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Comparison of palonosetron with combined palonosetron and midazolam for preventing postoperative nausea and vomiting after laparoscopic cholecystectomy

Eun Kyung Choi, MD, PhD[a,*], Sang-Jin Park, MD, PhD[a], Chanyang Park, MD[a], Jung A. Lim, MD[b]

Abstract

Background: Postoperative nausea and vomiting (PONV) is an undesirable complication in patients undergoing general anesthesia. Combination therapy via different mechanisms of action for antiemetic prophylaxis has been warranted for effective treatment of PONV. This study was designed to compare the prophylactic antiemetic effect between midazolam combined with palonosetron (group MP) and palonosetron alone (group P) after laparoscopic cholecystectomy surgeries.

Methods: A prospective randomized controlled trial was investigated in non-smoking female. Eighty-eight patients were randomly divided into 2 groups with 44 patients each. Group MP received 0.05 mg/kg of midazolam intravenously before induction of anesthesia whereas group P received the same volume of normal saline. Immediately after anesthetic induction, 0.075 mg of palonosetron was administered to both the groups. The incidence and severity of PONV were assessed during 2 time intervals (0–2 hours, 2–24 hours), postoperatively.

Results: The incidence of PONV during 24 hours after surgery was lower in group MP as compared to group P. There was also a significant difference in the use of rescue antiemetics. The severity of nausea was significantly lower in group MP as compared to group P, in the initial 2 hours after surgery. The incidence of side effects was similar between the 2 groups.

Conclusion: In the prevention of PONV, midazolam combined with palonosetron, administered during induction of anesthesia was more effective as compared to palonosetron alone.

Abbreviations: 5-HT_3 = 5-hydroxytryptamine, PONV = postoperative nausea and vomiting.

Keywords: laparoscopic cholecystectomy, midazolam, palonosetron, postoperative nausea and vomiting

1. Introduction

Postoperative nausea and vomiting (PONV) is an undesirable complication in patients undergoing general anesthesia, and its incidence is nearly 46% to 75% in laparoscopic cholecystectomy surgeries.[1,2] Antiemetic prophylaxis by a single pharmacological agent can partially reduce the incidence of PONV whereas combination therapy via different mechanisms of action has been warranted for more effective treatment of PONV,[3] in high-risk patients.[4,5]

Palonosetron, a 5-hydroxytryptamine (5-HT_3) receptor antagonist, is commonly used for the prophylaxis and treatment of PONV due to its better efficacy and favorable side effects. This agent has a greater receptor affinity with longer duration of action as compared to traditional antiemetics such as ondansetron.[6] However, incidence of PONV was up to 50% in patients given either palonosetron or ramosetron after laparoscopic surgery (or in high-risk patients).[7]

Midazolam is a short acting benzodiazepine that possesses anxiolytic, amnestic, and anesthetic properties. Benzodiazepines have been recently researched in clinical practice for their role as antiamnestics. Prophylactic intravenous administration of midazolam (0.05–0.075 mg/kg) reduced the incidence of PONV[8,9] and some of the reports showed that it is as effective as any other antiemetic drug.[10] Therefore, we hypothesized that midazolam in combination therapy with other antiemetics might have a better effect at reducing the incidence of PONV than the antiemetics alone.

In this study, we investigated the prophylactic antiemetic effect between midazolam combined with palonosetron and palonosetron alone in patients undergoing laparoscopic cholecystectomy surgery.

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

[a] Department of Anesthesiology and Pain Medicine, Yeungnam University College of Medicine, Daegu, Republic of Korea, [b] Department of Anesthesiology and Pain Medicine, School of Medicine, Catholic University of Daegu, Daegu, Republic of Korea.

[*] Correspondence: Eun Kyung Choi, Department of Anesthesiology and Pain Medicine, Yeungnam University College of Medicine, 170, Hyeonchung-ro, Nam-gu 42415, Daegu, Republic of Korea (e-mail: zzini0527@naver.com).

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2. Methods

This study was approved by the Institutional Review Board of Yeungnam University Hospital, Daegu, Republic of Korea and was registered in a ClinicalTrials.gov (NCV03933605). Written informed consent was obtained from all patients and 88 patients were assigned by computer-generated randomization with sealed-envelope method. The female, non-smoker patients (age 20–65 years) scheduled for laparoscopic cholecystectomy with American Society of Anesthesiologists (ASA) physical status classification of ASAI or ASAII, were administered either palonosetron alone (group P) or midazolam and palonosetron (group MP). Exclusion criteria included history of allergy to any other drug used in this study, gastrointestinal disorders, pregnancy, breastfeeding women, use of antiemetics within 24 hours, and body mass index >30 kg/m^2.

