Taylor & Francis
Taylor & Francis Group

Impact of timing of midazolam administration on incidence of postoperative nausea and vomiting in patients undergoing laparoscopic gynecological surgery: A randomized, double-blinded, controlled study

Samar Rafik Amin 🆔, Taghreed Elshahat Sakr and Shaimaa Ezzat Amin

Department of Anesthesia, Faculty of Medicine, Benha University, Benha, Egypt

ABSTRACT

Background: A frequently used anxiolytic, midazolam, has recently been recognized for its antiemetic activity during the perioperative period. This study sought to investigate the best time to provide midazolam in order to decrease the frequency of postoperative nausea and vomiting (PONV) without increasing the risk of sedation.

Methods: A total of 120 women aged 20–60 years who underwent laparoscopic gynecological surgeries were distributed randomly to three groups: group M1 (n = 40) received intravenous 2 mg midazolam 15 min prior anesthesia induction, group M2 (n = 40) received intravenous 2 mg midazolam approximately 30 min prior surgery conclusion, and group C (n = 40) received intravenous normal saline. The frequency of PONV and the rescue antiemetics needs were measured as the primary outcomes during the first 24 hr postoperatively. The secondary outcomes were the severity of nausea, timing of initial emetic attack, time of PACU discharge, patient sedation, and pain scores.

Results: The frequencies of vomiting and rescue antiemetic use were lower in midazolam groups than controls during early (0–2) and late (0–24) time periods after surgery (P < 0.05), with insignificant difference between M1 and M2 groups. The timing of the first emetic episode was significantly longer in M2 than in C groups (458.3 vs 128.8 minutes) (P < 0.01). Insignificant differences with regard to frequency and severity of nausea, time of PACU discharge, and sedation score were detected among the three groups.

Conclusion: Midazolam was effective in reducing PONV, whether it was given prior induction of anesthesia or prior end of surgery, without influencing recovery duration or sedation level of the patients.

1. Introduction

Postoperative nausea and vomiting (PONV) is a frequent incident following anesthesia and surgery. According to resources, up to 80% of the high-risk population and up to 30% of the general population suffered from PONV [1]. Patients who experience PONV find it upsetting, and it might extend their hospital stay and raise their medical expenses. In some circumstances, PONV can cause postoperative problems, particularly in patients who are unable to handle an increase in their blood pressure, intrathoracic pressure, or central venous pressure [2].

Different variables can affect the frequency of PONV including age, gender, non-smoking habit, postoperative opioid utilization, and history of previous PONV episodes or motion sickness. Furthermore, non-patient-associated variables include surgeries under laparoscopy, gases and drugs of anesthesia, and length of surgery [3].

The impact of PONV is clear, yet its optimal management seems to be a complex process. Antiemetics come in a variety of forms with different pharmacokinetics, efficiency, and side-effects. According to

recommended guidelines, individuals having two or more risk factors (≥2) for PONV should obtain antiemetic prophylaxis [4].

Midazolam is a widely used medication for anxiolysis during the perioperative phase, with antiemetic properties that has been introduced in several studies [5].

Midazolam is a short-acting sedative which attaches to benzodiazepine receptors placed on gamma-aminobutyric acid (GABA) type-A receptors within the central nervous system. Releasing GABA neurotransmitters restrains the central dopaminergic pathway, leading to sedation and anxiolysis. However, it is not entirely clear how midazolam acts as an antiemetic. Some hypothesized mechanisms involve reduced dopaminergic stimulation in the chemoreceptor trigger zone, along with reduced 5-hydroxytryptamine outflux by attaching to GABA-benzodiazepine complex [6]. Also, it is unclear whether midazolam antiemetic properties are correlated with its anxiolytic action. Previous research has revealed that preoperative anxiety increases stomach acidity and decreases gastric motility, which could raise the risk of PONV [7].

Since midazolam is a depressant agent; its sedation effect, breathing depression, and long recovery period could be the main safety concerns [5]. So, this comparative study was intended to find the optimal timing for midazolam application as an antiemetic agent in female patients undergoing laparoscopic gynecological surgeries under general anesthesia.

2. Methods

This trial was accepted by the Research Ethics Committee at the Faculty of Medicine, Benha University (study number: RC6-8-2021), and written informed consents were taken from participating patients. Online registration of the protocol was performed prospectively in the clinicaltrials.gov with a specific number (NCT05057767).

