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Comparison of efficacy between palonosetron-midazolam combination and palonosetron alone for prevention of postoperative nausea and vomiting in patients undergoing breast surgery and patient controlled analgesia

A prospective, randomized, double-blind study: A CONSORT-compliant study

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Abstract

Background: Postoperative nausea and vomiting (PONV) is a common complaint in patients following general anesthesia. Various antiemetics, including 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists, are effective but still have limited efficacy. Therefore, combination therapy is preferable to using a single drug alone in high-risk patients. We performed a comparative study on the antiemetic effect of palonosetron, a 5-HT_3 receptor antagonist, monotherapy vs palonosetron-midazolam combination therapy for the prevention of PONV.

Methods: A total of 104 female patients scheduled for breast cancer surgery were enrolled. They were randomly divided into 2 groups, a palonosetron monotherapy group (group P) and palonosetron-midazolam combination therapy group (group PM). Both groups received 0.075 mg palonosetron intravenously after induction of anesthesia. Patient-controlled analgesia (PCA) was applied according to the allocated group. Intravenous (IV)-PCA in group P consisted of fentanyl 20 μg/kg plus normal saline (total volume: 100 ml); IV-PCA in group PM consisted of fentanyl 20 μg/kg plus midazolam 4 mg plus normal saline (total volume: 100 ml). Efficacy parameters were collected during 0 to 1, 1 to 6, 6 to 24, and 24 to 48 hours postoperative time intervals. These measures included complete response (defined as no PONV and no rescue anti-emetic use) rate, incidence of PONV, sedation score, rescue antiemetic use, rescue analgesic use, and numerical rating scale (NRS) for pain. The complete response rate during the 0 to 24 hours interval was analyzed as the primary outcome.

Results: Although the complete response rate between 0 and 24 hours was higher in group PM (42.3% and 48.1% in group P and PM, respectively), there was no statistically significant difference ($P = .55$). The complete response rates in other time intervals were not different between the 2 groups as well. The sedation score and NRS score also showed no differences between the 2 groups.

Conclusions: The combination therapy of palonosetron with midazolam did not lead to a greater reduction in the incidence of PONV than monotherapy in patients undergoing breast surgery and receiving IV-PCA containing fentanyl.

Abbreviations: 5-HT_3 = 5-hydroxytryptamine type 3, CR = complete response, Group P = palonosetron monotherapy group, Group PM = palonosetron-midazolam combination therapy group, IV-PCA = intravenous patient-controlled analgesia, NK-1 = neurokinin-1, NRS = numerical rating scale, OAA/S = observer's assessment of alertness/sedation, PONV = postoperative nausea and vomiting.

Keywords: midazolam, palonosetron, patient-controlled analgesia, PONV

Editor: Young-Kug Kim.

The authors have no conflicts of interest to disclose.

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

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How to cite this article: Hong JM, Han YH, Lee D, Hwang BY, Baik J, Cho AR, Lee HJ, Kim E. Comparison of efficacy between palonosetron-midazolam combination and palonosetron alone for prevention of postoperative nausea and vomiting in patients undergoing breast surgery and patient controlled analgesia: a prospective, randomized, double-blind study: a CONSORT-compliant study. Medicine 2021;100:26(e26438).

Received: 21 January 2020 / Received in final form: 21 May 2021 / Accepted: 3 June 2021

http://dx.doi.org/10.1097/MD.0000000000026438

1. Introduction

Postoperative nausea and vomiting (PONV) is a common complaint following surgery under general anesthesia. The general incidence of vomiting and nausea is 30% and 50%, respectively, whereas PONV occurs in 80% or more of the cases involving high-risk patients.[1–3] Although most instances of PONV are self-limiting, resulting only in patient dissatisfaction or discomfort, PONV can sometimes cause serious complications, such as wound dehiscence, esophageal rupture, aspiration of gastric contents, retinal detachment, prolonged hospitalization, and increased costs.[4–6]

Various antiemetics, including 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, corticosteroids, butyrophenones, antihistamine, and anticholinergics, have been developed to reduce the incidence of PONV but drug monotherapy using these drugs has limited efficacy. Thus, combination therapies with drugs from different classes are preferred.[7–10] Various combination therapies using 5-HT_3 receptor antagonists, such as ondansetron or granisetron, with either droperidol or dexamethasone have been reported. However, much research is still needed on the proper combination and dosage of these combination therapies and there are no studies on the effects of the combination of palonosetron and midazolam.

