

Comparison of ramosetron with ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery

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Background. Ramosetron is a new selective 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist that reportedly has more potent antiemetic effects compared with other 5-HT₃ receptor antagonists. The purpose of this study was to evaluate the efficacy of ramosetron for the prevention of postoperative nausea and vomiting (PONV) with that of ondansetron or placebo in high-risk patients undergoing gynaecological surgery.

Methods. In this prospective, randomized, double-blinded, placebo-controlled study, 162 healthy patients who were undergoing gynaecological operation under general anaesthesia using sevoflurane were enrolled. Patients were divided into three groups: the ramosetron group (0.3 mg i.v.; $n=54$), the ondansetron group (8 mg i.v.; $n=54$), and the placebo group (normal saline i.v.; $n=54$). The treatments were given before the end of surgery. The incidence of PONV, severity of nausea, and the use of rescue antiemetic requirements during the first 24 h after surgery were evaluated.

Results. The incidence of nausea was lower in the ramosetron (50%) and ondansetron (44%) groups compared with the placebo group (69%) ($P<0.05$). In addition, the incidence of vomiting was lower in both the ramosetron (17%) and the ondansetron (20%) groups than in the placebo group (44%) during the first 24 h after surgery ($P<0.05$). The visual analogue scale score for nausea was also lower in the ramosetron and ondansetron groups compared with the placebo group ($P<0.05$). The proportion of patients requiring rescue antiemetics was significantly lower with ramosetron (15%) when compared with the placebo group (41%) during the 24 h after surgery ($P<0.05$). However, there were no significant differences in the incidence of nausea and vomiting, severity of nausea, and required rescue PONV between the ramosetron and the ondansetron groups.

Conclusions. Ramosetron 0.3 mg i.v. was as effective as ondansetron 8 mg i.v. in decreasing the incidence of PONV and reducing nausea severity in female patients during the first 24 h after gynaecological surgery.

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Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after anaesthesia and surgery, and may lead to serious postoperative complications. The overall incidence of PONV has been reported to be between 20% and 30%, but can increase up to 80% in high-risk patients. Patients undergoing gynaecological surgery have been associated with high risk for developing PONV.^{1,2}

For PONV prevention, selective serotonin 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists are considered one of the first-line therapy because of their efficacy and few side-effects compared with other antiemetics.³ Most research on the 5-HT₃ receptor antagonists has been on ondansetron, and its antiemetic efficacy has been well established in chemotherapy-induced emesis and the prevention and treatment of PONV.^{4–7}

Ramosetron is a recently developed selective 5-HT₃ receptor antagonist. It exhibits significantly greater binding affinity for 5-HT₃ receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5-HT₃ receptor antagonists.^{8,9}

It was reported that ramosetron is more potent with a longer duration of action than granisetron in the prevention of emesis after cisplatin chemotherapy, and in the prevention of PONV.^{10–12} However, there are few reports about the antiemetic effect of ramosetron compared with ondansetron for prevention of PONV. Choi and colleagues¹³ reported that ramosetron i.v. was superior to ondansetron i.v. in reducing the severity of nausea, incidence of vomiting, and the use of rescue antiemetics at 6–24 h after operation in patients who had undergone lumbar spine surgery, but this study was not placebo-controlled. However, the antiemetic efficacy of ramosetron i.v. to prevent PONV compared with that of ondansetron i.v. or placebo in patients undergoing gynaecological surgery has not yet been reported.

Therefore, we designed this prospective, randomized, double-blind, placebo-controlled study to evaluate the efficacy of ramosetron for preventing PONV compared with that of ondansetron or placebo in high-risk patients undergoing gynaecological surgery during the first 24 h after surgery.

Methods

An approval was obtained from IRB before study commencement. After receiving written informed consent, 162 female healthy patients, aged 21–71 yr, undergoing elective gynaecological surgery were enrolled in this randomized, placebo-controlled, double-blinded study. The duration of surgery ranged 35–190 min and the patient underwent hysterectomy, ovarian cystectomy, and salpingo-oophorectomy.