This is a prospective, randomized, controlled, double-blinded trial that enrolled 120 non-smoker female patients aged 20–60 years old, physical status (ASA) grade I/II, with previous history of motion sickness and/or PONV. They underwent laparoscopic gynecological surgeries (ovarian cystectomy, myomectomy, salpingo-oophorectomy, or hysterectomy) under general anesthesia. Exclusion criteria included patients with predicted difficult airway, diabetes mellitus, obesity (BMI > 30 kg/m^2), chronic vertigo, inner ear disease, or known hypersensitivity to midazolam. Also, patients who smoke, abuse alcohol, had gastrointestinal disease, or received any medication with antiemetic properties within 24 hr prior the study were excluded.

There are four indicators identified by the simplified Apfel risk score to expect PONV frequency: female gender, non-smoking, history of motion sickness and/or PONV, and opioids utilization postoperatively. Because all included patients were non-smoking, females, and with previous history of motion sickness and/or PONV, the simplified Apfel risk score was 3. The expected frequency of PONV was 61% in patients with at least three risk factors [1].

Eligible patients were randomly distributed into three groups: Group M1 (n = 40) received intravenous (IV) 2 mg midazolam in 3 ml volume 15 min prior anesthesia induction plus 3 ml normal saline approximately 30 min prior to end of surgery. Group M2 (n = 40) received 3 ml normal saline 15 min prior anesthesia induction plus IV 2 mg midazolam in 3 ml volume approximately 30 min prior to end of surgery. Group C (n = 40) received 3 ml normal saline 15 min prior anesthesia induction plus 3 ml normal saline approximately 30 min prior to end of surgery.

A well-trained nurse who was not participating in the study prepared the medications as directed by the manufacturers and put them in sealed envelopes with numbers randomly selected by a computer. Both anesthesiologists performing the procedure and gathering the postoperative data were blinded to the nature of the IV fluid. No pre-medication was used, and patients were told to stop eating solid food at least 6 hr before the procedure; however, clear fluids were permitted up to 2 hr before the procedure.

Standard monitoring equipment (pulse oximeter, non-invasive arterial blood pressure cuff, electrocardiography leads, and capnography cannula) was applied. Patients were anesthetized using fentanyl (1–2 μg/kg), propofol (2 mg/kg), and rocuronium (0.6 mg/kg), followed by endotracheal tube insertion. Concentration of isoflurane was set at 0.8% to 1.2% to maintain anesthesia. During the surgery, carbon dioxide was used for abdominal insufflation with intra-abdominal pressure below 15 mmHg. Ventilatory parameters were adjusted to maintain the partial pressure of end-tidal CO_2 at 35–40 mmHg. Intraoperative fentanyl (1 μg/kg bolus) was used for analgesia as determined by the attending anesthesiologist. At the end of the surgery, atropine (0.2 mg/kg) and neostigmine (0.04 mg/kg) were given to reverse the neuromuscular blocker, then the endotracheal tube was removed. The anesthesia emergence time (described as the period from termination of isoflurane till removal of endotracheal tube) was recorded.

For postoperative pain relief, all patients received IV paracetamol (1 gm), administered every 8 hr for 24 hr. When patient reported a pain score of more than 3, intravenous ketorolac (30 mg) was given. Two hours following surgery, patients were given liquid (water or juices) to drink. Six hours following surgery, solid oral meals could be allowed.

3. Measurements

Postoperatively, participants were instructed to inform about any incident of nausea, vomiting (emesis), or retching within three-time intervals: 0–2, 2–6, and 6–24 hr. Nausea was described as a subjectively non-pleasant feeling related to the desire to vomit, whereas vomiting was described as evacuation of gastric contents forcefully through the mouth. Retching and vomiting are the same but without evacuation of gastric contents. Absence of nausea, emesis, and the need for rescue antiemetic was considered as complete response.

The frequency of nausea, emetic episodes (retching or vomiting), complete responses, and antiemetic medications requirement was recorded during the determined time periods. The severity of nausea was noted on a scale of 0 = none, 1 = mild (patient can eat), 2 = moderate (oral intake was diminished greatly), and 3 = severe (absent oral intake, demanding IV fluids). Rescue antiemetic medications (metoclopramide 10 mg IV) were given when nausea lasted more than 15 min or an emetic episode occurred during the observed periods. If necessary, the medication was repeated. If metoclopramide proved ineffective, an IV

ondansetron 4 mg was administered as a second-line rescue antiemetic.

