Int Surg 2016;**101:**106–115
DOI: 10.9738/INTSURG-D-15-00147.1

Effect of Palonosetron, Dexamethasone, or Palonosetron and Dexamethasone in Postoperative Nausea and Vomiting in Highly Susceptible Thyroidectomy Patients: A Randomized Trial

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Our study aimed to compare the efficacy of dexamethasone added to palonosetron to both palonosetron and dexamethasone monotherapy for preventing postoperative nausea and vomiting in highly susceptible patients receiving opioid-based, intravenous patient-controlled analgesia after thyroidectomy. Nonsmoking women who underwent total thyroidectomy were randomly allocated to either the dexamethasone group (Group D), the palonosetron group (Group P), or to the dexamethasone plus palonosetron group (Group DP). The severity of nausea and pain, the number of episodes of vomiting, the administrations of rescue anti-emetics, and the side effects of the antiemetics were documented in the recovery room at 2, 4, 8, 12, 24, and 48 hours after surgery. The severity of nausea was lowest in Group DP, followed by Group P and Group D. But there was an overall difference only between Group D and Group DP. The overall differences in the time to the first administration of the rescue antiemetic were observed in a Kaplan-Meier analysis ($P = 0.017$), noting a significant difference between Group D and Group DP ($P = 0.003$). The combination of dexamethasone and palonosetron decreased the severity of nausea and increased the time to the first antiemetic dose compared with using

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dexamethasone or palonosetron alone in nausea-susceptible patients undergoing thyroidectomy.

Key words: Dexamethasone – Palonosetron – Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is one of the most common complications following surgery, and PONV often reduces patient satisfaction and delays recovery and hospital discharge. The chemoreceptor trigger zone in the brain, the vestibular system, the visceral afferents from the gastrointestinal tract, and the cerebral cortex are the known players associated with PONV.[1] Specifically, the many serotonin (5-HT3), neurokinin-1 (NK1), and dopamine (D2) receptors in the chemoreceptor trigger zone and the interactions among these various receptors and neurotransmitters influence the occurrence of PONV. Notably, risk factors for PONV include patient-related factors, such as female sex, a history of motion sickness or PONV, nonsmoking status, and the postoperative use of opioids. Surgical factors associated with PONV include the type of surgery and the anesthetic method used.[2]

The incidence of PONV after thyroidectomy was observed to be 63% to 84%, which is higher than that of other surgeries.[3,4] The occurrence of PONV causes complications, such as increased intracranial pressure, pulmonary aspiration, dehydration, and electrolyte imbalance. PONV after thyroidectomy can also cause life-threatening complications, such as wound bleeding and dehiscence, which was caused by tension on suture lines, resulting in airway compression.[5,6] As such, studies exploring the occurrence and prevention of PONV after thyroidectomy are very important.

Until now, 5-HT3 antagonists have been used as representative drugs in PONV prevention studies.[7–11] Among them, palonosetron is the most recently developed 5-HT3 antagonist, and it has higher binding affinity to the 5-HT3 receptor than the previous generation of 5-HT3 antagonists. Because of this higher binding affinity, palonosetron has many benefits, such as higher potency, a significantly longer half-life (~40 h, 4–5 times longer than that of dolasetron, granisetron, or ondansetron), and an excellent safety profile.[12,13]

Like palonosetron, dexamethasone has been reported to prevent PONV in patents who underwent thyroidectomy.[14] Additionally, a previous systematic review[15] reported that dexamethasone has similar effects to ondansetron in preventing PONV. Although its mechanism of action has not yet been established, it is assumed that the endogenous production of prostaglandins and opioids associated with the central antiemetic mechanism is involved.[15,16]

Combination therapy is more effective in preventing PONV in high-risk groups than monotherapy,[17] but there is still controversy surrounding which combination of drugs is most efficient. Furthermore, none of the combinations used so far have completely prevented PONV. Specifically, combination therapy with dexamethasone and other antiemetics has been used in various studies, but the results have been inconsistent.[16,18–20] Accordingly, our study aimed to explore the effects of monotherapy and combination therapy using dexamethasone and palonosetron on the prevention of PONV in a randomized, double-blind, comparative study for highly susceptible, nonsmoking, female patients undergoing thyroidectomy and using opioids for postoperative pain management.