Exclusion criteria were pregnancy, body weight more than 30% above the ideal body weight, vomiting or retching within 24 h before the operation, administration of antiemetics or steroids or psychoactive medications within 24 h before the operation, and respiratory, cardiovascular, renal, hepatic, endocrine, gastrointestinal, or neurological disease. Patients were asked to provide a detailed medical history and patient characteristic information, including age, weight, and any history of PONV, motion sickness, or smoking.

Patients were randomly allocated to receive one of the three study medications according to a computer-generated randomized number table: ramosetron group, ramosetron 0.3 mg i.v.; ondansetron group, ondansetron 8 mg i.v.; and placebo group, saline i.v. The envelopes were opened before induction of anaesthesia by a trained nurse not involved in the study. The nurse then prepared the

appropriate study medication diluted to 4 ml in identical syringes, and administered ~30 min before the end of surgery. All patients, investigators collecting the postoperative data, and nurses involved in the postoperative care of patients were blinded to the randomization.

A standardized anaesthesia regimen was followed. All patients received midazolam 3–5 mg i.m. for premedication 30 min before surgery. General anaesthesia was induced with propofol 2 mg kg⁻¹ and fentanyl 2–3 µg kg⁻¹. Rocuronium 0.6 mg kg⁻¹ was administered to facilitate tracheal intubation. Anaesthesia was maintained with sevoflurane (0.5–5%) and nitrous oxide (50%). At the end of surgery, residual neuromuscular block was reversed with pyridostigmine (0.2 mg kg⁻¹) and glycopyrrolate (0.005 mg kg⁻¹) in all patients. The study medication (ondansetron, ramosetron, or saline) was administered i.v. ~30 min before the end of surgery. For postoperative pain control, patients were administered fentanyl using i.v. patient-controlled analgesia (bolus dose fentanyl 15 µg, lockout interval of 5 min, and no background infusion). After surgery, patients were observed in the post-anaesthetic care unit (PACU) before ward transfer when stable.

The incidence of PONV, severity of nausea, and the need for rescue antiemetics were evaluated for 24 h after surgery, divided into two intervals: 0–6 and 6–24 h. Patients were monitored every 15 min in the PACU and every 2 h in the ward except when sleeping. 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 intensity of nausea episode was assessed using a 100 mm visual analogue scale (VAS) (0, none; 100, maximum). Patients were asked to evaluate their maximal degree of nausea during the interval assessments. When moderate or severe nausea (VAS score >50) or vomiting was present, patients were asked if they required rescue antiemetics. Rescue medication for PONV (metoclopramide 10 mg as an initial rescue drug, ondansetron 4 mg as a second rescue drug) was administered upon patient request or complaint of established nausea (VAS score >50) or vomiting. To minimize suffering from PONV, patients were informed and educated on how to request treatment when PONV occurred before, after surgery, or both. Adverse events were evaluated and recorded by the investigator during the entire observation period. Patients were also asked to rate their overall satisfaction with the anaesthetic experience on a three-point scale (satisfied, neutral, and dissatisfied) 24 h after surgery completion.

The primary outcome measure of this study was the incidence of nausea and vomiting during the first 24 h after operation, and the secondary outcome measures were the severity of nausea, need for rescue medication, and patient satisfaction.

Sample size was predetermined using a power analysis to achieve an 80% chance ($\beta=0.2$) of detecting a 40%

reduction in PONV from a basal incidence of 70% (from 70% to 42%) with an assumed significance level of $\alpha=0.05$.^{5 14} A calculated minimum sample size was 49 patients in each group. A larger number of patients were included to allow for possible incomplete data collection or patient dropout. Statistical analysis was performed using SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA). A one-way analysis of variance was used to compare the continuous variables among the groups. If a significant difference was noted, a Bonferroni multiple comparison test was used to determine intergroup differences. Categorical variables were analysed 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 mean (SD), numbers, or percentages.

Results

There were no significant differences among the three groups with respect to patient characteristics, type of surgery, duration of surgery or anaesthesia, motion sickness, smoking status, or previous PONV history (Table 1). No study patient was withdrawn from the study.

The incidence of nausea was significantly lower in the ramosetron (50%) and ondansetron (44%) groups compared with the placebo group (69%) ($P<0.05$). The incidence of vomiting was also noted to be significantly lower in the ramosetron (17%) and ondansetron (20%) groups when compared with the placebo group (44%) during the 24 h after surgery ($P<0.05$) (Table 2).

