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ORIGINAL ARTICLE

# Efficacy of palonosetron and ramosetron on postoperative nausea and vomiting related to intravenous patient-controlled analgesia with opioids after gynecological laparoscopic surgery (double-blinded prospective randomized controlled trial)

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**Abstract**
*Purpose* The study was designed to assess the efficacy of palonosetron and ramosetron in preventing postoperative nausea and vomiting (PONV) related to intravenous (IV) patient-controlled analgesia (PCA) with opioids after gynecological laparoscopic surgery.
*Methods* Patients were randomly allocated to 4 groups—C, P, R0.3 and $R_{PCA}$. At the end of surgery, group C received an infusion of 50 ml normal saline, group P received palonosetron 75 μg mixed in 50 ml normal saline, and groups R0.3 and $R_{PCA}$ received ramosetron 0.3 mg mixed in 50 ml normal saline. A PCA pump containing fentanyl was connected for all groups; however, ramosetron 0.6 mg was mixed with the PCA regimen for the $R_{PCA}$ group. PONV and postoperative pain were assessed.
*Results* PONV incidence and scale, and Rhodes index in $R_{PCA}$ group between 24 and 72 h after discharge from the post-anesthetic care unit (PACU) showed significantly lower values, compared with the other groups. PONV incidence and scale, and Rhodes index in P group and R0.3 group were lower than the corresponding values in C group at all times, without statistical significance.
*Conclusion* A single dose of palonosetron 75 μg or ramosetron 0.3 mg was unable to prevent PONV related to IV PCA with opioids in patients undergoing gynecological laparoscopic surgery. The combination of a single dose of ramosetron 0.3 mg, followed by ramosetron 0.6 mg mixed with PCA, significantly decreased PONV compared with a single dose of palonosetron 75 μg or ramosetron 0.3 mg.

**Keywords** Postoperative nausea and vomiting · Patient-controlled analgesia · Opioids

## Introduction

Intravenous (IV) patient-controlled analgesia (PCA) with opioids is an effective and safe method for the control of postoperative pain with a high level of patient satisfaction. However, postoperative analgesia with opioids is associated with a high incidence of postoperative nausea and vomiting (PONV) [1, 2].

Selective serotonin or 5-hydroxytryptamine type 3 ($5\text{-HT}_3$) receptor antagonists have a well-established role in prophylaxis and treatment of PONV. However, ondansetron has not shown better efficacy compared with traditional anti-emetics [3, 4], and has shown a limited effect on PONV related to IV PCA with opioids [5]. Palonosetron and ramosetron are newly developed $5\text{-HT}_3$ receptor antagonists, which are more potent at all doses below their therapeutic ceiling, with longer acting duration [6]. These pharmacologic properties are expected to contribute to better efficacy in preventing PONV related to IV PCA with opioids but clinical evidence is limited [6, 7]. In addition, continuous infusion of a newly developed $5\text{-HT}_3$ receptor

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antagonist with the PCA regimen, following a single injection of the same drug, is expected to sustain higher plasma concentrations than a single dose and allow more effective prophylaxis of PONV; however, palonosetron should not be mixed with other drugs, and must be used as a single injection (http://www.aloxi.com/hcp/about-aloxi/dosage.aspx).

The study was designed to assess the efficacy of palonosetron and ramosetron as a single dose in preventing PONV related to IV PCA with opioids after gynecological laparoscopic surgery. We also evaluated the effect of ramosetron mixed into the PCA regimen, following a single injection of ramosetron, on prophylaxis of PONV related to IV PCA with opioids, compared with a single injection of palonosetron or ramosetron.

