

Differences in midazolam premedication effects on recovery after short-duration ambulatory anesthesia with propofol or sevoflurane for gynecologic surgery in young patients

A randomized controlled trial

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Abstract

Background: Anxiolytic premedication requires careful consideration owing to potential side effects including delayed recovery after ambulatory anesthesia. We aimed to compare the effect of midazolam on recovery profiles postoperatively, depending on whether propofol or sevoflurane was the primary anesthetic.

Methods: We enrolled 226 patients (age, 18–50 years) undergoing ambulatory gynecologic laparoscopic surgery. Patients were categorized into propofol without midazolam (P), propofol with midazolam (MP), sevoflurane without midazolam (S), and sevoflurane with midazolam (MS) groups. As premedication, placebo or 0.02 mg/kg intravenous midazolam was used. The primary outcome was the difference in the time from anesthetic discontinuation to eye opening in response to verbal command. Secondary outcomes included postoperative nausea and pain occurrence and time to reach the discharge score.

Results: The time from anesthetic discontinuation to eye opening was longer in the MP group (n=49) than in the P group (n=50; $P < .001$) but was not significantly different between the MS (n=50) and S groups (n=49; $P = .1$). Midazolam premedication did not significantly affect postoperative nausea in the MP group compared with that in the P group ($P = .3$) but had a nausea prevention effect in the MS group compared with that in the S group ($P < .001$). The time to reach the discharge score was similar in all patients regardless of midazolam administration.

Conclusion: In the recovery from short-duration ambulatory gynecologic surgery in young patients, intravenous midazolam premedication showed positive effects on postoperative nausea without affecting the time from anesthetic discontinuation to eye opening with sevoflurane-based anesthesia but prolonged the time from anesthetic discontinuation to eye opening with propofol-based anesthesia. Because this difference between the propofol groups is not clinically significant, the results support midazolam premedication in young women. Further studies assessing larger populations are needed.

Abbreviations: BIS = bispectral index, MAC = minimum alveolar concentration, MOASS = Modified Observer's Assessment of Alertness/Sedation Scale, NRS = numerical rating scale, Nu-DESC = Nursing Delirium Screening Scale, PACU = postanesthesia care unit, PONV = postoperative nausea and vomiting.

Keywords: ambulatory care, anesthesia recovery period, midazolam, postoperative nausea and vomiting, premedication

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The authors have no conflicts of interest to disclose.

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

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1. Introduction

In the ambulatory setting in particular, both preoperative anxiolysis and early recovery are important and are a major concern for clinicians. Thus, anxiolytic premedication should be carefully selected to avoid delayed recovery after short-duration outpatient surgeries. Short-duration anesthesia may have different effects on the emergence from general anesthesia depending on the premedication status.

Midazolam is a drug that is commonly prescribed before surgery as premedication. The effects of midazolam premedication include reduced anxiety, postoperative nausea, and amnesia.^[1] Midazolam has a sedative effect and may affect the emergence from anesthesia.^[2,3]

We hypothesize that the presence or absence of midazolam premedication would have different effects on the emergence time if different primary anesthetics were used to achieve short-duration anesthesia. Hence, this prospective, randomized, controlled trial was designed to compare the effects of midazolam premedication on recovery depending on whether propofol or

sevoflurane was used as the primary anesthetic. In addition, postoperative nausea and pain were assessed. Midazolam was administered by an intravenous route with a faster onset.^[4] To reduce confusion due to surgery type and evaluate the effects of midazolam premedication on postoperative nausea, the study was restricted to laparoscopic surgery.

2. Materials and methods

2.1. Study design

The Institutional Review Board of Keimyung University Dongsan Hospital (DSMC 2017–07-021; September 12, 2017) approved this study. This study was designed as a prospective, randomized, controlled trial and was conducted at the Keimyung University Dongsan Hospital. Patients scheduled for ambulatory gynecologic laparoscopic surgeries under general anesthesia were enrolled and provided written informed consent for participation.