Patients and Methods

Patients

The Institutional Review Board of Chung-Ang University Hospital approved these study protocols, which were registered in the CRIS (KCT0000899). The study was conducted according to the principles of the Declaration of Helsinki, 2000. Written informed consent was obtained from all participants prior to inclusion in the trial.

All of the female, nonsmoking, American Society of Anesthesiologists physical status 1 to 2 patients who were between the ages of 20 and 60 years and undergoing thyroidectomy under general anesthesia at our institution between September 2013 and February 2014, were assessed for study eligibility. To minimize the confounding effects of the operation, only the patients undergoing total open thyroidectomy without radical neck dissection by the same team of surgeons were included in this study.

The exclusion criteria included severely impaired bowel motility, insulin-dependent diabetes mellitus, pregnancy or breastfeeding, administration of anti-

emetic medication within 24 hours before the operation, systemic treatment with steroids within 24 hours before the operation or 48 hours after the operation, a history of cardiovascular or respiratory disease, active alcohol or drug use, obesity (body mass index $\geq$35 kg/m^2), impaired renal function, and impaired hepatic function. The decision regarding whether or not to enroll or exclude patients was made by the investigator, who did not otherwise participate in conducting the study or in data collection.

Study design and randomization

This was a randomized, double-blind, placebo-controlled study. Randomization into one of the 3 groups [Group D (dexamethasone group), Group P (palonosetron group), or Group DP (dexamethasone and palonosetron group)] was based on a random table generated using PASS 11 (NCSS, Kaysville, Utah). Notably, a statistician not otherwise participating in the study generated this random computerized table. The details of the series were unknown to the investigators, and the group assignments were kept in a set of sealed envelopes that were labeled only with the case number. Prior to surgery, the nurse opened the appropriately numbered envelope to determine the patient's treatment and group classification. Dexamethasone (5 mg, DEXA S, Ilsung Pharmaceuticals Co Ltd, Seoul, Korea), palonosetron (0.075 mg, Aloxi, Helsinn Birex Pharmaceuticals Ltd, Dublin, Ireland), or dexamethasone (5 mg) and palonosetron (0.075 mg) were then prepared in equal volume syringes by the nurse and labeled with the case number. All of the parties involved, including the patients, the surgeon, the anesthesiologists, and the investigator collecting the data, were unaware of the study drugs or the patients' group assignments.

General anesthesia

The patients fasted for $\geq$8 hours for solid food and $\geq$2 hours for clear fluids, and were hydrated appropriately prior to surgery. All patients entered the operating room without receiving premedication. After recording noninvasive blood pressure, heart rate, and peripheral oxygen saturation measures, the randomly selected experimental medication was injected intravenously (IV) as a bolus during the course of 30 seconds immediately before anesthesia. Patients in Group D received dexamethasone (5 mg in 1 mL) and 1 mL of normal saline. Patients in Group P received palonosetron (0.075 mg in 1 mL) and 1 mL of normal saline. Patients in Group DP received dexamethasone (5 mg in 1 mL) and palonosetron (0.075 mg in 1 mL), administered separately.

Anesthesia was induced with 2 mg/kg propofol, and tracheal intubation was facilitated with 0.6 mg/kg rocuronium. To maintain normocarbia throughout the operation, mechanically controlled ventilation was adjusted to maintain a tidal volume of 6 to 8 mL/kg and an I/E ratio of 1:2 at a respiratory rate of 8 to 15 breaths per minute. Anesthesia was maintained using 2 to 3 vol% sevoflurane (end-tidal concentration of 1.2–1.8 minimum alveolar concentration) in 1.5 L/min nitrous oxide (N_2O) and 1.5 L/min O_2. During the surgery, the patients received an IV infusion of lactate Ringer solution at a rate of 3 to 6 mL/kg/h. No additional analgesics were injected during the surgery. At the end of surgery, muscle relaxation was antagonized with a combination of 0.4 mg IV glycopyrrolate and 15 mg IV pyridostigmine. Once fully awake, the patients were extubated.