## Methods

### Study population

The study was approved by the Institutional Review Board (approval number KUH1160025 granted by Institutional Review Board of Konkuk University Medical Center, Seoul, Korea) and registered at Clinical Research Information Service, Korea Centers for Disease Control and Prevention, Ministry of Health Welfare (https://cris.nih.go.kr) with registration number of KCT0000183. Written informed consent was obtained from patients and the study was conducted in a prospective, double-blinded and randomized fashion from September 2011 to February 2013. Patients, requesting IV PCA for pain control after gynecological laparoscopic surgery were enrolled for the study. Patients were excluded if any of the following criteria were present: (1) urgent or emergent case, (2) re-operation case, (3) allergy to egg or soybean oil, (4) QT prolongation on preoperative electrocardiography, (5) history of drug abuse, (6) any current medication, (7) other concurrent surgery, (8) surgery within 1 h and (9) discharge within 72 h. Patients were randomly allocated using a sealed envelope method to receive 50 ml of normal saline (C group), palonosetron (Aloxi®, CJ Cheiljedang Corp., Korea) 0.075 mg (P group), ramosetron (Nasea®, Astellas Pharma Inc., Japan) 0.3 mg (R0.3 group) or ramosetron 0.3 followed 0.6 mg mixed with the PCA regimen ($R_{PCA}$ group). Palonosetron 75 μg and ramosetron 0.3 mg were dissolved in 50 ml of normal saline. The normal saline for the study was administered over 10 min at the end of surgery. IV ketorolac 0.5 mg/kg for control of postoperative pain was administered and an IV PCA pump was connected at the end of surgery until discharge from the hospital in all patients. The PCA regimen consisted of fentanyl 1,500 μg diluted in normal saline with a total volume of 150 ml. The pump was programed to deliver a basal infusion rate of 0.02 ml/kg/h and an additional dose of 0.02 ml/kg on demand, with 15-min lockout time. All study drugs and PCA pumps were prepared with identical syringes or bags by registered nurses in the post-anesthetic care unit (PACU). All anesthesiologists, surgeons and nurses involved in the study were blinded to the allocation of groups. All data were collected by trained observers who were blinded to the study and did not participate in patient care.

### Anesthetic technique

Patients received no pre-anesthetic medication and were anesthetized with a standardized technique. Anesthesia was induced after establishing routine non-invasive monitoring with bispectral index (BIS) monitoring. The anesthesiologists, who were blinded to the study, were requested to anesthetize the patients as follows. Lidocaine 0.5 mg/kg was administered to decrease the pain induced by propofol. Propofol 2 mg/kg was administered to induce anesthesia. Remifentanil infusion was started after anesthesia induction using a target-controlled infusion (TCI) device to maintain a target plasma concentration of 5 mg/ml until the end of surgery. Rocuronium 0.6 mg/kg was administered for muscle relaxation under the guidance of peripheral neuromuscular transmission monitoring after loss of consciousness. Tracheal intubation was performed at a train-of-four count of zero. Anesthesia was maintained with sevoflurane, and titrated to maintain BIS values between 40 and 60. Sevoflurane and TCI of remifentanil were stopped at the end of the surgery. Residual neuromuscular paralysis was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg under the guidance of peripheral neuromuscular transmission monitoring. Patients were transferred to PACU after tracheal extubation.

### Measurement

PONV was assessed using a four-point ordinal scale (0, none; 1, nausea; 2, retching; 3, vomiting) [8] at the following times—on arrival at the PACU (T1), on discharge from the PACU (T2), 24 h after discharge from the PACU (T3), 48 h after discharge from the PACU (T4), and 72 h after discharge from the PACU (T5). The severity of PONV from T2 to T3, from T3 to T4 and from T4 to T5 was evaluated with the Rhodes index which described the severity of PONV using a numerical scale from 0−32, including subjective (the degree of severity) and objective (with/without nausea, retching and vomiting, and times of nausea, retching and vomiting) factors of PONV [9] (Fig. 1). Metoclopramide 10 mg was given on demand as the first-line anti-emetic treatment. Ondansetron 4 mg was given on demand as the