The VAS score for nausea was also lower for both the ramosetron and the ondansetron groups compared with the placebo group ($P<0.05$) (Table 2). The proportion of patients requiring rescue antiemetics was only significantly lower with ramosetron (15%), not ondansetron (30%), when compared with the placebo group (41%) during the 24 h after surgery ($P<0.05$) (Table 2). Patients who

Table 1 Patient characteristics. Data are mean (SD) or number of patients. PONV, postoperative nausea and vomiting; Lap., laparoscopic. There were no significant differences between the groups

	Ramosetron (n=54)	Ondansetron (n=54)	Placebo (n=54)
Age (yr)	42 (8.8)	42 (9.4)	41 (9.1)
Body weight (kg)	60 (8.6)	58 (8.3)	57 (8.7)
Duration of surgery (min)	86 (36.8)	80 (37.7)	89 (43.1)
Duration of anaesthesia (min)	111 (38.8)	105 (38.1)	114 (44.9)
Previous PONV history	1	1	3
Motion sickness history	16	18	23
Non-smoking status	51	47	47
Fentanyl consumption (μ g)	496 (344)	466 (327)	375 (281)
Types of surgery			
Abdominal hysterectomy	23	21	23
Vaginal hysterectomy	5	5	1
Lap. hysterectomy	14	13	15
Lap. ovarian cystectomy or salpingo-oophorectomy	12	15	15

Table 2 Incidences of nausea, vomiting, and the need for rescue antiemetics, and severity of nausea (VAS) during the first 24 h after surgery. Data are mean (SD) or number (%). VAS score for nausea (0, none; 100, the worst imaginable nausea). * $P<0.05$ compared with the placebo group

	Ramosetron (n=54)	Ondansetron (n=54)	Placebo (n=54)
0–6 h			
Nausea	18 (33%)*	19 (35%)*	34 (63%)
Vomiting	4 (7%)*	8 (15%)*	17 (31%)
Rescue antiemetics	6 (11%)*	9 (17%)*	18 (33%)
VAS for nausea	20 (32)*	21 (33)*	43 (39)
6–24 h			
Nausea	22 (41%)	17 (31%)	24 (44%)
Vomiting	7 (13%)*	8 (15%)*	18 (33%)
Rescue antiemetics	3 (6%)*	7 (13%)	10 (19%)
VAS for nausea	16 (24)	19 (32)	27 (36)
0–24 h			
Nausea	27 (50%)*	24 (44%)*	37 (69%)
Vomiting	9 (17%)*	11 (20%)*	24 (44%)
Total PONV	27 (50%)*	24 (44%)*	37 (69%)
Rescue antiemetics	8 (15%)*	16 (30%)	22 (41%)
VAS for nausea	28 (33)*	28 (38)*	48 (39)

Table 3 Incidences of adverse event and patient satisfaction. Data are number of patients (%). * $P<0.05$ compared with the placebo group

	Ramosetron (n=54)	Ondansetron (n=54)	Placebo (n=54)
Adverse event			
Dizziness	9 (17%)	8 (15%)	10 (19%)
Headache	11 (20%)	9 (17%)	8 (15%)
Satisfaction			
Satisfied	46 (85%)*	48 (89%)*	37 (69%)
Neutral	8 (15%)	4 (7%)	12 (22%)
Dissatisfied	0 (0%)	2 (4%)	5 (9%)

received ramosetron or ondansetron were more satisfied than those receiving placebo ($P<0.05$) (Table 3).

There were no significant differences with regard to the incidence of PONV, severity of nausea, incidences of requirement for rescue antiemetics, or patient satisfaction rating between the ramosetron and the ondansetron groups (Tables 2 and 3). Furthermore, there were no statistically significant differences in the incidence of adverse events among the three groups (Table 3). The most frequently reported adverse events were dizziness and headache.

Discussion

In our study, ramosetron was shown to be as effective as ondansetron in preventing nausea and vomiting, and decreasing the severity of nausea during the first 24 h in female patients after gynaecological surgery. However, ramosetron was more effective in reducing the need for additional rescue antiemetics after surgery.