Postoperative pain control

Thirty minutes before the end of the surgery, a computerized, IV, patient-controlled analgesia (IV-PCA) system (Automed 3300, ACE Medical Corp Ltd, Seoul, Republic of Korea) was connected to control postoperative pain. The IV-PCA regimen, which was prepared by the nurse, consisted of a 0.5 μg/kg fentanyl bolus with a 15-minute lockout interval without continuous infusion (total volume including saline: 100 mL) during the first 48 hours after surgery. One day prior to surgery, the patients were taught how to push the PCA system's button to deliver a bolus of medication as needed. In cases of persistent pain with visual analogue scale (VAS) pain scores of 3 or greater, the investigator injected an additional 50 μg of fentanyl intravenously until the pain was brought below a VAS score of 3.

The studied variables

The primary outcome variable was the severity of nausea during the first 48 hours after surgery.

The secondary outcome variables included the incidence of vomiting, the use of additional rescue antiemetic, pain intensity, and postoperative medication-associated complications. These variables

were evaluated 7 times, which included during the stay in the recovery room and then in the ward at approximately 2, 4, 8, 12, 24, and 48 hours after surgery. Nausea was defined subjectively as the unpleasant sensation of the urge to vomit, and vomiting was defined as the forceful expulsion of gastric contents through the mouth. The severity of nausea was graded on an 11-point numeric rating scale (NRS), with 0 being no nausea and 10 being the worst possible nausea. A single blinded investigator collected the nausea severity (NRS) scores.

Compared with using NRS to assess the need for an additional antiemetic to mitigate symptoms, PONV was a more objective method. Therefore, we also evaluated the number of rescue antiemetics and the times until the first rescue antiemetic therapy dose was administered in each group. The rescue antiemetic therapy (10 mg of metoclopromide, IV) was administered at the discretion of the attending physicians—who were blinded to the patient groups—if the patients complained of nausea with an NRS $\geq$5 or if they experienced vomiting. The IV-PCA was discontinued when severe nausea persisted or upon the patient's request after two consecutive boluses of metoclopromide. The most frequently reported side effects of the 5-HT3 antagonists used in conjunction with the opioid-based IV-PCA were headache, dizziness, drowsiness, constipation, flushing, heat, and general weakness, and these side effects were also assessed during the study period. Two investigators were responsible for data collection other than the severity of nausea measure during the postoperative period.

Statistical analysis

To estimate the group size for this study, a pilot study was conducted to measure the NRS for nausea severity in 10 patients who underwent thyroidectomy and were treated with palonosetron. The averages and the SDs of the NRSs in the recovery room and at postoperative hours 2, 4, 8, 12, 24, and 48 were 4.1 $\pm$ 0.9, 3.1 $\pm$ 0.8, 2.7 $\pm$ 0.7, 2.2 $\pm$ 0.7, 2.3 $\pm$ 0.9, 1.5 $\pm$ 0.8, and 1.1 $\pm$ 0.6, respectively.

The autocorrelation between the adjacent measurements of the same patient was 0.7. For our power calculation, we assumed that the first-order autocorrelation adequately represented the autocorrelation pattern. We wanted to detect a 10% increase in the dexamethasone group and a 10% decrease in dexamethasone and palonosetron group. Therefore, with an alpha of 0.05 and a power of 80%, we needed 26 patients per group. The PASS 11 software (NCSS) was used to calculate the sample size.

For intergroup comparisons, the distribution of the continuous data was first evaluated for normality using the Shapiro-Wilk test. Normally distributed data were compared using parametric tests, and data were presented as the mean $\pm$ SD. The abnormally distributed data were analyzed using nonparametric tests and were expressed as median (P_{25}–P_{75}).

