Original Article

Effects of adding intravenous midazolam to a dual postoperative nausea and vomiting regimen in patients undergoing breast surgery: A pragmatic randomized controlled trial

ABSTRACT

Background: For high-risk patients, adding a third antiemetic drug to dual postoperative nausea and vomiting (PONV) prophylaxis is controversial. Given the established antiemetic properties of midazolam, this study compared the combination of low-dose dexamethasone-ondansetron and midazolam with high-dose dexamethasone-ondansetron.

Methods: A total of 300 female patients scheduled for breast surgery were recruited and randomly assigned to two groups. The DO group received dexamethasone 8 mg and ondansetron 4 mg, whereas the DOM group received dexamethasone 4 mg, ondansetron 4 mg, and midazolam 0.04 mg/kg. The primary outcome was the incidence of PONV within 24 h. Secondary outcomes were PONV severity, antiemetic requirement, blood glucose levels, satisfaction and sedation scores, time to eye opening and extubation, pain outcome, and sore throat.

Results: Primary outcome analysis included 298 patients. Incidence of PONV within the first 24 h after surgery occurred in 52 of 150 (35%) patients in the DO group and 33 of 148 (22%) patients in the DOM group (adjusted risk ratio, 0.63; 95% confidence interval, 0.45–0.88; $P = 0.007$). The antiemetic requirement was significantly greater in the DO group compared with the DOM group ($P = 0.034$). However, a significantly higher sedation level and longer time for eye-opening and extubation were observed in the DOM group ($P < 0.05$).

Conclusion: Compared to high-dose dexamethasone and ondansetron alone, midazolam combined with low-dose dexamethasone and ondansetron decreased the incidence of PONV in patients undergoing breast surgery; however, it increased the sedation level in the early postoperative period.

Key words: Breast, dexamethasone, midazolam, nausea and vomiting, ondansetron, postoperative, surgery

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Introduction

In accordance with the Fourth Consensus recommendations, multimodal postoperative nausea and vomiting (PONV) prophylaxis was advised for high-risk patients, which included patients undergoing breast surgery.[1] Dexamethasone and ondansetron, constituted one of the most frequently used combined antiemetic prophylaxes.[1,2] The most administered and recommended doses are 8 mg of dexamethasone and 4 mg of ondansetron.[3] However, a meta-analysis examining the efficacy of dexamethasone in preventing PONV revealed that a dose ranging from 4 to 5 mg produced clinical effects comparable to those observed with a dose of 8–10 mg, whether dexamethasone was administered alone or in combination with other drugs.[4] Therefore, a dose of 4–8 mg of dexamethasone combined with 4 mg of ondansetron was administered within our institution, with the dosage of dexamethasone frequently determined by the risk of adverse events associated with high-dose dexamethasone.[5]

Nevertheless, despite receiving dual PONV prophylaxis, the incidence of PONV in patients undergoing breast surgery can reach up to 30–40%.[6] A recent guideline recommended administering a third or fourth antiemetic with a different mechanism of action compared to the dual preventive method to adult patients who were at an increased risk of PONV.[7] Several studies have demonstrated that intravenous midazolam can reduce the incidence of PONV.[8-10] However, the effectiveness of using midazolam as a third antiemetic prophylactic when combined with conventional dual antiemetic prophylaxis remains uncertain.

Thus, the primary aim of this study was to assess the effectiveness of combining midazolam with low-dose dexamethasone (4 mg)-ondansetron and high-dose dexamethasone (8 mg)-ondansetron in reducing PONV in patients undergoing breast surgery. We hypothesized that adding midazolam to low-dose dexamethasone-ondansetron would reduce the incidence of PONV within 24 h compared with high-dose dexamethasone-ondansetron alone.

Methods

This pragmatic, randomized, double-blind, multicenter controlled trial was conducted at the King Chulalongkorn Memorial Hospital and Chaophrayayommarat Hospital in Thailand. The study protocol was approved by the Institutional Review Board of Chulalongkorn University (No: 161/65, approval on April 12, 2022) and the Ethics Committee of Chaophrayayommarat Hospital (No: YM020/2565), and written informed consent was obtained from all subjects. The trial was registered before patient enrollment at the Thai Clinical Trial Registry (TCTR20220510001, date of registration: May 10, 2022).

Female participants aged 18–65 years who met the criteria for elective breast surgery according to the American Society of Anesthesiologists classification I–III were eligible for participation. Before participation, all the participants were provided with comprehensive information about the study. The exclusion criteria were body mass index (BMI) <18 or >40 kg/m^2, patient refusal, allergy or contraindication to drugs in this trial, chronic opioid use (>3 months), chronic benzodiazepine use, antipsychotic use, prior anticancer chemotherapy within 4 weeks, pregnancy, obstructive sleep apnea, poorly controlled DM (HbA1C > 9), or blood sugar level >180 mg/dL on the morning of surgery, and prior antiemetic use within 24 h.