Pain level was quantified by using the visual analog scale (VAS) which ranged from 0 = absent pain till 10 = worst pain. Sedation was evaluated in the post-anesthetic care unit (PACU) by the observer's Assessment of Alertness/Sedation (OAA/S) scale, which has a range of five points, with alert/awake being equal to 1 and deep sleep being equal to 5 [8]. To be eligible for discharge from the PACU, the patient had to be awake and alert, have stable hemodynamics, with no severe pain or persistent nausea or vomiting.

The primary outcome measures included the frequency of PONV and rescue antiemetic requirements during the first 24 hr after anesthesia. The secondary outcome measures included the nausea severity, the time of first emetic attack and first oral intake, time for PACU discharge, and patient sedation and pain scores.

4. Statistical analysis

The SPSS (Statistical Package for the Social Sciences) software version-26 for Windows was employed to tabulate, code, and analyze variables. The mean and standard deviation were used to summarize the quantitative data. Frequencies and percentages were used to express qualitative data. Numerical (parametric) data were compared between more than two groups using analysis of variance (ANOVA). Continuous (non-parametric) data were compared using the test of Kruskal-Wallis. Post-hoc analysis was performed to detect whether differences were statistically significant between each pair of groups (X2-test). A p-value of 0.05 or lower was interpreted as significant.

A power analysis was used to estimate the sample size before the trial started [9]. The estimated frequency of PONV in this trial was in the range of 60%, based on the risk score of Apfel [1]. We assumed that clinical relevance would be achieved if PONV frequency in the therapy groups decreased by 35%. The α error was decided at 0.05 (two-sided) and the β error at 0.2 (power = 0.8). The estimation revealed that each group needed 40 patients.

5. Results

One hundred and twenty-eight female patients were tested for eligibility. Eight patients were excluded due to rejection to participate, surgery postponement, or falling within the exclusion criteria. All 120 patients (40 in each group) completed the study and were analyzed (Figure 1).

Comparable differences were detected among the groups regarding demographic criteria (age, BMI, and ASA physical status) and operative data (length of the procedure, length of anesthesia, intraoperative opioid utilization, and emergence time) (Table 1). Also, the

time of PACU discharge and the sedation level among the three groups were comparable (Table 2).

Both midazolam groups (M1-M2) achieved significant shortening of the time passed until oral feeding start postoperatively compared to controls, but the intergroup difference between M1 and M2 groups was insignificant. However, only M2 group had a significant prolonged time till the first attack of vomiting compared to the controls, otherwise no significant intergroup differences were detected between (M1-M2) or (M1-C) (Table 2).

Pain scores (VAS) during the three time periods and postoperative rescue analgesia demand were comparable among the studied groups (Table 2) (Figure 2).

As regard PONV, the incidence of vomiting and antiemetics requirement was significantly less in midazolam groups (M1-M2) than control group during the time periods (0–2) and (0–24 hr) postoperatively. Also, the patients' number with complete response was significantly higher in both midazolam groups than controls during the first postoperative 2 hr (Table 3). Few patients needed more than one rescue antiemetic in the study groups: only one patient in each midazolam group and three patients in control group (P > 0.05).

Despite the increased number of patients with nausea in the control group, the frequency of nausea and its severity did not achieve any significant differences among the three groups in all time periods. All values were comparable between M1 and M2 groups (Table 3).

6. Discussion

Postoperative nausea and vomiting (PONV) is the second most frequent complaint after surgical pain [10]. The use of prophylactic antiemetic medication is a crucial component of well-managed anesthetic care, but the choice of which antiemetic to use is a frequent issue. Among all available antiemetic drugs, midazolam has proven its effectiveness as an emesis prophylaxis in various studies. Midazolam reduced overall postoperative vomiting, nausea, and rescue antiemetics need as stated by Ahn et al.'s systemic review and meta-analysis which explored 16 randomized controlled trials (RCT) to determine the efficiency of midazolam for avoidance of PONV in patients obtaining general anesthesia [11]. Also, Grant et al.'s meta-analysis reported that PONV can likely be inhibited at sub-hypnotic dosages (<0.05 mg/kg) of midazolam to avoid undesirable side effects. [12]