The 5-HT_3 antagonists are representative drugs used to prevent PONV. Palonosetron is a second-generation 5-HT_3 antagonist and has a long half-life of 40 hours.[11]

Midazolam is a short-acting benzodiazepine and bolus or continuous infusion of midazolam is effective in decreasing PONV. Furthermore, in 1 study, midazolam was reported to be effective in preventing nausea and vomiting when added to intravenous patient-controlled analgesia (IV-PCA).[12] The combined administration of ondansetron and midazolam in addition to IV-PCA was even more effective.[13]

We conducted this study to compare the anti-emetic effects of palonosetron monotherapy and palonosetron-midazolam combination therapy for the prevention of PONV in high-risk patients.

2. Methods

This prospective, double-blind study was approved by the institutional review board of Pusan National University Hospital, and written informed consent was obtained from all patients (institutional approval number H-1312-001-025). This study was registered at http://cris.nih.go.kr (KCT0001114). One hundred and four female patients, aged 18 to 60 years old, American Society of Anesthesiologists physical status I or II, and scheduled to undergo breast cancer surgery under general anesthesia with postoperative fentanyl IV-PCA were enrolled. Patients who had allergies to the study drugs, a history of drug abuse, or had received anti-emetic drugs 24 hours prior to the start of the study period were excluded.

Patients were randomly divided into 2 groups, a palonosetron monotherapy group (group P) and a palonosetron-midazolam combination therapy group (group PM), using a computer-generated sequence. Both groups received 0.075 mg palonosetron intravenously after induction of anesthesia. A different PCA regimen was applied according to the allocated group. The IV-PCA in group P consisted of fentanyl 20 μg/kg plus normal saline (total volume: 100 ml); IV-PCA in group PM consisted of fentanyl 20 μg/kg plus midazolam 4 mg plus normal saline (total volume: 100 ml). Before beginning anesthesia, the PCA regimen was prepared by another anesthesiologist who was not involved in anesthesia. The anesthesiologist involved in the anesthesia was not aware of the group classification. The IV-PCA drugs were administered as a continuous infusion at a rate of 1.0 ml/h with a bolus of 1 ml and a lockout time of 15 minutes.

All patients were pre-medicated with 0.2 mg glycopyrrolate intramuscularly 30 minutes prior to surgery. Anesthesia was induced with 1.5 μg/kg of propofol, 0.8 mg/kg of rocuronium, and 500 μg/h of remifentanil. After intubation, 0.075 mg of palonosetron was injected intravenously, and inhalation anesthesia was maintained with sevoflurane at 2.0–3.0 vol% and remifentanil 100–500 μg/h at O_2 0.8 L/min and air 1.5 L/min. During anesthesia, the tidal volume was regulated to maintain an end-tidal CO_2 pressure in the range of 30–35 mmHg and vital signs were maintained within 20% of normal values. Sevoflurane was reduced to 1 vol% at the start of skin suturing. At the end of the surgery, sevoflurane and remifentanil were stopped, and a 4 ml PCA loading dose and IV-PCA were provided.

All patients and the investigator who measured the outcomes were not aware of the allocated group. At least 1 episode of nausea or vomiting of the patient was considered a PONV incident. No nausea or vomiting while maintaining PCA was considered a complete response (CR). CR rate, nausea, vomiting, and PCA stop were measured during 0 to 1, 1 to 6, 6 to 24, and 24 to 48 hours postoperative time intervals. When a patient complained of PONV, 4 mg of ondansetron was administered intravenously. If the symptom was not relieved after 30 minutes, 10 mg of metoclopramide was given intravenously. If the symptom persisted, PCA was stopped. When the symptom improved, PCA was resumed. The pain was evaluated using the numerical rating scale (NRS). When the NRS was ≥6, 30 mg of ketorolac was administered intravenously. Sedation was assessed using the modified Observer's Assessment of Alertness/Sedation (OAA/S) score. If the OAA/S score was 3 or less, the respiratory rate per minute was 10 or less, or the oxygen saturation was 90% or less, PCA was stopped and flumazenil was administered. PONV, NRS, OAA/S, connection time of PCA, and the number of ondansetron, metoclopramide, and ketorolac injections were investigated from the chart and interview with the investigator blinded to the group classification. The total consumption volume was investigated through data from the PCA machine. We analyzed CR rate during the 0 to 24 hours interval as the primary outcome. The secondary endpoints of CR included postoperative time intervals of 0 to 1, 1 to 6, 6 to 24, 24 to 48, and 0 to 48 hours. Also, pain and sedation were analyzed as secondary outcomes.

Based on the findings of a previous study, we assumed the CR rate would be 43% with a single injection of palonosetron[14] and expected that the CR rate would be 70% when palonosetron administration was combined with midazolam in addition to IV-PCA. Based on an α error of 0.05 and power of 0.8, 52 patients would be needed in each group.