2.2. Inclusion/exclusion criteria

Patients who were undergoing ambulatory gynecologic laparoscopic surgeries under general anesthesia; were 18 to 50 years of age; were nonsmokers; had a surgery and anesthesia duration of ≤ 1 hour; and had an American Society of Anesthesiologists physical status class of I–II were included in the study. Those who were severely obese (body mass index ≥ 35 kg/m²)^[5]; were smokers; had a history of postoperative nausea and vomiting (PONV) or motion sickness; experienced nausea or vomiting within 48 hours before surgery; were taking psychotropic medications (benzodiazepines, antidepressants, antiepileptics, and antipsychotics); experienced depression, cirrhosis, heart failure, and renal failure; and were pregnant or lactating were excluded from the study.

2.3. Study procedures

The patients were categorized into 4 groups: propofol without midazolam (P), propofol with midazolam (MP), sevoflurane without midazolam (S), and sevoflurane with midazolam (MS) groups. A randomization sequence for the 4 groups in a 1:1:1:1 ratio was produced in blocks of 8 using a computer-generated random number sequence. Group allocation was conducted the day before the surgery using sealed, number-coded envelopes. In the outpatient center, where patients received the premedication before surgery and were prepared for discharge after surgery, an intravenous catheter was inserted and secured. The premedication drug was prepared and administered by a nurse who had no further study involvement. The purpose of premedication was to reduce anxiety from the time a patient entered the operating room until the induction of anesthesia. Thirty minutes before entering the operating room, intravenous midazolam 0.02 mg/kg (not exceeding 2.5 mg)^[6] or normal saline 2.5 mL (placebo) was administered over ≥ 15 seconds to each patient following pulse oximetry and noninvasive blood pressure monitoring. Decrease in arterial oxygen saturation ($SpO_2 < 92\%$), hypotension (decrease in systolic blood pressure of $>30\%$ from baseline), and other side effects were assessed and recorded.

2.4. Study assessments and medication

To evaluate preoperative anxiety and sedation levels, the numerical rating scale (NRS; from 0 = no anxiety to 10 = extreme

anxiety) and the Modified Observer's Assessment of Alertness/Sedation Scale (MOASS; 0 = no response to painful stimulation, 1 = responds only to painful stimulation, 2 = responds only after mild prodding or shaking, 3 = responds after name called loudly or repeatedly or both, 4 = lethargic response to name spoken in a normal tone, and 5 = responds readily to name spoken in a normal tone) (modified from Sun et al^[6]) were used twice: 30 minutes before the administration of the allocated premedication drug at the outpatient center and shortly after entering the operating room (30 minutes after the allocated premedication drug administration). The anxiety and sedation levels were evaluated by a designated investigator (JHS) who was blinded to the allocated groups. When the NRS score for a patient's anxiety level was >6 at the outpatient center, the patient was excluded from the study and stabilized by the administration of anxiolytics.

The patients' electrocardiography, noninvasive blood pressure, pulse oximetry, temperature, bispectral index (BIS), and train-of-four in the operating room were monitored. Vital signs were recorded at 3- to 5-minute intervals in the operating room and postanesthesia care unit (PACU), as appropriate. To induce anesthesia, intravenous propofol 1.5 to 2 mg/kg and sufentanil 0.1 μ g/kg were administered to all patients, and rocuronium 0.6 mg/kg was administered through tracheal intubation. To maintain the BIS value between 40 and 60 during anesthesia, a continuous intravenous infusion of propofol 4 to 6 mg/kg/h was applied in the P and MP groups, and the end-tidal concentration of sevoflurane was maintained at 0.8 to 1.2 minimum alveolar concentration (MAC) using an age-related iso-MAC chart^[7] in the S and MS groups. Intravenous dexamethasone 5 mg and sufentanil 0.1 μ g/kg were administered before incision. Before surgery completion, intravenous ketorolac 30 mg was administered. Propofol and sevoflurane were discontinued at surgery completion, and the fresh gas flow was increased to 10 L/min. Intravenous pyridostigmine 0.2 mg/kg and glycopyrrolate 0.01 mg/kg were administered when 3 twitch responses to train-of-four stimuli were observed.