Current study employed midazolam as a prophylactic agent for emesis and nausea. The dose was fixed as 2 mg intravenously, based on the dose employed in previous studies and was found to be effective in reducing PONV. [13,14]
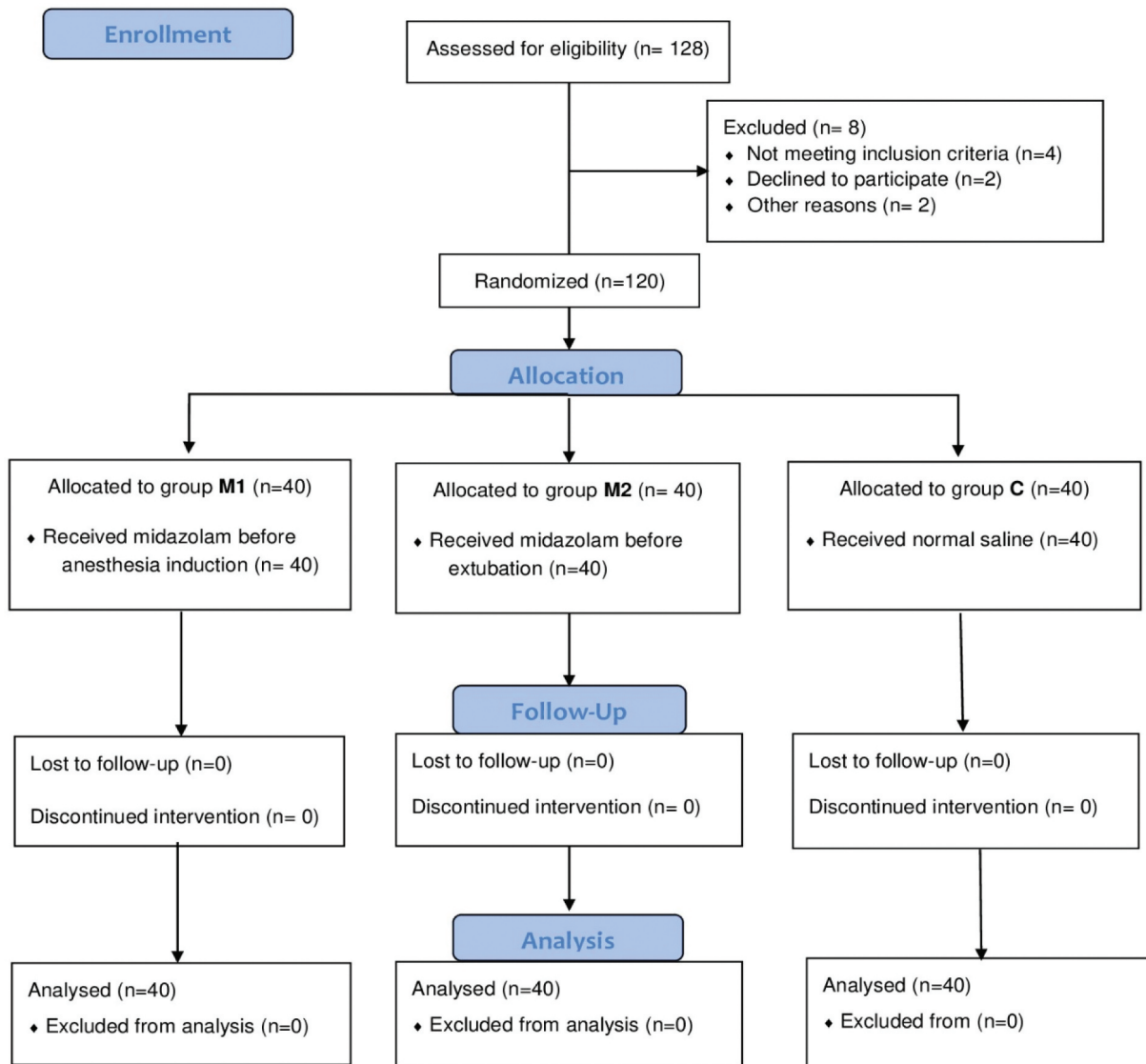
Figure 1. CONSORT flow diagram of the patients.

Table 1. Demographic and operative criteria of the studied groups.

