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Comparison of prophylactic anti-emetic effects of ramosetron between single bolus administration and continuous infusion following bolus administration

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Background: The authors hypothesized that the continuous infusion of ramosetron 0.15 mg following a 0.15 mg bolus administration would maintain higher 5-hydroxytryptamine type 3 receptor occupancy levels and be more effective in preventing postoperative nausea and vomiting (PONV) than a 0.3 mg single bolus administration. We conducted a study to compare the efficacy of single bolus ramosetron administration with the combination of continuous infusion following intravenous bolus administration for PONV prophylaxis.
Methods: One hundred and fifty female patients undergoing thyroidectomy were allocated randomly to one of three groups to receive a placebo (Group 1, n = 49), 0.3 mg of IV ramosetron (Group 2, n = 53), or the continuous infusion of 0.15 mg ramosetron following a bolus administration of 0.15 mg of ramosetron (Group 3, n = 48). Anesthesia was maintained with sevoflurane and N_2O. The incidence of PONV, nausea severity, and use of rescue antiemetics during the postoperative 24 hours were recorded.
Results: Group 1 showed higher incidences of PONV during the postoperative 24 hour than Group 2 (81% vs. 58%, P = 0.02) and Group 3 (81% vs. 48%, P < 0.01), but there was no difference between Groups 2 and 3 (P = 0.39). The use of rescue antiemetics was significantly lower in Groups 2 and 3 than Group 1 during the postoperative 6 to 24 hours.
Conclusions: There were no significant differences of incidence and severity of PONV between ramosetron 0.3 mg single bolus administration and the combination of ramosetron infusion after 0.15 mg bolus administration. **(Anesth Pain Med 2016; 11: 166-171)**

Key Words: Morphine, Patient-controlled analgesia, Postoperative nausea and vomiting, Ramosetron, Thyroidectomy.

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is a distressing adverse effect that follows general anesthesia and surgery [1]. The etiology of PONV remains unclear but the contributing factors are complex including gender, smoking, a history of motion sickness or previous PONV, anesthetic technique, type of surgery, and the use of opioids. PONV is common after thyroidectomy, with a reported incidence of up to 65% [2]. Although postoperative intravenous (IV) patient-controlled analgesia (PCA) based on opioids is an effective and widely used method for pain control after surgery, postoperative opioids usage is associated with increased incidence of PONV. Therefore, an appropriate prophylactic antiemetic treatment should be considered when opioid-based IV PCA is planned in high risk patients.

Ramosetron, a selective serotonin 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonist, has higher receptor occupancy after intravenous administration of standard doses compared with ondansetron and granisetron [3]. Because of its higher binding affinity to the receptor and slower dissociation rate, ramosetron is more potent and has longer-lasting antiemetic effects than older agents [3,4]. Ogata et al. [5] demonstrated that dividing the dosage of ramosetron (0.3 + 0.3 mg) maintained higher receptor occupancy for a longer time than a 0.6 mg single bolus dose. Additionally, approximately 100% of the $5\text{-}HT_3$ receptor was occupied after ramosetron 0.15 mg as well as 0.3 mg IV administration. The anti-emetic effect of ramosetron is known to persist for 24 h, but ramosetron cannot prevent PONV during postoperative 24 h completely. The authors focused on the fact that the incomplete resolution of PONV may be related to $5\text{-}HT_3$ receptor occupancy. Therefore, the

authors hypothesized that the continuous infusion of ramosetron 0.15 mg following a 0.15 mg bolus administration would maintain a higher 5-HT_3 receptor occupancy level for a longer time and be more effective in preventing PONV than a 0.3 mg single bolus administration. However, a few studies have investigated the effect of administration methods and doses of ramosetron on PONV [6,7].