Verbal commands were repeated at 30-second intervals to assess the patient's consciousness. The BIS value at the time of anesthetic discontinuation and the time from anesthetic discontinuation to eye opening were recorded by an investigator (JHS) who was blinded to the allocation. The endotracheal tube was removed when the patient could open their eyes on verbal command and when spontaneous ventilation was adequate. Upon arrival at the PACU, the severities of postoperative nausea and pain were graded using a 4-point NRS (0 = none, 1 = minimal, 2 = moderate, and 3 = severe), and the incidence of dizziness was assessed by a nurse who was unaware of the conditions of the study. Both vomiting and dry retching were considered as 3 points on the NRS. Intravenous ramosetron and paracetamol were administered for nausea and pain, respectively, when the relevant NRS scores were ≥ 2 or when the patient requested the medications. When the score on the modified Aldrete scoring system reached 9,^[8] an investigator unaware of the conditions of the study evaluated postoperative delirium using the Nursing Delirium Screening Scale (Nu-DESC)^[9,10] (5 items including disorientation, inappropriate behavior, inappropriate communication, hallucination, and psychomotor retardation are rated from 0 to 2; 0 = no symptom, 1 = mild, and 2 = pronounced), and the patients were transferred from the PACU to the outpatient center. Nausea, pain, and dizziness were assessed on arrival at the outpatient center. The patients were discharged after reaching 9 points in the discharge criteria.^[11] Nausea, pain, dizziness, and cognitive impairment were assessed in 3 follow-up

telephone calls to all patients at 24, 48, and 120 hours after surgery.^[12]

2.5. Study endpoints

The primary outcome was the difference in the time from anesthetic discontinuation to eye opening in response to verbal command. The secondary outcomes were the differences in anxiety NRS and MOASS scores before and after administration of the allocated premedication, incidence of PONV during the recovery period in the PACU and outpatient center, NRS scores for nausea/pain and the use of rescue antiemetics and analgesics in the PACU and outpatient center, Nu-DESC symptom scores ≥ 2 , time to reach a 9-point score on the modified Aldrete scale, time to reach a 9-point score in the discharge criteria, NRS scores for nausea/pain/dizziness, and the presence of cognitive impairment after discharge. The systolic blood pressure and heart rate values, measured on arrival at the outpatient center and operating room (i.e., before and after administration of the allocated premedication drug), and the incidence of intraoperative hypotension were also compared among the groups.

2.6. Statistical analyses

Statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY). The sample size was calculated from a pilot study, in which the time from anesthetic discontinuation to eye opening were (mean \pm standard deviation) 6.0 ± 1.3 , 6.9 ± 1.2 , 7.3 ± 1.5 , and 7.4 ± 1.2 minutes in the P, MP, S, and MS groups, respectively ($n = 10$ per group). Assuming a two-tailed α of 0.05 and power of 90%, the required sample size was determined as 98 (49 per group) for the time from anesthetic discontinuation to eye opening to demonstrate a statistically significant difference between the P and MP groups. Thus, assuming a dropout rate of 10%, a target sample size of 55 patients per group was planned. None of the patients in the pilot study were included in this study. To compare continuous variables, the independent Student *t* test or Mann–Whitney *U* test was performed according to the data distribution. Levene test was used to assess the homogeneity of variances. Categorical data in the cross-tabulation tables were compared using Pearson chi-square or Fisher exact test. $P < .05$ was considered to indicate statistical significance. No direct comparison was made between the anesthetic agents.

