

Comparison of ramosetron and ondansetron for the treatment of established postoperative nausea and vomiting after laparoscopic surgery: a prospective, randomized, double-blinded multicenter trial

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Background: Postoperative nausea and vomiting (PONV) is a common complication after surgery, which increases physical and psychological discomfort and delays recovery. The aim of this study was to test the hypothesis that ramosetron is comparable to ondansetron for the treatment of established PONV after laparoscopic surgery using a prospective, randomized, double-blinded, noninferiority study.

Methods: Patients who had at least two risk factors of PONV and underwent laparoscopic surgery under general anesthesia were assessed for eligibility. Patients who developed PONV within the first 2 h after anesthesia received ondansetron (4 mg) or ramosetron (0.3 mg) intravenously in a randomized double-blind manner. Patients were then observed for 24 h after drug administration. The incidence of nausea and vomiting, severity of nausea, rescue antiemetic necessity, and adverse effects at 0–2 or 2–24 h after drug administration was evaluated. The primary endpoint was the rate of patients exhibiting a complete response, defined as no emesis and no further rescue antiemetic medication for 24 h after drug administration.

Results: Among the 583 patients, 210 (36.0%) developed PONV and were randomized to either the ondansetron (n=105) or ramosetron (n=105) group. Patient's characteristics were similar between the groups. The complete response rate was 44.1% in the ondansetron group and 52.9% in the ramosetron group after 24 h of initial antiemetic administration. The incidence of adverse events was not different between the groups.

Conclusion: We found evidence to support the noninferiority of ramosetron (0.3 mg) compared to ondansetron (4 mg) for the treatment of established PONV in moderate to high-risk patients undergoing laparoscopic surgery.

Keywords: laparoscopic surgery, ondansetron, postoperative nausea and vomiting, ramosetron, non-inferiority, antiemetic

Introduction

Despite considerable effort in evaluating antiemetic strategies and the development of a new antiemetic class, postoperative nausea and vomiting (PONV) remains one of the most common and distressing complications after surgery. PONV not only increases physical and psychological discomfort but also causes wound dehiscence, dehydration, and electrolyte imbalance, which leads to delayed recovery, prolonged hospital stays, and life-threatening aspiration.^{1,2} Published evidence suggests that prophylactic

administration of antiemetic drugs should be considered for patients with two or more PONV risk factors, such as the female gender, nonsmoking, and the use of postoperative opioids.^{3,4} In addition, various approaches to prevent or treat PONV have been studied, especially for high-risk patients, which contribute to early recovery, increased patient satisfaction, and reduced side effects.

Among the currently available antiemetics, 5-hydroxytryptamine receptor 3 (5-HT₃) antagonists are frequently used for prophylaxis against PONV and treatment of established PONV. Ramosetron is a newly developed selective 5-HT₃ receptor antagonist with longer action duration (up to 48 h) and higher receptor affinity than its previously developed congeners, including ondansetron.⁵⁻⁷ Ondansetron is an effective prophylactic and therapeutic 5-HT₃ receptor antagonist for the treatment of PONV.⁸⁻¹⁰ Although ramosetron is superior to ondansetron for preventing PONV, ramosetron and ondansetron have never been compared with respect to their therapeutic efficacy in treating established PONV.

Therefore, we designed a randomized controlled trial to compare the therapeutic efficacy of ramosetron and ondansetron for the treatment of established PONV in patients following laparoscopic surgery under general anesthesia.

Methods

After obtaining approval from the institutional review boards of Yonsei University Severance Hospital, Seoul National University Bundang Hospital, and Ewha Womans University Mokdong Hospital, a total 610 patients undergoing laparoscopic surgery between July 2015 and September 2016 were assessed for eligibility. An independent institutional review board from all the institutions at which the participating anesthesiologists are affiliated has approved this study. This study was registered at <http://ClinicalTrials.gov> (registration number NCT03017222).

Written informed consent was obtained from all patients before they were recruited. Patient inclusion criteria were as follows: age 19–65 years, undergoing elective laparoscopic surgery under inhalation anesthesia, surgery duration between 30 min and 4 h, American Society of Anesthesiologists physical status I or II, and at least two of these risk factors: female gender, history of motion sickness or PONV, nonsmoking, and postoperative opioid use. Patient exclusion criteria were as follows: history of being allergic to 5-HT₃ receptor antagonists, anticancer chemotherapy history, chronic opioid use, alcohol abuse, drug abuse, administration of antiemetic medication within 24 h of surgery, steroids 24 h before or after surgery, presence of renal

(serum Cr >1.6 mg/dL) or hepatic (liver enzymes more than twice the normal value) insufficiency, conversion to open laparotomy, pregnant, breastfeeding, borderline QTc prolongation (>430 ms for male, >450 ms for female), and unable to understand pain scoring or express the PONV degree.