Continuous variables are expressed as the mean ± standard deviation and analyzed using the *t* test or Mann–Whitney *U* test. Categorical variables are expressed as the percentage of the number of patients (%) and analyzed using the chi-squared or Fisher exact test.

We used SPSS for statistical analysis and a P value $<.05$ was considered statistically significant.

3. Results

We enrolled 104 female patients (Fig. 1). No patient dropped out after randomization, and 52 patients in each group were included

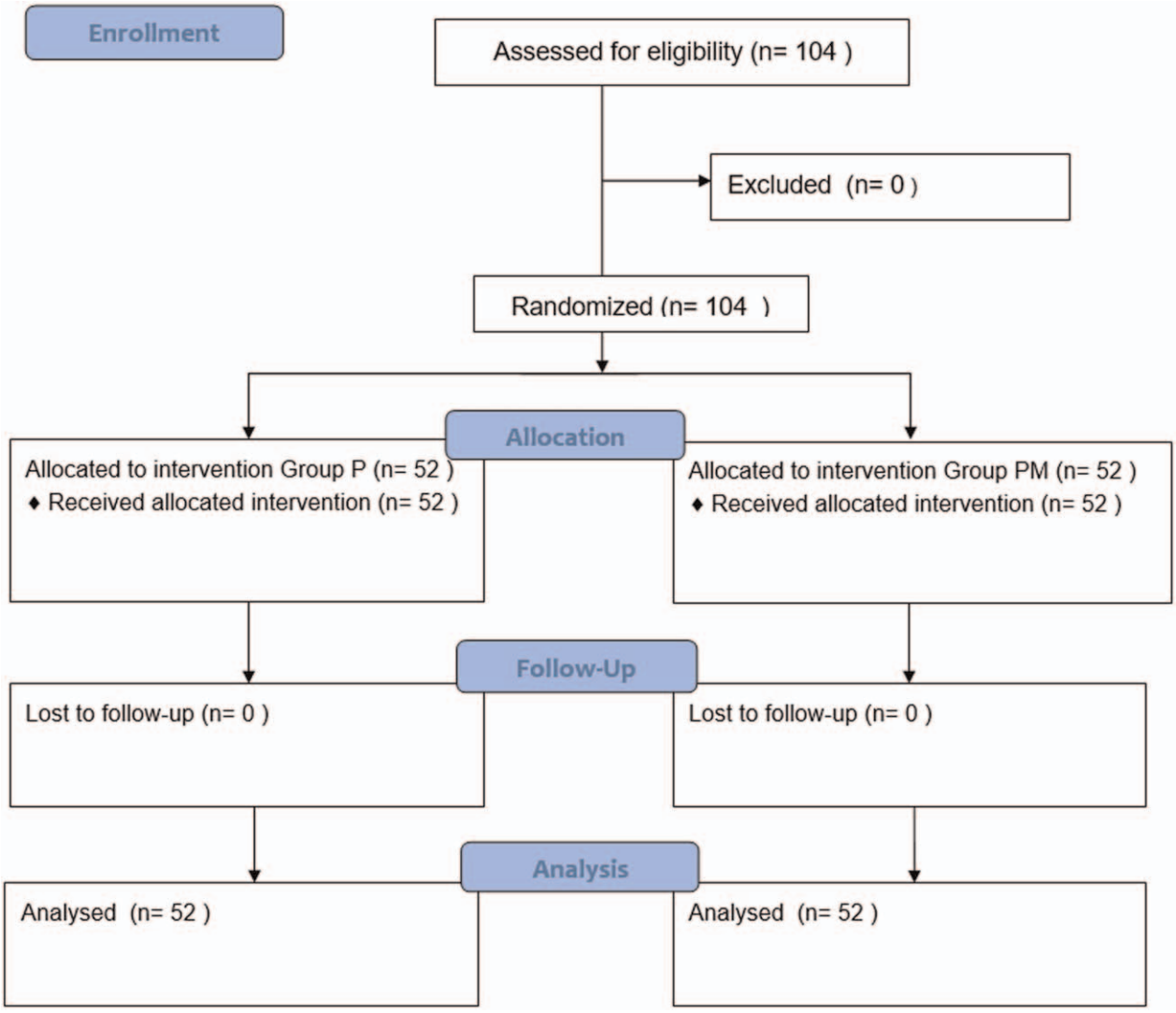

Figure 1. Flow chart indicating patient selection. Group P, palonosetron alone group (0.075 mg palonosetron intravenous administration) and Group PM, palonosetron-midazolam combination group (0.075 mg palonosetron intravenous administration + 4 mg midazolam added into patient-controlled analgesia). Group P = palonosetron monotherapy group, Group PM = palonosetron-midazolam combination therapy group.

in the analysis. There was no significant difference in age, weight, height, anesthetic time, history of PONV or motion sickness, smoking history, simplified Apfel score, the total volume of administered PCA, and PCA connection time between the 2 groups (Table 1). The simplified Apfel scores of the patients included in the study were all 3 or 4 points except for 2 patients in the PM group (2 points).

