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ORIGINAL ARTICLE

A prospective, randomized, double-blind, multicenter trial to evaluate the therapeutic efficacy and safety of palonosetron in the treatment of postoperative nausea and vomiting over a 72-h period

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Abstract
Purpose We performed a multicenter, randomized, double-blind trial to assess the efficacy and safety of a single, fixed, intravenous dose of palonosetron (0.075 mg) in the treatment of established postoperative nausea and vomiting (PONV).
Methods Three hundred and eighty-four patients who had at least one risk factors of PONV and underwent surgery under general anesthesia were screened. Those who developed PONV were randomized to receive either 0.075 mg intravenous palonosetron or a placebo. The incidence of nausea and vomiting, severity of nausea, requirements for rescue anti-emetics, and adverse effects at 2, 24, and 72 h after drug administration were evaluated. Complete response (CR) and complete control (CC) rate were compared for 24 and 72 h.
Results Among the 384 patients, 152 (39.6 %) developed PONV and were randomized to either the palonosetron ($n = 75$) or placebo ($n = 77$) group. The number of patients with CR at 24 and 72 h was higher in the palonosetron group than the placebo group [0–24 h: $n = 49$ (68.1 %) vs. $n = 30$ (40.5 %), $p < 0.001$; 0–72 h: $n = 47$ (65.3 %) vs. $n = 28$ (37.8 %), $p < 0.001$]. The incidence of PONV at 2, 24, and 72 h periods was lower in the palonosetron group than the placebo group (29.2, 45.8, and 50.0 % in the palonosetron group vs. 50.0, 62.2, and 66.2 % in the placebo group, $p = 0.010$, 0.048, 0.047, respectively). The incidence of adverse events was not different between the groups.
Conclusion A single 0.075 mg IV dose of palonosetron effectively increased the CR rates at 24 and 72 h in these moderate-risk patients with established PONV.

Keywords 5-HT_3 receptor antagonist · Palonosetron · Postoperative nausea and vomiting · Anti-emetic agent

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Introduction

Postoperative nausea and vomiting (PONV) is a frequent complication that affects approximately one-third of all patients receiving general anesthesia, and can lead to subject discomfort and dissatisfaction as well as considerable medical and economic consequences [1–3]. The incidence of PONV was reported to be as high as 80 % in high-risk populations, and the incidence of postdischarge nausea and vomiting after outpatient surgery was also reported to be greater than 30 % [4]. Prevention and treatment of PONV is reported to be a key concern for patients undergoing general anesthesia [5].

Palonosetron, a second-generation 5-hydroxytryptamine 3 receptor antagonist (5-HT_3 RA), has a different mechanism from previous drugs in this family. Palonosetron exhibits high potency and persistent effects [6–8]. The half-life of palonosetron is 40 h, compared with 3.5–5.5 h of ondansetron and 4.9–7.7 h of granisetron [9]. Palonosetron is thought to be clinically superior to other 5-HT_3 RAs such as ondansetron and dolasetron [10, 11], due to its unique mechanism of allosteric binding [12], which is different from standard 5-HT_3 RAs. The receptor binding affinity of palonosetron is 30 times higher than granisetron, and 100 times higher than ondansetron [13, 14]. Palonosetron acts on substance *P* receptor, which is involved in delayed nausea and vomiting, whereas other 5-HT_3 RAs do not have an activity on substance *P* receptor [15].

Although there are many previously published clinical evidences of efficacy of 5-HT_3 RAs including palonosetron on the prevention of PONV [10, 16–24], we could not find a study evaluating the efficacy of palonosetron on the treatment of established PONV symptoms. To our knowledge, very few studies have been performed to evaluate the therapeutic efficacy of 5-HT_3 RAs as a treatment in subjects who develop PONV in the post-anesthesia care unit (PACU) [25–28]. Furthermore, the therapeutic efficacy of 5-HT_3 RAs as a rescue medication has been evaluated only during acute phase (up to 24 h) [29]. Since the management of postdischarge nausea and vomiting is important for patients to resume their normal daily activities [3, 4], proper evaluation of therapeutic efficacy in delayed phase is necessary.

Therefore, we performed a randomized, double-blind, multi-center trial to evaluate the therapeutic efficacy and safety of a single, fixed, intravenous dose of palonosetron (0.075 mg) in the treatment of established PONV following surgery under general anesthesia. We evaluated the therapeutic efficacy during 72 h after study drug administration.