We conducted a prospective, randomized, double-blinded, placebo-controlled study to compare the efficacy of a single bolus ramosetron administration with the combination of continuous infusion following IV bolus injection of ramosetron for PONV prophylaxis in female patients undergoing thyroidectomy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the authors' institution. After obtaining informed consent, 150 female patients with the American Society of Anesthesiologists physical status I or II and aged 20-65 years, undergoing thyroidectomy were enrolled in this prospective study. Patients with diabetes mellitus, gastrointestinal disease, or a history of motion sickness or PONV, and those who were smoker, menstruating or had taken an antiemetic medication or steroids within 72 h before surgery were excluded from the study. The four risk factors proposed by Apfel et al. [8] were female gender, non-smoking, the use of postoperative opioids, and a prior history of motion sickness or PONV. The basic inclusion criteria for patients were female gender, non-smoking and anticipated use of opioids postoperatively; thus, the patients with 3 risk factors of PONV were selected. Patients were allocated randomly to one of three groups to receive a placebo (Group 1), 0.3 mg of IV ramosetron (Group 2), or the continuous infusion of 0.15 mg of ramosetron following a bolus administration of 0.15 mg of ramosetron (Group 3) using computer-generated random numbers.

The anesthetic regimen was standardized. No patient received preanesthetic medication. Electrocardiogram, noninvasive blood pressure, temperature, pulse oximetry, capnography, and neuromuscular monitoring were used for standard monitoring. Anesthesia was induced with thiopental sodium 5 mg/kg and rocuronium 0.8 mg/kg. Anesthesia was maintained with 1.5-3.0% sevoflurane and 50% N_2O in O_2. End-tidal carbon dioxide partial pressure was maintained at 30-35 mmHg. The arterial blood pressure and heart rate were kept within 20% of preanesthetic values. The nasopharyngeal temperature was maintained at 36.5 ± 0.5°C throughout the operation using a forced air warmer. Additional neuromuscular block was achieved with 10 mg of rocuronium when train-of-four (TOF) counts were more than 3. The balanced salt solution was infused at a rate of 3 to 5 ml/kg/h during surgery except in cases of overt intraoperative blood loss.

The study medications were prepared in identical 2 ml syringes. In a double-blind manner, the placebo (saline), 0.3 mg, or 0.15 mg of ramosetron in 2 ml preparations were given by a group-blinded anesthesiologist in Group 1, 2, and 3 after removal of the thyroid, respectively. At the completion of surgery, N_2O and sevoflurane were stopped. Residual neuromuscular blockade was antagonized with glycopyrrolate 0.4-0.6 mg and pyridostigmine 15-20 mg, and the trachea was extubated when the TOF ratio was greater than 0.7 and the patient showed purposeful movement. For postoperative PCA, each patient was equipped with a continuous balloon-type infuser (Ambix Anaplus™, E-wha Fresenius Kabi Inc., Korea). A total of 60 ml of analgesic solution contained 20 mg of morphine sulfate and 150 mg of ketorolac in normal saline. The analgesic solutions in the PCA device were prepared blindly by a research team member not involved in the anesthesia care and postoperative evaluation. In Group 3, ramosetron 0.15 mg was added to the analgesic solution of PCA and continuously infused. All patients received a bolus of 6 ml (morphine 2 mg and ketorolac 15 mg) of the prepared analgesic solution as a loading dose at the end of the surgery. The demand dose was 0.5 ml with a 0.5 ml/h background infusion and a 15-min lockout time.

To assess nausea and vomiting, patients were monitored for 2 h at a postanesthesia care unit and were interviewed in the ward at postoperative 6 and 24 h. PONV during the periods 0 to 2 h, 2 to 6 h, and 6 to 24 h after anesthesia was evaluated by an anesthesiologist blinded to the study group or by spontaneous complaints by the patients. Rescue antiemetics were given at the discretion of the attending anesthesiologists, who were also unaware of the group identities, in response to nausea, vomiting, or at the patient's request. The first-line rescue antiemetic was metoclopramide 10 mg.

Patients who experienced nausea or vomiting at least once during the 24 h following surgery were counted as positive for PONV incidence. The severity of nausea was recorded at postoperative 2, 6, and 24 h using a visual analog scale (nausea-VAS; where 0 cm = no nausea and 10 cm = worst possible nausea). In the same study period, patients were asked to evaluate their level of pain using a VAS (pain-VAS; where

0 cm = no pain and 10 cm = worst possible pain). The incidences of the most frequently reported side effects of the 5-HT_3 antagonists such as headache, dizziness, and drowsiness, were also assessed [9], although ramosetron may induce rare side effects such as involuntary movements [10]. The incidence and severity of PONV, pain score, administrations of rescue antiemetic, and side effects of the antiemetics during the first 24-hour period after surgery were recorded.

