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The effect of combination treatment using palonosetron and dexamethasone for the prevention of postoperative nausea and vomiting versus dexamethasone alone in women receiving intravenous patient-controlled analgesia

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Background: The purpose of this study was to evaluate the effect of palonosetron combined with dexamethasone for the prevention of PONV compared to dexamethasone alone in women who received intravenous patient-controlled analgesia (IV-PCA) using fentanyl.

Methods: In this randomized, double-blinded, placebo-controlled study, 204 healthy female patients who were scheduled to undergo elective surgery under general anesthesia followed by IV-PCA for postoperative pain control were enrolled. Patients were divided into two groups: the PD group (palonosetron 0.075 mg and dexamethasone 5 mg IV; n = 102) and the D group (dexamethasone 5 mg IV; n = 102). The treatments were given after the induction of anesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 48 hours after surgery were evaluated.

Results: The incidence of PONV was significantly lower in the PD group compared with the D group during the 0–24 hours (43 vs. 59%) and 0–48 hours after surgery (45 vs. 63%) ($P < 0.05$). The severity of nausea during the 6–24 hours after surgery was significantly less in the PD group compared with the D group ($P < 0.05$). The incidence of rescue antiemetic used was significantly lower in the PD group than in the D group during the 0–6 hours after surgery (13.1 vs. 24.5%) ($P < 0.05$).

Conclusions: Palonosetron combined with dexamethasone was more effective in preventing PONV compared to dexamethasone alone in women receiving IV-PCA using fentanyl.

Key Words: Dexamethasone, Palonosetron, Postoperative nausea and vomiting.

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Introduction

Postoperative nausea and vomiting (PONV) is one of the most common distressing complications after anesthesia and surgery. Serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are widely used as one of the first-line therapeutic agent for the prevention of PONV because of their good efficacy and minimal side effects [1].

Palonosetron, the latest 5-HT_3 receptor antagonist, has a higher receptor binding affinity and a longer plasma half-life than older 5-HT_3 receptor antagonist such as ondansetron, granisetron, dolasetron, and ramosetron. In contrast to the older 5-HT_3 receptor antagonists, palonosetron's allosteric binding and positive cooperativity triggers receptor internalization, which result in persistent inhibition of 5-HT_3 receptor function and long duration of action [2]. It was reported that palonosetron was more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting (CINV) [3], and PONV [4].

Patient-controlled analgesia (PCA) using opioid is widely used for postoperative pain control. Although safe and effective for controlling postoperative pain, PCA is associated with high incidence of PONV. Infrequently, severe PONV may be perceived as a failure of PCA for pain control, and patients may refuse to continue PCA treatment due to dissatisfaction [5].

It is recommended that patients at high risk of developing PONV receive a combination of two or more different classes of antiemetic agents rather than a single one, because none of the available antiemetic is entirely effective in preventing PONV [6].

One of the commonly used combinations for preventing PONV is a 5-HT_3 receptor antagonist with dexamethasone. It has been demonstrated that combining a 5-HT_3 receptor antagonist (ondansetron or ramosetron) with dexamethasone is more effective in preventing PONV than ondansetron, ramosetron or dexamethasone alone [7-10].

Recently, however, it was reported that the combination of palonosetron and dexamethasone is no more effective than palonosetron alone for the prevention of PONV [11,12].

Additionally, the effect of palonosetron and dexamethasone combination in patients at high-risk for PONV who received intravenous patient-controlled analgesia (IV-PCA) using fentanyl for postoperative pain control has not yet been reported.

The aim of this study was to determine whether combination therapy using palonosetron and dexamethsone was more effective in preventing PONV than monotherapy with dexamethasone in women who received IV-PCA using fentanyl for postoperative pain control.

Materials and Methods

Institutional Review Board approval was obtained prior to starting the research. After receiving written informed consent, 204 healthy female patients, aged 20–70 years with American Society of Anesthesiologists physical status of 1–2, who were scheduled for elective surgery under general anesthesia and wanted to receive IV-PCA for postoperative pain control, were included in our randomized, placebo-controlled, double-blinded study.

Exclusion criteria included pregnancy, body weight more than 30% above the ideal body weight, vomiting or retching within 24 hours before the operation, administration of antiemetics, steroids or psychoactive medications within 24 hours before the operation.

Patients were randomly allocated to one of the two groups according to a computer-generated random number table: 1) PD group, 0.075 mg of palonosetron plus 5 mg of dexamethasone IV; 2) D group, 5 mg of dexamethasone with normal saline IV. Study medications were administered immediately after the induction of anesthesia. The patients and the investigator who collected the postoperative data were blinded to the randomization.