Methods

After obtaining institutional review board (IRB) approval and written informed consent, we enrolled patients at four major university hospitals in South Korea. The present study was registered at www.clinicaltrials.gov (protocol ID NCT01568268). We enrolled adult patients with American society of anesthesiologists physical status classification I to II who were scheduled to undergo surgery under general anesthesia that was expected to last at least 30 min. The surgical procedure included predominantly gynecologic surgery, such as hysterectomy, myomectomy, ovarian cystectomy, salpingo-oopherectomy and other surgeries such as tympanoplasty, mastoidectomy, breast, or thyroid surgery.

We enrolled those who had at least one of the following risk factors for PONV [30]: history of PONV or motion sickness, and expected to use opioid analgesics intraoperatively. We excluded patients who had any of the following: a known hypersensitivity/contraindication to 5-HT_3 antagonists or study drug excipient; patients who were unable to understand the study procedures as determined by the investigators; women who were pregnant, breastfeeding, or planning to become pregnant, were not using effective birth control, or had a positive serum pregnancy test within 7 days prior to surgery; subjects who had received any investigational drug within 30 days before study enrollment, subjects who had taken any drug with potential anti-emetic efficacy within 24 h prior to anesthetic procedures; patients with known or suspected current history of alcohol abuse or drug abuse.

The anesthetic technique were controlled in all four institutions that participated in this study. Premedication was not administered. General anesthesia was induced using 5 mg/kg pentothal sodium, 0.5–1 μg/kg fentanyl and 0.8 mg/kg rocuronium. Anesthesia was maintained with 1.2–2.4 % (vol) isoflurane (end-tidal concentration) in 50 % nitrous oxide/oxygen [31, 32]. Nitrous oxide was not used in patients undergoing tympanoplasty or mastoidectomy. Ventilator setting was adjusted to keep end-tidal CO_2 at 35–45 mmHg throughout the surgery. Rocuronium was administered to maintain neuromuscular blockade. During the postoperative study period, patients were asked to report their level of pain verbally, using numerical rating scale (NRS, 0 = none, 10 = most severe). An IV bolus dose of ketorolac (30 mg, repeated if needed) was administered to the patients with NRS $\geq$ 2. We did not give any medication to prevent nausea and vomiting or with anti-emetic properties during the 24 h before anesthesia induction and study period.

We assessed the patients for study eligibility one day before surgery and performed a follow-up evaluation when the patients woke up and were able to respond to verbal

commands postoperatively. Screening test included electrocardiography, blood sample analysis, urinalysis and urine β-hCG test. Blood analysis included complete blood cell count with differential count, blood chemistry, and electrolytes. The written informed consent was provided before screening tests were undertaken and before they developed PONV.

Subjects experiencing nausea with NRS $\geq$ 4, or who developed retching or vomiting more than one time within two hours after the end of surgery at PACU were randomized to administration of 0.075 mg palonosetron intravenous injection or a placebo drug in 1:1 allocation ratio, using computer-generated random-number codes. To achieve a homogenous risk of PONV in each study group, stratified randomization was used according to gender, history of PONV or motion sickness. We used a dynamic adaptive stratification to balance the treatment group across the entire study. The hospital pharmacy independent of this study prepared the study drug according to this randomization code and confirmed that palonosetron was indistinguishable from its placebo. All study personnel, outcome assessor, care-provider and participants were blinded to group assignment during the study.

A single intravenous 0.075 mg of palonosetron (Aloxi®, Helsinn/CJ pharmaceutical) or placebo injectable volume of 1.5 ml was administered as IV by randomization code. If subjects still experienced nausea with NRS $\geq$ 4 or developed retching or vomiting after 30 min after study drug administration, they were given rescue anti-emetic medication at the investigator's discretion. The rescue anti-emetic used was IV metoclopramide (20 mg) or ondansetron (4 mg), and the use of rescue anti-emetic was recorded.

Patients or investigator (anesthesiologist) blinded to group allocation evaluated the following items 0, 0.5, 1, 2, 24, 48 and 72 h post-dose: incidence of nausea, retching and vomiting [33]; severity of nausea; need for additional anti-emetics; complete response (CR) rate; complete control (CC) rate; and quality of life (QoL) score measured by Osoba Nausea and Emesis module [34]. If the patient was discharged before 72 h, patients reported these outcomes in their provided diary cards. We evaluated the severity of nausea with a 10-point scale (NRS). CR was defined as no retching or vomiting and no administration of secondary rescue drug, and CC was defined as no nausea with NRS $\geq$ 4, in addition to complete response. Incidences of all adverse events were measured to evaluate the safety of palonosetron.

