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The incidences of nausea and vomiting after general anesthesia with remimazolam versus sevoflurane: a prospective randomized controlled trial

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Background: Postoperative nausea and vomiting (PONV) refers to nausea and vomiting that occurs within 24-h after surgery or in the post-anesthesia care unit (PACU). Previous studies have reported that the use of remimazolam, a newer benzodiazepine (BDZ) hypnotic, for anesthesia results in less PONV. In this study, we compared the rate of PONV between sevoflurane and remimazolam after general anesthesia.

Methods: In this prospective randomized controlled trial, participants aged 20–80 years who underwent elective laparoscopic cholecystectomy or hemicolectomy were randomized to either the remimazolam or sevoflurane group. The primary outcome was PONV incidence for 24-h after surgery. Secondary outcomes comprised of PONV at 30-min post-surgery, postoperative additional antiemetic use, and Quality of Recovery-15 (QOR-15) score at 24-h postoperatively.

Results: Forty patients were enrolled in the study. The remimazolam group exhibited significantly lower rates of PONV for 24-h after surgery than did the sevoflurane group (remimazolam group vs. sevoflurane group; 5% vs. 45%, P = 0.003, respectively). The use of dexamethasone, a rescue antiemetic administered within 24 h of surgery, was substantially lower in the remimazolam group than in the sevoflurane group (0% in remimazolam vs. 30% in sevoflurane, P = 0.020). The QOR-15 score at 24-h after surgery showed no significant difference between the two groups.

Conclusions: Compared to sevoflurane, opting for remimazolam as an intraoperative hypnotic may decrease the incidence of PONV and reduce antiemetic use for 24 h after laparoscopic surgery.

Keywords: Analgesics; Antiemetics; Benzodiazepines; Nausea; Sevoflurane; Vomiting.

Introduction

Remimazolam besylate is a new ultra-short-acting benzodiazepine (BDZ) agent. It is known as Byfavo in South Korea, Anerem® in Japan, Aptimyda™ in the EU, ByFavo™ in the United States of America, and Ruima® in China. Remimazolam is currently used in many countries as an anesthetic for surgery and as a sedative for medical procedures. Remimazolam offers advantages, such as minimal intravenous (IV) infusion pain and superior cardiovascular stability, when compared to other anesthetics, such as propofol that was previously used for monitored anesthesia care or total IV anesthesia. Notably, unlike

other anesthetics, the effects of remimazolam can be reversed with an antidote, allowing for patient awakening, if necessary [1]. Its pharmacokinetic and pharmacodynamic properties also make it suitable for anesthesia, similar to other commonly used sedatives, such as propofol and pentothal [2]. Existing meta-studies have demonstrated that a BDZ, midazolam, reduces postoperative nausea and vomiting (PONV) by acting on gamma-aminobutyric acid (GABA) receptors [3,4]. In particular, Heidari et al. [5] found that the midazolam premedication group had a lower incidence of PONV than did the non-premedication group after cholecystectomy.

PONV largely signifies nausea and vomiting that occurs within 24-h after surgery or in the post-anesthesia care unit (PACU) [6]. It still affects 20%–30% of patients even in the Enhanced Recovery after Surgery protocol. In high-risk patients, the incidence is reported to be as high as 70% [7]. Predisposing factors for PONV include female sex, a history of motion sickness or PONV, non-smoker status, and postoperative opioid use [8]. Additionally, cholecystectomy, gynecological surgery, and laparoscopic approaches increase the risk of PONV [9]. Earlier studies have examined the rates of PONV between propofol and remimazolam, as well as between desflurane and remimazolam [10–13]. Although desflurane and sevoflurane are similar inhalation anesthetics, the incidence of PONV differs between desflurane and sevoflurane [14]. No studies, to date, have compared PONV between sevoflurane and remimazolam.

We hypothesized that remimazolam, would reduce PONV compared to sevoflurane. Thus, this study aimed to compare the incidence of PONV between sevoflurane and remimazolam after general anesthesia. We surveyed PONV for 24-h postoperatively.

