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ORIGINAL ARTICLE

A randomized, double-blind trial evaluating the efficacy of palonosetron with total intravenous anesthesia using propofol and remifentanil for the prevention of postoperative nausea and vomiting after gynecologic surgery

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Abstract
Purpose Palonosetron has potent and long-acting antiemetic effects for postoperative nausea and vomiting (PONV). The aim of this study was to prospectively evaluate the efficacy of palonosetron when used with total intravenous anesthesia (TIVA) using propofol and remifentanil for the prevention of PONV in patients undergoing laparoscopic gynecologic surgery.
Methods This prospective double-blind study comprised 100 female American Society of Anesthesiologist physical status I and II patients who were undergoing laparoscopic gynecologic surgery under TIVA. The patients were randomly assigned to two groups—the palonosetron plus TIVA group (palonosetron 0.075 mg i.v., $n = 50$) and the TIVA group (normal saline 1.5 ml i.v., $n = 50$). The treatments were given before the induction of anesthesia. The incidence of PONV, severity, number of rescue antiemetics, adverse effects, and patient satisfaction during the first 24 h after surgery were evaluated.
Results The demographic profiles of the patients in the two groups were comparable. The overall incidence of PONV (0–24 h) was significantly lower in the TIVA plus palonosetron group than in the TIVA group (34 vs 58 %, $p = 0.027$). In particular, during the 6–24 h after surgery, the incidence of PONV (14 vs 30 %, $p = 0.03$) and the incidence of moderate to severe nausea (6 vs 22 %, $p = 0.041$) were significantly lower in the TIVA plus palonosetron group than in the TIVA group. There were no significant differences in adverse effects, use of rescue antiemetics or patient satisfaction.
Conclusion Combining palonosetron with TIVA can be considered as a good method to prevent PONV, not only during the short postoperative period but also especially during the 6–24-h period after anesthesia.

Keywords Palonosetron · Postoperative nausea and vomiting · Total intravenous anesthesia

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common adverse events after anesthesia. PONV is associated with adverse consequences, including dissatisfaction among patients, pulmonary aspiration, dehiscence of surgical wounds, and delayed recovery [1]. Additionally, because of the very high incidence of PONV (10–79 %) [2], the prevention and management of PONV is important to anesthesiologists.

Many researchers have investigated various modalities for preventing PONV, including dexamethasone, droperidol, total intravenous anesthesia (TIVA), 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists, and anticholinergics, among others [3]. Palonosetron, a second-generation 5HT-3 receptor antagonist, is widely used clinically, and many studies have investigated its efficacy and safety [4, 5]. However, although palonosetron is known to have both short- and long-term antiemetic effects after anesthesia [6, 7], there have been no investigations regarding whether and for how long palonosetron could reduce

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the incidence of PONV when added to TIVA. We anticipated a reduction in the incidence of PONV during the first 24 h after surgery when we combined palonosetron (which has long-term PONV prevention effects) with TIVA (which is known to have short-term PONV-preventing effects) [8]. The aim of this study was to determine whether the combination of TIVA with palonosetron is superior to TIVA only in the postoperative period.

Materials and methods

Consecutive patients scheduled to undergo elective gynecological laparoscopic surgery of >1 h duration at Incheon St. Mary's Hospital, Incheon, Republic of Korea between June and October 2015 were enrolled in the study. All patients were women aged 20–60 years with an American Society of Anesthesiologists physical status I or II. Approval for the study was obtained from the Incheon St. Mary's Hospital Institutional Review Board and the trial was registered with clinicaltrials.gov under #NCT01478165. Additionally, all patients provided verbal and written informed consent before enrollment. Patients who experienced vomiting or retching in the 24-h period before surgery, patients who underwent emetogenic radiotherapy within 8 weeks or cancer chemotherapy within 4 weeks before study entry, and patients who had received steroids, antiemetics or psychoactive medications 24 h before study initiation were excluded.

The patients, who received no premedication, were randomly assigned to two groups using a computer-generated number table as follows—(1) palonosetron 0.075 mg i.v. just before induction of anesthesia [TIVA plus palonosetron group]; and (2) normal saline 1.5 ml i.v. just before the induction of anesthesia [TIVA group]. Trained nurses, who were not involved in the study, prepared the study drugs before induction of anesthesia, according to directions in an envelope containing the allocation groups. Anesthesia was induced and maintained with propofol (target effect-site concentration 2.5–3.5 μg/ml) and remifentanil (target effect-site concentration 2.5–3.5 ng/ml) using a target-controlled infusion device (Orchestra® Base Primea; Fresenius Kabi, France). Tracheal intubation was facilitated with rocuronium 0.6 mg/kg i.v. and at the end of surgery, pyridostigmine 0.2 mg/kg i.v. and glycopyrrolate 0.008 mg/kg i.v. were given to all patients for the reversal of the neuromuscular blockade. In order to control postoperative pain, intravenous patient-controlled analgesia (PCA) devices, set to deliver a basal infusion of fentanyl at 20 μg/h with a 5-μg bolus and a lock-out time of 15 min, were used during the 24–48-h postoperative period.