The primary outcome was CR rate at 24 h. We hypothesized that the CR rate at 24 h after study drug administration would be higher in the palonosetron group than in the placebo group. The sample size was calculated based on an assumed CR rate difference of 24 % point between two groups. Baseline CR rate was expected to be 50 % in the control group. For a two-tailed test with a power of 0.8 difference and a type I error of 0.05, the sample size was determined to be 60 evaluable subjects per group. Allowing for a 20 % dropout rate, 75 patients per group was ultimately determined. A total of 150 patients who developed PONV were included in this study.

Data values are expressed as mean (SD), median (IQR) or number (%). SAS software (version 9.2, SAS Inc., Cary, NC, USA) was used for statistical analysis. The Shapiro–Wilk test was used to test the normality of the distribution of data. CR and CC rate were compared by Chi square test. The comparison of continuous variables between groups was performed with unpaired t test or the Mann–Whitney test. The comparison of incidence variables between groups was performed with the χ^2 test or Fisher's exact test. Multiple comparisons of variables over time were adjusted by Bonferroni correction. The total score of the modified Osoba module questionnaire items was analyzed by the χ^2 test.

Results

A total of 384 patients were screened and 152 (39.6 %) among them were enrolled in this study in two treatment groups between January 2012 and June 2012. Six patients were withdrawn after randomization (Fig. 1). The efficacy analysis population was conducted on 72 patients receiving palonosetron and 74 receiving placebo, and all patients received originally assigned intervention. The time sequence of measurements is shown in Fig. 2.

Patient characteristics, including history of PONV or motion sickness, time and type of surgery and anesthesia, were similar for both groups (Table 1). The number of patients reaching CR at 24 and 72 h was significantly different in favor of the palonosetron group at 24 h: $n = 49$, 68.1 % vs. $n = 30$, 40.5 % in the placebo group, $p < 0.001$; and at 72 h: $n = 47$, 65.3 % in the palonosetron group vs. $n = 28$, 37.8 % in the placebo group, $p < 0.001$ (Fig. 3). The number of patients reaching CC rates at 24 and 72 h was not different between groups ($p = 0.127$, $p = 0.168$, respectively, Fig. 3). Overall PONV incidence and incidences of emesis at 2, 24 and 72 h after administration of the study drug were significantly lower in the palonosetron group than the placebo group (Table 2). Although incidence of nausea did not differ significantly between groups (Table 2), severity of nausea using NRS was significantly lower in the palonosetron group at between 0.5 and 1 h after the administration of the study drug [3 (2–4) in the palonosetron group vs. 3 (3–5) in the placebo group, $p = 0.025$, Table 3]. The incidence of administration of rescue