Materials and Methods

Study design and patient selection

We conducted a single-center, prospective, single-blinded, randomized controlled trial conducted between April 2023 and November 2023. The study protocol was evaluated by the Institutional Review Board (IRB # 05-2023-089) of Pusan National University Yangsan Hospital and enrolled in the clinical research information service registry (KCT0008812). Forty patients, including those with American Society of Anesthesiologists (ASA) physical status grade I, II, or III, were enrolled. The study included adults aged 20–80 years undergoing elective laparoscopic cholecystectomy or hemicolectomy. Inclusion was limited to patients who provided voluntary preoperative consent to participate. Patients with ASA grade ≥ IV or a history of an allergic reaction, such as skin rash, constricted airway, or anaphylaxis in response to remimazolam, sevoflurane, or any of the study-related drugs were excluded. In addition, patients with renal or hepatic impairment using relevant medications, those habituated to psychoactive drugs, pregnant females, those with dementia or mental illness, and those with communication difficulties (such as hearing loss or non-native Korean speakers) were excluded. This study was conducted under ethical principles of Declaration of Helsinki, 2013.

Participants were randomly assigned to one of the two treatment groups using a simple randomization procedure with 1:1 allocation (computer-generated random numbers). Randomization was performed by a single researcher who was not involved in the study. The researcher assessing the study outcomes and the patients were blinded to the group allocation throughout the study. Before surgery, the patients attended a pre-anesthesia consultation at the outpatient clinic in the Department of Anesthesiology and Pain Medicine, to assess their pre-anesthesia status. Patients were admitted a day before the surgery, and a 20-Gauge catheter was placed in the patient's vein either the night before or on the morning of surgery. Immediately before anesthesia induction, patients were asked about their history of PONV, smoking, and motion sickness. Noninvasive arterial blood pressure (BP), oxygen saturation, electrocardiogram, and neuromuscular transmission were monitored in the operating room. The randomization envelope was opened immediately before anesthetization for intention-to-treat analysis, to decrease follow-up loss.

Anesthetic management

For anesthesia induction, the sevoflurane group was administered sevoflurane 5% and remifentanil 0.1–0.2 μg/kg/min. Anesthesia was maintained with a mixture of sevoflurane (ETSEVO) 1.6–2% and remifentanil 0.1–0.2 μg/kg/min. In the remimazolam group, anesthesia induction involved an IV infusion of remimazolam 6 mg/kg/h and remifentanil 0.1–0.2 μg/kg/min. Anesthesia maintenance was carried out using remimazolam 1–2 mg/kg/h and remifentanil 0.1–0.2 μg/kg/min via an IV injection. Anesthetic was administered while monitoring bispectral index to maintain a range between 40 and 60. Hypotension was defined as mean BP below 55 mmHg; if needed, ephedrine was used to maintain BP. If heart rate (HR) fell below 45 bpm, atropine was administered to maintain normal HR. In both groups, an IV injection of rocuronium 0.8 mg/kg was administered when the patient lost consciousness. Patients were intubated when the train-of-four (TOF) was ≤ 2. For postoperative analgesia, transabdominal plane block was performed after anesthetization and before skin incision.

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Pain management included the administration of fentanyl 0.7 μg/kg and ketorolac 30 mg at 15 min before the end of surgery. No additional opioid was administered in the PACU. All patients received the same regimen of patient-controlled analgesic consisting of ramosetoron 0.6 mg, nefopam 80 mg, ketorolac 120 mg in normal saline, totaling 60 ml.

Additionally, all patients received ramosetron 0.3 mg IV 30 min before the end of surgery. Upon emergence, sugammadex at 4 mg/kg or 2 mg/kg was administered for TOF 0, 1, or TOF ≥ 2, respectively. In case of insufficient recovery from anesthesia, irregular respiratory pattern, no gag reflex, and no purposeful movement, or a TOF ratio < 90%, an additional 2 mg/kg of the rescue dose was planned to be administered under neuromuscular transmission monitoring. The remimazolam group received 0.2 mg flumazenil (FLUNIL INJ in Korea). Endotracheal tube extubation was performed once the patient was deemed fully emerged with a cough reflex, purposeful movement, and TOF ratio ≥ 90%, after which they were transferred to the PACU.

PACU protocol

Upon admission to the PACU, a patient's PONV was checked, and the Numerical Rating Scale (NRS) for pain was used to assess pain. If the patient reported a pain score of ≥ 5 or requested additional analgesics, 1 g of acetaminophen premix or 20 mg of nefopam was administered intravenously at a slow rate. The patient's PONV and NRS for pain were reassessed 30-min postoperatively. In addition, dexamethasone 5 mg was administered as a rescue antiemetic if the patient vomited or experienced severe nausea. The patient, but not the attending anesthesiologist, was unaware of the hypnotic administered. The outcome was measured by another anesthesiologist who was blinded to the drugs administered. All patients were monitored for a minimum of 30 min and were discharged with a modified Aldrete score of ≥ 9.

