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Comparison of Ramosetron, Dexamethasone, and a Combination of Ramosetron and Dexamethasone for the Prevention of Postoperative Nausea and Vomiting in Korean Women Undergoing Thyroidectomy: A Double-Blind, Randomized, Controlled Study

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ABSTRACT

BACKGROUND: Thyroidectomy is associated with a relatively high incidence of postoperative nausea and vomiting (PONV), ranging from 51% to 76%. Because these symptoms are distressing for patients, prophylactic medication to avoid or reduce PONV is recommended.

OBJECTIVE: The aim of the present study was to compare the efficacy of ramosetron, dexamethasone, and a combination of ramosetron and dexamethasone in preventing PONV in Korean women undergoing thyroidectomy.

METHODS: In this double-blind, randomized, controlled trial, consecutive adult female patients who were scheduled to undergo thyroidectomy under general anesthesia at the Kyungpook National University Hospital (Daegu, Korea) were randomly assigned to receive ramosetron 0.3 mg alone, dexamethasone 8 mg alone, or a combination of ramosetron 0.3 mg and dexamethasone 8 mg administered intravenously as a single dose immediately after induction of anesthesia. The primary end point of this study was the total PONV rate up to 24 hours postanesthesia. The secondary end points were the incidence of nausea, incidence of vomiting, severity of nausea (0 = no nausea to 10 = nausea as bad as it could be), use of rescue antiemetic drugs, and the occurrence of adverse events (AEs) determined through interview or spontaneous patient report for 24 hours postanesthesia.

RESULTS: A total of 198 female patients were approached for study inclusion, 18 of whom were excluded. Therefore, 180 Korean women (mean [SD] age, 46.5 [12.6] years; height, 159.8 [2.7] cm; weight, 53.2 [3.6] kg) were enrolled and completed the study. The total PONV rates up to 24 hours postanesthesia were 35%, 13%, and 10% in the dexamethasone, ramosetron, and combination groups, respectively. The PONV rate was significantly lower in the combination group than in the dexamethasone alone group ($P = 0.006$). The PONV rate was not significantly different in the combination group compared with the ramosetron alone group. The PONV rate in the dexamethasone alone group was significantly higher than that in the ramosetron alone group ($P = 0.03$). The severity of nausea (median [25th–75th percentiles],

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0 [0–0] vs 0 [0–4]; $P = 0.009$) and rate of use of rescue antiemetic drugs (5% vs 27%; $P = 0.006$) were significantly lower in the combination group than in the dexamethasone alone group, whereas the severity of nausea (median [25th–75th percentiles], 0 [0–0] vs 0 [0–0]) and rate of use of rescue antiemetic drugs (5% vs 7%) were not significantly different between the combination and ramosetron alone groups. The severity of nausea (median [25th–75th percentiles], 0 [0–4] vs 0 [0–0]; $P = 0.033$) and the rate of use of rescue antiemetic drugs (27% vs 7%; $P = 0.018$) were significantly higher in the dexamethasone alone group than in the ramosetron alone group. The rates of AEs (headache: 15%, 20%, and 18%; dizziness: 18%, 22%, and 15%) were not significantly different in the dexamethasone alone, ramosetron alone, or combination groups, respectively.

CONCLUSIONS: The combination of ramosetron and dexamethasone was more effective in reducing PONV than was dexamethasone monotherapy. However, the combination did not show additional benefits compared with ramosetron alone in preventing PONV after thyroidectomy in these Korean women. (*Curr Ther Res Clin Exp.* 2010;71:78–88) © 2010 Excerpta Medica Inc.

KEY WORDS: thyroidectomy, nausea, vomiting, antiemetics, ramosetron, dexamethasone.

