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The effect of oral and IV ramosetron on postoperative nausea and vomiting in patients undergoing gynecological laparoscopy with total intravenous anesthesia

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Abstract
Purpose. Ramosetron can be administered orally as well as intravenously. We investigated the effect of oral ramosetron on postoperative nausea and vomiting (PONV) in patients undergoing gynecological laparoscopy.
Methods. One hundred and twenty women were allocated randomly to one of three groups ($n = 40$ in each) to receive saline (control), 0.1 mg oral ramosetron (PO), or 0.3 mg IV ramosetron (IV). Total intravenous anesthesia (TIVA) with propofol and remifentanil was used in all patients.
Results. The incidence of complete response (no PONV, no rescue) in the control, IV, and PO groups was: 65%, 90%, and 87.5%, respectively, during the first 1 h; and 67.5%, 87.5%, and 80%, respectively, during 1 to 24 h.
Conclusion. The effect of oral ramosetron 0.1 mg was comparable to that of IV ramosetron 0.3 mg on the prevention of PONV in women undergoing gynecological laparoscopy with TIVA. Both the oral and IV forms were effective at preventing PONV during the first 1 h after surgery.

Key words Gynecological laparoscopy · Postoperative nausea and vomiting · Ramosetron

Introduction

Postoperative nausea and vomiting (PONV) is common after general anesthesia. It is a significant cause of morbidity, especially in patients undergoing gynecological surgery [1]. The etiology of PONV is complex and depends on various factors, including patients' characteristics, underlying disease, type of operation, anesthetic technique, and postoperative care [2]. Because propofol is known to have an antiemetic effect, it has been used to decrease PONV [3,4]. However, White et al. [5] reported that because total intravenous anesthesia (TIVA) reduced the predicted rate of PONV in the early postoperative period only, a long-acting antiemetic drug might be necessary to prevent post-discharge nausea and vomiting in day-case surgery.

Ramosetron (Nasea; Astellas, Tokyo, Japan), is an antagonist of the 5-hydroxytryptamine type 3 (5-HT_3) receptor, and is reported to be effective for the prevention of PONV in gynecological surgery, with greater efficacy compared to granisetron [6]. However, these newly developed 5-HT_3 receptor antagonists have been criticized because of their high cost [7,8]. These drugs are much more expensive than other commonly used antiemetics such as droperidol and metoclopramide. In addition to its availability as an injection, ramosetron is also available as oral disintegrating tablets, which are less expensive than the injection. Yano et al. [9] demonstrated that oral ramosetron had the same antiemetic effects as IV granisetron in patients undergoing chemotherapy. However, no data have been available for the use of oral ramosetron as an antiemetic against PONV after TIVA. Therefore, this study investigated the effect of oral and IV ramosetron on PONV in patients undergoing gynecological laparoscopy with TIVA.

Patients, materials, and methods

This study was approved by the Institutional Research and Ethics Committee. After the obtaining of informed consent, 120 women, American Society of Anesthesiologists (ASA) physical status I or II, aged 18–60 years, undergoing general anesthesia for gynecological laparoscopy were enrolled in the study. Patients with gastrointestinal disease, a history of motion sickness, or a previous episode of PONV, and those who were menstruating or had taken an antiemetic medication within 24 h before surgery were excluded from the study.

Patients were allocated randomly to one of three groups ($n = 40$ in each), to receive saline (control group),

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0.3 mg IV ramosetron (IV group), or 0.1 mg oral ramosetron (PO group), using a sealed envelope system. An independent researcher prepared the study solutions, which consisted of a drinking cup containing 10 ml saline and a syringe with 2 ml normal saline in the control group, a cup containing 10 ml saline and a syringe with 0.3 mg ramosetron in the IV group, and a cup containing completely dissolved ramosetron tablets in 10 ml saline and a syringe with 2 ml saline in the PO group. The oral test drug was administered 1 h before surgery and the IV test drug was injected immediately after the induction of anesthesia by an investigator who was blinded to the study.

