers	3 (5.0)	0 (0)	0.324
Calcium channel blockers	0 (0)	0 (0)	< 0.001
Duration of surgery (min)	87.4 ± 41.4	95.9 ± 43.4	0.200
Duration of anesthesia (min)	120.8 ± 44.0	126.5 ± 44.5	0.130
Duration of PACU stay (min)	50.6 ± 15.0	52.1 ± 14.6	0.106
Postoperative hospital stay (d)	2.1 ± 0.4	2.1 ± 0.4	0.038

Values are presented as mean ± SD or number of patients (%). OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia, SMD: standardized mean difference, ASA: American Society of Anesthesiologists, PONV: postoperative nausea and vomiting, PACU: post-anesthesia care unit.

in the OSA group. Our results suggested that sympathetic responses to intraoperative nociceptive stimuli were efficiently blunted by sevoflurane, magnesium sulfate, and occasional β -blockers during laparoscopic gynecological surgery. Intraoperative administration of remifentanil may cause nausea in the immediate postoperative period. Therefore, even with short-acting remifentanil, reducing intraoperative opioid use as much as possible seems beneficial in preventing nausea in the PACU.

The postoperative opioid-free analgesic strategy included NSAIDs, acetaminophen, nefopam, and dexamethasone. Combining acetaminophen with either NSAID or nefopam has been reported to have a superior opioid-sparing effect compared to most non-opioid analgesics used alone. Dexamethasone has been

shown to have both analgesic and PONV-reducing effects [21,22]. Interestingly, the NRS score for pain and the incidence of rescue opioid requirement were significantly reduced only in the PACU, according to the restriction of remifentanil. To completely exclude the effects of postoperative opioids, a subgroup analysis was performed on patients who did not receive any postoperative opioids. OSA followed by opioid-free analgesia also significantly reduced the incidence of nausea in the PACU.

Intraoperative remifentanil has been reported to be associated with increased pain intensity and opioid requirement after discontinuation [23–25], despite being within the regular clinical dose range. However, the infusion rate of remifentanil in our OUA group, 0.05–0.06 µg/kg/min, was below the level known to

Table 2. Postoperative Nausea, Retching, Vomiting, and Antiemetic Administration

Variable	OSA group (n = 60)	OUA group (n = 60)	P value	ARD (95% CI)	NNT
Nausea					
PACU	19 (31.7)	31 (51.7)	0.026	20 (2.4, 36)	5
Postop 6 h	5 (8.3)	11 (18.3)	0.107	10 (−2.5, 22.5)	10
POD 1	1 (1.7)	5 (8.3)	0.207	6.7 (−1.9, 16.5)	15
Retching					
PACU	8 (13.3)	14 (23.3)	0.157	10 (−4, 23.7)	10
Postop 6 h	1 (1.7)	2 (3.3)	1.000	1.7 (−5.9, 9.8)	60
POD 1	0 (0)	2 (3.4)	0.496	3.3 (−3.2, 11.4)	30
Vomiting					
PACU	3 (5.0)	5 (8.3)	0.717	3.3 (−6.6, 13.6)	30
Postop 6 h	0 (0)	1 (1.7)	1.000	1.7 (−4.5, 8.9)	60
POD 1	0 (0)	1 (1.7)	1.000	1.7 (−4.5, 8.9)	60
Ramosetron administration					
PACU	16 (26.7)	24 (40.0)	0.121	13.3 (−3.5, 29.2)	7
Postop 6 h	4 (6.6)	2 (3.4%)	0.679	−3.3 (−12.9, 5.7)	−30
POD 1	0 (0)	2 (3.4)	0.496	3.3 (−3.2, 11.4)	30

Values are presented as number of patients (%). OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia, ARD: absolute risk difference, NNT: number needed to treat, PACU: post-anesthesia care unit, POD: postoperative day.