| Rhodes index at 24, 48 or 72 h after discharge from PACU | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Score | 4 | | 3 | | 2 | | 1 | | 0 | |
| 1. In the last 24 h, I threw up ( ) times. | 7 or more | ☐ | 5-6 times | ☐ | 3-4 times | ☐ | 1-2 times | ☐ | I did not throw up | ☐ |
| 2. In the last 24 h, from retching or dry heaves have felt ( ) distress. | Severe | ☐ | Great | ☐ | Moderate | ☐ | Mild | ☐ | No | ☐ |
| 3. In the last 24 h, from vomiting or throwing up, I have felt ( ) distress. | Severe | ☐ | Great | ☐ | Moderate | ☐ | Mild | ☐ | No | ☐ |
| 4. In the last 24 h, I have felt nauseated or sick at my stomach ( ). | More than 6 h | ☐ | 4-6 h | ☐ | 2-3 h | ☐ | 1 hour or less | ☐ | Not at all | ☐ |
| 5. In the last 24 h, from nausea/sickness at my stomach, I have felt ( ) distress. | Severe | ☐ | Great | ☐ | Moderate | ☐ | Mild | ☐ | No | ☐ |
| 6. In the last 24 h, each time I threw up I produced a ( ) amount. | Very large (3cups or more) | ☐ | Large (2-3 cups) | ☐ | Moderate (1/2-2 cups) | ☐ | Small (up to 1/2 cups) | ☐ | I did not throw up | ☐ |
| 7. In the last 24 h, I have felt nauseated or sick at my stomach ( ) times. | 7 or more | ☐ | 5-6 times | ☐ | 3-4 times | ☐ | 1-2 times | ☐ | No | ☐ |
| 8. In the last 24 h, I have had periods of retching or dry heaves without bringing anything up ( ) times. | 7 or more | ☐ | 5-6 times | ☐ | 3-4 times | ☐ | 1-2 times | ☐ | No | ☐ |

**Fig. 1** Questionnaire for Rhodes index. *PACU* post-anesthetic care unit

second-line anti-emetic treatment. Dexamethasone 5 mg on demand was reserved as the third-line anti-emetic treatment.

Postoperative pain was assessed at the same times using a visual analog scale (VAS) that ranged from 0−100 mm with 0 mm (no pain) and 100 mm (worst pain imaginable). Ketorolac 0.5 mg/kg and fentanyl 0.2 μg/kg were given on demand as first- and second-line additional rescue analgesic treatments.

The incidence of headache, dizziness and skin flushing was checked at the same time for evaluating the adverse effects of 5-$HT_3$ receptor antagonists.

## Statistics

PONV incidence (70 %) and scale (1.4 ± 1.2) at T3, and Rhodes index (4.4 ± 4.1) from T2 to T3 (4.4 ± 4.1) were observed from a pilot study of 10 patients who received the same PCA regimen without any 5-$HT_3$ receptor antagonist after gynecological laparoscopic surgery. Primary and secondary outcomes were Rhodes index from T2 to T3 and PONV scale at T3, respectively. The minimum difference of 75 % in Rhodes index and PONV scale among the groups was considered to be clinically significant and the sample sizes of 44 for Rhodes index and 36 for PONV scale, respectively, were calculated to obtain a power of 0.9 and an $\alpha$ value of 0.05.

Data were analysed using the Statistical Package for the Social Sciences ver. 18.0® software. The chi-squared test was performed for differences in PONV incidence among the four groups. The multiple type-I error level was guaranteed at the level of 0.05 by applying Bonferroni's correction. The intra-group changes in PONV scale were analysed using the Friedman test, while inter-group differences in PONV scale were analysed with the Kruskal–Wallis test. If significant, the Mann–Whitney *U* test was performed for multiple comparisons among groups. The intra-group changes in Rhodes index and VAS over time and the inter-group differences among the four groups were analysed using an analysis of variance by ranks for repeated measurements; if significant, the Tukey's test was performed for multiple comparisons among groups. All values were expressed as the number of patients or mean ± standard deviation. A value of $p < 0.05$ was considered statistically significant.