Intraoperative and postoperative management

The anesthetic techniques were controlled at all three institutions. Premedication was not administered. Anesthesia was induced using propofol (1.5–2 mg/kg) and fentanyl (1 µg/kg) or remifentanyl (0.5–1 µg/kg/min) under standard monitoring; rocuronium (0.6 mg/kg) was administered to facilitate tracheal intubation. The patient's lungs were ventilated with a tidal volume of 8 mL/kg of ideal body weight in 50% oxygen with air. Respiratory rate was adjusted to maintain an end-tidal CO₂ pressure of 35–45 mmHg. Anesthesia was maintained with sevoflurane or desflurane and remifentanyl (0.1–0.3 µg/kg/min). For management of postoperative pain, a single bolus dose of fentanyl (1 µg/kg) was administered intravenously 15 min before the end of surgery, and remifentanyl intravenous infusion was stopped. Fentanyl (15–20 µg/kg at 2 mL/h, 0.5 mL bolus, 15 min lock-out time, total 100 mL) was used in intravenous patient-controlled analgesia (PCA) pumps if indicated to control acute postoperative pain.

After extubation and transfer to the postanesthesia care unit (PACU), the patients were monitored with routine care and supplementary oxygen through a face mask. During PACU care, if patients developed nausea with numerical rating scale (NRS) ≥4 or vomiting within 2 h postoperatively, the therapeutic intervention designed to treat PONV ensued. The patients were randomly allocated into one of the two groups: the ondansetron group (Zofran® 4 mg) or ramosetron group (Nasea® 0.3 mg), using computer-generated random number codes. When nausea of NRS ≥4 or vomiting still existed, metoclopramide (10 mg) as additional rescue antiemetic was administered and recorded. If PONV did not develop within 2 h postoperatively, we excluded the patient from study enrollment and administered prophylactic antiemetic agents, given the presence of the relevant risk factors for PONV. The study drugs were prepared in identical syringes and administered by the personnel who were not involved in this study. All patients, physicians, and investigators collecting data were blinded to group assignments.

Outcomes

The primary outcome variable was a complete response rate, defined as no retching and/or vomiting and no secondary rescue antiemetic administration. The secondary outcome

variables were incidence and severity of nausea, incidence of retching and/or vomiting, need for additional antiemetics, pain score, and requirements of rescue analgesics. The intensity of nausea was graded on an NRS using an 11-point scale, with 0=no nausea to 10=worst possible nausea. The severity of nausea was determined according to NRS scores: mild (1–3), moderate (4–6), and severe (7–10). Pain intensity scores were measured on a visual analog scale (VAS) that ranged from 0 mm (no pain) to 100 mm (worst pain imaginable). The investigator blinded to group allocation evaluated incidence and severity of nausea, retching and/or vomiting, need for additional antiemetics, pain intensity, rescue analgesic, and adverse events for 24 h after administration of the study drug, which was divided into two intervals: 0–2 h and 2–24 h.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was performed as a non-inferiority trial, designating ondansetron, the commonly used drug for treating PONV, as the comparison for the effects of ramosetron toward established PONV. A previous study demonstrated a complete response rate of 45% with ondansetron (4 mg) treatment for established PONV.⁹ As there was no previous study regarding ramosetron treatment for established PONV, a complete response rate was assumed as 55% and defined the margin of non-inferiority at

an absolute risk difference of 10%. Therefore, we calculated that a study with 95 patients per group would have at least 80% power, with one-sided type I error of 0.025, using a non-inferiority test. Taking into consideration a 10% dropout rate, we decided to enroll 105 patients in each group. Categorical variables were analyzed using chi-square test or Fisher's exact test and shown as number and percentage. Continuous variables were expressed as mean \pm standard deviation or median [interquartile range] according to the normality, using Student's *t*-test or Mann-Whitney *U*-test, as appropriate. *P*-values of <0.05 were considered significant.