Although the CR rate between 0 and 24 hours was higher in group PM (42.3% and 48.1% in group P and PM, respectively), there was no statistically significant difference ($P = .55$). The CR rates in other time intervals were not different between the 2 groups as well (Table 2, Fig. 2). The incidence of nausea, vomiting, and the number of patients who stopped PCA were also not different between both groups (Table 2).

We evaluated the degree of sedation using the OAA/S score. Although light sedation (score 4) was greater in group PM during 1 to 24 hours, there was no statistical difference. In addition, no patient in either group scored ≤ 3 on the OAA/S score during the 48 hours postoperative period (Table 3).

Table 1

Characteristics of patients.

Variable	Group P (n = 52)	Group PM (n = 52)	*P* value
Age (yr)	48.1 (7.4)	45.9 (6.8)	.11
Weight (kg)	57.1 (7.8)	56.9 (7.6)	.88
Height (cm)	157.9 (5.1)	158.3 (5.1)	.74
Anesthesia time (min)	244.3 (66.9)	264.2 (86.7)	.19
PONV history	5 (9.6%)	9 (17.3%)	.39
Non-smoker	52 (100%)	50 (98.1%)	.49
Simplified Apfel Score			.73
2	0 (0%)	2 (3.8%)	
3	48 (92.3%)	43 (82.7%)	
4	4 (7.7%)	7 (13.5%)	
Patient-controlled analgesia			
Consumption volume (ml)	55.6 (23.7)	54.3 (24.7)	.71
Connection time (h)	48 (20–48)	48 (24.5–48)	.72

Group P = palonosetron alone group (0.075 mg palonosetron intravenous administration), Group PM = palonosetron-midazolam combination group (0.075 mg palonosetron intravenous administration + 4 mg midazolam added into patient-controlled analgesia), PCA, patient-controlled analgesia, PONV = postoperative nausea and vomiting. Data are mean ± SD, number of patients (%), or median (interquartile range).

Table 2

Incidence of complete response, nausea, and vomiting during the 48 hours after surgery.

	Group P (n = 52)	Group PM (n = 52)	*P* value
0–24 h			
CR	22 (42.3)	25 (48.1)	.55
Nausea	30 (57.7)	27 (51.9)	.55
Vomiting	6 (11.5)	10 (19.2)	.28
Stopped due to nausea	15 (28.8)	8 (15.4)	.10
Stopped due to sedation	0	0	
0–1 h			
CR	36 (69.2)	38 (73.1)	.66
Nausea	16 (30.8)	14 (26.9)	.66
Vomiting	1 (1.9)	2 (3.8)	>.99
Stopped due to nausea	0	0	
Stopped due to sedation	0	0	
1–6 h			
CR	35 (67.3)	38 (73.1)	.52
Nausea	17 (32.7)	14 (26.9)	.52
Vomiting	0	2 (3.8)	.49
Stopped due to nausea	4 (7.7)	2 (3.8)	.67
Stopped due to sedation	0	0	
6–24 h			
CR	26 (50)	30 (57.7)	.43
Nausea	26 (50)	22 (42.3)	.43
Vomiting	5 (9.6)	7 (13.5)	.76
Stopped due to nausea	15 (28.8)	8 (15.4)	.09
Stopped due to sedation	0	0	
24–48 h			
CR	32 (61.5)	31 (59.6)	.84
Nausea	20 (38.5)	19 (36.5)	.83
Vomiting	1 (1.9)	0	>.99
Stopped due to nausea	14 (26.9)	12 (23.1)	.65
Stopped due to sedation	0	2 (3.8)	.49

CR = complete response, Group P = palonosetron alone group (0.075 mg palonosetron intravenous administration), Group PM = palonosetron-midazolam combination group (0.075 mg palonosetron intravenous administration + 4 mg midazolam added into patient-controlled analgesia). Data are the number of patients (%). There are no significant differences between groups ($P > .05$).

Table 3

Degree of sedation.