INTRODUCTION

Thyroidectomy is associated with a relatively high incidence of postoperative nausea and vomiting (PONV), ranging from 51% to 76%.[1,2] The etiology of PONV after thyroidectomy is not fully understood, but may be associated with several factors, including age and sex (mostly middle-aged women), and intense preoperative vagal stimulation (surgical handling of neck structures).[3] Other factors, including a history of motion sickness, smoking, previous postoperative emesis, anesthetic technique, and postoperative pain are also considered to be associated with an increase in the incidence of PONV.[4] Because these symptoms are distressing for patients, prophylactic medication to avoid or reduce PONV is highly recommended.

Several studies have reported that dexamethasone, a corticosteroid, was an effective antiemetic drug for the prophylaxis of PONV.[5–7] In a comprehensive review based on available randomized trials (1996–2001), focused on the effects of perioperative single-dose steroid administration, Holte and Kehlet[5] reported that dexamethasone has antiemetic effects in various types of surgery. In a dose-ranging study in 225 women undergoing thyroidectomy, Wang et al[6] reported a significantly lower incidence of PONV in the dexamethasone group (5 mg) compared with the saline group (19% vs 51%; $P < 0.01$). Fujii and Nakayama[7] found that the rate of PONV during the first 24 hours after thyroidectomy was significantly lower in the dexamethasone (8 mg) group compared with the placebo group (28% vs 76%; $P < 0.01$). Several currently available 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists (ondansetron, granisetron, dolasetron, and ramosetron) are highly effective for PONV, with ramosetron being the newest, most potent, and most selective of these agents.[8–11] Fujii and Tanaka[8,11] reported that

85% to 88% of patients undergoing thyroidectomy were emesis-free with ramosetron treatment.

Although 5-HT_3 receptor antagonists and dexamethasone are effective for preventing PONV, none of the currently available pharmacologic interventions totally eliminates PONV. Studies have suggested that the combination of 5-HT_3 antagonists (eg, dolasetron, granisetron) and dexamethasone, as part of a multimodal approach, might reduce PONV more effectively than any drug alone in high-risk patient populations.[12–14] Fujii et al[13] and Biswas and Rudra[14] found that adding dexamethasone (8 mg) to granisetron (40 mg/kg) administered intravenously before induction of anesthesia was associated with improvements in antiemetic efficacy of 12% to 15% for 24 hours postanesthesia. A meta-analysis of data from a randomized controlled trial (1966–2005) found that combination therapy with a 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron, or tropisetron) and dexamethasone had a safety profile similar to that of any agent alone.[15]

The exact mechanism of action of the combination of dexamethasone with 5-HT_3 receptor antagonists is not yet known. However, dexamethasone may enhance the antiemetic efficacy of a 5-HT_3 receptor antagonist by inhibiting central or peripheral production or secretion of serotonin and by potentiating the main effects of other antiemetic drugs by sensitizing the pharmacologic receptors.[16]

Despite studies reporting on 5-HT_3 and steroid combination therapy, no evidence is available regarding the effects of a combination of ramosetron and dexamethasone for the prevention of PONV. MEDLINE was searched (inception–2009) using the following terms: *PONV, antiemetics, 5-HT_3 receptor antagonist, ramosetron,* and *dexamethasone*. The search did not identify any studies regarding the effects of a combination of ramosetron and dexamethasone for the prevention of PONV. Therefore, the present study was performed to compare the efficacy of a combination of ramosetron and dexamethasone with dexamethasone or ramosetron alone in the prevention of PONV in adult female patients undergoing thyroidectomy.

PATIENTS AND METHODS

This double-blind, randomized, controlled study was conducted at the Kyungpook National University Hospital (a tertiary care hospital) in Daegu, Korea. Consecutive adult female patients were categorized as being a normal healthy patient (American Society of Anesthesiologists status I) or a patient with mild systemic disease (status II).[17] All eligible patients were scheduled to undergo thyroidectomy under general anesthesia. The exclusion criteria were as follows: known hypersensitivity or contraindication to study medication; the use of antiemetics within 24 hours before surgery; the presence of gastrointestinal, renal, or liver disease; smoking; a history of motion sickness and/or previous postoperative emesis; pregnancy; or breastfeeding. Because risk factors such as sex may contribute to PONV episodes, we controlled the study design to include only women. All thyroidectomies were performed by the same team of anesthesiologists and surgeons. The study was approved by the institutional review board of Kyungpook National University Hospital, and all patients provided written informed consent prior to participation.