Without pre-medication, standardized monitoring was applied in the operating room. After monitoring, patients in the group MP received 0.05 mg/kg of midazolam IV, whereas patients in the group P received the same volume of normal saline IV. Anesthesia was induced with propofol (1.5–2.5 mg/kg) and remifentanil infusion (0.15–0.3 μg/kg/min). After administering rocuronium (0.6–1 mg/kg), tracheal intubation was done. Immediately after anesthetic induction, 0.075 mg of palonosetron was administered in the patients of both the groups. Anesthesia was maintained using sevoflurane in 50% oxygen with air and remifentanil infusion (0.05–0.2 μg/kg/min) throughout surgery, in order to maintain the hemodynamic stability and bispectral index between 40 and 50. At the end of surgery, administration of anesthetic maintenance drugs was stopped and ketorolac 30 mg IV was administered for postoperative pain control. Residual neuromuscular block was reversed using pyridostigmine and glycopyrrolate. An anesthesiologist who was blinded to group assignment performed all anesthetic procedures.

In the postanesthetic care unit, incidence of nausea and vomiting was assessed during 2 time intervals (0–2 hours, 2–24 hours) and severity of nausea was also assessed using a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe). A rescue antiemetic (metoclopramide 10 mg) was administered when the patient requested a rescue drug or had severe nausea or vomiting episode. Postoperative pain was assessed using a numerical rating scale (0–10) and additional analgesic administration (fentanyl 50 μg, when numerical rating scale ≥ 5 or patient requests) was also recorded. Side effects such as headache, dizziness, and skin flushing were evaluated and an anesthesiologist who was unaware of the study protocol did study assessments.

2.1. Statistical analysis

According to our preliminary study, the incidence rate of PONV up to 2 hours after surgery was 60% in patients receiving palonosetron only. While considering a 50% reduction in the incidence of PONV in combination group of midazolam and palonosetron would be clinically relevant, 40 patients were required in each group using power analysis with α error of 5% and a power of 80%. Total 92 patients were selected for study taking account of the possible dropouts. Data were expressed as number (%) or means ± SD. Statistical analysis was performed using SPSS software (Chicago, IL). Chi-square, Fisher exact, or Student *t* test was applied as appropriate. $P < .05$ was considered statistically significant ().

3. Results

Out of 92 patients screened, 4 were excluded based on exclusion criteria and refusal to participate. The demographic and operative data of patients were statistically not different in the

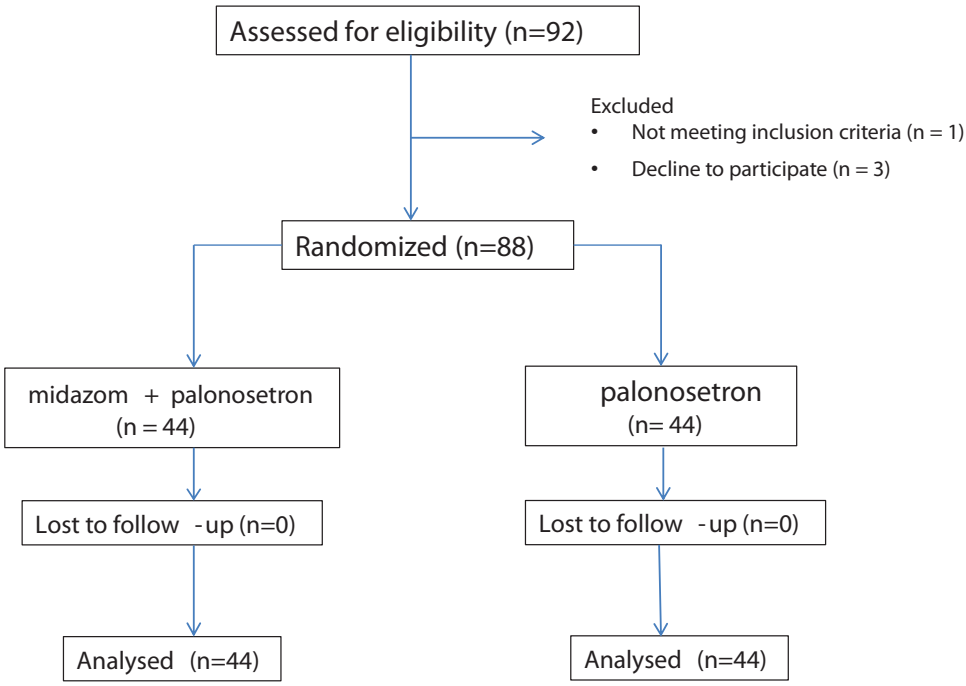

Figure 1. Flow diagram of the study.

Table 1

Patient characteristics and intraoperative data.