Sample size determination and statistical analysis

The sample size was predetermined by Chi-Square Sample Size using SigmaStat 3.5 (Systat Software Inc. San Jose, USA) based on assumptions that the incidence of no PONV, which was regarded as the primary endpoint, would be 30% in the control group and 60% in Group 2 (0.3 mg of ramosetron IV), and in anticipation of the incidence was improved to 80% in Group 3 (combination of 0.15 mg ramosetron IV and 0.15 mg infusion). It was ascertained that 46 patients were required in each group with a significance level of 0.05 (α = 0.05) and a power of 80% (β = 0.20). To allow for attrition, the sample size was enlarged to 150.

Statistical analysis was performed with SigmaStat version 3.5. Continuous variables such as patient demographics were analyzed with one-way analysis of variance (ANOVA), and incidence of PONV, use of rescue antiemetics, and incidence of side effects were analyzed using the chi-square test. All data are expressed as the means ± standard deviations (SDs), median (interquartile range) or the number of patients and percentages. A P value of less than 0.05 was considered statistically significant.

RESULTS

Of the 150 patients enrolled in this study, 1 patient in Group 1 was excluded because of protocol violation. In this case, the violation did not affect patient safety and was considered a minor violation. Consequently, 149 patients were included in the study. The final patients comprised 48 in Group 1, 53 in Group 2, and 48 in Group 3. The 3 groups were comparable in terms of patient characteristics and anesthesia time (Table 1).

There were no differences in the consumption of analgesic solution in PCA among the 3 groups during the postoperative 24 h (Group 1; 35 ± 14 ml, Group 2; 39 ± 11 ml, Group 3; 38 ± 13 ml, P = 0.266). The intensity of postoperative pain evaluated with VAS was similar among the 3 groups during postoperative 24 h (Table 2). The incidences of PONV, complete response (no PONV) and, the use of rescue antiemetics, and the severity of nausea are listed in Table 3. There were no significant inter-group differences in incidences of PONV and the use of rescue antiemetics, and the severity of nausea during the first postoperative 6 h. The incidences of

Table 1. Patient Characteristics and Anesthesia Time

	Group 1 (n = 48)	Group 2 (n = 53)	Group 3 (n = 48)	P values
Age (yr)	47.8 ± 9.5	46.6 ± 8.9	47.3 ± 9.5	0.825
Height (cm)	158.6 ± 4.6	159.0 ± 5.1	159.1 ± 5.1	0.866
Weight (kg)	59.5 ± 8.4	59.9 ± 8.7	60.1 ± 8.8	0.697
Anesthesia time (min)	143.9 ± 19.5	140.5 ± 26.5	145.7 ± 25.9	0.543
ASA PS (I/II)	39/9	47/6	39/9	0.498

Data are expressed as the means ± standard deviation (SD) or numbers. ASA PS: American Society of Anesthesiologists Physical Status.

Table 2. Intensity of Postoperative Pain and Analgesic Consumption in the Patient-Controlled Analgesia (PCA) during Postoperative 24 Hours

		Group 1 (n = 48)	Group 2 (n = 53)	Group 3 (n = 48)	P values
Pain VAS	2 h	3.6 (2.1–4.6)	3.5 (2.1–5.0)	3.6 (1.3–4.7)	0.903
	6 h	2.3 (1.2–3.0)	1.8 (0.7–3.7)	1.8 (0.9–3.5)	0.762
	24 h	2.1 (0.7–3.4)	1.3 (0.5–2.4)	1.4 (0.4–2.4)	0.183
Analgesic consumption in PCA (ml)		35 ± 14	39 ± 11	38 ± 13	0.266

Data are expressed as median (interquartile range) and mean ± SD. VAS: visual analog scale.

Table 3. Incidences of Postoperative Nausea and Vomiting (PONV), Requirements for Rescue Antiemetic Treatment, and Severity of Nausea