Table 3. Postoperative Pain and Analgesic Administration

Variable	OSA group (n = 60)	OUA group (n = 60)	P value	ARD (95% CI)	NNT
Maximum NRS for pain					
PACU	6.7 ± 1.7	7.5 ± 1.6	0.007	1.7 (−4.5, 8.9)	60
Postop 6 h	4.7 ± 2.3	4.4 ± 2.0	0.557	−5 (−17.3, 7.3)	−20
POD 1	3.4 ± 1.2	3.3 ± 1.4	0.889	−1.7 (−15, 11.7)	−60
Mean NRS for pain					
PACU	4.6 ± 1.2	5.4 ± 1.4	0.001	−3.3 (−12.1, 4.6)	−30
Postop 6 h	2.6 ± 1.9	2.4 ± 1.7	0.479	1.7 (−4.5, 8.9)	60
POD 1	2.0 ± 1.1	2.0 ± 1.2	0.935	−3.3 (−18.5, 12.1)	−30
Analgesic administration					
PACU	51 (85.0)	54 (90.0)	0.408	5 (−7.3, 17.3)	20
Postop 6 h	11 (18.3)	14 (23.3)	0.500	5 (−9.6, 19.4)	20
POD 1	10 (16.7)	14 (23.3)	0.361	6.7 (−7.8, 20.8)	15
Opioid administration					
PACU	2 (3.3)	11 (18.3)	0.008	15 (3.8, 26.8)	7
Postop 6 h	1 (1.7)	2 (3.3)	1.000	1.7 (−5.9, 9.8)	60
POD 1	1 (1.7)	2 (3.3)	1.000	1.7 (−5.9, 9.8)	60

Continuous values are shown as the mean ± SD. Categorical variables are expressed as number of patients (%). OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia, ARD: absolute risk difference, NNT: number needed to treat, NRS: numerical rating scale, PACU: post-anesthesia care unit, POD: postoperative day.

cause acute opioid tolerance or opioid-induced hyperalgesia (0.2–0.3 µg/kg/min) [26,27]. The analgesic effect of the magnesium sulfate used during surgery may have persisted in the PACU, leading to improved pain control in the OSA group [28,29]. Additionally, although used only once, the administration of alfentanil or high-maintenance dose of sevoflurane could be factors contribut-

ing to the relatively lower pain scores observed in the OSA group in the PACU.

This study has some limitations. First, patients undergoing laparoscopic gynecological surgery represent a high-risk group for PONV; therefore, it is questionable whether the results can be generalized to all surgical patients. Second, the assessment of in-

Table 4. Postoperative Nausea, Retching, Vomiting, and Antiemetic Administration in Patients Who did not Receive Postoperative Opioid Analgesics

Variable	OSA group (n = 56)	OUA group (n = 47)	P value	ARD (95% CI)	NNT
Nausea					
PACU	17 (30.4)	25 (53.2)	0.019	22.8 (4.2, 41.5)	4
Postop 6 h	4 (7.1)	7 (14.9)	0.205	7.8 (−4.5, 20.0)	13
POD 1	1 (1.8)	4 (8.5)	0.178	6.7 (2.0, 15.4)	15
Retching					
PACU	8 (14.3)	11 (23.4)	0.235	9.1 (6.1, 24.3)	11
Postop 6 h	1 (1.8)	1 (2.1)	1.000	0.3 (−5.0, 5.7)	292
POD 1	0 (0)	2 (3.4)	0.239	4.3 (−1.5, 10.0)	24
Vomiting					
PACU	3 (5.4)	5 (10.6)	0.464	5.3 (−5.3, 15.9)	19
Postop 6 h	0 (0)	1 (2.1)	0.456	2.1 (−2.0, 6.3)	47
POD 1	0 (0)	1 (2.1)	0.456	2.1 (−2.0, 6.3)	47
Ramosetron administration					
PACU	15 (26.8)	19 (40.4)	0.143	13.6 (−4.6, 31.8)	7
Postop 6 h	3 (5.4)	1 (2.1)	0.623	−3.2 (−10.4, 4.0)	31
POD 1	0 (0)	1 (2.1)	0.456	2.1 (−2.0, 6.3)	47

Values are presented as number of patients (%). OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia, ARD: absolute risk difference, NNT: number needed to treat, PACU: post-anesthesia care unit, POD: postoperative day.