Patients were randomized to treatment group using a computer-generated random number table; the group assignment was prepared by the enrolling anesthesiologist in sealed opaque envelopes. The enrolling anesthesiologist was not the same person as the treating anesthesiologist. A total of 180 sealed envelopes containing the names of the groups (60 for each) were prepared before initiation of the study. The envelopes were opened before induction of anesthesia, and the drugs were prepared by an independent nurse who was not participating in any other part of the study.

No premedication was administered. Anesthesia was induced with propofol 2 mg/kg, and rocuronium bromide 1 mg/kg was administered to facilitate tracheal intubation. After intubation, anesthesia was maintained with isoflurane titrated between 0.6% to 2.5% and nitrous oxide 50% in oxygen. Ventilation was mechanically controlled and adjusted to maintain the partial pressure of the end-tidal concentration of carbon dioxide at 35 to 40 mm Hg. Neuromuscular blockade was reversed with pyridostigmine and glycopyrrolate.

Immediately after induction of anesthesia, patients received ramosetron 0.3 mg, dexamethasone 8 mg, or a combination of both agents at the aforementioned doses administered intravenously as a single dose. Each drug, or placebo (normal saline) administered in lieu of active drug, was diluted in 5 mL of clear solution in identical syringes. Each patient received 2 syringes, active and placebo in the case of patients in the ramosetron alone and the dexamethasone alone groups and both ramosetron and dexamethasone in the patients in the combination group. The patients, the anesthesiologist present during surgery, and the anesthesiologist who collected the postoperative data were all blinded with respect to the randomization process and the identity of the study drugs.

The primary end point of this study was the total PONV rate up to 24 hours postanesthesia. The secondary end points were the incidence of nausea, incidence of vomiting, severity of nausea, use of rescue antiemetic drugs, and the occurrence of adverse events (AEs) for 24 hours postanesthesia. All episodes of PONV (nausea, retching, or vomiting) were recorded during the first 24 hours after anesthesia in 2 time periods (0–1 hour in the postanesthesia care unit and 1–24 hours in the general ward). In the postanesthesia care unit and general ward, an anesthesiologist directly questioned the patient every 30 minutes and 6 hours, respectively. The anesthesiologist, who was blinded to the study groups, asked patients if retching or vomiting had occurred and if they felt nauseated. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. For the purpose of data collection, retching (an involuntary effort to vomit without the actual expulsion of gastric contents) was considered vomiting. The presence and severity of nausea were assessed using a 10-point scale (0 = no nausea; 10 = nausea as bad as it could be). Metoclopramide 10 mg was administered intravenously as a rescue antiemetic drug when patients had a nausea score >6 for ≥15 minutes, when they experienced vomiting or retching episodes, or at the patient's request. Postoperative pain was assessed using a 10-point scale (0 = no pain to 10 = the worst pain imaginable). Ketorolac (30 mg) as an analgesic was administered on request for intolerable pain. The details of any other AEs were noted throughout the study and recorded by the treating anesthesiologist during surgery

and by the anesthesiologist interviewing patients after the surgery, whether obtained through general questioning or reported spontaneously by the patients.

Statistical Analysis

An a priori power analysis based on previous studies in similar surgical populations suggested that a group size of 60 would be adequate to determine a 15% difference in the incidence of PONV,[6,11] the primary end point, given an estimated baseline incidence of PONV in the dexamethasone or ramosetron group of 20% (power = 0.80, $\alpha = 0.05$).