3. Results

Overall, 226 patients were enrolled between March 2018 and June 2019 from a total of 318 patients assessed for eligibility. Sixty-eight patients were excluded based on the exclusion criteria, 24 declined to participate, and 9 were excluded as they had anxiety NRS scores of >6 at the outpatient center. Nineteen patients were not included in the analysis because the duration of their surgeries and anesthesia exceeded 1 hour. Thus, 198 patients were included in the analysis (P group, 50; MP group, 49; S group, 49; and MS group, 50; Fig. 1). The surgeries performed for the patients were ovarian cystectomy, salpingo-oophorectomy, excision of endometriosis, and myomectomy.

Demographic data and vital signs of the patients and procedure durations are presented in Table 1. The patients' age, height, weight, duration of anesthesia, systolic blood pressure, and heart rate on arrival at the outpatient center were not significantly

different in each comparison. Additionally, differences in blood pressure and heart rate before and after premedication drug administration were not statistically significant. No patient exhibited significant hypotension (decrease in systolic blood pressure of $>30\%$ from the baseline value). Two patients in the MS group showed decreases in SpO₂ (90%–91%), but no treatment was required and provided. The incidence of intraoperative hypotension was not significantly different in each comparison.

The preoperative anxiety and consciousness and postoperative variables in the P and MP groups are shown in Table 2. The data for the S and MS groups are shown in Table 3. When changes in anxiety NRS and MOASS scores before and after premedication drug administration were analyzed, the scores were significantly reduced in the midazolam-treated groups (i.e., MP vs P and MS vs S).

There was no statistically significant difference in the BIS values at surgery completion. The time from anesthetic discontinuation to eye opening was significantly longer in the MP group than in the P group but was not significantly different between the MS and S groups. The incidence of PONV (including at the PACU and outpatient center), nausea scores, and pain scores were not significantly different between the MP and P groups; however, the incidence of PONV and nausea scores were significantly lower in the MS group than in the S group, and both groups had similar pain scores during the postanesthesia recovery period. The time to reach 9-point ratings on the modified Aldrete scoring system at the PACU and the time to reach 9-point scores in the discharge criteria at the outpatient center were not significantly different in each comparison. No occurrence of delirium (evaluated using the Nu-DESC) was noted in the PACU, and the incidence of dizziness was not significantly different in each comparison. There was no difference in nausea, pain, and dizziness assessed through telephone calls after discharge in each comparison. No development of cognitive impairment was noted after discharge.

4. Discussion

This study differs from previous studies in that the effects of midazolam premedication on each patient under propofol-based and sevoflurane-based anesthesia were assessed and the differences were identified. Intravenous midazolam premedication reduced the patients' anxiety when the patients arrived at the operating room. The time from anesthetic discontinuation to eye opening was significantly longer in the group who received midazolam as premedication and propofol-based anesthesia, but there were no changes in the group who received midazolam as premedication and sevoflurane-based anesthesia. Midazolam premedication did not have an effect on the incidence of PONV in patients who received propofol-based anesthesia but had a nausea-preventing effect in patients who received sevoflurane-based anesthesia. The time to reach the satisfactory discharge score was similar in all groups regardless of whether midazolam premedication was administered.

Recently, a meta-analysis reported that the administration of benzodiazepine premedication does not seem to prolong the recovery time after ambulatory surgery under short-duration anesthesia.^[3] The studies included in this meta-analysis varied in the type and route of administration of the premedication drug, that is, oral midazolam, intramuscular midazolam, intravenous midazolam, oral temazepam, oral alprazolam, oral diazepam,

oral lorazepam, and intravenous lorazepam. Among the benzodiazepines, midazolam has a rapid onset of action and short half-life.^[4] It has a shorter duration of action when administered intravenously than when administered via other routes.^[4,13] In addition, intramuscular injections can cause pain, but intravenous administration does not make the patient uncomfortable if intravenous access is already available. These points confer validity on intravenous midazolam premedication for short-duration ambulatory anesthesia. As assessed and verified in this study, however, patients should be carefully monitored as midazolam can affect their level of consciousness. This study was conducted on patients aged <50 years, and there was no occurrence of delirium after surgery. However, midazolam premedication in elderly patients who will receive ambulatory anesthesia requires careful consideration.^[14]