	Group M1 (n = 40)	Group M2 (n = 40)	Group C (n = 40)	P-value
Age (yrs)	37.38 ± 12.19	38.15 ± 13.82	36.85 ± 11.77	0.9
BMI (kg/m^2)	28.50 ± 3.71	27.73 ± 3.99	27.18 ± 4.25	0.3
ASA (n%) I	31 (77.5%)	27 (76.5%)	29 (72.5%)	0.6
II	9 (22.5%)	13 (32.5%)	11 (27.5%)	
Duration of surgery (min)	77.58 ± 21.74	79.08 ± 24.13	76.75 ± 22.28	0.9
Duration of anesthesia (min)	95.28 ± 22.94	98.20 ± 23.00	96.18 ± 24.81	0.9
Intraoperative opioid need (n%)	23 (57.5%)	19 (47.5%)	21 (52.5%)	0.7
Emergence time (min)	11.2 ± 2.45	12.25 ± 2.69	12.05 ± 2.78	0.2

Data are presented as mean ± SD and n (%).

Following drugs and dosage, many anesthesiologists deal with another controversial issue of when to provide the antiemetic, whether pre-induction or intraoperative, to achieve the longest effect and stay away from its sedating action.

The current study showed a significant reduction in the frequency of PONV, as well as the rescue antiemetics requirements when midazolam was used compared to controls, during the early (0–2 hr) and total (0–24 hr) postoperative periods. However, results could not achieve significant difference between pre-induction and intraoperative midazolam groups.

Previous literature has also failed to determine the precise time of midazolam administration that could confirm efficacy in lowering PONV frequency. Two large meta-analysis and one RCT investigated the timing effect of midazolam administration, and no significant differences were found. The RCT conducted by Park et al. on 126 females underwent gynecological laparoscopic surgeries. The authors compared the pre-

Table 2. Postoperative clinical criteria of the studied groups.

	Group M1 (n = 40)	Group M2 (n = 40)	Group C (n = 40)	P-value
PACU discharge time (min)	18.98 ± 3.50	19.85 ± 4.34	17.75 ± 3.93	0.06
Sedation score	2 (1–3)	2 (1.25–3)	2 (1–2)	0.13
Time to oral intake (hr)	3.45 ± 1.91	3.08 ± 1.97	5.38 ± 2.96	<0.001*
First attack of vomiting (min)[1]	263.33 ± 220.79	458.33 ± 347.93	128.80 ± 106.76	0.009*
Rescue analgesic use n (%)	13 (32.5)	12 (30)	14 (35)	0.9

Data are presented as mean ± SD, n (%), and median (IQR). *Statistically significant (P < 0.05).
[1]M1 = 9, M2 = 6, C = 20
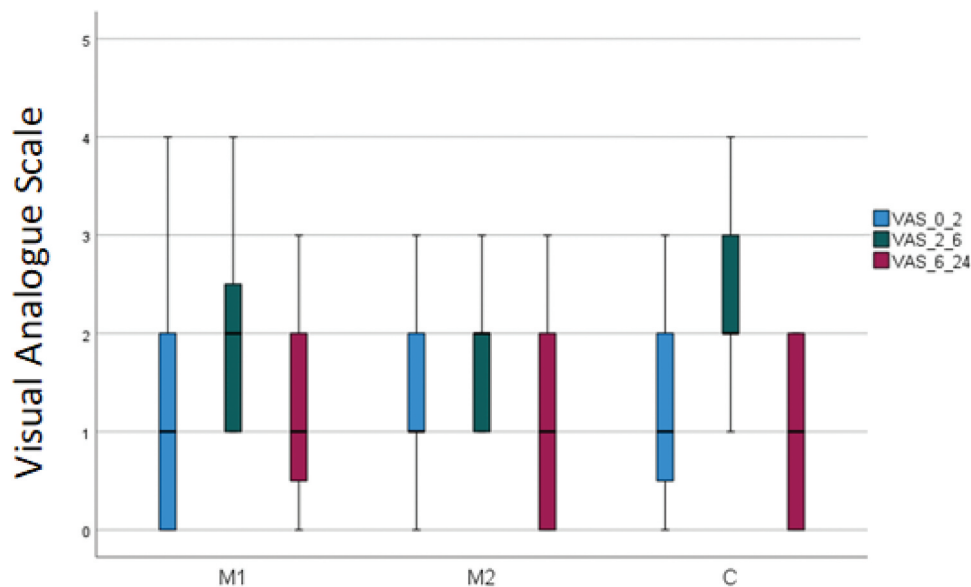
Figure 2. Visual Analog Scale in different time periods postoperative.

induction versus intraoperative administration of midazolam–ramosetron combination and did not observe significant differences in reducing PONV frequency between the two groups [15].