Eligible patients were randomly assigned to either the control group (DO) or the intervention group (DOM) using a computer-generated block of four randomizations that were centrally constructed through an online system. The allocation for randomization was obtained from both institutions through an online platform. A physician who was not involved in the study prepared sequentially numbered, sealed, opaque envelopes. Additionally, before the patient arrived in the operating room, the nurse anesthetist who prepared the study medications was informed of the group allocation; however, they did not participate in the data collection, evaluation, or analysis. The ward nurses, patients, statisticians, intraoperative anesthesiologists, surgeons, and research assistants who collected the data were blinded to the group allocation.

Before surgery, patients were not administered premedication consisting of benzodiazepines or antiemetics. Anesthetic management was the responsibility of the intraoperative anesthesiologist, which included airway management, induction agents, volatile agents, muscle relaxants, ventilator settings, fluid administration, and analgesia, except for nitrous oxide avoidance. The patients were administered the study medication, which was prepared by a nurse anesthetist who did not participate in patient care, following the standard procedure for inducing anesthesia. The dexamethasone doses for both groups were prepared in equal amounts by diluting with normal saline and were packed in a syringe labeled "Research drug no. 1." Subsequently, 30 min before the end of surgery, all patients in both groups received 4 mg of ondansetron and "Research drug no. 2," which in the DOM group consisted of midazolam 0.04 mg/kg (maximum of 2 mg) or the equivalent volume of normal saline in the DO group. To ensure patient safety, intraoperative anesthesiologists could request research drug identification in the event of

complications arising during the perioperative period, such as delayed awakening or failed extubation.

During the postoperative period, when the patient was admitted to the postanesthetic care unit (PACU), if a patient complained of nausea for more than 10 min or had a PONV score >1, 4 mg of ondansetron was administered as the first rescue antiemetic. In cases where the symptoms persisted for a duration exceeding 10 min or failed to respond to ondansetron, a secondary rescue antiemetic consisting of 10 mg of intravenous metoclopramide was administered. Multimodal analgesic regimens were used in the PACU and ward to manage postoperative pain, based on the surgeon's discretion. However, the pain score in the PACU remained >4 despite the administration of pain medication for >30 min. Additionally, a rescue therapy dose of 25 micrograms of intravenous fentanyl was provided to the patient.

The primary outcome was the incidence of PONV within 24 h. The secondary outcome assessments included the following: PONV was assessed at 0, 0–2, 2–6, 6–12, and 12–24 h postoperatively using the PONV score,[11] which ranged from 0 to 3 (0 = no nausea or vomiting, 1 = nausea, 2 = retching, which means an involuntary attempt to vomit without expulsion of gastric content, and 3 = vomiting); the severity of PONV at 0, 0–2, 2–6, 6–12, and 12–24 h postoperatively was measured using the visual analog scale (VAS) rated as 0–10 (0 = without symptom, 10 = worst possible nausea and vomiting); the requirement of an antiemetic was recorded and the time to first rescue antiemetic drug was defined as the interval from the end of surgery until the first rescue antiemetic administration; the VAS for pain score (0–10, with 0 indicating no pain and 10 the worst pain) was measured at 0, 0–2, 2–6, 6–12, and 12–24 h postoperatively; the satisfaction for relieving PONV was evaluated using the Likert scale 1–5; the sedation score was assessed using the observer's assessment of alertness/sedation scale[12] (range: 1–5; 5 = fully awake while a score of 1 represented unconsciousness) and was recorded on arrival at 0, 30, and 60 min postoperatively; the pre- and postoperative blood glucose levels were also measured by point-of-care testing glucose before the surgery and in PACU. In addition, we evaluated other parameters, as described below. The requirement for analgesic drugs was recorded, and the time to first rescue analgesia was defined as the interval from the end of surgery until the first intravenous opioid was administered. The quality of recovery (QoR) was assessed using the QoR-15 questionnaire developed by Stark *et al*.,[13] which was translated into Thai by Thosingha *et al*.[14] using the back-translation technique. The questionnaire was administered to the patients postoperatively in the ward and had to be completed at 6, 12, and 24 h after surgery. The time to eye opening and time to extubation after surgery were recorded, and incidences of sore throats and adverse events were assessed daily.

The sample size calculation was performed under the assumption that the incidence of PONV would occur in 35.1% of the patients in the DO group.[15] The clinical efficacy of the DOM group was determined based on a minimum 50% reduction in the incidence of PONV,[16] a significance level of 0.05 and a power of 0.9, and 270 patients would be required for the study. With an approximate 10% withdrawal rate, the target enrollment was 300 patients.