	Group P (n = 44)	Group MP (n = 44)
Age (yr)	49.6 ± 11.8	48.2 ± 10.9
Weight (kg)	61.1 ± 8.8	57.8 ± 7.4
Height (cm)	157.4 ± 6.9	157.3 ± 6.5
Operation time (min)	30.0 ± 9.7	31.9 ± 13.7
Anesthesia time (min)	53.8 ± 12.6	55.1 ± 14.9
Recovery time (min)	7.0 ± 2.3	6.6 ± 1.6
History of smoking (n)	0	0
History of PONV or motion sickness (n)	2 (4.5)	1 (2.3)

Data were expressed as mean ± SD or number (%).
PONV = postoperative nausea and vomiting, Group P = palonosetron group, Group MP = midazolam + palonosetron group.

both groups (Table 1). The incidence of PONV during 24 hours postsurgery was lower in the midazolam and palonosetron combination group as compared to palonosetron alone group ($P = .08$). There was a significant difference in the incidence of nausea during the first 2 hours ($P = .006$) whereas the incidence was not different between both groups during 2 to 24 hours after surgery. There was also a significant difference in use of rescue antiemetics during 24 hours after surgery ($P = .068$) and first 2 hours postoperatively ($P = .013$) (Table 2). The severity of nausea was significantly lower in the midazolam and palonosetron combination group as compared to palonosetron alone group in the initial 2 hours after surgery ($P = .013$) (Table 3). The degree of postoperative pain (numerical rating scale scores) and use of analgesics was not different between both the groups (Table 4). The incidence of side effects such as headache, dizziness, drowsiness, and skin flushing was similar between the 2 groups (Table 5).

4. Discussion

In the present study, midazolam and palonosetron in combination was more effective than palonosetron alone in lowering the incidence and severity of PONV in the initial 2 hours after laparoscopic cholecystectomy. Postoperative clinical complications such as headache, dizziness, drowsiness, and skin flushing were not different in both the groups.

Table 2

Incidence of postoperative nausea and vomiting and the usage of rescue antiemetic.

	Group P (n = 44)	Group MP (n = 44)	*P* value
0–2 h			
Nausea	29 (65.9)	16 (36.4)	.006*
Vomiting	1 (2.3)	0	.315
Rescue antiemetic	10 (22.7)	2 (4.5)	.013*
2–24 h			
Nausea	12 (27.3)	13 (29.5)	.813
Vomiting	0	0	1.000
Rescue antiemetic	1 (2.3)	1 (2.3)	1.000
0–24 h			
Nausea	31 (70.5)	23 (52.3)	.08*
Vomiting	1 (2.3)	0	.315
Rescue antiemetic	10 (22.7)	3 (6.8)	.068*

Values are number (%).
Group P = palonosetron group, Group MP = midazolam + palonosetron group.
* Statistically significant with a *P* value < .05.

Table 3

Severity of postoperative nausea.

	Group P (n = 44)	Group MP (n = 44)	*P* value
0–2 h			
None	15 (34.1)	28 (63.6)	
Mild	21 (47.7)	15 (34.1)	.013*
Moderate	4 (9.1)	1 (2.3)	
Severe	4 (9.1)	0	
2–24 h			
None	32 (72.7)	31 (70.5)	
Mild	7 (15.9)	12 (27.3)	.135
Moderate	5 (11.4)	1 (2.3)	
Severe	0	0	

Values are number (%).
Group P = palonosetron group, Group MP = midazolam + palonosetron group.
* Statistically significant with a *P* value < .05.

PONV incidence is higher after laparoscopic cholecystectomy than after other types of surgery.[1–2] PONV is influenced by multiple factors which are related to the patient (female, nonsmoker, history of motion sickness), surgery type (head, neck, laparoscopic, gynecologic), and anesthetic factors (opioid).[11] Although PONV may be considered an emotionally unpleasant problem to patients after general anesthesia, it can increase the morbidity of patients by causing a significantly distressing outcome.[12,13] Till date, wide range of research has been done to establish multimodal approach including pharmacological and non-pharmacological interventions for prevention of PONV.[14,15]

Selective 5-HT_3 antagonists have primarily been used for PONV prevention because of the fewer side effects such as extrapyramidal symptoms and sedation, than any other antiemetics. Palonosetron has greater potency and longer duration of action as compared to other agent in this class. Although the older 5-HT_3 antagonists such as ondansetron directly compete with serotonin receptor,[16] palonosetron is an allosteric 5-HT_3 antagonist that causes conformational change in the serotonin receptor, resulting in indirect inhibition of the serotonin receptor.[16] Additionally, it also inhibits substance P through 5-HT_3/neurokinin-1 receptor cross talk, which shows the effect of the drug on the delayed emesis after chemotherapy.[17] Apart from these unique pharmacodynamic properties of palonosetron, it has less effect on QTc prolongation in contrast to previous standard 5-HT_3 antagonists.[18]

Combination therapy for PONV is preferable to monotherapy.[3,19,20] As PONV occurs through various receptors related to nausea and vomiting, combined use of antiemetics with different sites of action may be more effective than using a solitary antiemetic, for preventing PONV. Hence, approach that is more

Table 4

The severity of pain and recovery variables.

