

CLINICAL PRACTICE

Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study

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Editor's key points

- Palonosetron is a novel potent anti-emetic with a unique mechanism that has potential advantages over current agents.
- The effects of palonosetron and ondansetron on postoperative nausea and vomiting (PONV) after thyroidectomy with opioid-based analgesia were compared in a randomized double-blind trial of 100 subjects.
- The incidence of PONV and the use of rescue anti-emetics were lower with palonosetron in the first 24 h after surgery.

Background. Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.

Methods. A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0–2 and 2–24 h.

Results. The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, $P=0.045$). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2–24 h. The only difference in the use of rescue anti-emetics was at 2–24 h (10% with palonosetron compared with 28% with ondansetron, $P=0.02$).

Conclusions. Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2–24 h after surgery.

Keywords: analgesia, patient-controlled; anti-emetics, ondansetron; anti-emetics, palonosetron; postoperative nausea and vomiting

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Among the various methods of controlling postoperative pain, patient-controlled analgesia (PCA) is known to be the most effective. PCA is used effectively for both major and minor surgeries for which postoperative pain is expected. Even though thyroid surgery is a short operation associated with relatively moderate pain, almost 90% of patients need opioids for pain control on the day of the operation and the first day afterwards.¹ Other studies have also proven the necessity of opioid analgesic pain control during the early postoperative phase.^{2–4} However, the use of opioid analgesics inevitably causes postoperative nausea and vomiting (PONV).⁵ In addition, thyroid surgery itself is

known to have a high incidence of PONV because of its high proportion of female patients and various surgery-related factors.⁶

Several clinical studies have examined the efficacy of anti-emetics in preventing PONV with opioid PCA.^{7,8} Selective 5-hydroxytryptamine 3 (5-HT₃) antagonists have been extensively studied and are currently the primary therapy for PONV prevention because they have fewer side-effects such as sedation or extrapyramidal symptoms compared with other anti-emetics. The efficacy of the 5-HT₃ antagonist ondansetron, the most commonly used drug for PONV prevention, is acknowledged in diverse postoperative situations.

Unfortunately, it is not always effective for reducing the incidence or severity of PONV related to opioid PCA.^{7–9}

Palonosetron, a newly developed 5-HT₃ antagonist, has a unique mechanism different from previously developed agents in this class with more potent and persistent effects. Its unique pharmacodynamic mechanism of allosteric binding, which is distinct from the standard 5-HT₃ antagonists, is thought to induce effects that are clinically superior to those of ondansetron, especially on PONV associated with opioid PCA. Nevertheless, clinical evidence is very limited. No study has compared the effects of palonosetron and ondansetron in high-risk patients receiving thyroidectomy. Therefore, we conducted a prospective, randomized, double-blind study to compare the effects of palonosetron and ondansetron on opioid PCA-related PONV in these high-risk patients.

Methods

The study was approved by the institutional review board of Seoul St Mary's Hospital, Catholic University (Ref: KC09MISI0373) and registered with CRiS (Ref: KCT0000012). All subjects provided written consent. The subjects were ASA physical status I and II aged 20–60 yr who underwent total thyroidectomy with central compartment node dissection under general anaesthesia between January 2010 and November 2010. Subjects had the following PONV risk factors: female, non-smoker, and use of opioid analgesics after surgery. We excluded patients receiving radical neck dissection because the operation time is longer than that of simple total thyroidectomy. We also excluded patients who took an anti-emetic within 1 day of surgery; took opioids or steroids within 1 week of surgery; were not able to use the PCA device; were not able to understand the visual analogue scale (VAS) of pain; abused alcohol or drugs; experienced diseases of the digestive system, kidneys, or liver; or developed insulin-dependent diabetes or obesity with a BMI of $>35 \text{ kg m}^{-2}$. The enrolled patients randomly received either ondansetron ($n=50$) or palonosetron ($n=50$), using computer-generated codes placed in sequentially numbered, opaque envelopes.

The same surgeon conducted all of the thyroid surgeries using the same surgical method. All subjects were in a eu-thyroid state before surgery. Premedication was omitted. General anaesthesia was induced using $1.5\text{--}2.5 \text{ mg kg}^{-1}$ propofol and $1\text{--}2 \text{ }\mu\text{g kg}^{-1}$ fentanyl, and 0.8 mg kg^{-1} rocuronium was injected to facilitate tracheal intubation. Anaesthesia was maintained with $1.5\text{--}2.5\%$ sevoflurane (end-tidal concentration) in 60% nitrous oxide/oxygen. Mechanically controlled ventilation was adjusted to keep end-tidal CO₂ at $4.6\text{--}5.9 \text{ kPa}$ throughout surgery. Additional rocuronium was administered as needed.