Intention-to-treat analysis, which counts all events in all randomized patients, was performed. A series of 1-way ANOVAs was conducted to examine differences among the 3 groups with respect to parametric variables. Primary and other categoric end points were compared between groups using the Fisher exact test and continuous end points (eg, nausea or pain scores) were compared using the nonparametric Kruskal-Wallis test. Where a 3-group treatment test was significant, post hoc pairwise group comparisons were made with the Fisher exact test and Mann-Whitney ranked sum test for categoric and nonparametric data (eg, severity variables), respectively. All follow-up analyses were corrected for the number of simultaneous contrasts using Bonferroni adjustments. $P < 0.05$ was considered statistically significant. Number needed to treat (NNT) was calculated by taking the reciprocal of the absolute risk reduction, and CIs were calculated for the NNT.[18]

RESULTS

A total of 198 female patients were approached for study inclusion, 18 of whom were excluded from the study based on the criteria described previously. One hundred eighty Korean women (mean [SD] age, 46.5 [12.6] years; height, 159.8 [2.7] cm; weight, 53.2 [3.6] kg) completed the study (**Table I**). No statistically significant between-group differences were found in the patients' demographic and clinical characteristics.

The total PONV rates up to 24 hours postanesthesia were 35%, 13%, and 10% in the dexamethasone alone, ramosetron alone, and combination groups, respectively. The PONV rate was significantly lower in the combination group compared with the dexamethasone alone group (95% CI, 0.02–0.18 vs 0.23–0.47; $P = 0.006$). PONV was not significantly different in the combination group than that in the ramosetron alone group (95% CI, 0.04–0.22). The incidence of PONV was significantly higher in the dexamethasone alone group than that in the ramosetron alone group ($P = 0.03$) (**Table II**).

Nausea was reported in 12 patients (20%) (95% CI, 0.10–0.30) in the dexamethasone alone group, 5 (8%) (95% CI, 0.01–0.15) in the ramosetron alone group, and 4 (7%) (95% CI, 0.01–0.13) in the combination group (all, P = NS). Vomiting was reported in 9 (15%) (95% CI, 0.06–0.24), 3 (5%) (95% CI, 0.00–0.11), and 2 (3%) (95% CI, 0.00–0.07) patients in the dexamethasone, ramosetron, and combination groups, respectively (all, $P < 0.01$). Nausea severity was significantly lower in the combination group than that in the dexamethasone alone group (median [25th–75th

Table I. Demographic and clinical characteristics of the study patients (N = 180).*

Characteristic	Ramosetron 0.3 mg (n = 60)	Dexamethasone 8 mg (n = 60)	Ramosetron 0.3 mg + Dexamethasone 8 mg (n = 60)
Age, mean (SD), y	44.9 (13.3)	45.4 (12.1)	49.1 (12.1)
Height, mean (SD), cm	159.5 (3.1)	160.2 (2.7)	159.8 (2.4)
Weight, mean (SD), kg	53.6 (3.9)	52.7 (3.6)	53.3 (3.3)
Duration of anesthesia, mean (SD), min	168.5 (23.1)	165.0 (18.9)	169.1 (21.1)
ASA status,[17] no. (%)			
I	43 (72)	42 (70)	46 (77)
II	17 (28)	18 (30)	14 (23)
Thyroid status, no. (%)			
Euthyroid	54 (90)	55 (92)	54 (90)
Treated euthyroid	6 (10)	5 (8)	6 (10)
Prior steroid use, no.	0	0	0

ASA = American Society of Anesthesiologists.
*No significant between-group differences were found.

percentiles], 0 [0–0] vs 0 [0–4]; $P = 0.009$), whereas no significant difference was found between the ramosetron alone and combination groups (0 [0–0] vs 0 [0–0]). Nausea severity was significantly higher in the dexamethasone alone group than in the ramosetron alone group (median [25th–75th percentiles], 0 [0–4] vs 0 [0–0]; $P = 0.033$). Rescue antiemetic drugs were required in 16 patients (27%) (95% CI, 0.16–0.38) in the dexamethasone alone group, 4 (7%) (95% CI, 0.01–0.13) in the ramosetron group, and 3 (5%) (95% CI, 0.00–0.11) in the combination group. The incidence of rescue antiemetic drug use was significantly lower in the combination group than the dexamethasone group ($P = 0.006$), whereas no significant difference was found between the ramosetron and the combination groups. The incidence of antiemetic rescue drug use was significantly higher in the dexamethasone group than in the ramosetron group ($P = 0.018$). Neither the postoperative pain scores nor the percentage of patients requiring ketorolac postoperatively differed significantly between the 3 groups (**Table II**).