Primary and secondary outcomes

The primary outcome of the study was the incidence of PONV for 24-h after surgery. Secondary outcomes included PONV at 30 min, postoperative use of additional antiemetics, assessment of the Quality of Recovery-15 (QOR-15; Supplementary Material 1) score at 24-h postoperatively, NRS for pain at 30-min and 24-h postoperatively, and the use of additional analgesics.

Statistical analysis

In earlier studies, PONV in the 24-h after surgery was observed in 60% of patients anesthetized with sevoflurane and in 11.7% of patients anesthetized with remimazolam [14,15].

The sample size was determined using G* Power software© (2021; Heinrich-Heine-Universität) based on the binomial enumeration of Fisher's exact test with $\alpha = 0.05$ and β (1-power) = 0.2. Eighteen patients were assigned to each group. Considering a 10% dropout rate for each group, a total of 40 patients were recruited.

Variables are presented as frequencies and percentages for categorical data, while numerical data are expressed as mean ± standard deviation (SD). Intergroup differences were assessed using the chi-square test or Fisher's exact test for categorical data and the independent *t*-test or Mann–Whitney *U* test for numerical data, as appropriate. The Shapiro–Wilk test was used to determine whether the distribution was normally distributed. All statistical analyses were carried out using R® statistical software (version 4.2.1; R Foundation, http://www.r-project.org/). $P < 0.05$ was considered to be statistically significant.

Results

Fifty-three patients were evaluated for eligibility. Among them, five patients declined participation, six did not meet the inclusion criteria, and in two cases, the surgery was either canceled or rescheduled, so that 40 patients were eventually enrolled. One patient in the remimazolam group refused QOR-15 measurement due to postoperative pain. In addition, one patient in the sevoflurane group violated the study protocol by mixing opioids with PCA during anesthesia and did not answer the QOR-15 questionnaire. This study performed an intention-to-treat analysis, including 20 patients in each of the remimazolam and sevoflurane groups for the final analysis (Fig. 1). The missing values were corrected by substituting the average value of each question in each group. None of the variables differed between the remimazolam and sevoflurane groups (Table 1) except for the amount of intraoperative fluid (Table 2). No other clinically serious adverse events occurred in this study, including symptoms, such as tachycardia or anaphylaxis [16] that are known adverse events of remimazolam.

Primary outcome

The remimazolam group exhibited a significantly lower incidence of PONV for 24-h after surgery than did the sevoflurane group (remimazolam group vs. sevoflurane group; 5% vs. 45%, respectively; $P = 0.003$) (Table 3).