All analyses were conducted in accordance with intention-to-treat principles. A descriptive analysis was used to describe the baseline characteristics. Standardized differences were presented, and variables with standardized differences >1.96 sqrt $[(1/n_1) + (1/n_2)]$ were considered imbalanced. In this study, standardized differences of ≥0.2 were considered imbalanced. A set of multivariable generalized linear regressions with binomial family was used to estimate the association of different prophylaxis drugs for PONV strategies (DO versus DOM group) with the primary and secondary outcomes and adjusted for study site, imbalanced variables, and additional potential risk factors ($P < 0.2$ in the univariable model, including younger age (<50 years), surgical time (>60 min), and Apfel score). The normality of the distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) according to the distribution. The independent Student's *t*-test or Mann–Whitney U test was applied for between-group comparisons of continuous variables, as appropriate. Categorical variables were presented as numbers and percentages. Outcomes were expressed as relative risks with 95% confidence intervals (CIs). All analyses were performed using STATA Statistics version 17.0 for Windows (STATA Corp., College Station, TX, USA). A two-sided P value < 0.05 was considered statistically significant.

Results

Of the 583 patients screened between April 2022 and June 2023, 300 were enrolled for randomization. Subsequently, two patients were excluded from the primary outcome analysis because of home discharge before 24 h. Therefore, the primary outcome data were available for 150 and 148 patients in the DO and DOM groups, respectively [Figure 1]. The clinical characteristics of the enrolled patients are shown in Table 1. All characteristics were balanced between the two groups, except for body weight, BMI, and underlying diseases,

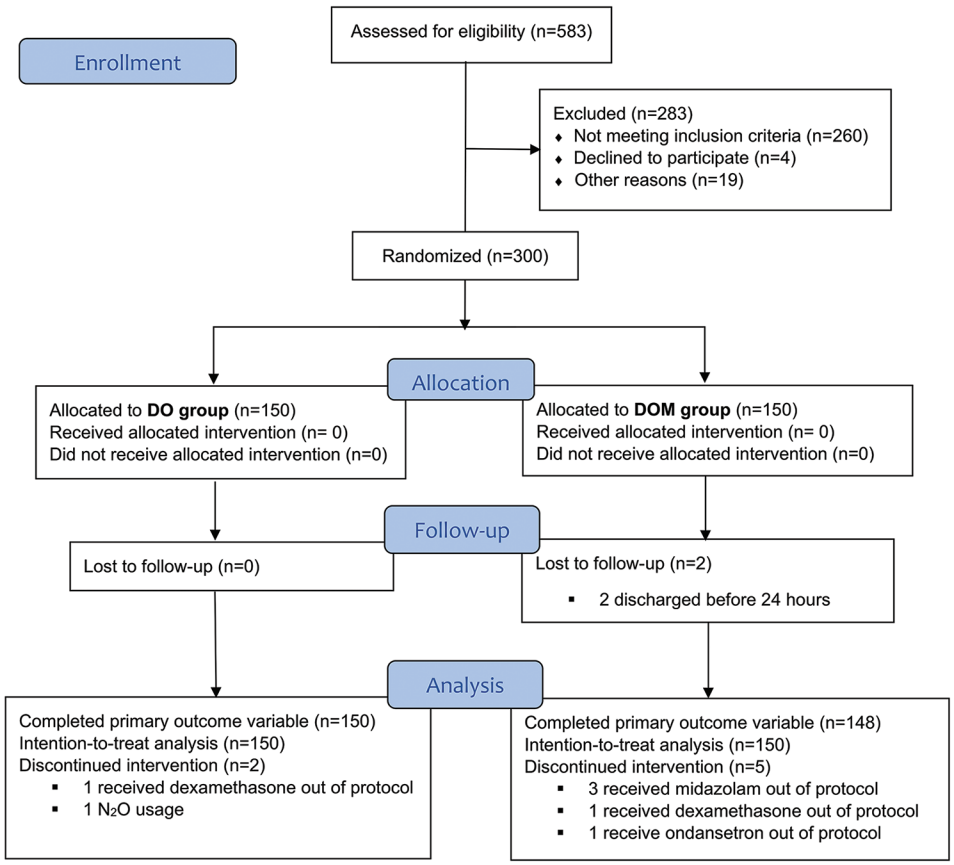

Figure 1: Consolidated standards of reporting trial statement flow diagram

which showed a potential imbalance, with a higher score in the DO group. Therefore, the primary analysis was adjusted to account for these variables.

The intraoperative and PACU characteristics are presented in Table 2 and the Appendix File. The data appeared to be well balanced between the groups, except for airway management (endotracheal tube), use of desflurane and neostigmine, and use of intravenous rescue morphine in the PACU. In addition, the times for eye opening (10 min [7–14] vs. 7 min [5–10]) and extubation (10 min [7–15] vs. 8 min [5–10]) were significantly longer in the DOM group than in the DO group ($P < 0.001$).