Results

A total of 610 patients were assessed for eligibility; 210 of the 583 patients observed for 2 h postoperatively at PACU were enrolled in this study and were randomly assigned to two treatment groups (Figure 1). After randomization, one patient withdrew consent, and three patients were excluded from the final analysis due to use of prohibited drugs without notification to the investigator; the remaining 206 patients completed the study. The baseline characteristics, including history of PONV or motion sickness, anesthetic, operative, and postoperative data, were similar between the groups (Table 1). Fentanyl-based intravenous PCA was used in 62.6% of all patients. Although there was a higher trend of intravenous PCA use in the ondansetron group, it was not statistically significant ($P=0.08$). The number of patients

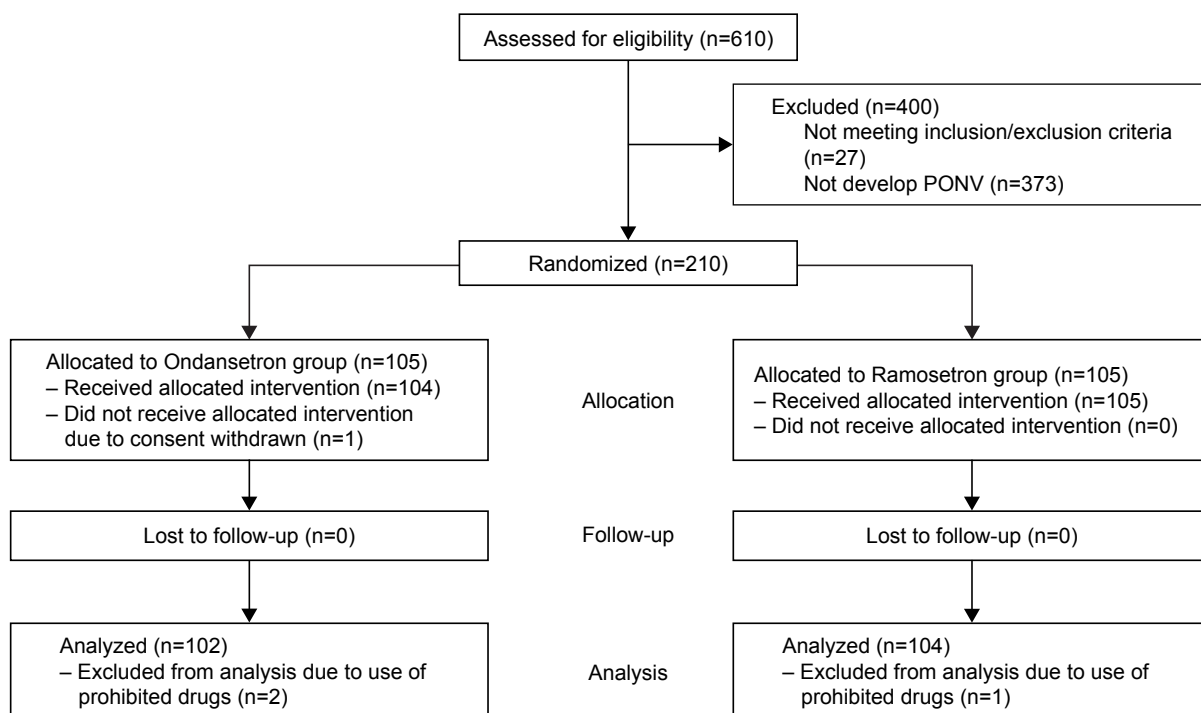


Figure 1 Flow diagram of the study.

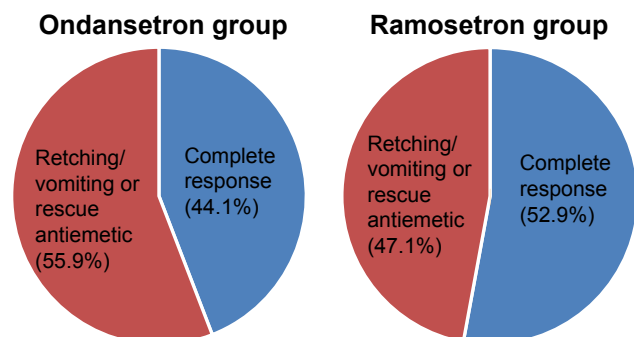
Table 1 Patient's characteristics

	Ondansetron group (n=102)	Ramosetron group (n=104)	P-value
Age (years)	42.6±10.9	43.7±11.9	0.50
Women	97 (95.1)	96 (92.3)	0.41
Body mass index (kg/m ²)	23.4±4.0	23.2±3.1	0.58
ASA physical status			0.44
1	83 (81.4)	79 (76.0)	
2	20 (19.6)	25 (24.0)	
History of PONV or motion sickness	38 (37.3)	42 (40.4)	0.65
Non-smoking	99 (97.1)	100 (96.2)	1.00
Simplified risk score			0.78
2	10 (10.2)	11 (10.6)	
3	57 (55.9)	59 (56.7)	
4	35 (34.3)	34 (32.7)	
Duration of anesthesia (min)	123.9±47.5	121.4±66.2	0.75
Duration of surgery (min)	94.1±45.2	92.2±64.6	0.81
Duration of PACU stay (min)	67.2±24.4	70.6±25.6	0.32
Use of fentanyl-based IV PCA	70 (68.6)	59 (56.7)	0.08
Type of surgical procedure			0.35
Cholecystectomy	34 (33.3)	43 (41.3)	
Hysterectomy	21 (20.6)	18 (17.3)	
Ovarian cystectomy	19 (18.6)	20 (19.2)	
Myomectomy	19 (18.6)	13 (12.5)	
Salpingo-oophorectomy	6 (5.9)	8 (7.7)	
Other gynecologic surgery	3 (2.9)	2 (1.9)	