The anesthetic regimen was standardized. All patients were premedicated with midazolam 0.05 $mg \cdot kg^{-1}$ intramuscularly 1 h before the induction. Anesthesia was induced and maintained with propofol (target blood concentration 2.5–3.5 $\mu g \cdot ml^{-1}$) and remifentanil (target blood concentration 2.5–3.5 $ng \cdot ml^{-1}$), using a target-controlled device (Orchestra; Fresenius Kabi, Bad Homburg, Germany). Rocuronium 0.6 $mg \cdot kg^{-1}$ was given to facilitate tracheal intubation. Ventilation was mechanically controlled with an O_2/air mixture (fractional inspired oxygen $[F_{I_{O_2}}] = 0.6$) and adjusted to keep an end-tidal concentration of CO_2 between 35 and 40 mmHg throughout the operation. A nasogastric tube was inserted to empty the stomach and it was removed before extubation of the trachea. Esophageal temperature was maintained at 36 ± 1°C using a warm mattress. Postoperative analgesia was provided intravenously with a mixture of 100 ml of ketorolac 240 mg and normal saline, which was started after surgery at a rate of 2 $ml \cdot h^{-1}$. First-line analgesic treatment was with ketorolac 30 mg IV when the patient experienced intolerable pain. If the patient did not respond to initial treatment, pethidine 25 mg IV followed as second-line treatment.

All episodes of PONV (nausea, retching, and vomiting) during the periods 0 to 1 h and 1 to 24 h after anesthesia were recorded by nursing staff who were unaware of which treatment each patient had been given. Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the labored, spastic, rhythmic contraction of the respiratory muscles without expulsion of the gastric contents; and vomiting was defined as the forceful expulsion of gastric contents from the mouth [2]. Complete response (i.e., emesis-free) was defined as no PONV and no need for another rescue antiemetic medication. At the end of each observation period, patients evaluated the severity of PONV using a modified Rhodes index (Table 1) [10,11]. At the end of study period, patients evaluated general satisfaction using a linear numerical scale ranging from 0 (complete dissatisfaction) to 10 (complete satisfaction). Any other adverse effects were also recorded. Rescue antiemetics were administered for active nausea and vomiting defined above. First line rescue treatment was with metoclopramide 10 mg IV. If the patient did not respond to the initial treatment, ondansetron 4 mg IV and dexamethasone 5 mg IV followed as second and third line treatments, respectively.

Table 1. Modified Rhodes index of nausea, vomiting, and retching (RINVR)

1. In the last ( ) hours, I threw up OO times.	7 or more (4)	5–6 (3)	3–4 (2)	1–2 (1)	I did not throw up (0)
2. In the last ( ) hours, from retching and dry heaves, I have felt OO distress.	No (0)	Mild (1)	Moderate (2)	Great (3)	Severe (4)
3. In the last ( ) hours, from vomiting and throwing up, I have felt OO distress.	Severe (4)	Great (3)	Moderate (2)	Mild (1)	No (0)
4. In the last ( ) hours, I have felt nauseated or sick to my stomach.	Not at all (0)	≤1 hour (1)	2–3 hours (2)	4–6 hours (3)	≥6 hours (4)
5. In the last ( ) hours, from nausea/sickness to my stomach, I have felt OO distress.	No (0)	Mild (1)	Moderate (2)	Great (3)	Severe (4)
6. In the last ( ) hours, each time I threw up, I produced a OO amount.	Very large (≥3 cups) (4)	Large (2–3 cups) (3)	Moderate (1/2–2 cups) (2)	Small (≤1/2 cups) (1)	I did not throw up (0)
7. In the last ( ) hours, I have felt nauseated or sick to my stomach OO times.	7 or more (4)	5–6 (3)	3–4 (2)	1–2 (1)	No (0)
8. In the last ( ) hours, I have had periods of retching or dry heaves without bringing anything up OO times.	No (0)	1–2 (1)	3–4 (2)	5–6 (3)	7 or more (4)

Total experience score is the sum of all scores

Statistical analyses were performed using the statistical package (SPSS 11.0 for Windows; SPSS, Chicago, IL, USA). Analysis of variance with Bonferroni's correction, the χ^2 test, Fisher's exact test, or the Mann-Whitney *U*-test was performed where appropriate. A *P* value of <0.05 was considered significant. Values were expressed as means (SD), or numbers of patients (%). Sample size was predetermined using a power analysis based on the assumptions that (a) the incidence of complete response (no nausea, no retching, no vomiting), which was regarded as the primary endpoint, in the control group would be 64% (based on the study by White et al. [5]), (b) an improvement from 64% to 90% was considered of clinical importance, and (c) $\alpha = 0.05$ with a power (1-β) of 0.8. The analysis showed that 39 patients per group would be sufficient to detect the antiemetic effect of ramosetron.