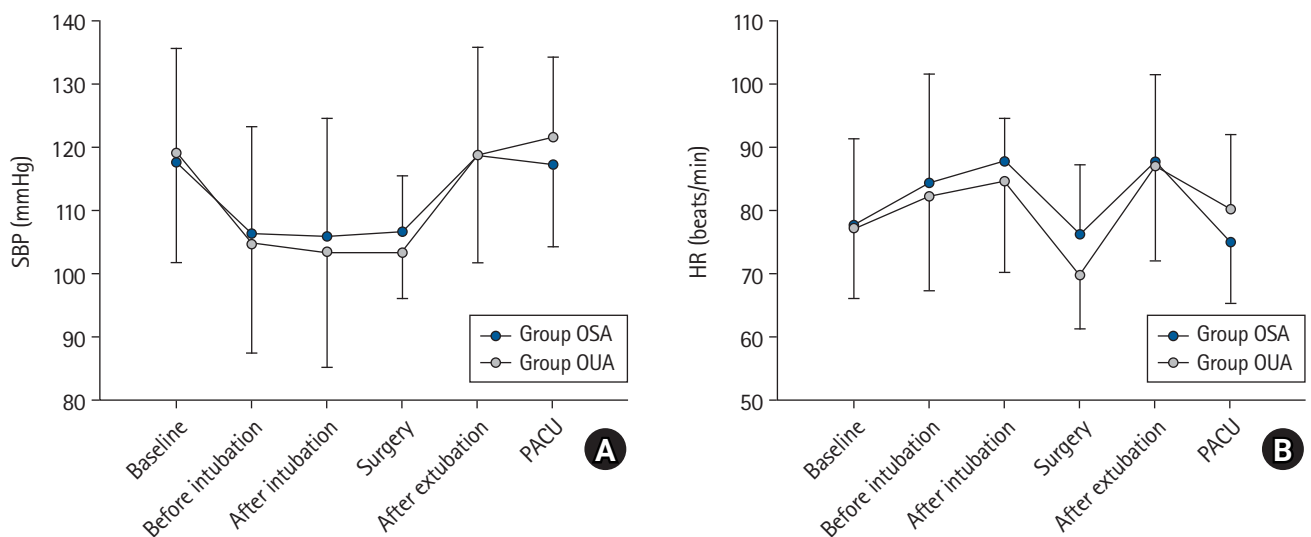


Fig. 2. Peri-operative systolic blood pressure (SBP) and heart rate (HR). (A) SBP, (B) HR. Average values of vital signs were calculated from measured values during surgery and PACU stay. OSA: opioid-sparing anesthesia, OUA: opioid-using anesthesia, PACU: post-anesthesia care unit.

traoperative nociception was based only on vital signs. Recent studies have introduced several objective indices to assess intraoperative nociception beyond vital signs. For example, the Analgesia Nociception Index (ANI) and Surgical Pleth Index (SPI) have been reported to be effective in guiding intraoperative analgesic administration, resulting in reduced opioid use [30,31]. Using supplementary indices such as ANI or SPI may enable a more accurate evaluation of whether OSA can sufficiently control noci-

ception.

In conclusion, OSA significantly reduced postoperative nausea, pain scores, and rescue analgesic requirements without increasing hemodynamic instability in patients undergoing laparoscopic gynecological surgery. This effect was limited to the immediate postoperative period in the PACU. Considering the high incidence of PONV after laparoscopic gynecological surgery, OSA may be a reasonable option in such cases.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the ethical restrictions of IRB but are available from the corresponding author on reasonable request.

Author Contributions

Sun Woo Nam (Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft)

Sang-Hwan Do (Methodology; Supervision; Writing – review & editing)

Jung-Won Hwang (Conceptualization; Data curation; Formal analysis; Writing – review & editing)

Insun Park (Data curation; Formal analysis; Investigation; Methodology)

Insung Hwang (Data curation; Methodology; Writing – review & editing)

Hyo-Seok Na (Conceptualization; Data curation; Funding acquisition; Project administration; Writing – review & editing)

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