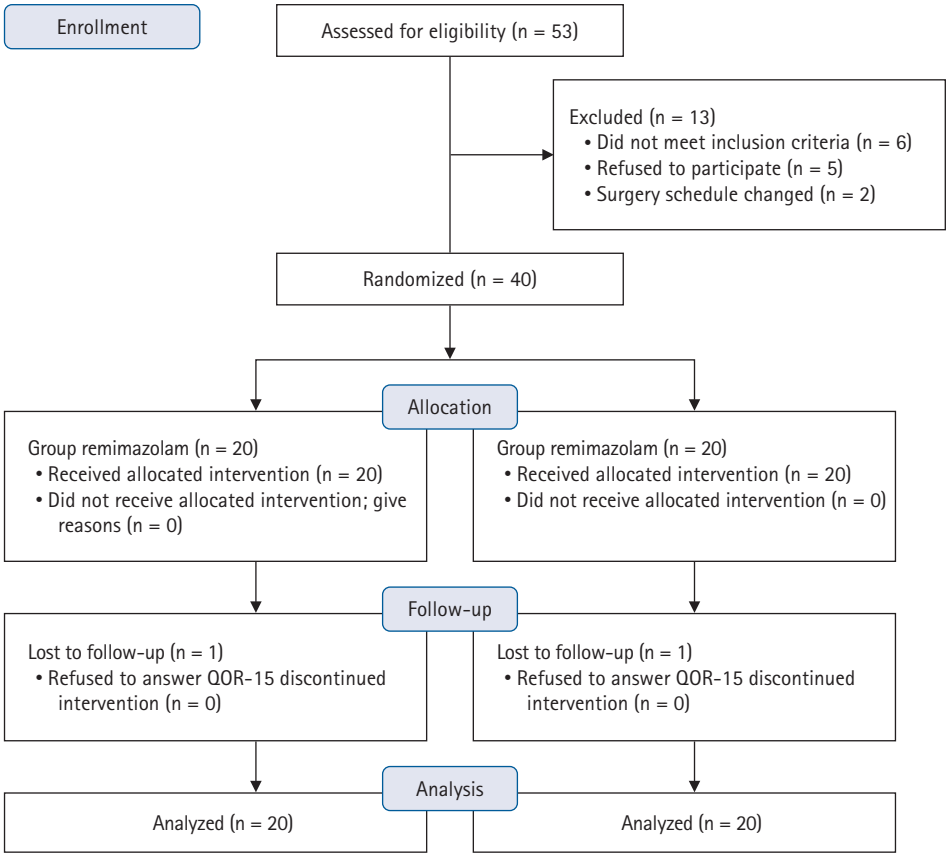

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Secondary outcomes

The incidence of PONV at 30 min after surgery was statistically significantly lower in the remimazolam group than in the sevoflurane group (remimazolam group vs. sevoflurane group; 0% vs. 45%, respectively; P = 0.001) (Table 3). Additionally, the use of dexamethasone, an antiemetic administered within 24-h postoperatively, was significantly less common in the remimazolam group than in the sevoflurane group (0% in remimazolam vs. 30% in sevoflurane, P = 0.020) (Table 3), and the number of patients administered dexamethasone for antiemetic purposes was statistically significantly lower in the remimazolam group (remimazolam group (n = 0) vs. sevoflurane group (n = 6), P = 0.02) (Table 4).

The QOR-15 consists of 15 items, and each response is on a scale of 0–10, i.e., an 11-point scale. Cronbach's α coefficient of the QOR-15 used in this study was 0.871, indicating high internal consistency among the QOR-15 items. In general, a Cronbach's α coefficient of 0.8 or higher is interpreted as being very reliable. The QOR-15 score at 24-h after surgery showed no significant difference between the two groups; however, scores for the 10th and 13th questions of the QOR-15 were statistically significantly different in the two groups. For the 10th question that measures the postoperative sense of overall well-being [17], the remimazolam group had a lower score than the sevoflurane group (remimazolam = 7.3 ± 2.3 vs. sevoflurane = 9.0 ± 1.4, MD [95% CI] = −1.6 [−2.9, −0.4], P = 0.018) that indicated that patients in the remimazolam group had a more reduced sense of general well-being than did those in the sevoflurane group (Table 5). Patients in the remimazolam group scored higher than did those in the sevoflurane group for the 13th question that measures PONV (remimazolam = 8.8 ± 2.4 vs. sevoflurane = 7.5 ± 2.8, MD [95% CI] = 1.3 [−0.3, 3.0], P = 0.036), indicating that patients in the remimazolam group had less PONV than those in the sevoflurane group (Table 5).

At 30-min after arriving at the PACU, the NRS for pain was statistically significantly higher in the remimazolam group (remimazolam = 6.7 ± 1.8 vs. sevoflurane = 5.4 ± 2.1, MD [95% CI] = 1.35 [0.0, 2.6], P = 0.045). A larger number of patients in the remimazolam group received rescue analgesics for 24-h postoperatively (75% in remimazolam vs. 35% in sevoflurane, P = 0.011) (Table 5). In addition, the number of patients administered post-

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Table 1. Patients' Baseline Characteristics