In the present study, the time from anesthetic discontinuation to eye opening in response to verbal command differed between the midazolam premedication group and placebo group when using propofol-based anesthesia. In a study of responses to verbal commands during sedation under BIS monitoring, the probability of responding was significantly higher in patients receiving propofol than that in patients receiving sevoflurane.^[15] The coexistence of midazolam with propofol-based anesthesia may have interfered with such early eye opening; that is, with midazolam, eye opening may have been delayed until after propofol concentrations rapidly decreased to very low levels. Based on the aforementioned results,^[15] the patients in the

present study might have opened their eyes when the effect-site sevoflurane concentration became very low, and it can be surmised that midazolam did not affect eye-opening time at this low sevoflurane concentration. Short-duration ambulatory anesthesia may be a key factor in this difference. For surgeries with longer durations, the effect of intravenously administered midazolam premedication may not last until surgery completion and is therefore less likely to affect recovery postoperatively. In addition, the synergistic sedation by the combination of midazolam and propofol may have affected the time from anesthetic discontinuation to eye opening in this study.^[16] Although the mean difference in eye-opening time from 4.9 to 7.0 minutes when using propofol-based anesthesia was statistically significant in the present study, this is not considered to indicate a clinically meaningful delayed recovery. The results of this study can contribute to the selection and decision making in various clinical situations because midazolam premedication may have different effects on the patients' recovery depending on the primary anesthetics used.

Midazolam premedication effectively reduces the incidence of postoperative nausea.^[1] However, in this study, administering midazolam as a premedication did not significantly affect postoperative nausea when propofol-based anesthesia was used; conversely, the severity of nausea was decreased postoperatively when midazolam premedication was administered and sevoflurane-based anesthesia was used. The predictors of postoperative nausea in this study were young age, female sex, and being