At the end of surgery, either ondansetron or palonosetron was injected according to the group assignment, and i.v. PCA was provided. In the ondansetron group, 8 mg of ondansetron in 4 ml was injected as a bolus and 16 mg in 8 ml was mixed with the PCA formulation. In the palonosetron

group, 0.075 mg of palonosetron in 4 ml was injected as a bolus and 8 ml of normal saline was added to the PCA formulation. The PCA formulation consisted of $12 \text{ }\mu\text{g kg}^{-1}$ fentanyl diluted to 100 ml in normal saline; the basal rate was set at 1 ml h^{-1} , with a bolus of 1 ml and lock-out time of 10 min. The study drug and PCA mixture were prepared in identical syringes. The subjects and individuals providing anaesthesia were blinded to group assignments.

Another anaesthesiologist blinded to the group assignments evaluated the following items 0–2 and 2–24 h after surgery: incidence of nausea and vomiting; severity of nausea; need for additional anti-emetics and additional analgesics; severity of pain; total amount of PCA fentanyl used; and side-effects. Nausea was defined as a subjectively unpleasant feeling associated with the awareness of the urge to vomit.¹⁰ Retching (defined as laboured, spasmodic contractions of the respiratory muscle without expulsion of gastric contents) and vomiting (defined as an actual physical phenomenon of the forceful expulsion of gastric contents from the mouth) were both defined as vomiting.¹⁰ The evaluation of nausea severity was based on a four-point scale (0, no nausea; 1, mild nausea; 2, moderate nausea; 3, severe nausea). When the patient felt severe nausea or requested rescue anti-emetic medication, metoclopramide (10 mg) was injected immediately after the nausea severity was recorded. When the patient suffered from pain with a severity greater than 5 on a 10 cm VAS (0, no pain; 10, worse intolerable pain), 25 mg of meperidine was injected i.v., and requests for rescue analgesics were recorded. Side-effects, such as headache, dizziness, and drowsiness, were also evaluated. The primary outcome was the incidence of nausea and vomiting during the study period.

In a preliminary study conducted with 23 patients who were given ondansetron and similar PCA as this study, 65% of subjects suffered from nausea and vomiting for up to 24 h after thyroidectomy. To obtain an 80% chance of finding a 30% decrease in PONV incidence ($65\%\rightarrow 35\%$) during the first 24 h after surgery with $\alpha=0.05$ (two-tailed) level, 43 patients were required for each group. Taking potential dropouts into consideration, 50 patients were included in each group. Student's *t*-test or the Mann-Whitney rank-sum test was used to compare inter-group differences. The χ^2 test or Fisher's exact test was used for categorical variables. Values of *P* were corrected by the Bonferroni method and *P* values <0.05 were considered to indicate statistical significance. SPSS software for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

A total of 191 patients were screened, and 100 among them were randomized into two groups. There were no dropouts among the 100 enrolled subjects (Fig. 1). Subject characteristics (including history of PONV, motion sickness, or both) and operative data were similar for both groups (Table 1).