Primary outcome

PONV within the first 24 h after surgery occurred in 52 of 150 (35%) patients in the DO group and in 33 of 148 (22%) patients in the DOM group (adjusted risk ratio [RR], 0.63; 95% CI, 0.45–0.88; $P = 0.007$) [Table 3], with a statistically significant difference in PONV incidence between the two groups at 0 (10% in the DO group vs. 4% in the DOM group, adjusted RR, 0.36; 95% CI, 0.14–0.93; $P = 0.034$), 0–2 (11% in the DO group vs. 5% in the DOM group, adjusted RR, 0.36; 95% CI, 0.15–0.83; $P = 0.016$), and 12–24 hours after surgery (7% in the DO group vs. 1% in the DOM group, adjusted RR, 0.18; 95% CI, 0.04–0.83; $P = 0.028$) [Figure 2].

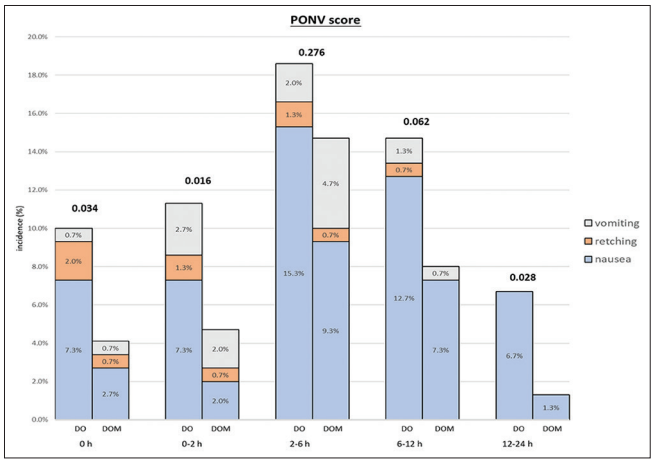

Figure 2: The bar graph of the incidence of postoperative nausea and vomiting in the DO and DOM groups from the end of surgery until 24 h postoperatively. PONV = postoperative nausea and vomiting. *P* <0.05 indicates statistical significance between two groups

Secondary outcomes

The results of the secondary outcomes are shown in Table 3. Overall, this study revealed that the VAS score for PONV

Table 1: Patient characteristics at baseline

Variables	DO group (*n*=150)	DOM group (*n*=150)	Standardized difference
Age, years, median (IQR)	50 (43-58)	51 (44-57)	0.035
Body weight, kg, median (IQR)	58 (52-66)	55 (51-61)	0.288
Height, m, median (IQR)	1.57 (1.53-1.61)	1.58 (1.54-1.61)	-0.066
BMI, kg/m^2, median (IQR)	23.8 (21.5-26.7)	22.4 (20.4-24.9)	0.324
ASA physical status, *n* (%)			
I	75 (50)	91 (61)	-0.215
II	71 (47)	58 (39)	0.175
III	4 (3)	1 (1)	0.156
History PONV, *n* (%)	18 (12)	12 (8)	0.133
Motion sickness, *n* (%)	31 (21)	42 (28)	-0.171
Non-smoking, *n* (%)	146 (97)	149 (99)	-0.156
Perioperative opioid, *n* (%)	148 (99)	149 (99)	-0.067
Apfel score, *n* (%)			
2	5 (3)	2 (1)	0.132
3	104 (69)	97 (65)	0.099
4	41 (27)	51 (34)	-0.144
Underlying diseases, *n* (%)	63 (42)	44 (29)	0.266
POCT preoperative, median (IQR)	94 (88-103)	93 (87-101)	0.102

Data are presented as the median (IQR), or number (percentage). ASA, American Society of Anesthesiologists; BMI, body mass index; GERD, Gastroesophageal Reflux Disease; IQR, interquartile range; POCT, point-of-care testing; PONV, postoperative nausea vomiting; Standardized differences ≥0.2 were considered imbalanced

Table 2: Intraoperative and PACU data

Variables	DO group (*n*=150)	DOM group (*n*=150)	Standardized difference
Intraoperative data			
Diagnosis, *n* (%)			
Breast cancer	103 (69)	97 (65)	0.085
Breast lesion	12 (8)	14 (9)	-0.047
Breast mass	23 (15)	30 (20)	-1.122
Other	12 (8)	9 (6)	0.078
Type of surgery, *n* (%)			
Mastectomy	5 (3)	8 (5)	-0.098
Mastectomy with ALND	32 (21)	29 (19)	0.050
Mastectomy with SLNB	19 (13)	11 (7)	0.178
Wide local excision/wide local excision with ALND	57 (38)	60 (40)	-0.041
Wide local excision with SLNB	26 (17)	23 (15)	0.054
Others	11 (7)	19 (13)	-0.178
Duration of anesthesia, min, median (IQR)	137 (90-180)	128 (75-170)	0.119
Duration of surgery, min, median (IQR)	102 (55-139)	90 (45-133)	0.160
Estimated blood loss, mL, median (IQR)	30 (10-60)	20 (10-50)	0.101
Postoperative blood transfusion, *n* (%)	1 (0.7)	1 (0.7)	0.000
PACU data			
PACU stay, min, median (IQR)	60 (60-60)	60 (60-60)	0.152
Use of analgesic drugs, *n* (%)			
Morphine	42 (28)	29 (19)	0.204
Fentanyl	32 (21)	27 (18)	0.084
Pethidine	4 (3)	1 (0.7)	0.156