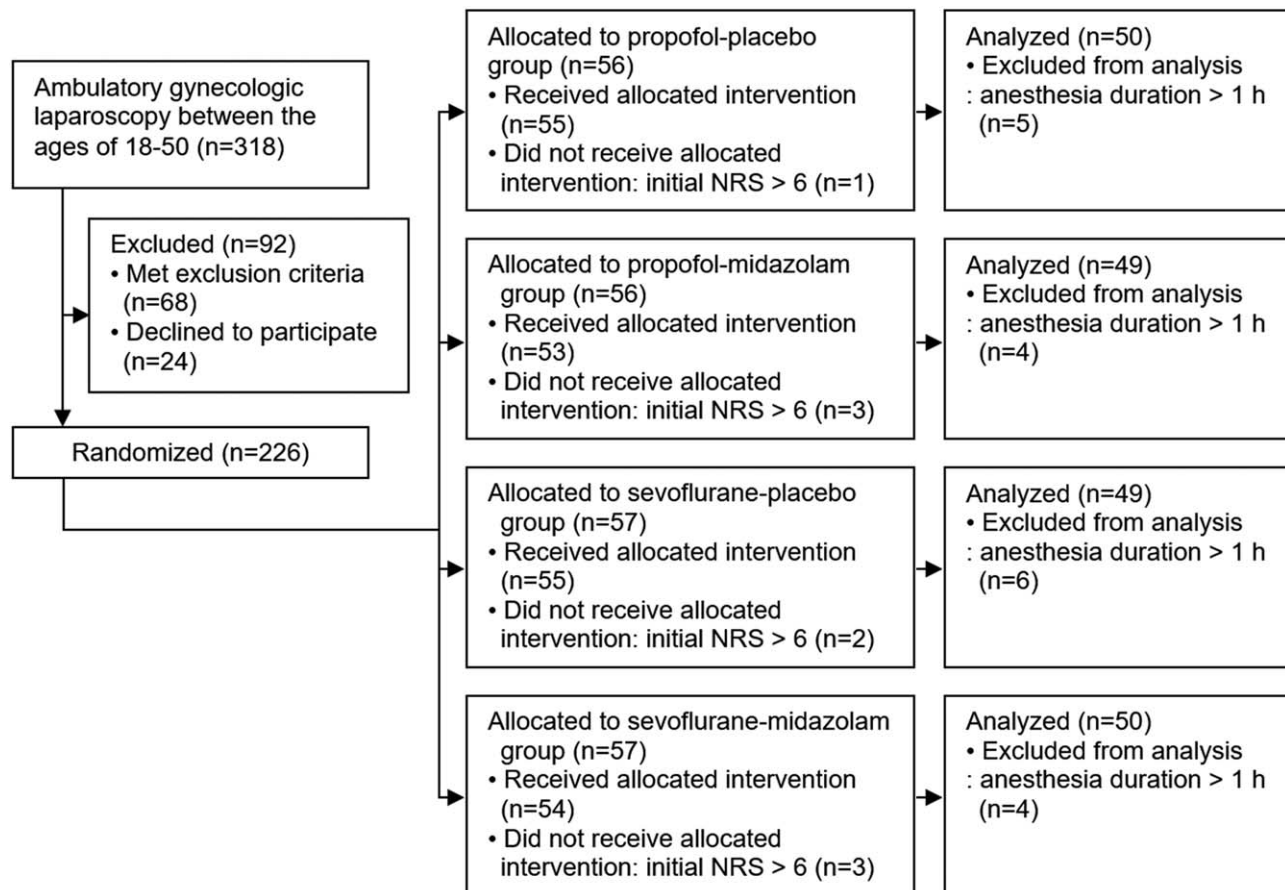


Figure 1. Patient flow diagram.

Table 1
Demographic data, blood pressure, and heart rate before and after premedication, and the duration of anesthesia.

	Group P (n=50)	Group MP (n=49)	P value (P vs PM)	Group S (n=49)	Group MS (n=50)	P value (S vs SM)	P value (all groups)
Age, y	42±5	41±7	.3	42±6	41±6	.6	.7
Height, cm	161±5	162±4	.2	162±4	162±4	.9	.6
Weight, kg	56±5	56±4	.8	57±4	56±5	.2	.1
BP at outpatient center, mmHg	118±14	117±13	.4	118±12	120±13	.3	.5
BP on arriving in operating room, mmHg	119±12	115±11	.3	118±12	120±13	.3	.5
HR at outpatient center, beats/min	80±9	82±9	.4	81±9	80±10	.6	.6
HR on arriving in operating room, beats/min	81±10	83±9	.6	84±10	82±9	.2	.6
Duration of anesthesia, min	45±6	44±8	.4	44±6	45±7	.6	.8

Data are presented as mean±SD.

nonsmokers.^[17] In contrast, the use of dexamethasone and short anesthesia durations were factors in reducing postoperative nausea. Because propofol-based anesthesia reduced the incidence of postoperative nausea, the combination of the abovementioned nausea-reducing factors and the use of propofol seemed to prevent statistically significant differences in nausea scores. Thus, sevoflurane-based anesthesia benefited from the nausea-reducing effect of midazolam in this study. In the group who received sevoflurane-based anesthesia in the present study, midazolam premedication reduced the postoperative nausea NRS scores by 0.7 on a 0 to 3 scale and the incidence of PONV by 21%. Short-duration surgeries, previous PONV, and dexamethasone administration were associated with the overall reduction in PONV incidence, which is thought to result in less significant clinical differences.