Time	Degree of sedation	Group P (N = 52)	Group PM (N = 52)	*P* value
0–1 h				.97
	5	48 (92.3)	49 (94.2)	
	4	4 (7.7)	3 (5.8)	
	3	0	0	
	2	0	0	
	1	0	0	
1–6 h				.07
	5	46 (88.5)	41 (78.8)	
	4	6 (11.5)	11 (21.2)	
	3	0	0	
	2	0	0	
	1	0	0	
6–24 h				.23
	5	51 (98.1)	49 (94.2)	
	4	1 (1.9)	3 (5.8)	
	3	0	0	
	2	0	0	
	1	0	0	
24–48 h				.57
	5	50 (96.2)	52 (100)	
	4	2 (3.8)	0	
	3	0	0	
	2	0	0	
	1	0	0	

Group P = palonosetron alone group (0.075 mg palonosetron intravenous administration), Group PM = palonosetron-midazolam combination group (0.075 mg palonosetron intravenous administration + 4 mg midazolam added into patient-controlled analgesia). Data are the number of patients (%). There are no significant differences between groups ($P > .05$).

Postoperative pain was most severe at 0 to 1 hours and decreased over time in both groups. There was no difference in pain score between the 2 groups during any period (Fig. 3).

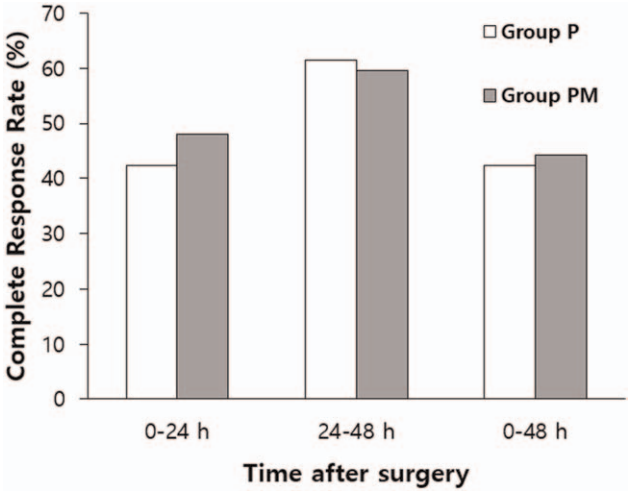

Figure 2. Complete response (no nausea and no vomiting) rate. Group P, palonosetron alone group (palonosetron 0.075 mg intravenous administration) and Group PM, palonosetron-midazolam combination group (palonosetron 0.075 mg intravenous administration + 4 mg midazolam added into patient-controlled analgesia). There is no significant difference between groups ($P > .05$). Group P = palonosetron monotherapy group, Group PM = palonosetron-midazolam combination therapy group.

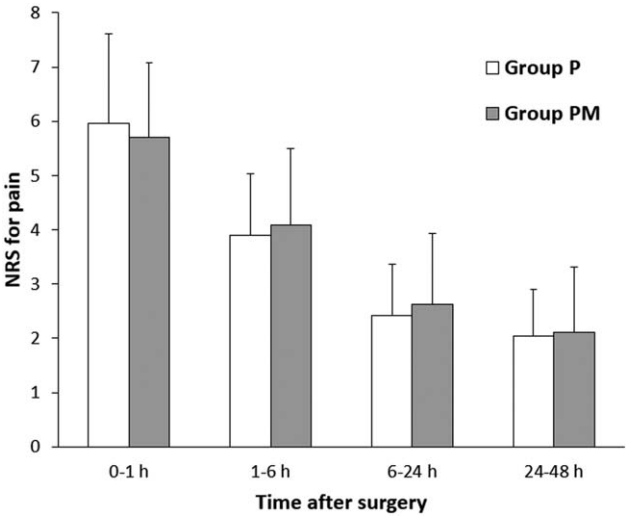

Figure 3. NRS for pain. Group P, palonosetron alone group (palonosetron 0.075 mg intravenous administration) and Group PM, palonosetron-midazolam combination group (palonosetron 0.075 mg intravenous administration + 4 mg midazolam added into patient-controlled analgesia). There is no significant difference between groups ($P > .05$). Group P = palonosetron monotherapy group, Group PM = palonosetron-midazolam combination therapy group, NRS = numerical rating scale.

4. Discussion

In this study, we found that there was no significant difference in preventing PONV between palonosetron monotherapy and palonosetron-midazolam combination therapy in patients undergoing breast cancer surgery and receiving IV-PCA using fentanyl.