For among-group comparisons, height was evaluated using analysis of variance and a post hoc Tukey test, and age, weight, body mass index, time for operation and anesthesia, and total fentanyl dose were analyzed by Kruskal-Wallis test with Bonferroni correction.

Because the severity ratings of nausea and pain were abnormally distributed ($P < 0.05$ according to Shapiro-Wilk test), they were analyzed using Friedman repeated-measures analysis of variance, followed by a Tukey test for multiple pairwise comparisons.

Interval before the administration of the first dose of rescue antiemetic was assessed using the Kaplan-Meier method, and the difference was evaluated by the log-rank test.

Descriptive variables were presented as n (%) and analyzed using a χ^2 test or a Fisher exact test as appropriate. A P value <0.05 was considered statistically significant. All analyses were performed using the SPSS statistical software, version 18.0 (IBM Corp, Armonk, New York) for Windows.

Results

Among the 95 patients who were eligible for the study from September 2013 to February 2014, a total of 9 patients refused to participate and 8 patients were excluded due to ineligibility. A total of 78 patients were randomized to 1 of 3 study groups (Fig. 1). The patient characteristics and operative data were similar between the 3 groups (Table 1).

The results of the severity of nausea measured using the NRS are shown in Fig. 2. In all of the groups, the highest NRS score was registered in the recovery room, and the nausea diminished gradually with time. The severity of nausea was reduced first in Group DP, followed by Group P and Group

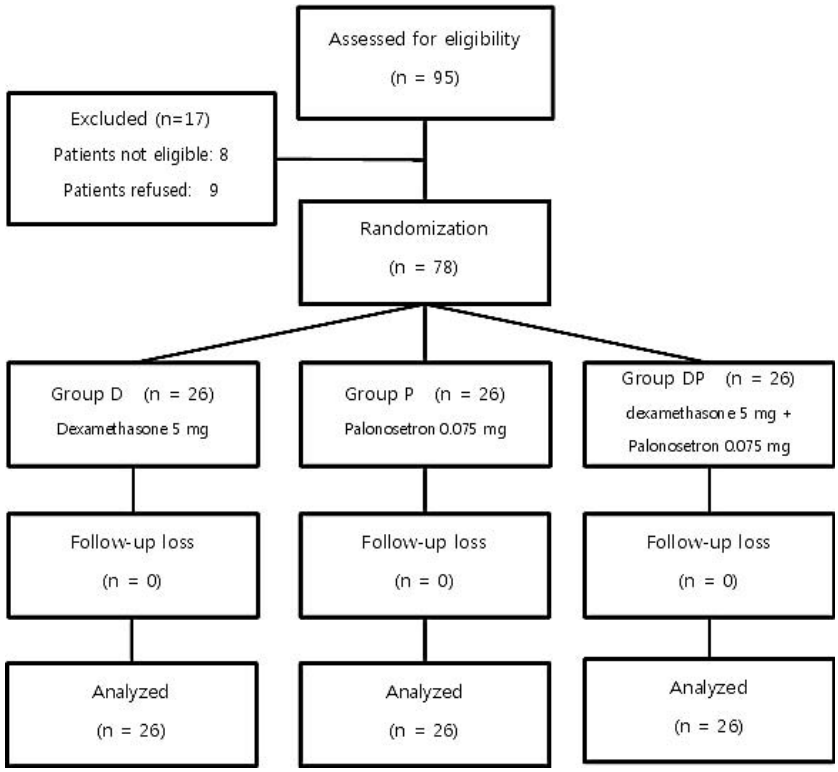

Fig. 1 Flow diagram of the patient population.

D. There was an overall difference in nausea severity between Group D and Group DP, but no difference was found between Group D and Group P or between Group P and Group DP. There were statistically significant differences between Group D and Group DP in the recovery room, at 2 hours postop, and at 12 hours postop. However, there were no significant differences between Group D and Group P or between Group P and Group DP at any time point (Fig. 2).