		Group 1 (n = 48)	Group 2 (n = 53)	*P value	Group 3 (n = 48)	*P value	†P value
0–2 h	Nausea	19 (40%)	19 (36%)	0.856	18 (38%)	1.0	0.972
	Vomiting	4 (8%)	4 (8%)	0.972	8 (17%)	0.355	0.268
	No PONV	29 (60%)	34 (64%)	0.856	30 (63%)	0.928	0.972
	Rescue antiemetics	13 (27%)	15 (28%)	0.932	12 (25%)	1.0	0.881
	Nausea-VAS	1.9 (0–3.7)	1.6 (0–2.4)	0.760	1.7 (0–4.6)	0.784	1.0
2–6 h	Nausea	27 (56%)	20 (38%)	0.096	18 (38%)	0.102	0.856
	Vomiting	18 (38%)	9 (17%)	0.036	6 (13%)	0.010	0.725
	No PONV	21 (44%)	33 (62%)	0.096	30 (63%)	0.183	0.856
	Rescue antiemetics	14 (29%)	9 (17%)	0.222	8 (17%)	0.225	0.823
	Nausea-VAS	2.2 (0–4.5)	1.6 (0–2.2)	0.097	1.6 (0–2.3)	0.076	0.988
6–24 h	Nausea	24 (50%)	12 (23%)	0.008	10 (21%)	0.006	0.983
	Vomiting	14 (29%)	4 (8%)	0.010	5 (10%)	0.040	0.876
	No PONV	24 (50%)	41 (77%)	0.008	38 (79%)	0.002	0.983
	Rescue antiemetics	12 (25%)	2 (4%)	0.005	3 (6%)	0.025	0.909
	Nausea-VAS	2.4 (0–4.6)	1.0 (0–2.0)	0.004	0.7 (0–1.5)	0.003	0.929
0–24 h	Nausea	39 (81%)	31 (58%)	0.024	23 (48%)	0.001	0.387
	Vomiting	27 (56%)	13 (25%)	0.002	14 (29%)	0.013	0.763
	No PONV	9 (19%)	22 (42%)	0.024	25 (52%)	0.003	0.387
	Rescue antiemetics	28 (58%)	22 (42%)	0.136	16 (33%)	0.024	0.521

Data are express as number of patients (percent) or median (interquartile range). VAS: visual analog scale. *P value: compared to Group 1. †P value: compared to Group 2.

PONV and rescue antiemetic use were significantly lower in Groups 2 and 3 than Group 1 during the postoperative 6 to 24 hours. However, there were no differences in the incidence of PONV, nausea severity, and rescue antiemetic use between Groups 2 and 3. In overall PONV incidence, Group 1 showed a higher incidence during postoperative 24 h than Group 2 (81% vs. 58%, P = 0.02) and Group 3 (81% vs. 48%, P < 0.01), but there was no difference between Groups 2 and 3 (P = 0.39).

The most frequently observed adverse symptoms were headache and dizziness during the study period. The number of patients who complained of headache and dizziness were 6 and 3 in Group 1, 5 and 4 in Group 2, and 7 and 3 in Group 3. There were no differences in the incidences of headache and dizziness among the 3 groups.

DISCUSSION

This study was conducted to compare the efficacy of prophylactic anti-emetic effects of the single bolus administration of ramosetron 0.3 mg with the continuous infusion of ramosetron 0.15 mg following a bolus administration of ramosetron 0.15 mg in female patients undergoing thyroidectomy with morphine-based IV PCA. In the current study, ramosetron showed prophylactic anti-emetic effects, but there were no significant differences in the incidence of PONV, severity of nausea, and requirement of rescue antiemetics in patients receiving the combination of bolus administration and continuous infusion of ramosetron (Group 3) compared with the patients receiving the single bolus administration (Group 2).

When the patient has emesis, venous pressure is increased which may induce postoperative bleeding and airway obstruction [11]. A high incidence of PONV has been reported in female patients undergoing thyroidectomy without antiemetic treatment. Although the reason for the high incidence of PONV after thyroidectomy is not clear, several factors are probably related to including middle-age, the female gender of patients, and vagal stimulation by the surgical handling of the neck [2,12]. In the current study, we reported that 81% of patients in the control group (Group 1) had PONV during the postoperative 24 h. This incidence was higher than that of previous studies of PONV in patients without prophylactic antiemetic treatment who underwent thyroidectomy with inhalation anesthesia (60–65%) [2,11-13]. The difference in PONV incidence compared with previous studies could be due to the number of risk factors. The patients with a history of motion sickness and/or previous postoperative PONV were excluded in the previous studies and our study, but morphine

was given to the patients postoperatively in the current study. Therefore, populations in the previous studies had 1 or 2 major risk factors, but all patients had 3 risk factors in the current study. According to the Apfel's risk scoring system, the presence of 1, 2, or 3 risk factors corresponds to approximately a 20%, 40%, and 60% incidence of PONV, respectively. In our result, as in previous thyroidectomy studies, the incidences of PONV were approximately 20% higher than the predicted incidence according to Apfel's risk scoring system after general surgery. This may be due to the surgical property of thyroidectomy. Because most of the contributing factors of PONV, including gender, a history of motion sickness and/or previous PONV, smoking, postoperative opioid administration, anesthetic technique and time, and surgery type, were well controlled in this study, the current results could be attributed to the study design.