The limitations of this study include the fact that all the selected study subjects were young women, although the reason for this selection was that the anti-anxiety effects of midazolam premedication are particularly useful in young women.^[6] Thus, further research is needed to determine sex-related and age-related differences in the effects of midazolam premedication when using different primary anesthetics. Another limitation is the fact that the blood pressure and heart rate of the patients were only measured once before and after the administration of the

allocated premedication. A single measurement of the patients' blood pressure may have large intra-individual variability and may lead to inconclusive interpretation of the study outcomes. In the present study, midazolam reduced the patients' anxiety (as measured by the subjective expressions of the patients), but the study was unlikely to identify how midazolam premedication affected blood pressure or heart rate changes associated with preoperative anxiety.

In conclusion, anxiolytic premedication with midazolam in young women showed different effects on postoperative recovery depending on whether the primary anesthetic used was propofol or sevoflurane. When the postoperative period was compared after short-duration ambulatory anesthesia, midazolam premedication prolonged the time from anesthetic discontinuation to eye opening but did not affect postoperative nausea when propofol-based anesthesia was used; however, midazolam premedication had a positive effect on postoperative nausea without affecting the time from anesthetic discontinuation to eye opening when sevoflurane-based anesthesia was used. The difference in eye-opening time when propofol-based anesthesia is used is not considered to exhibit a clinically meaningful delay in recovery. Thus, the results presented in this study can be interpreted as providing additional evidence for the clinical application of midazolam as premedication without discrediting its use in young

Table 2
Preoperative anxiety and consciousness and postoperative variables in patients receiving propofol-based anesthesia.

	Group P (n=50)	Group MP (n=49)	P value	Difference or odds ratio (95% CI)
Anxiety severity at outpatient center (NRS, 0–10)	3.7±0.8	3.8±0.8		
Anxiety severity on arriving in operating room (NRS, 0–10)	4.1±0.9	1.8±1.2		
NRS difference	0.4±0.5	−2.0±1.1	<.001*	2.4 (2.1, 2.7)
MOASS difference between outpatient center and operating room	0	0.2±0.4	.001*	−0.2 (−0.3, −0.1)
Incidence of intraoperative hypotension	9 (18)	13 (27)	.3	1.6 (0.6, 4.3)
BIS at surgery completion	51.0±3.1	49.8±3.9	.2	1.1 (−0.3, 2.5)
Eye opening time, min	4.9±1.3	7.0±1.8	<.001*	−2.1 (−2.8, −1.5)
PACU+outpatient center				
Incidence of PONV	24 (48)	16 (33)	.15	0.5 (0.2, 1.2)
Nausea NRS (0–3)	0.5±0.4	0.4±0.5	.3	0.1 (−0.1, 0.4)
Pain NRS (0–3)	1.3±0.7	1.2±0.7	.57	0.8 (−0.2, 0.3)
Rescue antiemetics	4 (8)	3 (6)	1.0	0.8 (0.2, 3.5)
Rescue analgesics	13 (26)	13 (27)	1.0	1.0 (0.4, 2.5)
Time to Aldrete 9 points, min	15.7±3.0	15.8±3.6	.6	−0.3 (−1.6, 0.9)
Time to discharge score, min	71.3±12.2	74.9±13.7	.3	−2.8 (−8.0, 2.4)

Data are presented as mean±SD or number (%). BIS=bispectral index, MOASS=Modified Observer's Assessment of Alertness/Sedation Scale score, NRS=numerical rating scale, PACU=postanesthesia care unit, PONV=postoperative nausea and vomiting.

*P<.05.

Table 3
Preoperative anxiety and consciousness and postoperative variables in patients receiving sevoflurane-based anesthesia.