One patient in Group D and one patient in Group P were required to discontinue the IV-PCA because of severe nausea and vomiting, even after receiving two consecutive boluses of metoclopramide, but no patients in Group DP were required to discontinue IV-PCA. The incidence of vomiting was 23.1% in Group D, 15.3% in Group P, and 7.7% in Group DP; these results were not statistically different ($P = 0.307$). In Group D, 61.5% of patients received antiemetic medications, 42.3% in Group P received them, and 30.8% in Group DP received them; these results were marginally different ($P = 0.079$; Table 2).

The Kaplan-Meier analysis of the interval before the administration of the first dose of rescue antiemetic highlights the overall differences among

Table 1 Patient characteristics[a]

	Group D (n = 26)	Group P (n = 26)	Group DP (n = 26)	*P* value
Age, y, median (P_{25}–P_{75})	41.00 (37.00–51.25)	47.00 (40.00–51.50)	48.00 (40.00–53.25)	0.242[b]
Height, cm, mean ± SD	160.24 ± 5.87	158.6 ± 5.06	157.33 ± 4.50	0.133
Weight, cm, median (P_{25}–P_{75})	57.50 (52.45–67.25)	57.50 (53.75–64.25)	58.50 (48.75–61.50)	0.875[b]
BMI, median (P_{25}–P_{75})	22.60 (21.58–24.40)	22.85 (21.55–24.75)	22.85 (20.18–24.70)	0.92[b]
ASA, No.	22/4	21/5	21/5	0.917
Operation time, min, median (P_{25}–P_{75})	120.00 (103.75–141.25)	130.00 (98.75-136.25)	120.00 (103.75–135.00)	0.999[b]
Ane time, min, median (P_{25}–P_{75})	140.00 (128.75–165.00)	150.00 (128.50-161.25)	140.00 (128.75–150.00)	0.81[b]

Ane, anesthesia; ASA, American Society of Anesthesiologists; BMI, body mass index.

[a]Group D, IV dexamethasone 5 mg alone; Group P, IV palonosetron 0.075 mg alone; Group DP, IV dexamethasone 5 mg combined with palonosetron 0.075 mg.

[b]Compared using Kruskal-Wallis test due to abnormal distribution.

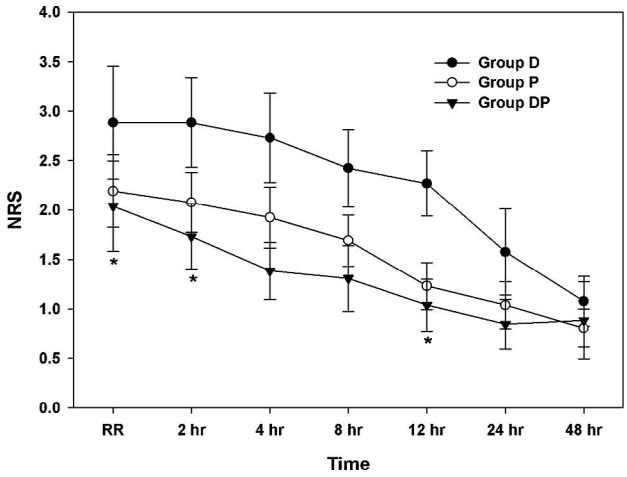

Fig. 2 Postoperative nausea intensity score assessed with an 11-point NRS. Group D, dexamethasone; Group P, palonosetron; Group DP, dexamethasone with palonosetron. *Statistically different points between group D and group DP