Data are presented as the mean (SD), median (IQR), or number (percentage). ALND, axillary lymph node dissection; IQR, interquartile range; PACU, post anesthetic care unit; SLNB, sentinel lymph node biopsy; Standardized differences ≥0.2 were considered imbalanced

severity in the DO group was marginally higher than that in the DOM group. Furthermore, these differences were shown to be significantly greater at 0 h (P = 0.024) and 12–24 h after surgery (P = 0.029). These results indicate that the DO group exhibited a notably higher need for intravenous rescue antiemetic drugs compared with the DOM group (P = 0.034). Additionally, the DO group had a shorter time to first rescue antiemetic drugs than the DOM group, although this difference was not statistically significant (P = 0.569). However, in the initial post-anesthesia phase (0 min), the

Table 3: Clinical outcomes

Variables	DO group (*n*=150)	DOM group (*n*=150)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	*P*
Primary Outcome					
Incidence PONV, *n* (%)	52 (35)	33 (22)	0.63 (0.44, 0.92)	0.63 (0.45, 0.88)	0.007*
Secondary outcomes					
VAS for PONV severity, median (IQR; min-max)					
0-h	0 (0-0; 0-10)	0 (0-0; 0-5)	-	-	0.024*
0-2 h	0 (0-0; 0-9)	0 (0-0; 0-10)	-	-	0.099
2-6 h	0 (0-0; 0-10)	0 (0-0; 0-10)	-	-	0.23
6-12 h	0 (0-0; 0-9)	0 (0-0; 0-8)	-	-	0.33
12-24 h	0 (0-0; 0-8)	0 (0-0; 0-4)	-	-	0.029*
Rescue antiemetic drug use, *n* (%)	23 (15)	15 (10)	0.65 (0.35, 1.2)	0.71 (0.38, 1.32)	0.277
Use of metoclopramide, *n* (%)	15 (10)	11 (7)	0.73 (0.35, 1.54)	0.77 (0.36, 1.64)	0.492
Metoclopramide dose, mg, median (IQR)	10 (10-10)	10 (10-10)	-	-	-
Use of ondansetron, *n* (%)	15 (10)	5 (3)	0.33 (0.12, 0.89)	0.34 (0.12, 0.92)	0.034*
Ondansetron dose, mg, median (IQR)	4 (4-4)	4 (4-4)	-	-	-
Time to first rescue antiemetic drug, min, median (IQR)	50 (10-225)	100 (45-240)	-	-	0.569
Sedation score, median (IQR)					
0 min	5 (4-5)	4 (4-5)	-	-	0.003*
30 min	5 (5-5)	5 (4-5)	-	-	0.504
60 min	5 (5-5)	5 (5-5)	-	-	0.488
POCT post-op, mg/dL, median (IQR)	115 (102-134)	108 (97-127)		-	-
Changed POCT from preoperative, mg/dL, median (IQR)	18 (8-36)	16 (6-29)	-3 (-8, 3)	1 (-4, 6)	0.636

Data are presented as the median (IQR), or number (percentage). *$P<0.05$ significant. CI, confidence interval; IQR, interquartile range; PONV, postoperative nausea vomiting; POCT, point-of-care testing

DOM group exhibited notably elevated levels of sedation than the DO group, as indicated by lower sedation scores ($P = 0.003$). In addition, there was no difference between the two groups in terms of postoperative blood glucose levels or alterations in blood glucose levels relative to preoperative levels.

Pain scores and other outcomes

The pain assessment and other variables are shown in Table 4. No statistically significant differences were observed between the two groups in terms of postoperative VAS pain scores or the incidence of sore throat. This was consistent with the finding that the times to first rescue analgesia and postoperative analgesic showed no substantial difference between the two groups. In addition, neither the QoR nor patient satisfaction differed significantly between the two groups.