A standardized anesthesia regimen was followed. All patients received midazolam 3–5 mg IM as premedication 30 min before surgery. General anesthesia was induced with propofol 2 mg/kg and fentanyl 2 μg/kg. Rocuronium 0.6 mg/kg was administered to facilitate endotracheal intubation. Anesthesia was maintained with desflurane or sevoflurane and nitrous oxide in oxygen (50%). At the end of surgery, residual neuromuscular block was reversed with pyridostigmine and glycopyrrolate. For postoperative pain control, patients were given fentanyl using IV-PCA (bolus dose 15 ug fentanyl with background infusion [15 ug fentanyl/h], lockout interval of 6 minutes). After surgery, patients were observed in the postanesthetic care unit (PACU) for 1 hour, and then transferred to the ward.

The incidence of nausea and vomiting, severity of nausea, and use of rescue antiemetic were evaluated at 1 hour after the surgery while in the PACU, then at 6, 24 and 48 hours after the surgery while at the ward. Evaluation was made by the investigator blinded to the treatment. An episode of vomiting was defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents). The severity of nausea was assessed using a four point verbal rating scale (none, mild, moderate, and severe). Rescue medication for PONV (metoclopramide 10 mg as an initial rescue drug, ondansetron 4 mg as a second rescue drug) was administered upon the patient's request, or upon complaint of moderate to severe nausea or vomiting. For inadequate pain control in spite of sufficient use of IV-PCA, additional analgesic medications were allowed at the discretion of the surgeon. The pain intensity was not assessed in this study.

Adverse events were evaluated and recorded during the entire observation period. Patients were also asked to rate their overall

satisfaction with the anesthetic experience on a three point scale (satisfied; neutral; dissatisfied) at 48 hours postoperatively.

The primary outcome measured in this study was the incidence of PONV during the 0–24 hours postoperative period, and the secondary outcome measured were the incidence of PONV during the 24–48 hours postoperative period, 0–48 hours postoperative period, the severity of nausea, the use of rescue antiemetics and patient's satisfaction.

The sample size was calculated based on the incidence of PONV (approximately 60%) among patients receiving dexamethasone alone for antiemetic prophylaxis while on IV-PCA [7]. A risk reduction from 60 to 40% in the incidence of PONV by palonosetron combined with dexamethasone would be clinically relevant [13]. For a two-sided test of difference, using $\alpha = 0.05$ and $\beta = 0.2$, the sample size was estimated at 97 patients per group. We enrolled 102 patients per group to allow for possible patient dropout.

Statistical analysis was performed using SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA). The student's t-test was used to compare the continuous variables between the groups. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. A P value of < 0.05 was considered statistically significant. Data are presented as means ± standard deviation (SD), numbers, or percentages.

Results

Among the 204 patients enrolled in this study, 11 were withdrawn from the study for insufficient data collection due to them being discharged before 48 hours after the operation. Data obtained from the remaining 193 patients were analyzed, with 94 patients in the D group and 99 patients in the PD group.

There were no significant differences between the groups with respect to patient characteristics, motion sickness, previous PONV history, smoking status, duration of surgery, duration of anesthesia, and type of surgery (Table 1).

The incidence of PONV was significantly lower in the PD group than in the D group during the 0–24 hours (43 vs. 59%) (P = 0.036), and the 0–48 hours postoperative period (45 vs. 63%) (P = 0.016) (Table 2).

The severity of nausea during the 6–24 hours postoperative period was significantly less in the PD groups compared with the D group (P = 0.010) (Table 3).

The incidence of rescue antiemetic used was significantly lower in the PD group than in the D group during the 0–6 hours after the operation (13 vs. 24%) (P = 0.043) (Table 2).

There were no significant differences in the patient's satisfaction rating between the groups (Table 4).

Headache occurred more frequently in the PD group than the D group, but it was not statistically significant (P = 0.067) (Table 4).

Table 1. Demographic Data and Baseline Characteristics of Patients

	D group (n = 94)	PD group (n = 99)
Age (yr)	50.6 ± 10.8	51.6 ± 12.2
Body weight (kg)	60.2 ± 8.9	59.8 ± 9.6
History of PONV (n)	7	4
History of motion sickness (n)	20	25
Non-smoker (n)	92	93
Duration of surgery (min)	119 ± 80.3	104 ± 60.8
Duration of anesthesia (min)	168 ± 84.7	151 ± 69.8
Type of surgery (n)		
General	20	26
Orthopedic	66	64
Gynecological	8	9

Values are expressed as mean ± SD, or number of patients (n). D group: 5 mg of dexamethasone with normal saline IV, PD group: 0.075 mg of palonosetron plus 5 mg of dexamethasone IV.