The incidence of nausea and vomiting, the severity of nausea in accordance with a categorical verbal rating scale (VRS) (none, mild, moderate, or severe), and rescue antiemetic use were recorded immediately after the end of surgery and at 0–2, 2–6 and 6–24 h after surgery. The total dosage of fentanyl using PCA was also checked up to 24 h after surgery. Nausea was defined as a subjectively unpleasant sensation associated with an awareness of the urge to vomit, whereas an episode of vomiting was defined as vomiting (forceful expulsion of gastric contents from the mouth) and retching (spasmodic, labored, rhythmic contractions of the respiratory muscles without expulsion of gastric contents) [9]. When the patients either vomited or retched, or requested treatment, 10 mg i.v. metoclopramide was injected as a rescue treatment.

The types of adverse events (including headache, dizziness, constipation and myalgia) and overall patient satisfaction scored on a 3-point scale (satisfied, neutral, and dissatisfied) were investigated 24 h after surgery. Every assessment and interview was performed by doctors blinded to treatment group enrollment.

The primary outcome was the overall incidence of nausea and vomiting during the first 24 h after anesthesia. Secondary outcomes included the severity of nausea, the need for a rescue drug, patient satisfaction, and the incidence of adverse events.

The sample size was calculated via power analysis while designing the study. By allowing an α error of 5 % and a β error of 20 %, a minimum of 49 patients would be needed in each group to show a 30 % difference in the incidence of PONV [10, 11]. Student's *t* test was used to compare continuous variables, chi-squared test was used for the severity of nausea and Fisher's exact test was used for other categorical variables. A difference was defined as significant at $p < 0.05$. All statistical analyses were carried out using SPSS® statistical package version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows®.

Results

One hundred patients were enrolled (50 per group) and all completed the study. Patient demographic data, risk factors and operative data were comparable between the two groups (Table 1). The overall incidence of PONV (0–24 h) was significantly lower in the TIVA plus palonosetron group than in the TIVA group (34 vs 58 %, $p = 0.027$). In particular, during the 6–24-h period following surgery, the incidence of PONV (12 vs 30 %, $p = 0.030$) and the incidence of moderate to severe nausea (6 vs 22 %, $p = 0.041$) were significantly lower in the TIVA plus palonosetron group than in the TIVA group (Table 2). In contrast, at 0–2 h and 2–6 h following surgery, the incidence of PONV and the severity of nausea were not significantly different between the two groups.

Table 1 Baseline demographic data and clinical characteristics of patients undergoing laparoscopic gynecologic surgery under total intravenous anesthesia with and without palonosetron

Characteristic	TIVA group ($n = 50$)	TIVA plus palonosetron group ($n = 50$)	p value
Age (years)	45 ± 11	43 ± 8	0.356
Weight (kg)	59.4 ± 7.9	59.8 ± 7.1	0.816
Height (cm)	156.7 ± 5.5	158.4 ± 5.1	0.122
ASA physical status			
I	38 (76)	38 (76)	>0.999
II	12 (24)	12 (24)	
Risk factors			
PONV history and/or motion sickness	25 (50)	28 (56)	0.689
Non-smoker	46 (92)	43 (86)	0.525
Type of surgery			
Laparoscopic ovarian cystectomy	14 (28)	15 (30)	
Laparoscopic salpingo-oophorectomy	2 (4)	1 (2)	
Laparoscopic hysterectomy	30.0 (60)	32 (64)	0.777
Laparoscopic myomectomy	4 (8)	2 (4)	
Duration of surgery (min)	90 ± 21	93 ± 21	0.652
Duration of anesthesia (min)	123 ± 33	126 ± 42	0.644

Data are presented as mean ± SD or *n* (%)

Student's *t* test was used for continuous variables and Fisher's exact test or chi-squared test was used for categorical variables

ASA American Society of Anesthesiologists, *PONV* postoperative nausea and vomiting

Table 2 Incidence and severity of postoperative nausea and vomiting (PONV), need for rescue antiemetics, and postsurgical fentanyl consumption after laparoscopic gynecologic surgery under total intravenous anesthesia with and without palonosetron