Variable	Overall (n = 40)	Remimazolam group (n = 20)	Sevoflurane group (n = 20)	P value
Age (yr)	53.0 ± 11.1	55.1 ± 11.9	50.9 ± 10.0	0.231
Sex (F)	21 (52.5)	11 (55.0)	10 (50.0)	0.752
ASA classification				
I or II	39 (97.5)	19 (95.0)	20 (100.0)	1.000
III	1 (2.5)	1 (5.0)	0 (0.0)	
Weight (kg)	71.2 ± 15.5	69.2 ± 16.3	73.3 ± 14.8	0.415
BMI (kg/m^2)	26.0 ± 3.9	24.9 ± 3.9	27.1 ± 3.8	0.075
OP				
Laparoscopic hemicolectomy	1 (2.5)	0 (0.0)	1 (5.0)	1.000
Laparoscopic cholecystectomy	39 (97.5)	20 (100.0)	19 (95.0)	
Apfel score (0-4)				
0	10 (25.0)	5 (25.0)	5 (25.0)	0.678
1	7 (17.5)	3 (15.0)	4 (20.0)	
2	12 (30.0)	8 (40.0)	4 (20.0)	
3	9 (22.5)	3 (15.0)	6 (30.0)	
4	2 (5.0)	1 (5.0)	1 (5.0)	
Smoking status				
Smoker	15 (37.5)	8 (40.0)	7 (35.0)	0.744
Non-smoker	25 (62.5)	12 (60.0)	13 (65.0)	
Motion sickness				
Yes	18 (45.0)	8 (40.0)	10 (50.0)	0.525
No	22 (55.0)	12 (60.0)	10 (50.0)	

Values are presented as mean ± SD, number (%). ASA: American Society of Anesthesiologists, BMI: body mass index, OP: operation. Shapiro–Wilk's test was employed to assess normality assumption.

Table 2. Clinical Characteristics and Perioperative Variables

Variable	Overall (n = 40)	Remimazolam group (n = 20)	Sevoflurane group (n = 20)	P value
Duration of anesthesia (min)	90.0 (90.0, 90.0)	90.0 (86.2, 90.0)	90.0 (90.0, 93.7)	0.441
Intraoperative fluid (ml)*	300.0 (200.0, 400.0)	200.0 (200.0, 312.5)	400.0 (250.0, 462.5)	0.001*
Remifentanil use (g)	0.4 (0.3, 0.5)	0.5 (0.3, 0.5)	0.4 (0.3, 0.5)	0.871
FTN for post OP pain (μg)	50.0 (49.0, 60.0)	50.0 (40.0, 60.0)	55.0 (50.0, 60.0)	0.233
Postoperative meperidine				
Yes	4 (10.0)	2 (10.0)	2 (10.0)	1.000
No	36 (90.0)	18 (90.0)	18 (90.0)	

Values are presented as median (Q1, Q3) or number (%). FTN: fentanyl, OP: operation. Shapiro–Wilk's test was employed to assess normality assumption.

operative diclofenac was statistically significantly higher in the remimazolam group (remimazolam group (n = 13) vs. sevoflurane group (n = 6), P = 0.026) (Table 4).

Discussion

Considering the primary outcome, the remimazolam group had a lower PONV incidence than the sevoflurane group (5.0% in remimazolam vs. 45.0% in sevoflurane, P = 0.003) within 24-h after surgery. Meta-analyses have shown that the use of midazolam in the perioperative period leads to a 38%–55% reduction in PONV [3,4]. Midazolam is thought to reduce the action of dopamine in the chemoreceptor trigger zone and decrease adenosine reuptake [18]. It also acts on the GABA–BDZ receptor complex that is believed to prevent PONV by diminishing dopaminergic neuronal activity and 5-hydroxytryptamine release [19]. Remimazolam, be-

Table 3. Comparison of PONV at 30 minutes and 24 hours

Variable	Remimazolam group (n = 20)	Sevoflurane group (n = 20)	Relative risk (95% CI)	P value
Number of patients	20 (50.0)	20 (50.0)		
PONV				
30 min	0 (0.0)	9 (45.0)	0.030 (0.000, 0.270)	0.001*
24 h	1 (5.0)	9 (45.0)	0.064 (0.003, 0.408)	0.003*
Rescue antiemetic	0 (0.0)	6 (30.0)	0.054 (0.000, 0.522)	0.020*

Values are presented as number (%). PONV: postoperative nausea and vomiting. *P value was statistically significant. Shapiro–Wilk's test was used to assess normality assumption.

Table 4. Type and Dosage of Rescue Analgesics and Antiemetics

Variable	Remimazolam group (n = 20)	Sevoflurane group (n = 20)	Mean difference (95% CI)	P value
Nefopam	2	2		1.000
Acetaminophen	1	1		1.000
Diclofenac	13	6	2.85 (1.56, 16.63)	0.026
Meperidine	2	2		1.000
Dexamethasone	0	6	3.33 (2, 10)	0.020

Values are presented as number of patients. NNT: number needed to treat. P values < 0.05: statistically significant.