Table 2. Incidence of Nausea and Vomiting, and Use of Rescue Antiemetics during the First 48 Hours after Surgery

	D group (n = 94)	PD group (n = 99)	P values
0–6 h			
Nausea	43 (46%)	38 (38%)	0.300
Vomiting	14 (15%)	10 (10%)	0.313
PONV	43 (46%)	38 (38%)	0.300
Rescue antiemetics	23 (24%)	13 (13%)*	0.043
6–24 h			
Nausea	30 (32%)	20 (20%)	0.063
Vomiting	12 (13%)	6 (6%)	0.109
PONV	30 (32%)	21 (21%)	0.092
Rescue antiemetics	11 (12%)	11 (11%)	0.897
0–24 h			
Nausea	55 (59%)	42 (42%)*	0.025
Vomiting	20 (21%)	16 (16%)	0.362
PONV	55 (59%)	43 (43%)*	0.036
Rescue antiemetics	29 (31%)	21 (21%)	0.127
24–48 h			
Nausea	22 (23%)	16 (16%)	0.206
Vomiting	4 (4%)	6 (6%)	0.572
PONV	22 (23%)	17 (17%)	0.281
Rescue antiemetics	7 (7%)	5 (5%)	0.491
0–48 h			
Nausea	59 (63%)	44 (44%)*	0.011
Vomiting	23 (24%)	18 (18%)	0.286
PONV	59 (63%)	45 (45%)*	0.016
Rescue antiemetics	31 (33%)	21 (21%)	0.066

Data are presented as number of patients (percentage). PONV: postoperative nausea and vomiting. D group: 5 mg of dexamethasone with normal saline IV, PD group: 0.075 mg of palonosetron plus 5 mg of dexamethasone IV. *P < 0.05.

Table 3. Severity of Nausea during the First 48 Hours after Surgery

	D group (n = 94)	PD group (n = 99)	P values
0–6 h			
None	51 (54%)	61(62%)	0.125
Mild	10 (11%)	12 (12%)	
Moderate	6 (6%)	9 (9%)	
Severe	27 (29%)	17 (17%)	
6–24 h			
None	63(67%)	79 (80%)	0.010
Mild	9 (10%)	10 (10%)	
Moderate	5 (5%)	4 (4%))	
Severe	17 (18%)	6 (6%)	
24–48 h			
None	72 (77%)	83 (84%)	0.606
Mild	13 (14%)	5 (5%)	
Moderate	4 (4%)	6 (6%)	
Severe	5 (5%)	5 (5%)	

Data are presented as number of patients (percentage). D group: 5 mg of dexamethasone with normal saline IV, PD group: 0.075 mg of palonosetron plus 5 mg of dexamethasone IV.

Table 4. Incidence of Adverse Events and Patient Satisfaction during the First 48 Hours after Surgery

	D group (n = 94)	PD group (n = 99)	P value
Adverse effect			
Dizziness	17 (18%)	19 (19%)	0.844
Headache	10 (11%)	20 (20%)	0.067
Satisfaction			
Satisfied	77 (82%)	80 (81%)	0.873
Neutral	11 (12%)	15 (15%)	
Dissatisfied	6 (6%)	4 (4%)	

Data are presented as number of patients (percentage). D group: 5 mg of dexamethasone with normal saline IV, PD group: 0.075 mg of palonosetron plus 5 mg of dexamethasone IV.

Discussion

In this study, the combination of palonosetron 0.075 mg and dexamethasone 5 mg was significantly more effective in preventing PONV than dexamethasone 5 mg alone during the first 48 hours after surgery in women who received IV-PCA using fentanyl for postoperative pain control.

Although the exact etiology of PONV is not well known, many factors may be involved; which include age, gender, obesity, anxiety, prior history of motion sickness or PONV, non-smoking state, anesthetics, type of surgery, duration of surgery and anesthesia, use of opioids, postoperative ambulation, dizziness, postoperative pain, and oral intake [14].

Apfel et al. [15] reported four important independent risk factors that can be used to predict PONV: female gender, history of motion sickness or PONV, non-smoking, and the use of postoperative opioids. Based on these four risk factors, a simplified risk score for predicting PONV was developed. If none, 1, 2, 3, or 4 of these four risk factors are present, the incidence of PONV is approximately 10, 20, 40, 60 and 80%, respectively.