Time after operation (h)	TIVA group ($n = 50$)	TIVA plus palonosetron group ($n = 50$)	p value
0–2			
Nausea (mild, moderate, severe)	5 (2, 1, 2)	5 (3, 1, 0)	0.525
Vomiting	1 (2.0)	1 (2.0)	>0.999
Overall PONV	5 (10.0)	5 (10.0)	>0.999
2–6			
Nausea (mild, moderate, severe)	17 (5, 9, 3)	8 (3, 4, 1)	0.212
Vomiting	2 (4.0)	1 (2.0)	>0.999
Overall PONV	17 (34.0)	8 (16.0)	0.063
6–24			
Nausea (mild, moderate, severe)	14 (3, 7, 4)	6 (3, 3, 0)	0.041
Vomiting	1 (2.0)	2 (4.0)	>0.999
Overall PONV	15 (30.0)	6 (12.0)	0.030
0–24			
Nausea	29 (58.0)	17 (34.0)	0.027
Vomiting	4 (8.0)	4 (8.0)	>0.999
Overall PONV	29 (58.0)	17 (34.0)	0.027
Rescue antiemetics	6 (12.0)	2 (4.0)	0.269
Postsurgical fentanyl consumption (μg)	536.8 ± 27.1	540.9 ± 23.7	0.245

Data are presented as *n* (%) of patients except for severity of nausea

Severity of nausea presented as a four-point verbal rating scale (VRS)—none, mild, moderate, severe

The chi-squared test was used for severity of nausea, while Fisher's exact test was used for other categorical variables. Student's *t* test was used for postsurgical fentanyl consumption

Table 3 Incidence of adverse events and level of satisfaction in patients who underwent laparoscopic gynecologic surgery and received only total intravenous anesthesia (TIVA) and those who received palonosetron 0.075 mg i.v. before TIVA

	TIVA group ($n = 50$)	TIVA plus palonosetron group ($n = 50$)	p value
Adverse events			
Headache	8 (16.0)	11 (22.0)	0.580
Dizziness	11 (22.0)	8 (16.0)	
Myalgia	1 (2.0)	0 (0)	
Patient satisfaction			
Satisfied	26 (52.0)	25 (50.0)	0.856
Neutral	21 (42.0)	23 (46.0)	
Dissatisfied	3 (6.0)	2 (4.0)	

Data presented as n (%) of patients

TIVA total intravenous anesthesia

There were no significant differences with respect to the use of rescue antiemetics, post-surgical fentanyl consumption during the 24 h after surgery (Table 2), adverse effects or patient satisfaction (Table 3).

Discussion

Despite advances in anesthesia, PONV remains a challenge for anesthesiologists. Numerous anesthesia-, patient-, and surgery-related risk factors are associated with a high incidence of PONV. The mechanism triggering PONV is associated with peripheral and/or centrally located receptors; however, the exact etiology remains unclear. Various receptor and neurotransmitter systems, including cholinergic, histaminergic, neurokininergic, dopaminergic, and serotonergic are involved in triggering PONV. Among these systems, the 5-HT3 receptors in the peripheral vagal terminals are known to be connected to the vomiting center, and competitive 5-HT3 antagonists can suppress the initiation of the vomiting reflex at these sites [3]. A 5-HT3 receptor antagonist is typically prescribed to prevent PONV, not only because of comparable efficacy to dexamethasone or droperidol [12], but also due to a lack of known adverse effects, such as extrapyramidal symptoms, dry mouth, excessive sedation or dysphoria [4, 13].

Palonosetron is a recently developed second-generation 5-HT3 receptor antagonist and has a longer elimination half-life (approximately 40 h) and greater binding affinity for 5-HT3 receptors than previous 5-HT3 receptor antagonists [6, 7]. Palonosetron exhibits allosteric binding to 5-HT3 receptors with concomitant receptor internalization, as well as negative cooperativity with neurokinin-1 receptors [14, 15]. In addition, palonosetron does not influence the QT interval [16] and, therefore, may be safer for patients at risk of cardiac arrhythmias. Like other 5-HT3 receptor antagonists, palonosetron (0.075 mg) has been associated with a relative risk reduction for PONV of approximately 30 % [17, 18].