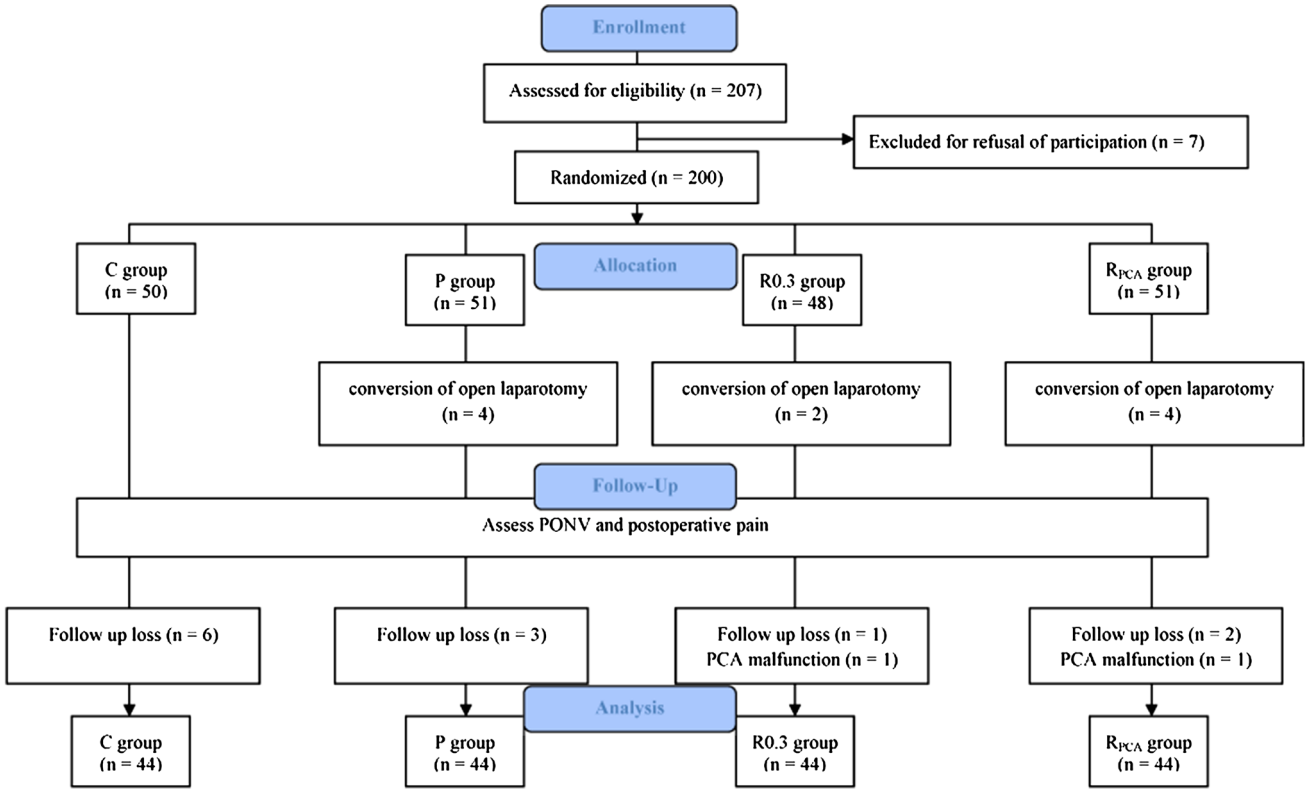


**Fig. 2** CONSORT flow diagram for the study. *PONV* postoperative nausea and vomiting, *PCA* patient-controlled analgesia

## Results

Of the two hundred and seven patients who were eligible for the study, 31 were excluded for the following reasons—7 patients refused to participate in the study, 10 patients were converted to open laparotomy (4 patients in P group, 2 patients in R0.3 group and 4 patients in $R_{PCA}$ group), 12 patients were discharged early (6 patients in C group, 3 patients in P group, 1 patient in R0.3 group and 2 patients in $R_{PCA}$ group), and 2 patients had a malfunctioning PCA (1 patient in R0.3 group and 1 patient in $R_{PCA}$ group). Thus, 176 patients were included in the final analysis (Fig. 2).