In this study, the patients were at high risk for PONV with 3 or 4 Apfel's risk factors for PONV. The patient characteristics and Apfel's risk factors were similar between the two groups. Therefore, the observed differences of the results were due to the treatment provided.

Many antiemetic agents such as dopamine receptor antagonists, serotonin 5-HT_3 receptor antagonists, histamine receptor antagonists, cholinergic receptor antagonists, NK 1 receptor antagonists, and dexamethasone are already available [1].

The serotonin 5-HT_3 receptor antagonists, such as ondansetron, tropisetron, granisetron, dolasetron, and ramosetron, exert their antiemetic effect via competitive binding at the 5-HT_3 receptor sites which antagonize the effect of serotonin (5-HT), centrally and peripherally [6]. Palonosetron, the latest 5-HT_3 receptor antagonist, has a stronger binding affinity and longer plasma half-life (exceeding 40 h) than the older 5-HT_3 receptor antagonists (5–12 h) which results in prolonged inhibition of receptor function. In addition, palonosetron has significantly different characteristics from the older 5-HT_3 receptor antagonists. First, palonosetron differs in chemical structure compared to the older 5-HT_3 receptor antagonists. The older drugs are based on a 3-substituted indole structure resembling serotonin, while palonosetron is based on a fused tricyclic ring system attached to a quinuclidine moiety. Second, palonosetron interacts with 5-HT_3 receptors very differently. Palonosetron exhibits allosteric binding and positive cooperativity when binding to the 5-HT_3 receptor, and triggers a receptor internalization resulting in prolonged inhibition of receptor function, whereas older 5-HT_3 receptors antagonists exhibits simple bimolecular competitive binding at the 5-HT_3 receptor [16].

Kovac et al. [13] showed that palonosetron 0.075 mg effectively reduced PONV up to 72 hours after an operation compared to placebo. During the first 24 hours after surgery, palonosetron 0.075 mg reduced the incidence of nausea (from 71 to 50%) and vomiting (from 60 to 40%) compared to placebo which correspond to a relative risk reduction of nausea by 31%, and relative risk reduction of vomiting by 34% [13]. In addition, palonosetron 0.075 mg was more effective than ondansetron 4 mg and ramosetron 0.3 mg in the prevention of PONV during the first 48 hours after laparoscopic surgery in high risk women receiving fentanyl-based IV-PCA [17]. Moon et al. [4] also reported that palonosetron was more effective in preventing PONV than ondansetron during 24 hours after surgery (42 vs. 62%). In a dose-ranging study compared with placebo, palonosetron 0.075

mg IV was found to be the effective dose for preventing PONV up to 24 hours after surgery [13]. Therefore, we used palonosetron 0.075 mg IV in this study.

Dexamethasone is an inexpensive, effective and safe antiemetic. Although the exact mechanism for dexamethasone's antiemetic effect is not well known, dexamethasone may exert central antiemetic actions mainly through activation of the glucocorticoid receptors in the nucleus of the solitary tract, the nucleus of raphe, and the area postrema [18]. Dexamethasone is widely used for CINV and PONV. Additionally, dexamethasone can prevent nausea and vomiting associated with intravenous or epidural opioid for postoperative pain control [18-21]. Lee et al. [19] reported that dexamethasone 8 mg IV reduced PONV significantly from 57% (placebo group) to 28% during the first 24 hours after surgery in patients receiving morphine IV-PCA for pain control. A meta-analysis to assess the efficacy of dexamethasone in reducing PONV showed that a single IV dose of dexamethasone 5 to 10 mg was effective in reducing PONV in women receiving neuraxial morphine for cesarean delivery or abdominal hysterectomy [21]. Additionally, the Society for Ambulatory Anesthesia guidelines recommended 4–5 mg dexamethasone IV for prevention of PONV [22]. Dexamethasone 5 mg IV was chosen in this study and was administered in all patients who received IV-PCA using fentanyl for postoperative pain control.

Even though new antiemetic drugs have been introduced, there are no agents that can completely prevent or treat PONV because of the multifactorial etiology and various receptor sites involved in PONV. Therefore, in patients at high risk for PONV, it is recommended that combination therapy using several antiemetics targeting different receptor sites be employed rather than using a single antiemetic agent [6]. It was reported that combination therapy using a 5-HT_3 receptor antagonist with either droperidol or dexamethasone, and droperidol with dexamethasone were more effective than therapy using a single antiemetic agent [23-25].