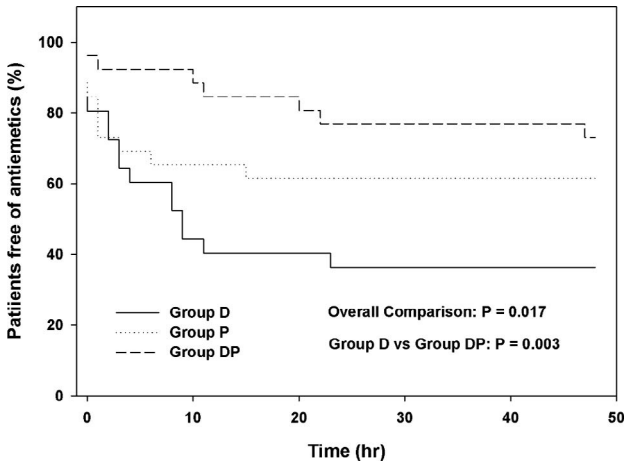

Fig. 3 Kaplan-Meier analysis of the interval before the first dose of rescue antiemetic. Group D, dexamethasone; Group P, palonosetron; Group DP, dexamethasone with palonosetron.

groups ($P = 0.017$). Specifically, there was a significant difference between Group D and Group DP ($P = 0.003$). However, no differences were found between any other groups (Fig. 3).

The VAS measure for postoperative pain showed Group P to have the highest level of pain, followed by Group D and Group DP. There was an overall difference between Group P and Group DP, but no difference between Group D and Group P or between Group D and Group DP. Significantly lower pain scores were found in Group D and Group DP compared with Group P, and these effects persisted up to 2 hours after the surgery (Fig. 4). Notably, there was no significant difference in the amount of total fentanyl used via PCA and rescue analgesic among the 3 groups (Table 2).

During the 48-hour postoperative period, the patients were observed for medication side effects. The most commonly reported adverse effects related to the 5-HT3 antagonists were headache and dizziness. The overall incidence of these side effects was low and did not significantly differ among the groups.

Discussion

Our study showed that Group DP had more mild nausea and the time to the first administration of rescue medication was longer, followed by those of Group P and Group D. In particular, the time to the first administration of rescue medication and the severity of nausea showed significant differences between Group D and Group DP. In addition, the postoperative pain was reduced in Group DP compared with Group P.

PONV is one of the most frequently occurring and distressing postoperative complications. Its incidence varies between 10% and 79%,[2] with some studies showing an incidence up to 84%[3] depending on the type of surgery, the anesthetic method, and risk factors. In particular, the occurrence of PONV after thyroidectomy can be quite dangerous. PONV after thyroidectomy can cause emergent events, such as airway compression from hematoma formation due to bleeding at the surgical site.[21] As such, the prevention of PONV in patients at high risk, such as patients undergoing thyroidectomy, is very important.

Table 2 Perioperative parameters[a]

	Group D	Group P	Group DP	*P* value
Total fentanyl dose, median (P_{25}–P_{75})	360.00 (180.47–404.20)	387.39 (257.50–454.45)	369.50 (335.14–415.31)	0.593
Vomiting, n (%)	6 (23.1)	4 (15.3)	2 (7.7)	0.307
Rescue antiemetics, n (%)	16 (61.5)	11 (42.3)	8 (30.8)	0.079

[a]Group D, IV dexamethasone 5 mg alone; Group P, IV palonosetron 0.075 mg alone; Group DP, IV dexamethasone 5 mg combined with palonosetron 0.075 mg.

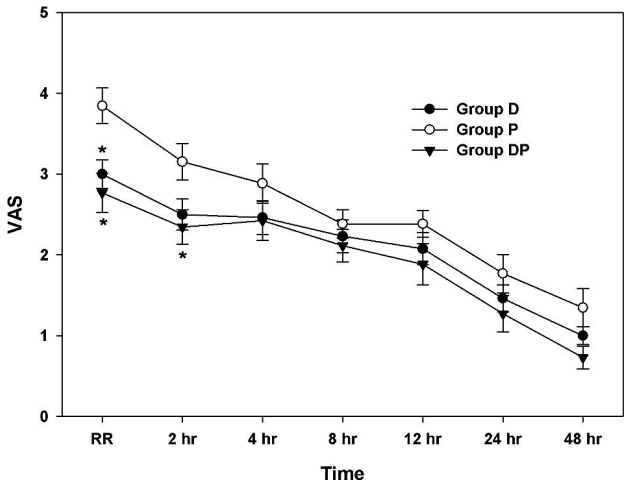

Fig. 4 Postoperative pain intensity score assessed with VAS. Group D, dexamethasone; Group P, palonosetron; Group DP, dexamethasone with palonosetron. *Statistically different points