The demographic profiles of the patients were similar among the groups (Table 1).

PONV incidence and scale at T3, T4 and T5, and Rhodes index from T2 to T3, from T3 to T4 and from T4 toT5 in $R_{PCA}$ group showed significantly lower values compared with the other groups (Table 2; Fig. 3). No patient in $R_{PCA}$ group complained of PONV at T5 (Table 2). There were no significant differences in PONV incidence and scale, and Rhodes index among the C, P and R0.3 group (Table 2; Fig. 3). The number of patients who required metoclopramide in C group was significantly larger than in the other groups at T1 (8, 3, 2 and 0 patients in C, P, R0.3 and $R_{PCA}$ group, respectively). However, there were no differences between T2 and T5. There were no differences in the number of patients requiring ondansetron or dexamethasone among the groups. No patient in $R_{PCA}$ group required either ondansetron or dexamethasone. The PONV incidence and scale, and Rhodes index showed the highest values at T3 in all groups (Table 2; Fig. 3). PONV incidence and scale, and Rhodes index decreased with the passage of time after discharge from the PACU (Table 2; Fig. 3).

There were no significant differences among the groups in terms of VAS (Table 3). There were no differences in the number of patients requiring ketolorac among the groups. No patient in any group required additional fentanyl. There were no significant differences in the number of additional doses of PCA on demand among the groups. Postoperative VAS decreased with the passage of time after discharge from the PACU in all groups (Table 3).

No patient complained of headache, dizziness or skin flushing after the administration of the study drugs.

## Discussion

The study showed that palonosetron 75 μg or ramosetron 0.3 mg as a single dose was not effective; however, the

**Table 1** Demographic data

| | C group ($n = 44$) | P group ($n = 44$) | R0.3 group ($n = 44$) | $R_{PCA}$ group ($n = 44$) | $p$ |
|---|---|---|---|---|---|
| Age (years) | 40 ± 11 | 37 ± 12 | 39 ± 14 | 40 ± 12 | 0.653 |
| Height (cm) | 158 ± 5 | 160 ± 6 | 159 ± 5 | 158 ± 5 | 0.283 |
| Weight (kg) | 59 ± 9 | 61 ± 11 | 59 ± 9 | 59 ± 8 | 0.627 |
| Smoking (pack × years) | 0.2 ± 0.8 | 0.2 ± 0.9 | 0.1 ± 0.4 | 0.5 ± 3.0 | 0.616 |
| History of motion sickness | 9 | 5 | 3 | 3 | 0.144 |
| History of PONV | 3 | 1 | 3 | 2 | 0.732 |
| Anesthesia time (min) | 146 ± 44 | 133 ± 39 | 151 ± 54 | 136 ± 35 | 0.195 |
| Operation time (min) | 119 ± 44 | 105 ± 36 | 122 ± 50 | 108 ± 30 | 0.139 |
| Surgical procedures | | | | | |
| Ovarian cystectomy | 26 | 23 | 30 | 25 | 0.523 |
| Uterine myomectomy | 8 | 11 | 5 | 12 | 0.264 |
| Vaginal hysterectomy | 10 | 10 | 9 | 7 | 0.897 |

Values are expressed as number of patients or mean ± standard deviation

*PONV* postoperative nausea and vomiting

**Table 2** Postoperative nausea and vomiting (PONV) incidence

| | C group ($n = 44$) | P group ($n = 44$) | R0.3 group ($n = 44$) | $R_{PCA}$ group ($n = 44$) |
|---|---|---|---|---|
| T1 | 10 | 8 | 4 | 4 |
| T2 | 10 | 7 | 3 | 7 |
| T3 | 33 | 22 | 27 | 8* |
| T4 | 22 | 17 | 19 | 4* |
| T5 | 12 | 14 | 13 | 0* |

Values are expressed as number of patients

*T1* on arrival at PACU, *T2* on discharge from PACU, *T3* 24 h after discharge from PACU, *T4* 48 h after discharge from PACU, *T5* 72 h after discharge from PACU

* $p < 0.05$ compared with C group, P group and R0.3 group

addition of ramosetron 0.6 mg to the PCA regimen was effective in preventing PONV related to IV PCA with opioids.