Discussion

This pragmatic randomized controlled trial investigated the additive antiemetic effect of midazolam when combined with a commonly-applied dual antiemetic prophylaxis course of, dexamethasone and ondansetron, in the context of breast surgery among female patients. Despite the absence of clinical importance, the findings of our study indicate that the administration of intraoperative intravenous midazolam (0.04 mg/kg with a maximum of 2 mg) when combined with 4 mg of dexamethasone and 4 mg of ondansetron resulted in a lower incidence of PONV within the first 24 h (22% vs. 35%) and at 0 h, 0–2 h, and 12–24 h after surgery than the use of 8 mg of dexamethasone and 4 mg of ondansetron alone. Moreover, the addition of midazolam decreased the intensity of PONV, specifically in the PACU and within 12–24 h postoperatively, while also decreasing the need for antiemetic medications. However, a notable increase in sedation levels was observed during the early postoperative period, as well as a prolonged time for eye opening and extubation.

Although the precise mechanisms underlying their antiemetic effects remain unknown, the potential benefits of benzodiazepines at reducing PONV are associated with their anxiolytic properties.[2,17,18] The antiemetic properties of midazolam have been documented as early as 2004 in the context of cardiac surgery and potentially even earlier in patients undergoing chemotherapy.[19,20] Furthermore, several studies have previously documented the antiemetic effects of midazolam, both as a standalone treatment and as a supplementary antiemetic medication in combination therapy for the prevention of PONV.[8-10,21] When combined with dexamethasone or ondansetron for dual PONV prophylaxis, midazolam exhibited greater efficacy compared with standard monotherapy.[8] However, as a

Table 4: Pain score and other outcomes

Variables	DO group (*n*=150)	DOM group (*n*=150)	*P*
VAS pain score, median (IQR)			
0 h	2 (0-5)	2 (0-5)	0.709
0-2 h	3 (1-4)	3 (1-4)	0.89
2-6 h	2 (1-4)	3 (1-4)	0.359
6-12 h	2 (1-3)	2 (1-3)	0.176
12-24 h	1 (0-3)	2 (0-3)	0.109
Rescue analgesic drug at ward, *n* (%)	6 (4)	4 (3)	0.75
Use of morphine, *n* (%)	4 (3)	4 (3)	1.000
Morphine dose, mg, median (IQR)	3 (3-5)	3 (3-4)	-
Use of pethidine, *n* (%)	1 (1)	0 (0)	1.000
Pethidine dose, mg, median (IQR)	25	-	-
Use of tramadol, *n* (%)	1 (1)	0 (0)	1.000
Tramadol dose, mg, median (IQR)	50	-	-
Time to first rescue analgesia, min, median (IQR)	123 (90-380)	138 (98-179)	0.914
Incidence of sore throat, *n* (%)			
0-h	40 (27)	43 (29)	0.699
0-2 h	31 (21)	29 (19)	0.773
2-6 h	8 (5)	17 (11)	0.060
6-12 h	3 (2)	6 (4)	0.335
12-24 h	1 (1)	3 (2)	0.369
Quality of recovery, median (IQR)			
6 h	132 (120-142)	134 (123-143)	0.307
12 h	138 (129-146)	141 (132-147)	0.196
24 h	142 (134-147)	144 (136-148)	0.293
Patient satisfaction, Likert scale[a], median (IQR)	5 (5-5)	5 (5-5)	0.184

Data are presented as the median (IQR), or number (percentage). $P<0.05$ significant; Mann–Whitney U test, Fisher's exact test, Chi-squared test. [a]Likert scale: 1=very dissatisfied, 2=somewhat dissatisfied, 3=neutral, 4=somewhat satisfied, 5=very satisfied. CI, confidence interval; IQR, interquartile range; PONV, postoperative nausea vomiting

third antiemetic, our results were inconsistent with those of a recent study that compared the efficacy of midazolam when administered with dual PONV prophylaxis following gynecologic laparoscopy.[16] Overall, it found that the dual prophylactic treatment comprising dexamethasone (4 mg) and ondansetron (4 mg) did not result in any additional preventive effect on PONV when pre-induction midazolam at 0.05 mg/kg was added. The lack of an antiemetic effect of midazolam may be attributable to the fact that all patients were routinely administered a postoperative intravenous patient-controlled analgesia mixture of ondansetron and sufentanil for pain management. In addition, while our study was underpowered to detect clinical differences in 24-h PONV incidence between groups, the efficacy of midazolam appeared promising. As the third antiemetic drug, midazolam can be administered alongside ondansetron and dexamethasone at varying dosages to alleviate PONV severity in the early postoperative phase (<2 h), which may have a substantial impact on delayed PONV (>12 h).[22]

A recent meta-analysis supported our finding, with results indicating that the administration of midazolam before or near the end of surgery was associated with a decreased incidence of PONV.[8,23] According to a study by Grant *et al*.,[8] midazolam was found to be effective in preventing PONV at doses of either 2 mg or 0.04–0.075 mg/kg. To avoid undesirable sedative effects, we elected to use a low, subhypnotic dose of midazolam (0.04 mg/kg) and a maximum dose of 2 mg in our protocol. However, the findings of our study indicate that patients who were administered midazolam still had elevated levels of sedatives. Although this effect was observed during the immediate post-anesthesia phase, none of the patients developed respiratory depression, severe sedation (score <1), or a prolonged stay in the PACU.