	Group P (n = 44)	Group MP (n = 44)	*P* value
NRS pain score			
0–2 h	4.13 ± 1.33	4.70 ± 1.02	.175
2–24 h	2.04 ± 1.01	2.79 ± 0.76	.525
Rescue analgesic use	16 (36.4)	23 (52.3)	.133

Data were expressed as mean ± SD or number (%).
Group P = palonosetron group, Group MP = midazolam + palonosetron group, NRS = numerical rating scale.
* Statistically significant with a *P* value < .05.

Table 5

Side effects.

	Group P (n = 44)	Group MP (n = 44)	*P* value
Headache	2 (4.5)	4 (9.1)	.398
Dizziness	1 (2.3)	2 (4.5)	.557
Drowsiness	1	1	
Skin flushing	0	0	

Values are number (%).

Group P = palonosetron group, Group MP = midazolam + palonosetron group.

comprehensive is needed in patients with high risk of PONV to prevent it. With this regard it has been recently demonstrated that intravenous midazolam as a part of combination therapy has better efficacy than single therapy.[8] Midazolam is commonly used as hypnotic agent in the general anesthesia due to its anesthetic and amnestic properties. Moreover, it is widely used as pre-medication agent because of its anxiolytic property. The mechanism of midazolam in prevention of PONV over and above its traditional hypnotic and anxiolytic effect is not clear, although some probable mechanisms of action have been suggested till now. Firstly, inhibition of dopaminergic output from chemoreceptor trigger zone area, through direct antagonism of adenosine or inhibition of γ-amino butyric acid.[21,22] Secondly, reduction in the use of postoperative opioid when midazolam was administered, might lessen PONV.[23,24]

According to systemic review, dose range of midazolam as a prophylactic antiemetic is 0.04 to 0.075 mg/kg.[25] Relatively low drug dosing of midazolam can provide prevention of PONV as well as anxiolysis.[25] In this study, we administered 0.05 mg/kg of midazolam for prevention of PONV, which was effective at reducing PONV without potentiating the side effects during the recovery period. Regarding the timing of midazolam administration, antiemetic effect of midazolam was similar during 3 time periods (pre-operative, intraoperative, and postoperative),[25] therefore, we administered midazolam during anesthetic induction. Although some side effects such as delayed recovery time and drowsiness have to be considered regarding the use of midazolam, the results of this study showed that these adverse effects were not significant. Moreover, typical side effects of 5-HT_3 receptor antagonists such as headache, dizziness, and skin flushing did not differ in the both groups. This suggests that intravenous midazolam and palonosetron as a multimodal approach to PONV prevention would be useful and tolerable in patients who undergo laparoscopic cholecystectomy.

This study has several limitations. Firstly, we did not check the incidence of PONV in the placebo group because withholding prophylactic antiemetics would be ethically unjustified. Secondly, data from this study revealed the effectiveness of midazolam as a part of combined approach for preventing PONV. Although the results are encouraging in the laparoscopic cholecystectomy, they may not be applicable to other types of surgery and anesthetic plans. Thirdly, we observed the incidence and severity of PONV only during postoperative 24 hours. Although 0.075 mg of palonosetron is an approved dose for the control of PONV for 24 hours after surgery,[26] the efficacy of single injection would be maintained for much longer time after treatment, due to its long half-life of 40 hours.[27] Especially, palonosetron is known to work better in delayed nausea and vomiting.[6] Additional studies would be needed for validation. Fourthly, we checked some side effects related to the use of midazolam including drowsiness, headache, and dizziness. However, we did not evaluate the values related to delayed postoperative recovery such as cognitive test and stay time in postanesthetic care unit although there was no difference in the emergence and recovery time.

5. Conclusion

Combination of palonosetron and midazolam had superior antiemetic efficacy as compared to a single injection of palonosetron in female patients undergoing laparoscopic cholecystectomy. Especially, combined use of both agents is associated with reduced postoperative nausea and antiemetic administration in the initial 2 hours after surgery.

Author contributions

Conceptualization: Eun Kyung Choi.
Data curation: Chanyang Park.
Formal analysis: Chanyang Park.
Funding acquisition: Eun Kyung Choi.
Methodology: Sang-Jin Park, Chanyang Park.
Software: Jung A Lim.
Supervision: Eun Kyung Choi, Jung A Lim.
Validation: Jung A Lim.
Writing – original draft: Sang-Jin Park.
Writing – review & editing: Eun Kyung Choi.

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