Note: Values are presented as mean ± standard deviation or number (%) of patients.
Abbreviations: ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting; PACU, postanesthesia care unit; IV PCA, intravenous patient-controlled analgesia.

with ≥3 risk factors for PONV was 92 (90.2%) patients in the ondansetron group and 93 (89.4%) patients in the ramosetron group.

Our primary outcome was ramosetron noninferiority in comparison with ondansetron based on the complete response rate for 24 h after administration of the study drug. The complete response rate was 44.1% (45 of 102 patients) and 52.9% (55 of 104 patients) in the ondansetron and ramosetron group, respectively, for 24 h after administration of the study drug (absolute difference 8.8%, 95% CI −4.8 to −22.4) (Figure 2). The incidence and severity of nausea

**Figure 2** Complete response rate for 24 h after administration of the study drug.**Table 2** Incidence of nausea, retching/vomiting, and requirement for rescue antiemetic treatment

	Ondansetron group (n=102)	Ramosetron group (n=104)	P-value
Patients with nausea			
0–2 h	70 (68.6)	64 (61.5)	0.29
2–24 h	59 (57.8)	57 (54.8)	0.66
0–24 h	83 (81.4)	77 (74.0)	0.21
Nausea severity			
0–2 h (mild/moderate/severe)	28/27/15	27/27/10	0.53
2–24 h (mild/moderate/severe)	21/31/7	24/24/9	0.84
Patients with retching/vomiting			
0–2 h	10 (9.8)	15 (14.4)	0.31
2–24 h	14 (13.7)	16 (15.4)	0.74
0–24 h	22 (21.6)	27 (26.0)	0.46
Patients requiring rescue antiemetic			
0–2 h	27 (26.5)	20 (19.2)	0.22
2–24 h	27 (26.5)	23 (22.1)	0.47
0–24 h	46 (45.1)	39 (37.5)	0.27

Note: Values are presented as number (%) of patients.

were similar between the two groups during the study period (Table 2). No differences were observed between the groups with respect to the incidence of retching and/or vomiting during the study period. The overall incidence of PONV during 24 h after administration of the study drug was 83 (81.4%) in the ondansetron group and 78 (75.0%) in the ramosetron group.

No patient withdrew from the study due to adverse events. There were no differences in the incidences of headache, dizziness, or drowsiness between the groups (Table 3). There were no significant differences with regard to the postoperative pain intensity and the rescue analgesic requirement during the study period (Table 4).

Discussion

In this prospective, randomized, double-blinded multicenter trial, we compared the therapeutic efficacy of a single dose of ramosetron (0.3 mg) with that of a single dose of ondansetron (4 mg) in the treatment of established PONV in a moderate to high-risk population undergoing laparoscopic surgery

Table 3 Side effects of antiemetic drugs

	Ondansetron group (n=102)	Ramosetron group (n=104)	P-value
Headache	7 (6.9)	2 (1.9)	0.10
Dizziness	11 (10.8)	14 (13.5)	0.56
Drowsiness	15 (14.7)	17 (16.3)	0.75

Note: Values are presented as number (%) of patients.

Table 4 Pain intensity scores and requirement of rescue analgesic

	Ondansetron group (n=102)	Ramosetron group (n=104)	P-value
Pain scores			
0–2 h	54.3±19.7	51.5±20.5	0.32
2–24 h	32.5±15.9	34.9±16.8	0.30
Patients requiring rescue analgesic			
0–2 h	72 (70.6)	74 (71.2)	0.93
2–24 h	49 (48.0)	54 (51.9)	0.58

Note: Values are presented as mean ± standard deviation or number (%) of patients.

under general anesthesia. Noninferiority analysis revealed that ramosetron appears to be noninferior to ondansetron for the treatment of established PONV in this subset of patients for 24 h after administration of the study drug.