The effects of low and high doses of dexamethasone on PONV prophylaxis appear to be comparable. However, the impact of these doses on changes in blood glucose levels remains a topic of continuous concern, particularly in diabetic patients. A recent meta-analysis indicated that a single dose of 4–12 mg of intraoperative dexamethasone raised the blood glucose to 36 mg/dL within 24 h following surgery, suggesting that diabetic patients could safely apply a varied dosage for PONV prevention.[24] Conversely, one prior study found that patients with type II DM taking 8 mg of dexamethasone as opposed to 4 mg had substantially

elevated blood glucose levels by 25 mg/dL.[5] Our secondary findings corroborated this finding, revealing that patients with DM experienced higher postoperative blood sugar values (up to 40–44 mg/dL) than non-diabetic patients (an increase of only 16–18 mg/dL). Hence, midazolam may be a viable option for individuals with poorly managed diabetes, or those who cannot receive high-dose dexamethasone, particularly when undergoing surgery with a high risk of PONV.

This study had several limitations. First, the generalizability of the findings may be limited in this randomized, double-blind, two-center, superiority-controlled trial. However, the only limitation of our pragmatic protocol was the avoidance of nitrous oxide; this adaptability enhanced the generalizability of the study. Moreover, several inconsistent baseline variables in our results may represent PONV risk factors. Therefore, to statistically standardize them, we employed a generalized linear regression model. Hence, multicenter clinical studies with large sample sizes are required to corroborate our findings. Second, treatment with insulin was administered to certain patients with DM found to have elevated intraoperative blood glucose levels, in accordance with the established local practice. Further, it was observed that the postoperative blood glucose levels were diminished from their actual values. Finally, we did not include male patients or those who underwent breast reconstruction with flap surgery; therefore, the findings do not apply to this subgroup of patients.

In summary, this pragmatic randomized trial involving female patients undergoing breast surgery, adding a third antiemetic drug (midazolam) to the PONV prophylaxis of low-dose dexamethasone and ondansetron, can reduce the incidence of PONV within 24 h after surgery, when compared with the dual PONV prophylaxis with high-dose dexamethasone and ondansetron. Moreover, our results showed that this regimen may reduce the intensity of PONV, and the requirement of an antiemetic. However, an increase in sedation level in the initial postoperative phase was observed. Future studies are needed to assess the efficacy of midazolam as an alternative route, particularly in the ambulatory setting.

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Conflicts of interest

There are no conflicts of interest.