	Group S (n = 49)	Group MS (n = 50)	P value	Difference or odds ratio (95% CI)
Anxiety severity at outpatient center (NRS, 0–10)	3.9 ± 0.8	3.9 ± 0.9		
Anxiety severity on arriving in operating room (NRS, 0–10)	4.5 ± 0.8	1.7 ± 1.2		
NRS difference	0.6 ± 0.8	−2.2 ± 1.4	<.001*	2.8 (2.3, 3.2)
MOASS difference between outpatient center and operating room	0	0.2 ± 0.4	.002*	−0.2 (−0.3, −0.1)
Incidence of intraoperative hypotension	15 (31)	10 (20)	.3	0.6 (0.2, 1.4)
BIS at surgery completion	48.3 ± 3.3	50.1 ± 3.7	.09	−1.4 (−2.8, −0.1)
Eye opening time, min	7.4 ± 1.3	7.8 ± 1.5	.1	−0.45 (−1.0, 0.1)
PACU + outpatient center				
Incidence of PONV	32 (65)	22 (44)	.04*	0.4 (0.2, 0.9)
Nausea NRS (0–3)	1.2 ± 0.5	0.5 ± 0.5	<.001*	0.7 (0.4, 1.1)
Pain NRS (0–3)	1.4 ± 0.7	1.3 ± 0.7	.8	−0.03 (−0.3, 0.2)
Rescue antiemetics	10 (20)	5 (10)	.2	0.4 (0.1, 1.4)
Rescue analgesics	15 (31)	16 (32)	1.0	1.1 (0.5, 2.5)
Time to Aldrete 9 points, min	17.0 ± 3.6	16.4 ± 3.0	.5	0.5 (−0.9, 1.8)
Time to discharge score, min	77.1 ± 12.3	77.9 ± 14.3	.9	−0.2 (−5.5, 5.1)

Data are presented as mean ± SD or number (%). BIS = bispectral index, MOASS = Modified Observer's Assessment of Alertness/Sedation Scale score, NRS = numerical rating scale, PACU = postanesthesia care unit, PONV = postoperative nausea and vomiting.

* $P < .05$.

women. As benzodiazepines should be carefully selected in consideration of their side effects, further studies involving a broader patient population are needed.

Author contributions

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References

- [1] Bauer KP, Dom PM, Ramirez AM, et al. Preoperative intravenous midazolam: benefits beyond anxiolysis. *J Clin Anesth* 2004;16:177–83.
- [2] Steiner C, Steurer MP, Mueller D, et al. Midazolam plasma concentration after anesthesia premedication in clinical routine - an observational study: midazolam plasma concentration after anesthesia premedication. *BMC Anesthesiol* 2016;16:105.
- [3] Mijderwijk H, Vanb S, Duivenvoorden HJ, et al. Effectiveness of benzodiazepine premedication on recovery in day-case surgery: a systematic review with meta-analysis. *Minerva Anesthesiol* 2016;82:438–64.
- [4] Reves JG, Fragen RJ, Vinik HR, et al. Midazolam: pharmacology and uses. *Anesthesiology* 1985;62:310–24.
- [5] Consultation WHOE Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–63.
- [6] Sun GC, Hsu MC, Chia YY, et al. Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study. *Br J Anaesth* 2008;101:632–9.
- [7] Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth* 2003;91:170–4.
- [8] Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth* 1995;7:89–91.
- [9] Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med* 2010;38:409–18.
- [10] Bilotta F, Lauretta MP, Borozdina A, et al. Postoperative delirium: risk factors, diagnosis and perioperative care. *Minerva Anesthesiol* 2013;79:1066–76.
- [11] Marshall SI, Chung F. Discharge criteria and complications after ambulatory surgery. *Anesth Analg* 1999;88:508–17.
- [12] Knopman DS, Roberts RO, Geda YE, et al. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology* 2010;34:34–42.
- [13] Fragen RJ. Pharmacokinetics and pharmacodynamics of midazolam given via continuous intravenous infusion in intensive care units. *Clin Ther* 1997;19:405–19. discussion 367–408.
- [14] Lepouse C, Lautner CA, Liu L, et al. Emergence delirium in adults in the post-anaesthesia care unit. *Br J Anaesth* 2006;96:747–53.
- [15] Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. *Anesthesiology* 2001;95:1151–9.
- [16] Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991;67:539–45.
- [17] Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth* 2012;109:742–53.