The NNT to prevent PONV by administering the combination of ramosetron plus dexamethasone compared with dexamethasone or ramosetron alone were 4 (95% CI, 2.55 to 9.30) and 30 (95% CI, –12.29 to 6.75), respectively. The NNT for ramosetron compared with dexamethasone was 5 (95% CI, 2.74 to 14.61) (**Table III**).

The most common AEs observed were headache (9 [15%], 12 [20%], and 11 [18%] patients) and dizziness (11 [18%], 13 [22%], and 9 [15%] patients) in the dexamethasone alone, ramosetron alone, and combination groups, respectively. There

Table II. Emetic episodes and analgesic requirements in Korean women who underwent thyroidectomy (N = 180).

Variable	Ramosetron 0.3 mg (n = 60)	Dexamethasone 8 mg (n = 60)	Ramosetron 0.3 mg + Dexamethasone 8 mg (n = 60)	*P* Overall (P_1, P_2)
Total PONV, no. (%) (95% CI)	8 (13) (0.04–0.22)	21 (35) (0.23–0.47)	6 (10) (0.02–0.18)	0.002 (0.03, 0.006)
Nausea, no. (%) (95% CI)	5 (8) (0.01–0.15)	12 (20) (0.10–0.30)	4 (7) (0.01–0.13)	0.064
Vomiting, no. (%) (95% CI)	3 (5) (0.00–0.11)	9 (15) (0.06–0.24)	2 (3) (0.00–0.07)	0.066
Nausea severity, median (25th–75th percentiles)*	0 (0–0)	0 (0–4)	0 (0–0)	0.003 (0.033, 0.009)
Rescue antiemetic drugs, no. (%) (95% CI)	4 (7) (0.01–0.13)	16 (27) (0.16–0.38)	3 (5) (0.00–0.11)	0.001 (0.018, 0.006)
Postoperative pain, median (25th–75th percentiles)†	4 (3–5)	4 (3–5)	5 (4–5)	–
Postoperative ketorolac use, no. (%)	27 (45)	26 (43)	29 (48)	–

P_1 = dexamethasone group versus ramosetron group; P_2 = dexamethasone group versus dexamethasone + ramosetron group; PONV = postoperative nausea and vomiting.
*Scale: 0 = no nausea to 10 = nausea as bad as it could be.
†Scale: 0 = no pain to 10 = the worst pain imaginable.

was no significant difference between any of the groups in the incidence of these AEs, which were all relatively mild (**Table IV**).

DISCUSSION

In the present study, the treatment groups were similar in terms of patient demographic characteristics, surgical procedure, anesthetic administered, pain intensity, and postoperative analgesic use. In addition, patients with a history of motion sickness, smoking, and previous postoperative emesis had been excluded from the study. Therefore, the difference in incidence of PONV between the groups might be attributable to the variation in antiemetic drugs administered.

Fujii and Tanaka[8,11] reported that 85% to 88% of patients undergoing thyroidectomy were free of emesis with ramosetron 0.3-mg prophylaxis, which was comparable with the results of the present study.

Table III. Calculation of absolute risk reduction and number needed to treat (NNT) to prevent postoperative nausea and vomiting with the combination of dexamethasone and ramosetron.