According to Grant et al.'s systematic review and meta-analysis, patients who received midazolam preoperative, at anesthesia induction, or prior to the end of surgery, all experienced significantly lower frequencies of PONV without significant differences in timing [12]. Also, Ahn et al.'s meta-analysis reviewed 11 studies that applied midazolam pre-induction, three at the end of surgery, and two studies compared both timings of application. They reported a statistically significant decline in total PONV whenever midazolam was applied at the induction or the surgery conclusion [11].

In contrast, Safavi and Honarmand study, which used midazolam solely in lower abdominal surgeries before induction (MP) and before extubation (MI), reported that the frequency of PONV decreased in MI group more than in MP and control groups at 6, 12, 18, and 24 hr after surgery [16].

Current study results also observed that time to first oral intake was shortened significantly when midazolam was used whenever the timing of administration. However, only the intraoperative administration of midazolam (group M2) succeeded to delay the time of the first attack of vomiting compared to controls. These outcomes agree with Safavi and Honarmand study that reported a longer time of first emetic episode when midazolam was administered intraoperative (3.1 hr) versus pre-induction (1.36 hr) versus controls (0.90 hr) [16].

On the other hand, the reduced PONV frequency with midazolam was not achieved in all trials. Ozcan et al. performed an RCT on 66 children undergoing tonsils removal in which one group obtained IM midazolam (0.1 mg/kg) and the other did not. Although the midazolam group had fewer cases of PONV than the controls, these differences were not statistically significant. A potential weakness and power of this RCT is the intramuscular application of midazolam against the intravenous route used in other studies [17].

The second issue that needs attention when applying midazolam as an emetic prophylaxis, is its hypnotic effect. The current study recorded the emergence time from anesthesia, PACU discharge time, and sedation score. Values were comparable among the three groups without significant delay in discharge from PACU or sedation time with midazolam. The study outcomes agree with both meta-analyses mentioned previously which investigated sedation and reported

Table 3. Incidence and severity of PONV and rescue antiemetics need in the studied groups.

Variables	M1 (n = 40)	M2 (n = 40)	C (n = 40)	p-value
0–2 hr				
Nausea	6 (15)	5 (12.5)	13 (32.5)	0.06
Severity	34/2/1/3	35/2/1/2	27/4/4/5	0.4
Vomiting	3 (7.5)	2 (5)	9 (22.5)	0.03*
Rescue antiemetics	4 (10)	2 (5)	10 (25)	0.02*
Complete response	34 (85)	35 (87.5)	27 (67.5)	0.006*
2–6 hr				
Nausea	9 (22.5)	7 (17.5)	15 (37)	0.1
Severity	31/2/4/3	33/3/2/2	25/4/7/4	0.5
Vomiting	4 (10)	2 (5)	9 (22.5)	0.06
Rescue antiemetics	4 (10)	3 (7.5)	10 (25)	0.06
Complete response	31 (77.5)	33 (82.5)	25 (62)	0.1
6–24 hr				
Nausea	5 (12.5)	4 (10)	5 (12.5)	0.9
Severity	35/3/1/1	36/2/1/1	34/2/1/2	0.9
Vomiting	1 (2.5)	2 (5)	2 (5)	0.8
Rescue antiemetics	2 (5)	2 (5)	3 (7.5)	0.9
Complete response	35 (87.5)	36 (90)	34 (85)	0.8
0–24 hr				
Severe nausea	7 (17.5)	5 (12.5)	13 (32.5)	0.07
Vomiting	9 (22.5)	6 (15)	20 (50)	0.004*
Rescue antiemetics	10 (25)	7 (17.5)	22 (55)	0.002*
Complete response	20 (50)	23 (57.5)	13 (32.5)	0.07

Data are presented n (%). *Statistically significant (P < 0.05).

neither prolongation of PACU stay time nor increased risk of sedation scores with midazolam. [11,12]

In contrast, Abdelhamid and Kamel evaluated the antiemetic action of midazolam following intra-gastric balloon placement and reported that postoperative sedation scores in the first 3 hr were significantly higher with midazolam compared to ondansetron only [18].