Table 5. Comparison of NRS for Pain and QOR-15

Group	Remimazolam group (n = 20)	Sevoflurane group (n = 20)	Mean difference (95% CI)	P value
NRS for pain				
Post OP 30 min	6.7 ± 1.8	5.4 ± 2.1	1.3 (0.0, 2.6)	0.045
Post OP 24 h	3.2 ± 1.6	3.0 ± 1.3	0.2 (−0.7, 1.1)	0.509
Rescue analgesics	15 (75.0)	7 (35.0)	5.5 (1.4, 23.7)	0.011
QOR-15 items				
1. Able to breathe easily	9.3 ± 1.1	8.6 ± 2.5	0.6 (−0.5, 1.9)	0.629
2. Been able to enjoy food	8.0 ± 2.2	7.1 ± 2.6	0.8 (−0.7, 2.4)	0.287
3. Feeling rested	8.1 ± 2.2	7.2 ± 0.5	0.9 (−0.6, 2.4)	0.185
4. Have had a good sleep	6.5 ± 2.4	6.8 ± 2.4	−0.2 (−1.8, 1.3)	0.870
5. Able to look after personal toilet and hygiene unaided	8.5 ± 1.6	8.1 ± 2.6	0.4 (−0.9, 1.8)	0.966
6. Able to communicate with family or friends	9.2 ± 1.2	9.1 ± 1.7	0.1 (−0.8, 1.1)	0.845
7. Getting support from hospital doctors and nurses	8.5 ± 2.1	8.8 ± 2.3	−0.3 (−1.8, 1.0)	0.383
8. Able to return to work or usual home activities	6.7 ± 3.0	7.2 ± 2.7	−0.4 (−2.3, 1.3)	0.610
9. Feeling comfortable and in control	8.5 ± 2.0	9.1 ± 1.3	−0.5 (−1.7, 0.5)	0.409
10. Having a feeling of general well-being	7.3 ± 2.3	9.0 ± 1.4	−1.6 (−2.9, −0.4)	0.018*
11. Moderate pain	4.7 ± 2.9	5.4 ± 2.8	−0.7 (−2.6, 1.1)	0.426
12. Severe pain	6.5 ± 2.5	6.4 ± 3.0	0.1 (−1.6, 1.8)	0.905
13. Nausea and vomiting	8.8 ± 2.4	7.5 ± 2.8	1.3 (−0.3, 3.0)	0.036*
14. Feeling worried and anxious	7.6 ± 2.8	7.2 ± 3.0	0.4 (−1.4, 2.3)	0.684
15. Feeling sad and depressed	8.6 ± 2.8	8.1 ± 3.1	0.5 (−1.3, 2.4)	0.481
Total QOR-15 score	117.5 ± 22.0	116.2 ± 22.4	1.3 (−12.9, 15.5)	0.839

Values are presented as mean ± SD or number (%). NRS: Numeric Rating Scale, QOR-15: Quality of Recovery-15, OP: operation. *P value was statistically significant. Shapiro–Wilk's test was used to assess normality assumption.

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ing an ultra-fast-acting BDZ that works on GABA receptors, may thus lower the incidence of PONV. The mechanism by which volatile anesthetics, such as sevoflurane, cause PONV is thought to be due to the emetogenic effect of volatile anesthetic agents [20]. Volatile anesthetics, such as sevoflurane, increase the 5-hydroxytryptamine-3 (5-HT_3) receptor function. The 5-HT_3 receptors within the nucleus tractus solitarius (NTS) are associated with autonomic reflexes, including vomiting, BP, and HR. Enhancement of the 5-HT_3 receptors within the NTS by volatile anesthetics has been presented as a mechanism underlying PONV [21].

To the best of our knowledge, no previous study has compared the incidence of PONV when sevoflurane or remimazolam alone was used as a hypnotic throughout the anesthesia process, considering the various PONV risk factors. PONV was defined as at least one episode of nausea or vomiting in the 24-h postoperative period. The overall probability of PONV in the current study was 25%, which is like that in previous studies [7].