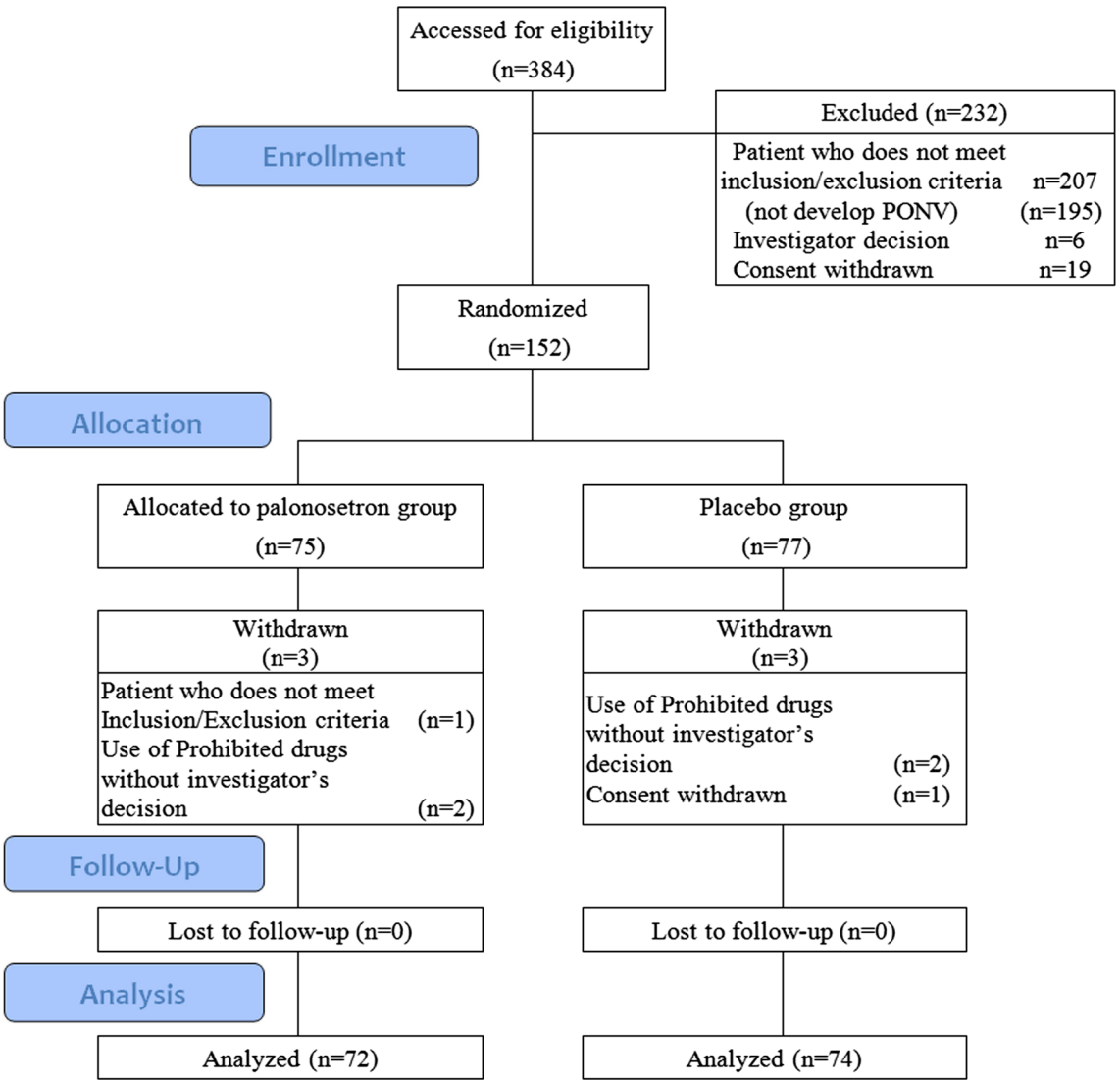

Fig. 1 Flow diagram of the study according to the CONSORT 2010

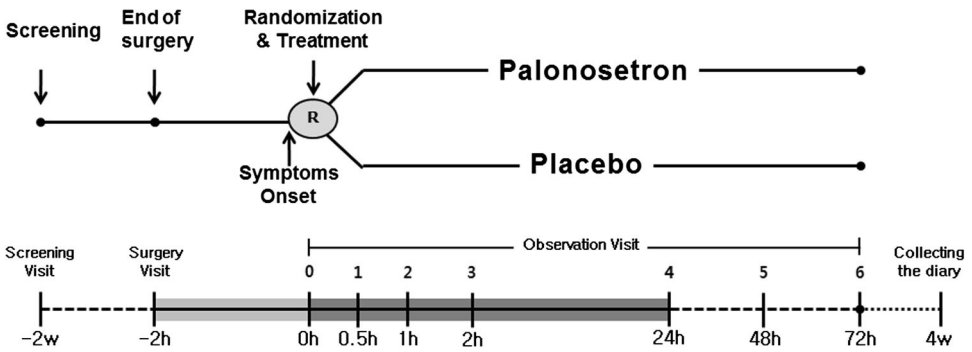

Fig. 2 Flow diagram showing the time sequence of measurements of the study

medication was significantly lower in the palonosetron group at 2 h after administration of the study drug (Table 2). At 72 h after study drug administration, quality of life was significantly better in the palonosetron group than in the placebo group (QoL score at 72 h: 5.2 ± 1.1 in the palonosetron group vs. 6.0 ± 2.5 in the placebo group, $p < 0.001$), and there were significantly more patients with QoL score of five (no functional

Table 1 Demographic and clinical characteristics in patients who received palonosetron or placebo