Consensus guidelines for PONV management recommend that adult patients at moderate risk of PONV should receive combination therapy with drugs from different classes because efficacy is optimized when a combination of drugs with different mechanisms of action is used.[3]

Risk factors for PONV reported by Apfel et al include female sex, history of PONV and motion sickness, non-smoking status, young age, use of volatile anesthetics, duration of anesthesia greater than 1 hours, postoperative opioid use, and nitrous oxide use.[15,16] Additionally Apfel et al presented a simplified risk score. In this report, risk factors for PONV included female sex, non-smoking status, history of PONV, and postoperative opioid use, and they showed that when the number of risk factors present is 0, 1, 2, 3, or 4, the risk for PONV is approximately 10%, 20%, 40%, 60%, and 80%, respectively.[1]

In our study, patients had a moderate to severe risk of PONV. Most patients in our study had an Apfel score of 3 with common factors of the female sex, non-smoking status, and postoperative opioid use, and some patients had an Apfel score of 4 due to a history of PONV in addition to the other risk factors. In addition, the use of volatile anesthetics and the long duration of anesthesia (group P: 242.65 min, group PM: 264.23 min) may also increase the risk of PONV. Moreover, the enrolled patients underwent breast cancer surgery. Although it is known that cholecystectomy, gynecological surgery, and laparoscopic surgery are associated with a higher incidence of PONV, breast cancer surgery also has a high PONV incidence.[17,18]

A variety of combination therapies have been studied for patients at high risk of PONV.[3] In particular, first-generation 5-HT_3 antagonists, such as ondansetron or granisetron, were found to be effective when used in combination with dexamethasone.[19,20] Ondansetron was also more effective when used in combination with casopitant, transdermal scopolamine, haloperidol, and midazolam than single-drug therapy.[21–24] However, there was no significant difference in PONV prevention between combination therapy and single therapy in this study. We compared palonosetron-midazolam combination therapy with palonosetron monotherapy.

Palonosetron has a higher receptor affinity and longer half-life (40 h) than other 5-HT_3 antagonists. Palonosetron is known to be more effective in preventing PONV than granisetron, and ondansetron although they have the same mechanism of action.[25,26] Unlike the first-generation 5-HT_3 antagonists, there has not been much research on combination therapy using the second-generation 5-HT_3 antagonist, palonosetron. Only a few studies have reported the effect of palonosetron-dexamethasone combination therapy preventing PONV. Bala et al reported that the combination therapy of palonosetron 0.075 mg and dexamethasone 8 mg was more effective in preventing PONV than palonosetron monotherapy.[27,28] However, other studies reported that combination therapy using palonosetron and dexamethasone did not show a significant difference from using palonosetron monotherapy.[29,30] Cho et al[27] suggested that this lack of difference was due to the fact that the dose of dexamethasone used was just 4 mg, which was not optimal. Therefore, it seems to be important to determine the optimal dose for combination therapy.

In the present study, we added midazolam instead of dexamethasone to increase the chances of PONV prevention. Although dexamethasone has effective antiemetic properties, it can cause many side effects, such as adrenal insufficiency, increased wound infection, hyperglycemia, and diabetes.[31,32]

Midazolam is known to have an antiemetic effect and decrease the incidence of PONV even though its mechanism of action is not fully understood. Suggested antiemetic mechanisms include intensification of the adenosine effect in the chemoreceptor trigger zone, reduction of 5-HT secretion by binding to the GABA receptor, and reduction of preoperative anxiety.[13,33,34] Midazolam 2 mg given 30 minutes before the end of surgery was as effective as ondansetron 4 mg, and midazolam 1 mg/h given at the end of surgery was also effective.[35,36] Midazolam was also effective in reducing the incidence of PONV when midazolam was added to fentanyl or morphine PCA, and mixed administration of ondansetron and midazolam is reported to be more effective in preventing PONV.[12,13] However, in the present study, we found no significant difference between the PM and P groups.

We suspect that the dose of midazolam we used might account for this finding. We employed the lowest concentration that showed a positive antiemetic effect at the design stage to minimize side effects, such as over-sedation, caused by midazolam. Kim study used a small dose of midazolam (0.0415 mg/h) and showed that midazolam added to PCA was more effective than ondansetron.[13] Therefore, we used 0.04 mg/h of midazolam in this study. The average total amount of PCA injected during the study period (median 48 h) including the demand amount was 54.3 ml. Considering that a loading dose of 4 ml was administered, a total of 2.33 mg of midazolam was administered in our study. However, other previous studies showed positive antiemetic effect have used much higher concentrations of midazolam than our study. Di Florio and Goucke used 1 mg/h of midazolam (total of 10 mg during 9 h) and Sanjay and Tauro used 0.02 mg/kg/h of midazolam (total of 33.64 mg during 24 h).[37,38] Although there was no statistical difference, our result showed that the CR rate was higher in the first 24 hours in the PM group. Therefore, if we increase the dose of midazolam, the difference may become significant. However, this requires further study and in this case, side effects caused by midazolam may also increase. In this study, we were concerned that midazolam would cause over-sedation and delay recovery from general anesthesia. Respiratory depression, which can occur when midazolam and opioids are administered together, was another concern. However, there was no difference in the OAA/S score. Furthermore, no patient experienced respiratory depression or had an OAA/S score of $\leq$3. Kim study showed similar results.[13] However, these side effects will occur more frequently when increased doses of midazolam were added to IV-PCA or this regimen is administered to high-risk patients, such as the elderly. Huh study showed a significant increase in sedation although mild, in the PCA group with midazolam 0.4 mg/ml.[12]