A single dose of palonosetron 75 μg or ramosetron 0.3 mg has been shown to provide effective prophylaxis against PONV in previous studies [10–12]. Palonosetron, with its long half-life of 40 h and a greater receptor-binding affinity [13], has been more effective than other 5-$HT_3$ receptor antagonists in preventing PONV during the first 24 h after surgery [14, 15]. Thus, we had expected that palonosetron would show the better results, compared with ramosetron. However, there was no significant statistical difference between palonosetron 75 μg and ramosetron 0.3 mg in the present study, even though there was a trend towards a lower PONV incidence and scale, and Rhodes index with palonosetron. Although the reason is not clear, various causes could be related to the anti-emetic effect of 5-$HT_3$ receptor antagonists, including receptor-binding affinity, the type of surgery, etc., as shown in previous reported studies [10, 11, 16].

The dose of palonosetron for prevention of PONV should also be considered. As the dose of palonosetron is increased, the prevention of PONV is increased [10]. However, palonosetron 75 μg was the most effective dose for prevention of PONV and doses >75 μg showed increased side-effects with decreased efficacy. A higher dose of palonosetron is required to prevent chemotherapy-induced nausea and vomiting (CINV), compared with the dose for PONV [17, 18]. Therefore, the correct dose of palonosetron for prevention of PONV should be re-evaluated in various clinical conditions.

Previously, the concentration of fentanyl in the blood through PCA regimen was expected to increase after surgery, although it was dependent on pain intensity. On the contrary, however, the concentration of ramosetron after a single-dose injection in the blood was decreased. To obtain the most benefit from the drug, it is essential to maintain blood levels within the therapeutic range for the correct length of time. The total accumulative dose, including a single injection, continuous infusion mixed in PCA and an additional dose of PCA on demand of ramosetron 0.47, 0.62 and 0.74 mg in $R_{PCA}$ group, were administered until T3, T4 and T5 with better results. Therefore, a higher dose of ramosetron as a single dose would be needed to achieve the same results with the $R_{PCA}$ group, although pharmacokinetics and pharmacodynamics should be considered.

5-$HT_3$ receptor antagonists have various tolerable adverse effects such as headache, dizziness, skin flushing, constipation, diarrhoea, QT prolongation on electrocardiography, etc [19]. In the present study, only the symptomatic adverse effects of 5-$HT_3$ receptor antagonists were assessed; gastrointestinal adverse effects were ignored because the enrolled patients underwent intra-abdominal procedures. No patient complained of headache, dizziness or skin flushing in the present study. Adverse effects should