Parameters	Palonosetron group ($n = 72$)	Placebo group ($n = 74$)
Gender (male/female), (*n*)	2 (3)/70 (97)	3 (4)/71 (96)
Age (years)	42 (10)	41 (10)
Weight (kg)	60 (11)	59 (8)
Height (cm)	160 (5)	161 (6)
Body Mass Index (kg/m^2)	23.5 (4.2)	23.0 (2.9)
Time from PONV until study drug administration (min)	5.2 (4.5)	5.9 (5.9)
History of PONV or motion sickness (*n*)	28 (39)	25 (34)
ASA physical status classification		
1	55 (76)	61 (82)
2	17 (24)	13 (18)
3	0	0
Number of risk factors for PONV		
1	2 (3)	10 (14)
2	44 (61)	41 (55)
3	26 (36)	23 (51)
Surgical procedure		
Hysterectomy	22 (31)	15 (20)
Ovarian cystectomy	18 (25)	14 (19)
Myomectomy	14 (19)	23 (31)
Cholecystectomy	8 (11)	7 (10)
Salpingo-oophorectomy	4 (6)	1 (1)
Tympanoplasty or mastoidectomy	2 (3)	4 (5)
Other gynecologic surgery	4 (6)	3 (4)
Other breast, thyroid surgery	0 (0)	7 (10)
Duration of surgery (min)	104 (45)	103 (40)

Data are presented as mean (SD) or number (%)

p values are the results of unpaired *t*-test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. Number of risk factors for PONV was counted for female gender, history of PONV or motion sickness, and use of intraoperative opioid

PONV Postoperative nausea and vomiting, *ASA* American Society of Anesthesiologist

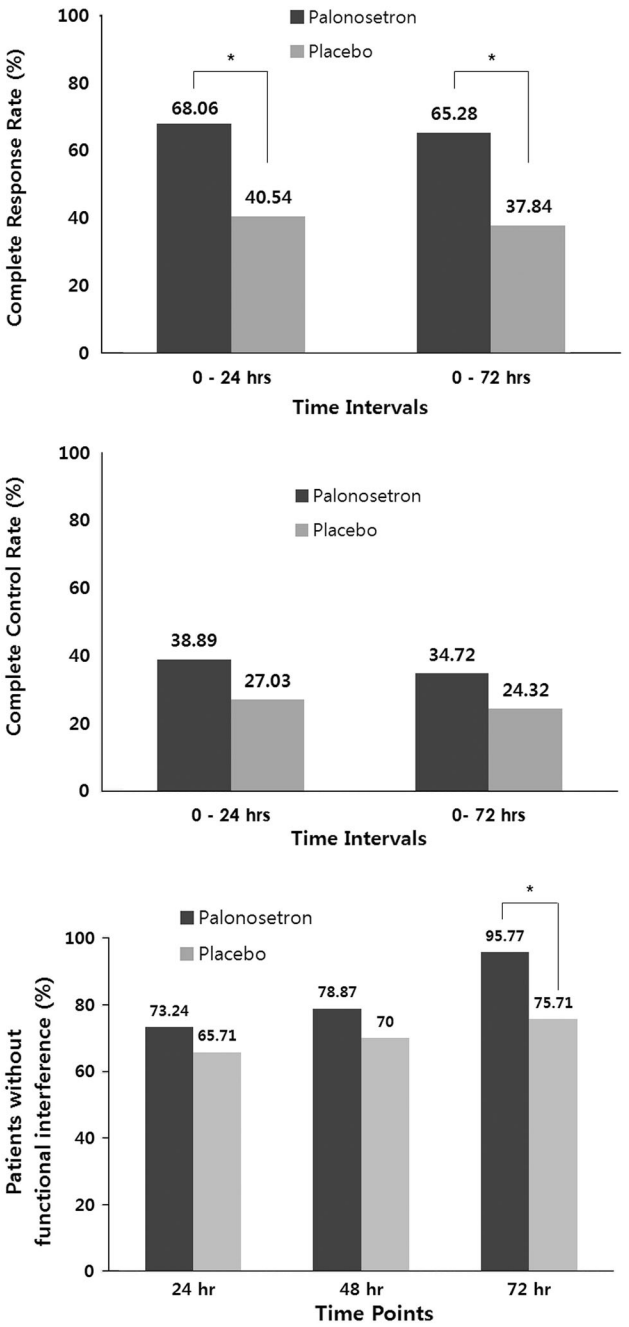

Fig. 3 Complete response rate for 24 h (*left*) and 72 h (*right*) after randomization (*upper*). Complete control rate for 24 h (*left*) and 72 h (*right*) after randomization (*middle*). Number of patients without functional interference at 24, 48 and 72 h after randomization (*lower*). *$p < 0.05$ (χ^2 test for comparisons of palonosetron vs. placebo). Functional interference due to nausea and vomiting was measured utilizing an Osoba Nausea and Emesis module consisting of five four-point Likert subscales (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much) for each category. The percentages represent those patients with final point score of five (score of one on any individual subscale)

interference) in the palonosetron group than in the placebo group (Fig. 3).