The pharmacological difference would be 1 of the reasons for the different results of this palonosetron study with the previous ondansetron study. While other previous 5-HT_3 receptor antagonists directly compete with serotonin, palonosetron uniquely acts indirectly by allosteric binding with the 5-HT_3 receptor.[39] As a result, palonosetron has a higher affinity with the 5-HT_3 receptor, which causes greater potency and longer

duration than previous 5-HT_3 receptor antagonists. Moon et al described these characteristics of palonosetron could decrease the need for combination therapy required for PONV prevention.[40]

Although combination therapy is recommended to prevent PONV, the addition of drugs may increase the potential side effects and cost of the drug. Thus, palonosetron monotherapy seems to have advantages regarding its equivalent effect in preventing PONV while reducing the risk of side effects in this study.

There were no significant differences in NRS for pain between the groups. There was also no difference in ketorolac requirements between the 2 groups. Although the combination of fentanyl and midazolam is known to have a synergic effect,[41] our study did not show any group difference. These results also appear to be due to the low dose of midazolam administered.

There were some limitations to this study. We investigated only CR, which did not reflect the degree of PONV. If we used a standardized score system, such as the Rhodes index of nausea, vomiting, and retching, we might have found significant differences. We performed this study only in breast cancer surgery patients to avoid the effects of heterogeneity of surgery type. Therefore, if we repeat this study in other operations, such as laparoscopic surgery or gynecological surgery, we might obtain a different result.

In conclusion, the addition of low doses of midazolam in PCA did not significantly reduce PONV more than using palonosetron alone in patients undergoing breast surgery and receiving IV-PCA using fentanyl. Further study on the proper combination and optimal dosing for different systems of combination therapy to prevent PONV without any side effects of the drugs used is necessary.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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References

[1] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999;91:693–700.
[2] Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999;91:109–18.
[3] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118:85–113.
[4] Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery – a prospective study. Can J Anaesth 1998;45:612–9.
[5] Schumann R, Polaner DM. Massive subcutaneous emphysema and sudden airway compromise after postoperative vomiting. Anesth Analg 1999;89:796–7.
[6] Zhang GS, Mathura JRJr. Images in clinical medicine. Painless loss of vision after vomiting. N Engl J Med 2005;352:e16.
[7] Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441–51.
[8] Arslan M, Cicek R, Kalender HÜ, Yilmaz H. Preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a prospective, randomized, double-blind study. Curr Ther Res Clin Exp 2011;72:1–12.
[9] Chan MT, Choi KC, Gin T, et al. The additive interactions between ondansetron and droperidol for preventing postoperative nausea and vomiting. Anesth Analg 2006;103:1155–62.
[10] Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. Can J Anaesth 2004;51:311–9.
[11] Stoltz R, Cyong JC, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in U.S. and Japanese healthy subjects. J Clin Pharmacol 2004;44:520–31.
[12] Huh BK, Jung S, White W, Jeon Y. Anti-emetic effect of midazolam added to morphine patient-controlled analgesia after total abdominal hysterectomy. Anaesth Intensive Care 2010;38:481–5.
[13] Kim DS, Koo GH, Kang H, et al. The antiemetic effect of midazolam or/and ondansetron added to intravenous patient controlled analgesia in patients of pelviscopic surgery. Korean J Anesthesiol 2012;62:343–9.
[14] Candiotti KA, Kovac AL, Melson TI, et al. Palonosetron 04-06 Study Group. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting. Anesth Analg 2008;107:445–51.
[15] 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.
[16] Apfel CC, Philip BK, Cakmakkaya OS, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? Anesthesiology 2012;117:475–86.
[17] Singhal AK, Kannan S, Gota VS. 5HT3 antagonists for prophylaxis of postoperative nausea and vomiting in breast surgery: a meta-analysis. J Postgrad Med 2012;58:23–31.
[18] Sadhasivam S, Saxena A, Kathirvel S, Kannan TR, Trikha A, Mohan V. The safety and efficacy of prophylactic ondansetron in patients undergoing modified radical mastectomy. Anesth Analg 1999;89:1340–5.
[19] Bano F, Zafar S, Aftab S, Haider S. Dexamethasone plus ondansetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a comparison with dexamethasone alone. J Coll Physicians Surg Pak 2008;18:265–9.
[20] Biswas BN, Rudra A. Comparison of granisetron and granisetron plus dexamethasone for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2003;47:79–83.
[21] Altorjay A, Melson T, Chinachoit T, et al. Casopitant and ondansetron for postoperative nausea and vomiting prevention in women at high risk for emesis: a phase 3 study. Arch Surg 2011;146:201–6.
[22] Singla NK, Singla SK, Chung F, et al. Phase II study to evaluate the safety and efficacy of the oral neurokinin-1 receptor antagonist casopitant (GW679769) administered with ondansetron for the prevention of postoperative and postdischarge nausea and vomiting in high-risk patients. Anesthesiology 2010;113:74–82.
[23] Gan TJ, Sinha AC, Kovac AL, et al. A randomized, double-blind, multicenter trial comparing transdermal scopolamine plus ondansetron to ondansetron alone for the prevention of postoperative nausea and vomiting in the outpatient setting. Anesth Analg 2009;108:1498–504.
[24] Grecu L, Bittner EA, Kher J, Smith SE, Rosow CE. Haloperidol plus ondansetron versus ondansetron alone for prophylaxis of postoperative nausea and vomiting. Anesth Analg 2008;106:1410–3.
[25] Bhattacharjee DP, Dawn S, Nayak S, Roy PR, Acharya A, Dey R. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2010;26:480–3.
[26] Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and