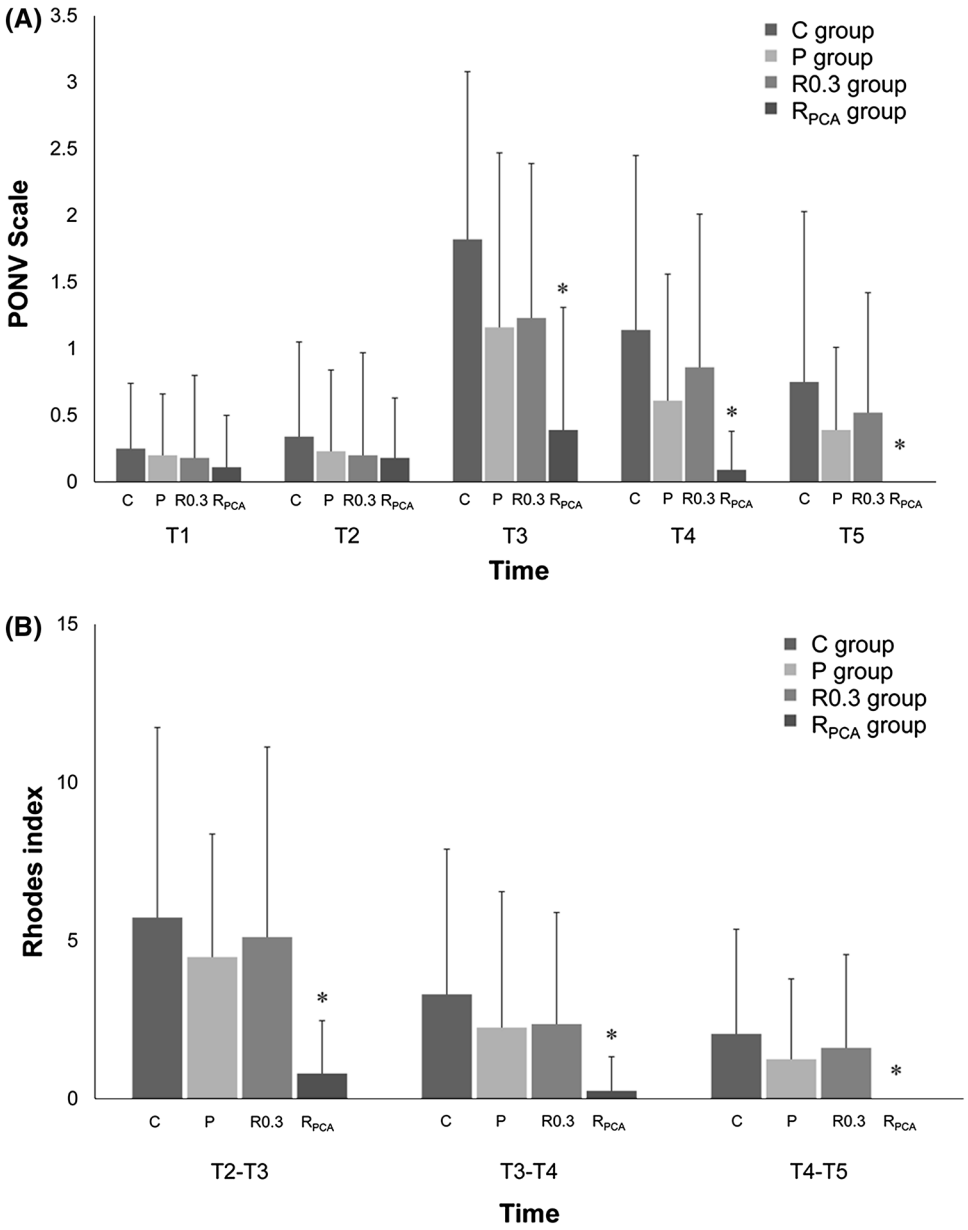


**Fig. 3** Severity of postoperative nausea and vomiting (PONV). **a** PONV scale. **b** Rhodes index. *T1* on arrival at PACU, *T2* on discharge from PACU, *T3* 24 h after discharge from PACU, *T4* 48 h after discharge from PACU, *T5* 72 h after discharge from PACU

be taken into consideration when using higher doses of 5-$HT_3$ receptor antagonists [20].

In the present study, PONV showed no significant differences among the groups at T1 and T2 but there were significant PONV differences between $R_{PCA}$ group and other groups at T3, T4 and T5, which was comparable with a previous study [14]. The time to reach the plasma concentration of the anti-emetic for effective PONV prevention was associated with no significant differences of PONV at T1 and T2. If the anti-emetic injections and the connection of the PCA pump occurred before the end of surgery, better results would be seen in the $R_{PCA}$ group at T1 and T2.