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Appendix File

Table 1: Intraoperative period- Anesthesia/procedural characteristics

Intraoperative characteristics	DO group (*n*=150)	DOM group (*n*=150)	Standardized difference	*P*
Airway, *n* (%)				0.080
Endotracheal tube	93 (62)	78 (52)	0.202	
Laryngeal mask airway	57 (38)	72 (48)	-0.202	
Drugs				
Use of propofol, *n* (%)	149 (99)	149 (99)	0.000	1.00
Propofol dose, mg, median (IQR)	180 (140-200)	180 (130-200)	-	-
Use of succinylcholine, *n* (%)	42 (28)	33 (22)	0.138	0.23
Succinylcholine dose, mg, median (IQR)	100 (40-100)	50 (25-100)	-	-
Use of atracurium, *n* (%)	25 (17)	25 (17)	0.000	1.00
Atracurium dose, mg, median (IQR)	30 (25-40)	35 (30-40)	-	-
Use of cisatracurium, *n* (%)	68 (45)	55 (37)	0.176	0.13
Cisatracurium dose, mg, median (IQR)	12 (10-14)	12 (10-16)	-	-
Use of rocuronium, *n* (%)	4 (3)	1 (1)	0.156	0.18
Rocuronium dose, mg, median (IQR)	24 (11-58)	8 (8-8)	-	-
Sevoflurane/Desflurane use, *n* (%)				0.009
Sevoflurane use	81 (54)	103 (69)	-0.304	
Desflurane use	69 (46)	47 (31)	0.304	
Use of neostigmine, *n* (%)	88 (59)	70 (47)	0.241	0.037
Neostigmine dose, mg, median (IQR)	2.5 (2.5-2.5)	2.5 (2.5-2.5)	-	-
Use of sugamadex, *n* (%)	1 (0.7)	0 (0)	0.115	0.32
Sugamadex dose, μg	200	-	-	-
Use of atropine, *n* (%)	54 (36)	45 (30)	0.127	0.27
Atropine dose, mg, median (IQR)	1.2 (1.2-1.2)	1.2 (1.2-1.2)	-	-
Use of glycopylorrate, *n* (%)	34 (23)	25 (17)	0.151	0.19
Glycopylorrate dose, mg, median (IQR)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	-	-
Use of ephedrine, *n* (%)	12 (8)	10 (7)	0.051	0.66
Ephedrine dose, mg, median (IQR)	8 (6-15)	8 (6-12)	-	-
Use of parecoxib, *n* (%)	68 (45)	77 (51)	-0.120	0.30
Parecoxib dose, mg, median (IQR)	40 (40-40)	40 (40-40)	-	-
Use of paracetamol, *n* (%)	57 (38)	69 (46)	-0.162	0.16
Paracetamol dose, mg, median (IQR)	1000 (1000-1000)	1000 (1000-1000)	-	-
Use of ketamine, *n* (%)	1 (0.7)	1 (0.7)	0.000	1.00
Ketamine dose, mg, median (IQR)	25	85	-	-
Use of ketorolac, *n* (%)	0 (0)	1 (1)	-0.115	0.32
Ketorolac dose, mg, median (IQR)	-	30	-	-
Use of nefopam, *n* (%)	3 (2)	4 (3)	-0.044	0.70
Nefopam dose, mg, median (IQR)	20 (20-20)	20 (20-20)	-	-
Use of morphine, *n* (%)	68 (45)	70 (47)	-0.027	0.82
Morphine dose, mg, median (IQR)	6 (5-8)	6 (4-8)	-	-
Use of fentanyl, *n* (%)	91 (61)	92 (61)	-0.014	0.91
Fentanyl dose, μg, median (IQR)	75 (50-100)	63 (50-100)	-	-
Use of pethidine, *n* (%)	5 (3)	4 (3)	0.039	0.74
Pethidine dose, mg, median (IQR)	35 (20-35)	25 (15-40)	-	-
Use of acetar, *n* (%)	142 (95)	141 (94)	0.029	0.80
Acetar dose, mL, median (IQR)	500 (400-700)	500 (350-700)	-	-
Use of normal saline, *n* (%)	12 (8)	8 (5)	0.107	0.35
Normal saline, mL, median (IQR)	517±286	475±255	-	-
Use of lactated ringer's solution, *n* (%)	0 (0)	1 (0.7)	-0.115	0.32
Lactated ringer's solution, mL, median (IQR)	-	400	-	-
Use of colloid, *n* (%)	2 (1.3)	1 (0.7)	0.067	0.56
Colloid, mL, median (IQR)	500 (500-500)	500 (500-500)	-	-
Use packed red cell, *n* (%)	1 (0.7)	1 (0.7)	0.000	1.00
Packed red cell, mL, median (IQR)	278	290	-	-

Data are presented as the median (IQR), or number (percentage)

Table 2: Pain score and other outcomes

Variables	DO group (*n*=150)	DOM group (*n*=150)	*P*
VAS pain score, median (IQR)			
0 h	2 (0-5)	2 (0-5)	0.709
0-2 h	3 (1-4)	3 (1-4)	0.89
2-6 h	2 (1-4)	3 (1-4)	0.359
6-12 h	2 (1-3)	2 (1-3)	0.176
12-24 h	1 (0-3)	2 (0-3)	0.109
Rescue analgesic drug at ward, *n* (%)	6 (4)	4 (3)	0.75
Use of morphine, *n* (%)	4 (3)	4 (3)	1.000
Morphine dose, mg, median (IQR)	3 (3-5)	3 (3-4)	-
Use of pethidine, *n* (%)	1 (1)	0 (0)	1.000
Pethidine dose, mg, median (IQR)	25	-	-
Use of tramadol, *n* (%)	1 (1)	0 (0)	1.000
Tramadol dose, mg, median (IQR)	50	-	-
Time to first rescue analgesia, min, median (IQR)	123 (90-380)	138 (98-179)	0.914
Incidence of sore throat, *n* (%)			
0-h	40 (27)	43 (29)	0.699
0-2 h	31 (21)	29 (19)	0.773
2-6 h	8 (5)	17 (11)	0.060
6-12 h	3 (2)	6 (4)	0.335
12-24 h	1 (1)	3 (2)	0.369
Quality of recovery, median (IQR)			
6 h	132 (120-142)	134 (123-143)	0.307
12 h	138 (129-146)	141 (132-147)	0.196
24 h	142 (134-147)	144 (136-148)	0.293
Patient satisfaction, Likert scale[a], median (IQR)	5 (5-5)	5 (5-5)	0.184

Data are presented as the median (IQR), or number (percentage). $P<0.05$ significant; Mann–Whitney U test, Fisher's exact test, Chi-squared test. [a]Likert scale: 1=very dissatisfied, 2=somewhat dissatisfied, 3=neutral, 4=somewhat satisfied, 5=very satisfied. CI, confidence interval; IQR, interquartile range; PONV, postoperative nausea vomiting