The first drugs proven to prevent PONV were 5-HT3 receptor antagonists, and they are used widely in clinical practice.[22] Palonosetron is a second-generation 5-HT3 receptor antagonist that has a longer effective period compared with the first-generation 5-HT3 receptor antagonists, such as ondansetron, dolasetron, and granisetron. This longer period of efficacy is achieved by blocking 5-HT binding to the orthosteric site of the receptor, which is due to palonosetron's strong affinity for the 5-HT3 receptor's allosteric site.[23–25] This mechanism may then explain palonosetron's preventive effects on both early PONV (0–24 hours postoperatively) and delayed PONV (24–72 hours postoperatively).

Another drug with antiemetic effects is dexamethasone, a glucocorticoid.[26] Its mechanism of action has not yet been fully established, but it is assumed to be associated with the central inhibition of prostaglandin synthesis, the inhibition of endogenous opioid release, reduced serotonin turnover in the central nervous system, and changes in the permeability of the blood-brain barrier to serum proteins.[15,16]

This study did not show statistically significant differences in the severity of nausea between Group D and Group P, which is in contrast to the results of Song *et al*.[26] Song *et al* showed that, compared with dexamethasone, the 5-HT3 antagonist ramosetron reduced the severity of nausea and the need for administration of rescue antiemetic drugs in female patients who underwent thyroid surgery. In addition, D'Souza *et al*[20] also reported conflicting results compared with the current study, reporting that dexamethasone was more effective at decreasing PONV than ondansetron in female patients who underwent laparoscopic gynecologic surgery. These differing results may be attributed to the differences in the types of 5-HT3 antagonists and their administration time, the type of surgery, and the types of induction and maintenance anesthetics used.

Comparing Group P and Group DP, the severity of nausea and the time to the first dose of rescue antiemetic were not significantly different. This result was in line with the results of Park *et al*,[19] which reported no difference in the incidence of PONV between palonosetron monotherapy and combination therapy with palonosetron and dexamethasone in patients with a high emetogenic risk. These results suggest that combination therapy with palonosetron and dexamethasone provides no significant additive or synergistic effect to reduce the severity of nausea compared with palonosetron alone.

However, Elhakim *et al*[16] and Bhattarai *et al*[18] reported results contradictory to those of the present study. Their studies showed that the incidence of PONV was reduced with dexamethasone and ondansetron combination therapy compared with ondansetron monotherapy in patients who underwent laparoscopic surgery. This differing result was attributed to several differences in the study methods. First, the two previous studies targeted patients who underwent laparoscopic surgery, but this study targeted patients who underwent thyroidectomy. Thus, the surgery type may affect the incidence and severity of PONV. Second, the two previous studies used midazolam[16] and diazepam[18] as premedications, unlike this study. These two premedications are known to prevent PONV,[27,28] which may have confounded the results. Third, the two previous studies used ondansetron, whereas this study used palonosetron, which is known to be effective in the prevention of PONV. As such, the combination of dexamethasone and palonosetron might have shown less significant synergistic effects on the prevention of PONV. However, we believe that these factors did not strongly affect the study results, considering that Group D and Group P did not show significant differences in this study.

Finally, when comparing Group D and Group DP, Group DP showed a significant reduction in severity of nausea, and an increased interval before administration of the first dose of rescue antiemetic. Our results comparing Group D and Group DP were consistent with the study conducted by Zhou *et al*,[29]

which reported that combination therapy with tropisetron, a 5-HT3 antagonist, and dexamethasone decreased the incidence of PONV compared with dexamethasone monotherapy in patients who underwent thyroidectomy. Our results were also consistent with the study by Jo *et al*,[30] which reported that the combination of dexamethasone and ramosetron better decreased the severity of nausea than dexamethasone monotherapy in patients who underwent laparoscopic cholecystectomy. However, our study showed statistically significant differences between groups in the recovery room and at postoperative hours 2 and 12, whereas Zhou *et al*[29] showed significant differences in the late postoperative period (6–48 hours), and the study of Jo *et al*[30] showed significant differences for 6 to 12 hours after surgery.