The etiology of PONV is multifactorial, with risk factors that include age, sex, obesity, a history of motion sickness or previous PONV, smoking habits, anesthetic technique, and postoperative use of opioids.¹¹ Type of surgery as a risk factor is still debated; laparoscopic surgery is associated with a higher incidence of PONV when compared with open surgery due to CO₂ insufflation, residual pneumoperitoneum, peritoneal distension, and diaphragm and visceral organ irritation.¹² Several meta-analyses report that ondansetron is one of the most effective antiemetic agents available for prevention and treatment of PONV, suggesting that intravenous ondansetron 4 mg was the optimal dose for treating established PONV.^{9,13} However, little information exists on the therapeutic efficacy of a newly developed 5-HT₃ receptor antagonist in patients with established PONV after laparoscopic surgery. In this study, we compared the clinical evidence for therapeutic response to ramosetron with that of ondansetron for established PONV treatment. There was no statistically significant difference between ramosetron and ondansetron as a treatment for established PONV after laparoscopic surgery in moderate to high-risk patients for 24 h after administration of the study drug.

In a recent meta-analysis comparing ramosetron to ondansetron for preventing PONV during various types of surgery, there was no difference in incidence of nausea, need for rescue antiemetics, and incidence of side effects, but there was significantly less vomiting in patients receiving ramosetron during early (0–6 h) and late (6–24 h) time periods.^{14–16} In this study, we had expected that ramosetron would have an advantage over ondansetron in treating vomiting or preventing further retching or vomiting in the late period because differences exist in receptor affinity, pharmacokinetics, and the half-life between ramosetron and ondansetron (9 vs 3.5 h, respectively).¹⁷ Although differences did not reach statistical

significance, 53% of patients receiving ramosetron treatment were prevented from further retching or vomiting without secondary rescue antiemetic administration compared to 44% of patients receiving ondansetron treatment. The current findings with ondansetron (4 mg) are consistent with previous results evaluating ondansetron use for treating established PONV; the complete response rate at 24 h after ondansetron administration was 45%–47%.^{9,18}

The incidence of PONV increases exponentially from 10% when no risk factors are present to 78% when all four risk factors are present,³ and identified risk factors include female gender, nonsmoking, the use of postoperative opioids, and prior history of motion sickness or PONV. The present study was designed to evaluate the therapeutic efficacy of ramosetron and ondansetron in patients at moderate to high risk of PONV, and thus we planned to include patients with two or more risk factors. However, after randomization and treatment allocation, we found that 90% of the enrolled patients had at least three risk factors, making our study unintentionally focused on high-risk patients. This may be due to the fact that the present study was done on the “treatment” of established PONV rather than its prevention, and theoretically, treatment studies are usually more difficult to perform. For instance, if a baseline risk of 40% PONV is expected, then of 100 patients who have given their informed consent to take part in a treatment trial, roughly 40 will eventually suffer from PONV symptoms and then be randomized and treated. The baseline risk for PONV after randomization could be increased compared to the general population, as patients with higher baseline risk of PONV would be more likely to develop PONV during the observation period for treatment decision. Although the 36% incidence of PONV during the first 2 h postrecovery of our study was found to rather accurately reflect common clinical practice,¹⁹ the observed complete response rates after treatment for established PONV may have led to different results if the enrolled patients had been more evenly distributed in terms of risks for PONV. Future studies are needed to validate the therapeutic efficacy of ramosetron in patients at relatively low risk of PONV.

In this study, there were no differences in the incidence of adverse events such as headache, dizziness, and drowsiness between the groups. Excessive sedation and extrapyramidal symptoms also were not observed in any patients. VAS scores of postoperative pain and requirement of rescue analgesics were similar in both groups.

Our study had limitations. First, we compared two 5-HT₃ antagonists and did not use a placebo control group. However, given the high risk of PONV associated with

patient-related factors and surgery type, having a placebo arm was considered unethical. Valid data on the therapeutic efficacy and dose-response of other classic antiemetics are needed. Second, we observed therapeutic responses during 24 h after administration of the study drug. Since the longer efficacy of ramosetron compared with ondansetron has been demonstrated, ramosetron could prevent further PONV development longer than 24 h after administration of the study drug.

Conclusion

We observed evidence to support the noninferiority of ramosetron (0.3 mg) compared to ondansetron (4 mg) for the treatment of established PONV in moderate to high-risk patients undergoing laparoscopic surgery.

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Disclosure

Sang-Hwan Do and Hee Jung Baik report consultancy payment from Astellas Pharma Korea, Inc. Yong Seon Choi, Sang-Hwan Do, Kyeong Tae Min, and Hee Jung Baik report payment for lectures from Astellas Pharma Korea, Inc. All authors report no other conflicts of interest in this work.

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