vomiting after gynaecological laparoscopic surgery. J Int Med Res 2011;39:399–407.
[27] Cho E, Kim DH, Shin S, Kim SH, Oh YJ, Choi YS. Efficacy of palonosetron-dexamethasone combination versus palonosetron alone for preventing nausea and vomiting related to opioid-based analgesia: a prospective, randomized, double-blind trial. Int J Med Sci 2018;15: 961–8.
[28] Bala I, Bharti N, Murugesan S, Gupta R. Comparison of palonosetron with palonosetron-dexamethasone combination for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiol 2014;80:779–84.
[29] Park JW, Jun JW, Lim YH, et al. The comparative study to evaluate the effect of palonosetron monotherapy versus palonosetron with dexamethasone combination therapy for prevention of postoperative nausea and vomiting. Korean J Anesthesiol 2012;63:334–9.
[30] Blitz JD, Haile M, Kline R, et al. A randomized double blind study to evaluate efficacy of palonosetron with dexamethasone versus palonosetron alone for prevention of postoperative and postdischarge nausea and vomiting in subjects undergoing laparoscopic surgeries with high emetogenic risk. Am J Ther 2012;19:324–9.
[31] Busti AJ, Hooper JS, Amaya CJ, Kazi S. Effects of perioperative antiinflammatory and immunomodulating therapy on surgical wound healing. Pharmacotherapy 2005;25:1566–91.
[32] Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Ann Nutr Metab 2014;65:324–32.
[33] Racke K, Schworer H, Kilbinger H. Effects of the benzodiazepine receptor agonist midazolam and antagonist flumazenil on 5-hydroxytryptamine release from guinea-pig intestine in vitro. Indirect support for a "natural" benzodiazepine-like substance in the intestine. Naunyn Schmiedebergs Arch Pharmacol 1990;341:1–7.
[34] Phillis JW, Bender AS, Wu PH. Benzodiazepines inhibit adenosine uptake into rat brain synaptosomes. Brain Res 1980;195:494–8.
[35] Tarhan O, Canbay O, Celebi N, et al. Subhypnotic doses of midazolam prevent nausea and vomiting during spinal anesthesia for cesarean section. Minerva Anestesiol 2007;73:629–33.
[36] Lee Y, Wang JJ, Yang YL, Chen A, Lai HY. Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. Anaesthesia 2007;62:18–22.
[37] Di Florio T, Goucke CR. The effect of midazolam on persistent postoperative nausea and vomiting. Anaesth Intensive Care 1999;27:38–40.
[38] Sanjay OP, Tauro DI. Midazolam: an effective antiemetic after cardiac surgery – a clinical trial. Anesth Analg 2004;99:339–43.
[39] Rojas C, Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. Anesth Analg 2008;107:469–78.
[40] Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. Br J Anaesth 2012;108:417–22.
[41] Ben-Shlomo I, Abd-el-Khalim H, Ezry J, Zohar S, Tverskoy M. Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth 1990;64:45–7.