Combination therapy using a 5-HT_3 receptor antagonist with dexamethasone became widely used after the issuance of a Food and Drug Administration black box warning on droperidol. A number of studies have reported that combination therapy using the older 5-HT_3 receptor antagonists such as ondansetron, tropisetron, or ramosetron with dexamethasone were more effective in reducing PONV than monotherapy [7-10,26,27]. The authors thought that the combination of palonosetron and dexamethasone may reduce PONV more effectively than monotherapy using either palonosetron or dexamethasone, similar to the effect offered by combination of the older 5-HT_3 receptor antagonists and dexamethasone.

However, there were two published studies claiming that combination therapy using palonosetron with dexamethasone did not reduce the incidence of PONV compared to palonosetron alone [11,12]. A study by Blitz et al. [11], involving elective outpatient laparoscopic abdominal or gynecological surgery with subjects having at least 3 Apfel's risk factors for PONV, showed that the combination of palonosetron 0.075 mg and dexamethsone 8 mg did not significantly reduce the incidence of PONV compared to using palonosetron 0.075 mg alone during the first 72 hours postoperative period (postoperative 0–2 h: 19 vs. 16%, 0–6 h: 44 vs. 42%, 6–72 h: 42 vs. 28%, palonosetron vs. palonosetron plus dexamethasone respectively) [11]. A study by Park et al. [12] showed that the combination of palonosetron 0.075 mg with dexamethasone 4 mg did not reduce the incidence of PONV in patients with at least 2 risk factors for PONV during the 24 hours after operation compared to palonosetron 0.075 mg alone (14 vs. 9.8%) [12].

It is unknown whether palonosetron, when used in combination with dexamethasone, acted differently in contrast to the older 5-HT_3 receptor antagonists because of palonosetron's different chemical structure and different interaction with the 5-HT_3 receptors. Therefore, this study was conducted to determine whether combination therapy using palonosetron and dexamethsone was more effective in preventing PONV than monotherapy with dexamethasone.

The result of our study demonstrated that combination therapy using palonosetron 0.075 mg and dexamethsone 5 mg was more effective in preventing PONV than monotherapy with dexamethsone 5 mg. This result was comparable to the results of previous studies claiming that combination of dexamethasone plus ondansetron is more effective in preventing PONV than dexamethasone alone [7,10]. A study by Wang et al. [7] showed that ondansetron 4 mg with dexamethasone 5 mg significantly reduced PONV compared to dexamethasone 5 mg alone in women receiving postoperative morphine PCA (30 vs. 57%) in the first 24 hours after surgery [7].

Apfel et al. [28] reported that dexamethasone 4 mg reduced PONV risk for 24 hours after an operation by about 26%, similar to ondansetron 4 mg or droperidol 1.25 mg. These antiemetic interventions were similarly effective and acted independently of one another and independently of the patients' baseline risk.

Base on the result of our study, it seems that palonosetron and dexamethasone also acted independently as did other older antiemetics [28].

More recently, Bala et al. [29] reported that combination of palonosetron 0.075 mg and dexamethasone 8 mg was more effective than palonosetron 0.075 mg alone in reducing PONV after laparoscopic cholecystectomy. Nausea occurred in 42.9% and vomiting occurred in 33.3% of patients who received palonosetron alone, while nausea occurred in 14.3% and vomiting occurred in 11.9% of patients who received combination of palonosetron and dexamethasone, during the first 24 hours after

surgery. The requirement for rescue antiemetic was also significantly less in the combination treatment group than palonosetron alone group. This result is contrary to the results of studies by Blitz et al. [11] and Park et al. [12] It is believed that palonosetron and dexamethasone acted independently.

Accordingly, the combination of palonosetron and dexamethasone was beneficial in preventing PONV compared to dexamethasone alone in patients at high risk for PONV.

Headache, one of the side effects of 5-HT_3 receptor antagonist, occurred more frequently in patients who received palonosetron combined with dexamethasone than dexamethasone alone in this study, but the difference was not significant. Known adverse effects of dexamethasone such as wound infection and delayed wound healing should be watched out for, but a single perioperative dose of dexamethasone is considered to be relatively free of side effects [30]. The adverse effects of dexamethasone were not evaluated in this study.

A limitation of this study was the absence of a placebo group which is required for calculation of absolute risk reduction. Since it is unethical to withhold antiemetics in patients at high risk for PONV, a placebo group was not included.

In conclusion, the combination of palonosetron with dexamethasone was more effective in preventing PONV compared to dexamethasone alone in women receiving IV-PCA using fentanyl.

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