There are few limitations in the current study. First, the concentrations of inhalational anesthetic and the supplemented doses of fentanyl intraoperatively were modified according to bispectral index and hemodynamics, without measuring the exact amounts. However, the duration of anesthesia did not vary substantially across the three groups, indicating that the amount of provided anesthetics was most likely a minor contributing factor to the development of PONV. Second, in high-risk population for PONV, studies recommended employing a multimodal strategy of two or three antiemetics that act at various receptors [19]. Our findings must therefore be taken cautiously when only midazolam is used as an emesis prophylaxis. Before we can reliably use it alone, more research is required to compare its efficacy to other antiemetics.

7. Conclusion

In high-risk patients for PONV following gynecological laparoscopic surgeries, midazolam revealed a significant antiemetic effect whether it was administered prior induction or prior the end of surgery without inversely affecting the recovery time or level of sedation. Midazolam is a medication that is both low-cost and widely accessible for use. It is a useful tool when applied as an anxiolytic or antiemetic drug.

References

[1] Apfel CC, Läärä E, Oivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999; 91:693–700.

[2] Smith HS, Smith EJ, Smith BR. Postoperative nausea and vomiting. Ann Palliat Med. 2012 Jul 1;1(2):94–102.

[3] Ebell MH. Predicting postoperative nausea and vomiting. Am Fam Physician. 2007;75(10):1537–1538.

[4] Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesthesia Analg. 2019 Jul 17;131 (2):411–448.

[5] Greene NH, Habib AS. Midazolam for anxiolysis and postoperative nausea and vomiting prophylaxis: can we kill two birds with one stone? Anesthesia Analg. 2016 Mar 1;122(3):590–592.

[6] Habib AS. Midazolam—an anti-emetic? Anaesthesia. 2002;57:725.

[7] Bauer KP, Dom PM, Ramirez AM, et al. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth. 2004;16:177–183.

[8] Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's assessment of alertness/ sedation scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990 Aug.

[9] Lerman J. Study design in clinical research: sample size estimation and power analysis. Can J Anaesth. 1996;43:84–91.

[10] Shaikh SI, Nagarekha D, Hegade G, et al. Postoperative nausea and vomiting: a simple yet complex problem. Anesth Essays Res. 2016 Sep-Dec;10(3):388–396.

[11] Ahn EJ, Kang H, Cho GJ, et al. The effectiveness of midazolam for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. Anesth Anal. 2016;122(3):664–676.

[12] Grant MC, Kim J, Page AJ, et al. The effect of intravenous midazolam on postoperative nausea and vomiting: a meta-analysis. Anesthesia Analg. 2016 Mar 1;122 (3):656–663.

[13] Prakash K, Meshram T, Jain P. Midazolam versus dexamethasone-ondansetron in preventing post-operative nausea-vomiting in patients undergoing laparoscopic surgeries. Acta Anaesthesiol Scand. 2021 Aug;65(7):870–876.

[14] Honarmand A, Safavi M, Khalili G, et al. Prophylactic administration of haloperidol plus midazolam reduces postoperative nausea and vomiting better than using each drug alone in patients undergoing middle ear surgery. Saudi J Anaesth. 2012 Apr;6(2):145.

[15] Park EY, Lee SK, Kang MH, et al. Comparison of ramosetron with combined ramosetron and

midazolam for preventing postoperative nausea and vomiting in patients at high risk following laparoscopic gynaecological surgery. J Int Med Res. 2013;41:654–663.

[16] Safavi MR, Honarmand A. Low dose intravenous midazolam for prevention of PONV, in lower abdominal surgery—preoperative vs intraoperative administration. Middle East J Anaesthesiol. 2009;20:75–81.

[17] Özcan AT, Özcan E, Çanakçi E, et al. Prophylactic midazolam for prevention of post-operative nausea and vomiting following adenoidectomy or adenotonsillectomy. Ortadogu Med J. 2017;9(4):177–182.

[18] Abdelhamid SA, Kamel MS. A prospective controlled study to assess the antiemetic effect of midazolam following intragastric balloon insertion. J Anaesthesiol Clin Pharmacol. 2014;30:383–386.

[19] Habib AS, White WD, Eubanks S, et al. A randomized comparison of a multimodal management strategy versus combination antiemetics for the prevention of post-operative nausea and vomiting. Anesth Analg. 2004;99:77–81.