Results

There were no differences in patient characteristics among the three groups (Table 2). The incidences of postoperative nausea, retching, vomiting, and complete responses are listed in Table 3. The incidence of complete response in the control, IV, and PO groups was: 65%, 90%, and 87.5%, respectively, during the first 1 h; and 67.5%, 87.5%, and 80%, respectively, during 1 to 24 h. The incidence of complete responses was higher in both the IV and PO groups compared to that in the

Table 2. Patient characteristics

	Control (*n* = 40)	IV (*n* = 40)	PO (*n* = 40)
Age (years)	41 (8)	41 (9)	41 (8)
Weight (kg)	57 (5)	58 (8)	57 (8)
Height (cm)	159 (4)	159 (5)	159 (6)
Duration of anesthesia (min)	110 (45)	111 (43)	105 (33)
Duration of operation (min)	77 (39)	76 (38)	74 (29)
Duration of pneumoperitoneum (min)	58 (27)	61 (37)	54 (27)
Type of laparoscopy (*n*)			
Hysterectomy	24	26	23
Myomectomy	2	3	3
Salpingo-oophorectomy	14	11	14
Analgesic used postoperatively (*n*)			
Ketorolac 30 mg IV	4	5	4
Pethidine 25 mg IV	2	3	2

Values are means (SD) or number of patients. No significant differences among the groups were noted
IV, Ramosetron 0.3 mg IV; PO, ramosetron 0.1 mg PO

Table 3. Incidences of postoperative nausea, retching, vomiting, and complete responses

		IV		PO	
	Control (*n* = 40)	(*n* = 40)	*P* value	(*n* = 40)	*P* value
During 0–1 h					
Complete response	26 (65%)	36 (90%)	0.014	35 (87.5%)	0.034
Nausea	13 (32.5%)	4 (10%)	0.027	4 (10%)	0.027
Retching	4 (10%)	2 (5%)	0.675	2 (5%)	0.675
Vomiting	2 (5%)	1 (2.5%)	1.00	2 (5%)	1.00
Rescue antiemetics	3 (7.5%)	1 (2.5%)	0.615	1 (2.5%)	0.615
Rhodes index	3.0 (5.3)	0.7 (2.4)	0.013	0.8 (2.5)	0.021
During 1–24 h					
Complete response	27 (67.5%)	35 (87.5%)	0.059	32 (80%)	0.31
Nausea	12 (30%)	5 (12.5%)	0.099	6 (15%)	0.18
Retching	7 (17.5%)	1 (2.5%)	0.057	5 (12.5%)	0.755
Vomiting	3 (7.5%)	1 (2.5%)	0.615	2 (5%)	1.00
Rescue antiemetics	2 (10%)	1 (2.5%)	1.00	1 (2.5%)	1.00
Rhodes index	3.6 (6.4)	1.1 (3.5)	0.041	1.4 (3.0)	0.058
Patient satisfaction	7.8 (1.6)	9.3 (1.4)	<0.001	9.1 (1.4)	<0.001

P value, compared with control group
Values are means (SD) or number of patients (%)
IV, Ramosetron 0.3 mg IV; PO, ramosetron 0.1 mg PO; complete response, no nausea, no retching and no vomiting

control group during the first 1 h, but not during 1 to 24 h. There was no significant difference in complete response between the IV and PO groups during the study period. Although the incidence of nausea was decreased in both the IV and PO groups (12.5% and 15%, respectively) compared to that in the control group (30%) during 1–24 h, the differences were not statistically significant ($P = 0.099$ for IV vs control group and $P = 0.18$ for PO vs control group). Except in the PO group during 1–24 h, the Rhodes index was lower in both the IV and PO groups compared to that in the control group during the study period. At the end of the study period, the patient satisfaction scale was significantly higher in both the IV and PO groups compared to that in the control group. There were no statistically significant differences in the Rhodes index or satisfaction scale between the IV and PO groups during the study period.

One patient in the PO group had dizziness and one in the IV group had headache. There was no difference in the incidence of side effects among the three groups.