As a secondary outcome, the reported influence of postoperative pain on PONV [22] prompted us to measure NRS for pain in both remimazolam and sevoflurane groups postoperatively. A statistically significant difference in the NRS for pain was observed between the two groups at 30-min postoperatively, with the remimazolam group exhibiting a higher NRS for pain at 30-min postoperatively. Additional postoperative analgesics were administered to 15 patients in the remimazolam group and seven patients in the sevoflurane group (Table 5). This was due to the analgesic effect of sevoflurane [23]. The analgesic effect of sevoflurane might be responsible for the statistically significantly lower NRS score for pain in the early postoperative period and for the less-frequent use of postoperative analgesics in the sevoflurane group. Nevertheless, the lower incidence of PONV in the remimazolam group with higher pain scores than the sevoflurane group provide supporting evidence that remimazolam is extremely effective in suppressing PONV.

In the QOR-15 questionnaire, the remimazolam group scored higher in response to the question related to nausea and vomiting after anesthesia (13th question) than did the sevoflurane group. This can be interpreted as a lower incidence of PONV in the remimazolam group and was consistent with the primary outcome. In the QOR-15 questionnaire, the remimazolam group scored significantly lower for the response to the 10th question about the postoperative feeling of general well-being than did the sevoflurane group. This is because not only PONV, but also postoperative pain affects postoperative feelings of general well-being [24]. Based on our results, we believe that pain affects the postoperative feeling of general well-being more than PONV does that may explain why the remimazolam group reported a lower postoperative feeling of general well-being in response to the 10th question.

Previous studies have reported lower PONV in a group with higher use of intraoperative fluid [25]. In this study, we used a restrictive fluid strategy in both groups. Any practice that administered less than the standard range of perioperative fluid therapy minus 10% was considered restrictive [26]; however, the amount of fluid used in the two groups was significantly different. This was because of more patients in the sevoflurane group than in the remimazolam group experiencing intraoperative hypotension that led to more use of ephedrine and fluids in the sevoflurane group. Nevertheless, the rate of PONV was significantly lower in the remimazolam group than in the sevoflurane group. Therefore, the ability of remimazolam to prevent PONV is very potent.

Hari et al. [13] compared desflurane and remimazolam and found that patients receiving desflurane had a higher incidence of PONV at 2-h and at 24-h after surgery. However, their study included only female patients undergoing gynecological surgery, without consideration of PONV incidence in male patients. Although previous studies on laparoscopic surgery similar to ours exist, propofol was used for induction in these studies, making it challenging to isolate the effect of inhalational agents on PONV in both induction and maintenance of anesthesia [27]. In this study, unlike other studies, we administered flumazenil to all patients who were anesthetized with remimazolam. It is possible that flumazenil has an effect on the potential development of PONV. A previous study involving 100 female patients who underwent anesthesia induction with midazolam for induced abortion reported a higher incidence of PONV in the group administered with flumazenil (Ro 15-1788) at the end of anesthesia than did the group without flumazenil [28]. However, in the current study, despite flumazenil administration in the remimazolam group, the sevoflurane group exhibited a significantly higher frequency of PONV. Therefore, the effect of remimazolam on preventing PONV is significantly superior to that of sevoflurane.

This study has several limitations. First, we included a small sample size of only 40 patients that limits the generalizability of our findings to a larger patient population. Second, we did not measure baseline QOR-15 scores (Table 2), making it difficult to assess the true impact of the intervention on patients' quality of postoperative recovery. Third, we did not distinguish opioid-induced nausea and vomiting from PONV that could have confounded the results, particularly considering that fentanyl and meperidine were used equally in both groups. Finally, the study was single-blinded that could have introduced bias if patient perception influenced symptom reporting or if blinding was accidentally compromised.

In conclusion, compared to sevoflurane, the use of remimazolam as an intraoperative hypnotic helped decrease PONV and reduce antiemetic use, particularly during the postoperative intensive care unit stay. Although more postoperative rescue analgesics were used and restrictive fluids therapy was used in the remimazolam group, the incidence of PONV in remimazolam group was significantly lower than that in the sevoflurane group. Consequently, for patients undergoing laparoscopic surgery with a high risk of PONV, choosing remimazolam instead of sevoflurane may help to reduce PONV.

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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 available from the corresponding author on reasonable request.

Author Contributions

Yeong Min Yoo (Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)
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Supplementary Material

Supplementary Material 1. Quality of Recovery-15 (QOR-15) questionnaire.

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