In general, 5-$HT_3$ receptor antagonist was recommended as first-line anti-emetic treatment [21–24]. However, the present study investigated the efficacy of palonosetron and ramosetron on PONV, and metoclopramide, independent of 5-$HT_3$ receptor, was used as the first-line anti-emetic treatment. As described in the introduction, ondansetron has shown a limited effect on PONV related to IV PCA with opioids. However, we used ondansetron as the second-line anti-emetic treatment for the following reasons. At first, we regarded the serum level of the 5-$HT_3$ receptor antagonist not reaching the therapeutic range when the first-line anti-emetic treatment failed although it could not completely cure the PONV because the mechanism of PONV is not entirely associated with only 5-$HT_3$ receptor. Secondly, ondansetron proved to be more effective than metoclopramide

**Table 3** Postoperative pain

| | C group ($n = 44$) | P group ($n = 44$) | R0.3 group ($n = 44$) | $R_{PCA}$ group ($n = 44$) |
|---|---|---|---|---|
| VAS (mm) | | | | |
| T1 | 40 ± 19 | 39 ± 14 | 35 ± 19 | 35 ± 17 |
| T2 | 36 ± 15 | 33 ± 11 | 31 ± 11 | 32 ± 12 |
| T3 | 25 ± 10* | 25 ± 10* | 22 ± 12* | 22 ± 12* |
| T4 | 17 ± 8*† | 18 ± 11*† | 16 ± 10*† | 16 ± 9*† |
| T5 | 12 ± 10*†‡ | 12 ± 6*†‡ | 11 ± 8*†‡ | 12 ± 9*†‡ |
| PCA on demand | | | | |
| T1 | 0.3 ± 0.4 | 0.1 ± 0.3 | 0.1 ± 0.3 | 0.2 ± 0.4 |
| T2 | 0.4 ± 0.5 | 0.3 ± 0.5 | 0.4 ± 0.5 | 0.4 ± 0.5 |
| T3 | 13.5 ± 4.2 | 14.2 ± 3.0 | 13.9 ± 3.0 | 12.6 ± 2.8 |
| T4 | 7.2 ± 4.3 | 8.4 ± 3.9 | 7.8 ± 3.2 | 6.6 ± 3.2 |
| T5 | 1.3 ± 2.5 | 1.8 ± 2.7 | 1.1 ± 2.0 | 1.1 ± 2.1 |

Values are expressed as mean ± standard deviation

*VAS* visual analog scale, *PCA on demand* number of additional doses of patient-controlled analgesia on demand, *T1* on arrival at PACU, *T2* on discharge from PACU, *T3* 24 h after discharge from PACU, *T4* 48 h after discharge from PACU, *T5* 72 h after discharge from PACU

* $p < 0.05$ compared with T1 and T2

† $p < 0.05$ compared with T3

‡ $p < 0.05$ compared with T4

in PONV related to IV PCA with opioids [25]. Thirdly, the effective anti-emetic treatment as a single agent on PONV related to IV PCA with opioids were droperidol, ramosetron and ondansetron as shown in new guidelines for the management of PONV [26]; however, droperidol is no longer available in Korea. The new guidelines also suggest the futility of repeat anti-emetic treatment when administered within 6 h of previous anti-emetic treatment [26]. Moreover, the adverse effects should be considered when ramosetron is used as a rescue anti-emetic treatment, especially in the $R_{PCA}$ group. The Korean Food and Drug Administration does not allow ramosetron >0.6 mg. Therefore, ondansetron, an additional 5-$HT_3$ receptor antagonist, was used as second-line anti-emetic treatment. Even dexamethasone has been shown to have good efficacy for PONV, it was used as the third-line anti-emetic treatment in the present study for the risk of infection [26].

In conclusion, the study demonstrated that a single dose of palonosetron 75 μg or ramosetron 0.3 mg was unable to prevent PONV related to IV PCA with opioids in patients undergoing gynecological laparoscopic surgery. The combination of a single dose of ramosetron 0.3 mg, followed by ramosetron 0.6 mg mixed with PCA, significantly decreased PONV compared with a single dose of palonosetron 75 μg or ramosetron 0.3 mg.

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**Conflict of interest** None.

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