A total of 342 adverse events (AEs) in 117 patients among 151 patients who administered the study drugs were reported during study period. The number of total AEs was not different between the palonosetron group and the placebo group (152 and 190, respectively, $p = 0.410$). AEs reported in more than 5 % of the subjects were dizziness, headache, fatigue, diarrhea, procedural pain of operation site, insomnia, and constipation. All AEs were recovered without any sequelae. Twelve abnormal laboratory results were reported in eight participants, but they were not considered to be related to the study drug. There was no clinically significant change in corrected QT interval of

Table 2 Proportion of patients with nausea or episodes of emesis and who required rescue anti-emetic therapy among the patients administered with palonosetron or placebo

Parameters (h)	Palonosetron group	Placebo group	*p* value
Patients with PONV[a]			
0.5–2	21 (29.2)	37 (50.0)	0.010
0.5–24	33 (45.8)	46 (62.2)	0.048
0.5–72	36 (50.0)	49 (66.2)	0.047
Patients with episodes of emesis			
0.5–2	6 (8.3)	17 (23.0)	0.015
0.5–24	14 (19.4)	29 (39.2)	0.009
0.5–72	17 (23.6)	33 (44.6)	0.008
Patients with nausea[a]			
0.5–2	20 (27.8)	30 (40.5)	0.104
0.5–24	27 (37.5)	39 (52.7)	0.065
0.5–72	31 (43.1)	43 (58.1)	0.069
Patients who required rescue antiemetics[b]			
0.5–2	10 (13.9)	20 (27.0)	0.049
0.5–24	19 (26.4)	25 (33.8)	0.330
0.5–72	21 (29.2)	26 (35.1)	0.440

p values are the results of χ^2 test

PONV Postoperative nausea and vomiting, *emesis* Vomiting and retching

[a] The incidence of nausea was counted for nausea with NRS $\geq$ 1

[b] Rescue antiemetics were considered to be given for the patients who develop nausea with NRS $\geq$ 4 or emesis

Table 3 Severity of nausea in patients who received palonosetron or placebo

Parameters (h)	Palonosetron group	Placebo group	*p* value
0	7 (5–8)	7 (5–8)	0.149
0–0.5	4 (3–5)	5 (3–7)	0.054
0.5–1	3 (2–4)	3 (3–5)	0.025
1–2	2 (1–3)	3 (2–5)	0.184
2–24	5 (2–6)	4 (2–6)	0.708
24–48	3 (2–5)	4 (2–5)	0.589
48–72	3 (1–6)	2 (1–5)	0.797

Severity of nausea was measured using numerical rating scale

Data are presented as median (IQR)

p values are the result of Mann–Whitney *U* test

electrocardiography in both groups. There were no differences in vital signs between the two groups.

Discussion

We evaluated the therapeutic efficacy of a single dose of palonosetron (0.075 mg) in the treatment of established PONV following surgery under general anesthesia. Palonosetron significantly decreased the incidence of PONV and increased the CR rates up to 72 h compared with the placebo group. To the best of our knowledge, this is the first placebo-controlled study to evaluate the therapeutic efficacy of palonosetron for the subjects who develop PONV over a 72 h-period. There is a relatively small number of trials for 5-HT_3 RAs on the treatment of established PONV symptoms and a lack of evidence on the therapeutic efficacy of palonosetron [25–28]. This may be due to the difficulty and expense of performing a placebo-controlled study evaluating therapeutic efficacy for established PONV.

The CR rate at 72 h after randomization was higher in the palonosetron group than in the placebo group in this study. This confirms the long-lasting effect of palonosetron, which may be related to its peculiar mechanism of action and long half-life. The half-life of palonosetron is ten times longer than ondansetron and 5–8 times longer than granisetron [9]. The long duration of therapeutic efficacy found in this study could be attributed to several experimental findings. Palonosetron has been reported to exhibit allosteric binding and to cooperate positively to the 5-HT_3 receptor, while ondansetron or granisetron bind to the 5-HT_3 receptor bimolecularly [12]. 5-HT_3 receptor is internalized by palonosetron and its function was inhibited for a long period [14].