Group	NNT (95% CI)
Ramosetron 0.3 mg + dexamethasone 8 mg vs dexamethasone 8 mg	4 (2.55 to 9.30)
Ramosetron 0.3 mg + dexamethasone 8 mg vs ramosetron 0.3 mg	30 (–12.29 to 6.75)
Ramosetron 0.3 mg vs dexamethasone 8 mg	5 (2.74 to 14.61)

Table IV. Incidence of adverse events (AEs) in Korean women who underwent thyroidectomy (N = 180). Data are shown as number (%) (95% CI).

AE	Ramosetron 0.3 mg (n = 60)	Dexamethasone 8 mg (n = 60)	Ramosetron 0.3 mg + Dexamethasone 8 mg (n = 60)	*P*
Headache	12 (20) (0.10–0.30)	9 (15) (0.06–0.24)	11 (18) (0.08–0.28)	0.831
Dizziness	13 (22) (0.12–0.32)	11 (18) (0.08–0.28)	9 (15) (0.06–0.24)	0.677
Other AEs (eg, constipation, myalgia)	1 (2) (0.00–0.06)	2 (3) (0.00–0.07)	2 (3) (0.00–0.07)	>0.99

Our findings indicated that the efficacy of the combination of ramosetron and dexamethasone was significantly better than that of dexamethasone alone. Contrary to our expectation, no significant difference was found between the effect of the combination and that of ramosetron alone, which was inconsistent with previous observations of other 5-HT_3 antagonists.[14,19,20] These observations may have resulted from our using these drug combinations only in a selected population undergoing thyroidectomy rather than other major surgeries or chemotherapy associated with high risks of emesis. Therefore, further studies are required to verify the efficacy of the combination of ramosetron and dexamethasone in other medical settings.

Dexamethasone has been used as an antiemetic in patients receiving highly emetogenic cancer chemotherapy[21,22]; it has been associated with significant reductions in the incidence of PONV.[1,6,7,23,24] Meta-analysis of the results obtained in 5613 patients receiving moderately or highly emetogenic chemotherapy in 32 studies suggested that dexamethasone was significantly more effective than placebo or no treatment for complete protection against both acute (odds ratio [OR] = 2.22; 95% CI, 1.89–2.60) and delayed emesis (OR = 2.04; 95% CI, 1.63–2.56). The results were similar for complete protection against nausea.[25] In the present study, we found that dexamethasone was significantly less effective in controlling PONV than ramosetron. Several studies have examined the effects of a single-dose application of dexamethasone before

or after thyroidectomy on PONV.[1,6,7,24] These studies indicated a reduced incidence of PONV after thyroidectomy in the dexamethasone groups (20%–28%) compared with controls who received placebo (51%–76%). The incidence of PONV in dexamethasone groups in these studies was comparable to that in the present study.

This study had several limitations. The original design included a placebo control group, but the institutional review board at our center decided that this would not be ethical, as the patients studied were at high risk of developing PONV. In addition, a limited population was recruited according to exclusion criteria, and therefore the results may not be widely applicable to men or to patients undergoing other procedures. Therefore, definitive conclusions regarding the effectiveness of the dexamethasone and ramosetron combination treatment relative to either agent alone cannot be reached. Other studies are required to address this issue.

The high cost of ramosetron may limit its widespread clinical application. Further studies are required to assess the cost savings or increased expenditure with the use of ramosetron in addition to antiemetic prophylaxis. Patients consider PONV to be one of the most undesirable postoperative symptoms, and it is one of the most common reasons for poor patient satisfaction rating in the postoperative period. Therefore, prophylactic antiemetic medication is highly recommended. In one study, patients associated a value with the avoidance of PONV and were willing to pay between US $56 and US $100 (2001) for a completely effective antiemetic.[26] In our study, ramosetron appeared to be more effective than dexamethasone. Therefore, prophylactic use of ramosetron or another potent antiemetic should be considered when treating patients at high risk for PONV.

CONCLUSIONS

The combination of ramosetron and dexamethasone was more effective in reducing PONV than was dexamethasone monotherapy. However, the combination did not show additional benefits compared with ramosetron alone in preventing PONV after thyroidectomy in these Korean women.

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