Discussion

This study demonstrated that the effect of oral ramosetron 0.1 mg was comparable to that of IV ramosetron 0.3 mg on the prevention of PONV in patients undergoing gynecological laparoscopy with TIVA. Both the oral and IV forms of ramosetron were effective at preventing PONV during the first 1 h after surgery but not from 1 to 24 h after surgery.

Ramosetron, a specific 5-HT_3 receptor antagonist, lacks the sedative, dysphoric, and extrapyramidal symptoms associated with non-5-HT_3 receptor antagonists such as droperidol and metoclopramide [2]. IV ramosetron 0.3 mg was reported to be an effective antiemetic in patients undergoing various surgeries [12,13]. Despite these results, the widespread use of ramosetron is limited, because, as with ondansetron, IV ramosetron is much more expensive than traditional antiemetics. On the other hand, the cost of ramosetron tablets is one-third that of the IV drug and the tablets can be taken without water. A previous study reported that oral ramosetron 0.1 mg was as effective as granisetron 3.0 mg for reducing nausea in patients receiving chemotherapy [9]. Another study comparing the antiemetic effects of IV ramosetron 0.3 mg and granisetron 2.5 mg in major gynecological surgery reported that although IV ramosetron lasted longer, the efficacy of the two drugs was similar for up to 24 h. The IV and oral doses of ramosetron that we used in the present study were based on the doses used in the previous two studies [12,13] and on a study reporting that the efficacy of granisetron 40 $\mu g \cdot kg^{-1}$ (2.4 mg for 60-kg patients) and 60 $\mu g \cdot kg^{-1}$ (3.6 mg for 60-kg patients) was reported to be similar in the prevention of PONV after major gynecological surgery [14]. The result of the present study showed that oral ramosetron 0.1 mg and IV ramosetron 0.3 mg were equally effective at preventing PONV in patients undergoing gynecological laparoscopy under TIVA during the first 1 h after surgery. Although there was no significant difference in the effect on complete response during 1–24 h, the change in the Rhodes index score during 1–24 h was significant only in the IV ramosetron group. This can be explained by the difference in the onset and duration of the effect of ramosetron depending on the route of administration. The plasma level of ramosetron after IV administration reaches the maximum within 2 h and then decreases to half maximum at 6 h [9]. On the other hand, the peak plasma level is reached 15 min after oral administration and then decreases with a terminal half-life of 2.1 h [15].

PONV comprises a mixture of symptoms different from the nausea and/or vomiting associated with other high-risk events such as pregnancy or chemotherapy. This difference supports the application of a different approach in assessing PONV. Rhodes et al. [16] developed an index of nausea and vomiting to capture the multidimensional features of upper gastrointestinal distress. The Rhodes index was tested and found to be a valid and reliable instrument for measuring upper gastrointestinal distress in ambulatory surgical patients [10]. In the present study, a modified Rhodes index was used instead of a simple numeric rating scale to measure the efficacy of ramosetron. The Rhodes index in both the IV and PO groups was lower compared to that in control group except for the PO group during 1–24 h after surgery. However, there was no difference in the Rhodes index between the IV and PO groups during the study period.

Several reports have been published regarding the question of whether late PONV needs to be distinguished from early PONV. A systematic review of 84 randomized controlled trials comparing propofol with inhalational agents demonstrated that the effect of propofol in preventing PONV was significant only in high-risk patients during early PONV (<6 h) [17]. Apfel et al. [18] reported, in a randomized controlled study of 1180 patients at high risk of PONV, that late PONV (2–24 h) had different risk factors from early PONV (<2 h). In addition, even though it was strongly predictive of early PONV, the anesthetic technique (inhalation vs TIVA) was not a risk factor for late PONV. White et al. [5] suggested that a longer-acting antiemetic might be necessary to reduce late PONV (especially post-discharge nausea and vomiting) in patients with TIVA. In the present study, the early PONV period was defined as 0–1 h after surgery, because the residual

plasma concentration of propofol that is effective against PONV does not last after 1 h, and the average time that patients stay in the postanesthetic care unit in our institution is 1 h.

In conclusion, prophylactic oral ramosetron 0.1 mg may be considered in patients with a high risk of developing PONV, such as patients undergoing gynecological laparoscopy, because it is simple, less expensive, and equally effective in terms of patient satisfaction compared to IV ramosetron 0.3 mg.

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