In this study, the difference in CR rate at 24 h after study drug administration in the palonosetron group and the placebo group was 27.6 %, comparable with previous placebo-controlled studies with ondansetron or granisetron that evaluated the first 24 h after drug administration [29, 35]. However, we cannot compare the CR rate at 72 h after palonosetron administration with other 5-HT_3 RAs.

The CC rate at 24 and 72 h after study drug administration was not different between the groups. Only the severity of nausea during the first 0.5 h was significantly lower in the palonosetron group than in the placebo group in our study, although the total incidence of PONV and emesis was significantly lower in the palonosetron group than the placebo group. Nausea is not controlled by the serotonin pathway only, although the mechanism of nausea has not been fully explained. Previous articles reported that 5-HT_3 receptor antagonists are more effective for retching and vomiting than nausea, which explains our finding in this study [13, 26].

The number of patients who developed PONV during 72 h after study drug administration was significantly lower in the palonosetron group than in the placebo group. The incidence of administration of rescue medication at 2 h post-dose was significantly lower in the palonosetron group. These results support that the palonosetron is associated with rapid onset, low recurrence rate, low incidence of requirement for rescue medication, and ultimately a high CR rate. The improved

QoL score at 72 h post-dose in the palonosetron group also indicates the long duration of action.

There are several limitations to our study. First, the anesthesia regimen of this study for these patients with moderate risk of PONV was not consistent with modern practice, which uses PONV prophylaxis for these patients. Inhalational anesthetics and nitrous oxide are seldom used for these patients. Therefore, we cannot confirm whether palonosetron is still efficacious when an anesthetic regimen designed to limit PONV is implemented. However, prophylactic use of anti-emetics was not allowed for the purpose of our study, and the anesthesia regimen used in this study was routine in our center, and was explained well before obtaining written informed consent. Second, we did not compare palonosetron with other kinds of 5-HT_3 receptor antagonists. We did not provide a direct comparison of therapeutic efficacy of different 5-HT_3 receptor antagonists. Third, as the therapeutic efficacy of only a single dose of bolus-injected palonosetron was evaluated, we could not evaluate the effect of different doses of palonosetron. However, we administered the commonly used dosage of palonosetron [10, 16, 17], and the objective of this study was achieved with this single dose.

In conclusion, a single 0.075 mg IV dose of palonosetron effectively increased the CR rates at 24 and 72 h after drug administration in moderate risk patients who developed PONV at PACU within 2 h after surgery. Palonosetron also decreased PONV incidence at 2, 24 and 72 h after drug administration, with significantly lower incidence of administration of rescue medication at 2 h after drug administration. We demonstrate for the first time the long-lasting therapeutic efficacy of palonosetron in the treatment of established PONV in moderate risk patients after surgery under general anesthesia.

This study was conducted with written informed consent from the study subjects.