Although the precise aetiology of PONV is unknown, it has been suggested to be of multifactorial origin. A number of factors, including age, gender, obesity, prior history of motion sickness or PONV, non-smoking,

anaesthetic techniques, surgical procedure and duration, the use of postoperative opioids, and ambulation, were associated with an increased incidence of PONV.^{1 2 15} In this study, patient characteristics and risk factors were similar among the study groups, allowing for the observed differences between the groups to be caused by the treatments provided.

Although ondansetron 4 or 8 mg has been recommended for preventing PONV, the meta-analysis by Tramer and colleagues¹⁶ suggested that an 8 mg dose of ondansetron was optimal for prevention of PONV. Therefore, ondansetron 8 mg was chosen for this study. Our results demonstrated that ondansetron 8 mg was effective in decreasing the incidence of PONV from 69% to 44% (absolute reduction of 25%) during the 24 h after surgery, which is comparable with the previous reports of ondansetron use for the prevention of PONV.^{4 5 16}

Ramosetron is a newly developed 5-HT₃ receptors antagonist with a more potent and longer receptor antagonizing effect compared with older 5-HT₃ receptors antagonists.⁹ In addition, the elimination half-life of ramosetron (9 h) is longer than that of ondansetron (3.5 h) or granisetron (4.9 h).^{8 17} Because of these pharmacological properties, ramosetron is reportedly more potent with a longer duration of action than older 5-HT₃ receptor antagonists clinically.^{8 12}

The reported efficacy of ramosetron is similar to that of granisetron in the prevention of cisplatin-induced emesis. However, ramosetron appears to have a longer duration of action during the 24 h after cisplatin chemotherapy.^{10 11} In addition, it has been reported that ramosetron was comparable with granisetron to prevent PONV 0–24 h after surgery, but ramosetron was more effective than granisetron for preventing PONV 24–48 h after surgery.^{12 18 19}

According to Fujii and colleagues,^{20 21} ramosetron is effective in preventing PONV after major gynaecological surgery, and ramosetron 0.3 mg is an effective dose for preventing PONV. In addition, the manufacturer's recommended dose is 0.3 mg i.v. once a day. Therefore, ramosetron at 0.3 mg dose was chosen for this study. Our results demonstrated that ramosetron 0.3 mg was effective in decreasing the incidence of PONV from 69% to 50% (absolute reduction of 19%) during the 24 h after surgery, which was equally effective to ondansetron in the prevention of PONV.

Although the efficacy of ramosetron was shown to be similar to ondansetron in reducing the incidence of PONV and severity of nausea, ramosetron appeared superior to ondansetron in minimizing the need for additional rescue antiemetic during the first 24 h after operation. Ramosetron significantly reduced the need for additional rescue antiemetic over the 24 h after operation (0–6 and 6–24 h). Ondansetron also significantly reduced the need for additional rescue antiemetic during 0–6 h after operation. However, it did not significantly decrease the need for additional rescue antiemetic use during 6–24 h after

operation and, consequently, did not significantly decrease rescue antiemetic need over the total 24 h postoperative period. As a result, it appears that ramosetron has a more potent, longer lasting antiemetic effect when compared with ondansetron, even though the treatment effect difference did not reach statistical significance. Therefore, we suggest ramosetron is a more favourable antiemetic than ondansetron in the prevention of PONV.

The most frequently reported adverse events of 5-HT₃ receptor antagonists are dizziness and headache.⁷ Adverse events observed in our study were similar among all three groups.

The limitation of this study was that we compared the efficacy of ramosetron and ondansetron by their known optimal doses because their equipotent doses were unknown at the time of study commencement. Further studies are needed to investigate the equipotency of ramosetron and ondansetron to prevent PONV.

In conclusion, ramosetron 0.3 mg i.v. and ondansetron 8 mg i.v. were equally effective in decreasing incidence of PONV and severity of nausea in high-risk female patients during the first 24 h after surgery. Although there were no significant differences between ramosetron and ondansetron in decreasing incidence of PONV, severity of nausea, need for additional rescue antiemetics, or patient satisfaction rate, ramosetron appears to be a more effective antiemetic agent because it requires less additional rescue antiemetics after surgery.

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