Our study focused on whether the combination of TIVA (which is already known to have an antiemetic effect) with palonosetron can prevent PONV more effectively over the entire postoperative period. As mentioned above, the TIVA plus palonosetron group showed a lower incidence of PONV over the entire postoperative period, and the severity of PONV was milder than in the TIVA group, most notably during the 6–24-h window following surgery. Xiong et al. [5] in their systematic review and meta-analysis reported that palonosetron was more effective in preventing early postoperative nausea (PON), late PON, and late postoperative vomiting (POV) compared with ondansetron. They explained the outcomes as being due to the long half-life of palonosetron compared with ondansetron. In our study, the characteristically long half-life of palonosetron was also demonstrated by the low incidence of PONV, especially at 6–24 h postoperatively. In contrast to the 6–24-h postoperative period, the incidence of PONV during the 0–6-h postoperative period was not significantly different between the two groups. This finding may be explained by the antiemetic effect of TIVA. Previous meta-analyses have demonstrated the superior antiemetic effect of propofol compared with inhaled anesthetic predominantly in the first 2–6 h after surgery [19–21]. The results of the present study support the previous finding that TIVA is effective in preventing PONV up to 6 h postoperatively. Interestingly, the incidence of PONV in the 0–2-h period after surgery was the same between the two groups, but it was lower in the TIVA plus palonosetron group at 2–6 h after surgery, albeit no statistical significance. These results imply that the antiemetic effect of TIVA is as potent as adding palonosetron to TIVA over a short-term period, especially 0–2 h postoperatively, and has a smaller effect on PONV prevention as time passes. On the whole, the long-term antiemetic effect (6–24 h) is due to palonosetron, which has a long-half life.

There have been some reports comparing various 5-HT3 receptor antagonists [22]. Lee et al. [23] compared palonosetron, granisetron, and ramosetron in the prevention of PONV after laparoscopic gynecologic surgery. They maintained anesthesia with sevoflurane and nitrous oxide and used diclofenac to control postoperative pain. The results of this prior study concluded that there were no significant differences in the overall incidence of PONV (33.3 %) among the groups. Our present study is unique in that, to date, there have been no studies conducted using only TIVA and palonosetron. Although our study regimen included opioid-based PCA, the overall incidence of PONV (34.0 %, TIVA plus palonosetron group) was similar to that reported

in the previous study by Lee et al. [23]. We found that the incidence of PONV during the early postoperative period (0–6 h) was also similar (17.1 % in Lee et al. vs 16.0 % in the TIVA plus palonosetron group of our study). This may be explained by the different agents used for anesthesia. Lee et al. used sevoflurane to maintain anesthesia, while we used opioids to control pain postoperatively. Both are known to have negative effects on the prevention of PONV, and both therefore seemed to show similar results.

Apfel's simplified risk score for PONV (risk factors being female gender, nonsmoking, history of PONV, and postoperative opioids) is widely accepted as a way to assess PONV risk [2]. In accordance with Apfel's simplified risk score, the risk factors influencing PONV were well balanced between the two groups in our study. All enrolled patients were female and were able to use opioid-based PCA. Most patients were nonsmokers and some had a history of motion sickness or PONV. Therefore, almost all patients had three or four risk factors which related to a 60−80 % incidence of PONV. Patients having a moderate-to-high risk of PONV should receive multimodal prophylaxis [24]. Thus, we evaluated the efficacy of TIVA and palonosetron compared with TIVA in preventing PONV. The relative risk reduction of palonosetron was known to be 30 % at 0.075 mg [17, 18]. In our study, the relative risk reduction in the TIVA plus palonosetron group relative to the TIVA group was 41 % for the first 24 h postoperatively.

The adverse effects associated with 5-HT3 receptor antagonists are not clinically serious, with headache and dizziness being most common [4, 25]. The incidence of adverse effects was not different between the TIVA and TIVA plus palonosetron groups and most of the symptoms were mild and transient.

There are some limitations to our study. The power analysis used to determine the number of patients required in this study was not based on the same type of surgery. It also would have been useful to have included a contrast group in which ondansetron was added to TIVA. We used a VRS in which patients describe their symptoms as none, mild, moderate, or severe. Although Apfel et al. suggested that a visual analog scale (VAS, 0−10 or 0−100), an 11-point numerical rating scale (0−10), or a VRS can be used to quantify symptoms [26], pain studies have found that the VRS is not as sensitive as the VAS [27]. Most of the previous literature investigated the effect of palonosetron up to 72 h after surgery. However, because surgeons of our institution tended to discharge patients at 2–4 days after surgery, we could not follow-up PONV in every patient up to 72 h equally. Further studies will be needed to generate data from a sufficient number of patients and to compare other 5HT-3 receptor antagonists in combination with TIVA.

In conclusion, combining palonosetron with TIVA can be considered as a good method to prevent PONV, not only during the short postoperative period but also especially during the 6–24-h period after anesthesia, without any serious adverse effects.

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Compliance with ethical standards

Conflict of interest There are no financial or other relationships to disclose that might lead to a conflict of interest regarding this article.

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