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References

1. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
2. Tramer MR. Strategies for postoperative nausea and vomiting. Best Pract Res Clin Anaesthesiol. 2004;18:693–701.
3. Gan TJ, Franiak R, Reeves J. Ondansetron orally disintegrating tablet versus placebo for the prevention of postdischarge nausea and vomiting after ambulatory surgery. Anesth Analg. 2002; 94:1199–200.
4. Carroll NV, Miederhoff P, Cox FM, Hirsch JD. Postoperative nausea and vomiting after discharge from outpatient surgery centers. Anesth Analg. 1995;80:903–9.
5. Eberhart LH, Morin AM, Wulf H, Geldner G. Patient preferences for immediate postoperative recovery. Br J Anaesth. 2002;89:760–1.
6. Wong EH, Clark R, Leung E, Loury D, Bonhaus DW, Jakeman L, Parnes H, Whiting RL, Eglen RM. The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. Br J Pharmacol. 1995;114:851–9.
7. van Wijngaarden I, Tulp MT, Soudijn W. The concept of selectivity in 5-HT receptor research. Eur J Pharmacol. 1990;188:301–12.
8. Fero KE, Jalota L, Hornuss C, Apfel CC. Pharmacologic management of postoperative nausea and vomiting. Expert Opin Pharmacother. 2011;12:2283–96.
9. Stoltz R, Cyong JC, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in US and Japanese healthy subjects. J Clin Pharmacol. 2004;44:520–31.
10. 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.
11. Shah A, DeGroot T, Apseloff G. Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects. J Clin Pharmacol. 2006;46: 1139–45.
12. Rojas C, Stathis M, Thomas AG, Massuda EB, Alt J, Zhang J, Rubenstein E, Sebastiani S, Cantoreggi S, Snyder SH, Slusher B. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. Anesth Analg. 2008;107:469–78.
13. Muchatuta NA, Paech MJ. Management of postoperative nausea and vomiting: focus on palonosetron. Ther Clin Risk Manag. 2009;5:21–34.
14. Rojas C, Thomas AG, Alt J, Stathis M, Zhang J, Rubenstein EB, Sebastiani S, Cantoreggi S, Slusher BS. Palonosetron triggers 5-HT(3) receptor internalization and causes prolonged inhibition of receptor function. Eur J Pharmacol. 2010;626:193–9.
15. Rojas C, Li Y, Zhang J, Stathis M, Alt J, Thomas AG, Cantoreggi S, Sebastiani S, Pietra C, Slusher BS. The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. J Pharmacol Exp Ther. 2010;335:362–8.
16. Kovac AL, Eberhart L, Kotarski J, Clerici G, Apfel C. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. Anesth Analg. 2008;107:439–44.
17. 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.
18. Kim SH, Hong JY, Kim WO, Kil HK, Karm MH, Hwang JH. Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study. Korean J Anesthesiol. 2013;64:517–23.
19. Hanaoka K, Toyooka H, Kugimiya T, Ohashi Y. Efficacy of prophylactic intravenous granisetron in postoperative emesis in adults. J Anesth. 2004;18:158–65.
20. Metaxari M, Papaioannou A, Petrou A, Chatzimichali A, Pharmakalidou E, Askitopoulou H. Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents. J Anesth. 2011;25:356–62.
21. Jo YY, Kwak HJ, Lee MG, Lim OK. Effect of palonosetron on postanesthetic shivering after propofol-remifentanil total intravenous anesthesia. J Anesth. 2013;27:535–40.

22. Lee D, Kim JY, Shin JW, Ku CH, Park YS, Kwak HJ. The effect of oral and IV ramosetron on postoperative nausea and vomiting in patients undergoing gynecological laparoscopy with total intravenous anesthesia. J Anesth. 2009;23:46–50.
23. Mitsunari H, Ashikari E, Tanaka K. The use of droperidol decreases postoperative nausea and vomiting after gynecological laparoscopy. J Anesth. 2007;21:507–9.
24. Song YK, Lee C. Effects of ramosetron and dexamethasone on postoperative nausea, vomiting, pain, and shivering in female patients undergoing thyroid surgery. J Anesth. 2013;27:29–34.
25. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. BMC Anesthesiol. 2001;1:2.
26. Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. Am J Health Syst Pharm. 2005;62:1247–60.
27. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anaesth. 2004;51:326–41.
28. Ormel G, Romundstad L, Lambert-Jensen P, Stubhaug A. Dexamethasone has additive effect when combined with ondansetron and droperidol for treatment of established PONV. Acta Anaesthesiol Scand. 2011;55:1196–205.
29. Taylor AM, Rosen M, Diemunsch PA, Thorin D, Houweling PL. A double-blind, parallel-group, placebo-controlled, dose-ranging, multicenter study of intravenous granisetron in the treatment of postoperative nausea and vomiting in patients undergoing surgery with general anesthesia. J Clin Anesth. 1997;9:658–63.
30. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiol. 1999;91:693–700.
31. Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, Heineck R, Greim CA, Roewer N. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth. 2002;88:659–68.
32. Morino R, Ozaki M, Nagata O, Yokota M. Incidence of and risk factors for postoperative nausea and vomiting at a Japanese Cancer Center: first large-scale study in Japan. J Anesth. 2013;27:18–24.
33. Scuderi PE. Pharmacology of antiemetics. Int Anesthesiol Clin. 2003;41:41–66.
34. Martin CG, Rubenstein EB, Elting LS, Kim YJ, Osoba D. Measuring chemotherapy-induced nausea and emesis. Cancer. 2003;98:645–55.
35. Claybon L. Single dose intravenous ondansetron for the 24-hour treatment of postoperative nausea and vomiting. Anaesthesia. 1994;49(Suppl):24–9.