The differences between our results and the above-mentioned results may be explained by several factors. First, their studies used midazolam as the premedication, but we did not. Midazolam is known to prevent early PONV,[28] which may have concealed the differences occurring in the early period. Second, their studies used fentanyl bolus or remifentanil maintenance infusion as supplementary analgesia during the surgeries. The use of intraoperative opioids might have affected the study results because intraoperative opioid administration is one of the risk factors for increased PONV. In addition, our study used opioid-based IV-PCA for postoperative pain control, unlike the other studies, which might also have affected the study results.

The 5-HT3 receptor antagonists are known to have analgesic effects related to nociceptive or facilitatory signal transmission. In models of cancer-induced bone pain, inflammatory pain, and neuropathic pain, descending serotonergic neurons from the rostral ventromedial medulla stimulate nociceptive signaling, and 5-HT3 antagonists inhibit this signal pathway and seem to show analgesic effects. Also, gamma-aminobutyric acid–mediated (GABAergic) inhibitory signaling is thought to be associated with such analgesic effects.[31]

In addition, dexamethasone is also known to have analgesic effects. Several randomized controlled studies and meta-analyses have reported that single-dose dexamethasone is effective in postoperative pain control after various surgeries, including laparoscopic, breast, and thyroid surgeries.[29,32–36] The mechanism of dexamethasone's analgesic effect seems to be associated with its anti-inflammatory action and modulation of its systemic physiologic responses.[26]

The VAS score on postoperative pain was lower in Group DP than in Group P. This is attributed to the synergistic analgesic effects of dexamethasone and palonosetron. Such analgesic effects might indirectly decrease the incidence of PONV caused by opioid use through reduction of the required bolus dose of opioid-based PCA.

The side effects of dexamethasone and palonosetron were observed up to 48 hours after the surgery. The incidence of side effects did not differ among the 3 groups. Notably, no patients showed side effects that required additional treatment during the observation period.

This study had several limitations. First, we observed patients for only 48 hours postoperatively. If the observation period were longer, we would have been able to analyze the effect of dexamethasone and palonosetron on postdischarge nausea/vomiting, because these drugs are known to be effective in preventing late-onset PONV. Furthermore, we could have obtained information regarding the long-term complications of glucocorticoids, including wound infection and impaired wound healing. Second, we could not investigate the direct effect of the administration of each drug because there was no placebo group. Because this study was conducted with high-risk patients, we considered having a placebo group to be unethical. Third, this study used a minimal dose of dexamethasone, 5 mg, for the prevention of PONV after thyroidectomy in order to minimize the adverse effects of dexamethasone, such as an increased blood glucose level and delayed wound healing, based on the results of the study by Wang *et al*.[14]

Some advantages of this study are worth highlighting. We included only open total thyroidectomy without radical neck dissection in this study in order to limit the type, nature, and duration of nausea and vomiting associated with different types of surgery. Moreover, all of the surgeries were conducted by the same team of surgeons in order to minimize the differences among surgeon teams. Furthermore, all of the postoperative measurements of the severity of nausea were carried out by a single blinded observer in order to eliminate any interobserver variability. Thus, we can assume that the measured differences in the severity of postoperative nausea accurately reflect the efficacy of the drugs used.

In conclusion, the combination of dexamethasone and palonosetron decreased the severity of nausea compared with dexamethasone or palonosetron alone in highly susceptible patients undergoing

thyroidectomy. Furthermore, these differences were observed in a Kaplan-Meier analysis of the interval before the administration of the first dose of rescue anti-emetic.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science and Technology (2012R1A1A1003700)

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