Two previous studies compared the prophylactic antiemetic effects of the continuous infusion of ondansetron and palonosetron following the single bolus administration of antiemetics and concluded that the continuous infusion of the antiemetics reduced the PONV incidence compared with the placebo infusion group [14,15]. However, the studies were designed that the total doses of antiemetics were different, unlike the present study, between the placebo and antiemetic infusion groups. Antiemetics were additionally infused in study groups. Therefore, the antiemetic effects could be affected by total doses rather than the administration methods of the antiemetics. The results of the present study and previous studies suggest that the prophylactic antiemetic effect may be related to total dose rather than methods of administration.

Ramosetron is an effective treatment for vomiting in cancer patients receiving chemotherapy [16-18] and many studies have concluded that prophylactic therapy with ramosetron is effective for preventing PONV after various surgical procedures [7,19,20]. The precise antiemetic mechanism of ramosetron remains unclear, but it may act on sites containing 5-HT_3 receptors that have demonstrated antiemetic effects [18]. Many studies have examined the prophylactic antiemetic effects of ramosetron compared with other 5-HT_3 receptor antagonists including ondansetron and granisetron [21,22]. Choi et al. [6] concluded that ramosetron 0.3 mg was effective in preventing PONV after thyroidectomy, but 0.45 mg had no demonstrable additional benefit. Yamada et al. [3] demonstrated a linear relationship between 5-HT_3 receptor occupancy and the clinical efficacy of 5-HT_3 receptor antagonists and the higher receptor occupancy indicated more extensive antiemetic action. The initial 5-HT_3 receptor occupancy was approximately 100% after ramosetron 0.15 mg administration, similar to ramosetron 0.3 mg. Furthermore, the receptor occupancy decreased to approximately 60% 24 h after IV ramosetron 0.6 mg administration, but the receptor occupancy was maintained at over 70% when adding ramosetron 0.3 mg 3 h after 0.3 mg bolus administration [5]. Therefore, the authors hypothesized that ramosetron 0.15 mg infusion with PCA after ramosetron 0.15 mg bolus administration may be shown to have antiemetic effects during a longer period than ramosetron 0.3 mg single bolus administration. However, there were no significant differences in antiemetic effects between Groups 2 and 3 although the ramosetron groups showed anti-emetic effects. The authors speculated about the reasons there was no difference between Groups 2 and 3. Firstly, the amount and rate of the continuous infusion of ramosetron may not have been enough to fill the occupancy of the 5-HT_3 receptor in Group 3. Secondly, there may have been the ceiling effect of antagonism preventing PONV although the anti-emetic effect of 5-HT_3 receptor antagonists is linearly related to inhibition of the 5-HT_3 receptor.

There are several limitations in this study. First, there is a discrepancy between the action duration of ramosetron and the time for postoperative opioid use. The action duration of single bolus ramosetron is approximately 24 h, but the patients were given postoperative morphine for 48 h in this study. Although there was a low incidence of PONV after postoperative 24 h and most PONV studies observed PONV for 24 h, this discrepancy is a limitation of the study. Second, the baseline incidence of PONV was evaluated by a control group without prophylactic anti-emetic drugs in this study. No prophylactic anti-emetic treatment in high PONV risk patients could be considered unethical. However, the patients were under close observation during the study period and received antiemetic rescue medications immediately when they showed vomiting or required rescue medications. Third, although the amount of continuously infused ramosetron was expected to be 0.15 mg, the actual infused dose of ramosetron was approximately 0.1 mg because 60% of analgesic solution of PCA was used for 24 h.

In conclusion, ramosetron was effective in preventing PONV during the postoperative 24 h in high-risk female patients undergoing thyroidectomy, but there were no significant differences of incidence and severity of PONV between a single bolus ramosetron 0.3 mg administration and ramosetron infusion with PCA after 0.15 mg bolus administration.

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