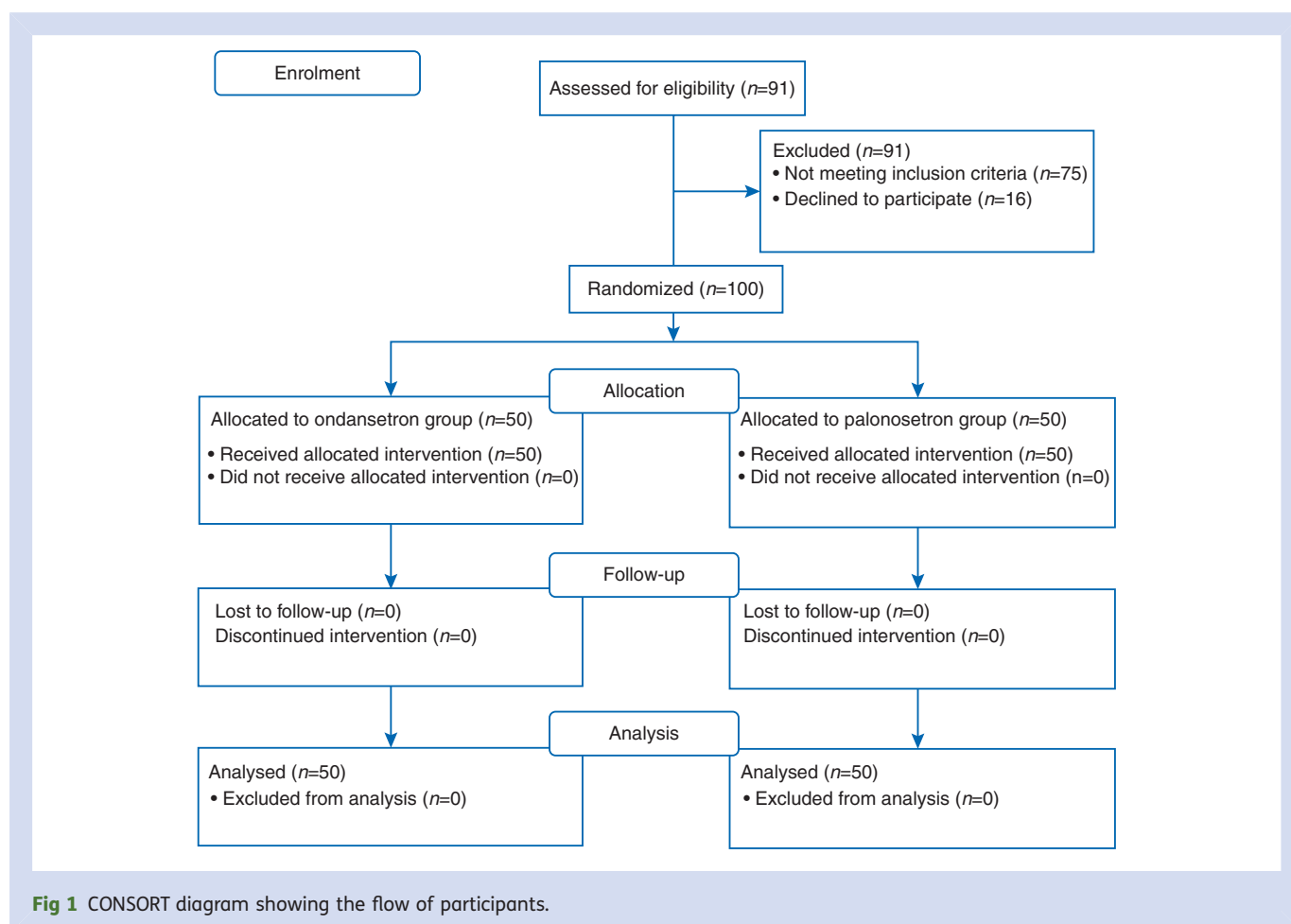


Table 1 Subject and anaesthetic characteristics. Values are number, mean (sd), or number (%). PONV, postoperative nausea and vomiting

| | Ondansetron (n=50) | Palonosetron (n=50) |
|------------------------------------|-----------------------|------------------------|
| Mean age (range) (yr) | 43.8 (20–60) | 45.9 (20–60) |
| Weight (kg) | 58.1 (7.5) | 59.3 (8.4) |
| Height (cm) | 159 (4.9) | 159 (5.5) |
| ASA I/II | 38/12 | 39/11 |
| Anaesthesia time (min) | 122 (28.2) | 118 (28.1) |
| History of motion sickness or PONV | 18 (36%) | 17 (34%) |

Overall, PONV incidence during the 24 h after surgery was lower in the palonosetron group compared with the ondansetron group (42% vs 62%, $P=0.045$). There was no significant difference between the groups during the first 2 h after surgery. On the other hand, the incidence of nausea and vomiting was significantly lower in the palonosetron group than in the ondansetron group 2–24 h after surgery (Fig. 2). The severity of nausea did not differ at 2 h after surgery, but was significantly lower in the palonosetron group compared with the ondansetron group 2–24 h after

surgery ($P=0.03$; Fig. 3). The only difference in the use of anti-emetics was at 2–24 h (10% in palonosetron group vs 28% in ondansetron group, $P=0.02$).

There was no significant difference in the degree of postoperative pain, total consumption of PCA fentanyl, and rescue analgesic used within 24 h after surgery (Table 2). The incidence of side-effects, such as headache, dizziness, or drowsiness, was similar between groups (Table 3).

Discussion

We found that bolus injection of palonosetron was more effective in lowering the incidence of nausea and vomiting and the severity of nausea 2–24 h after surgery than the combination of bolus injection and addition of ondansetron to i.v. PCA in subjects at high risk for PONV.

PCA using opioid analgesic is an effective, safe, and convenient method to control postoperative pain. Many clinical studies and reviews have already proven the superiority of i.v. PCA using opioids over methods using intermittent i.m. injection or hypodermic injection of opioid.¹¹ PCA has been reported to provide better analgesic efficacy and less sedation with higher patient satisfaction, compared with traditional opioid analgesia in postoperative settings. This method keeps plasma opioid concentration within the

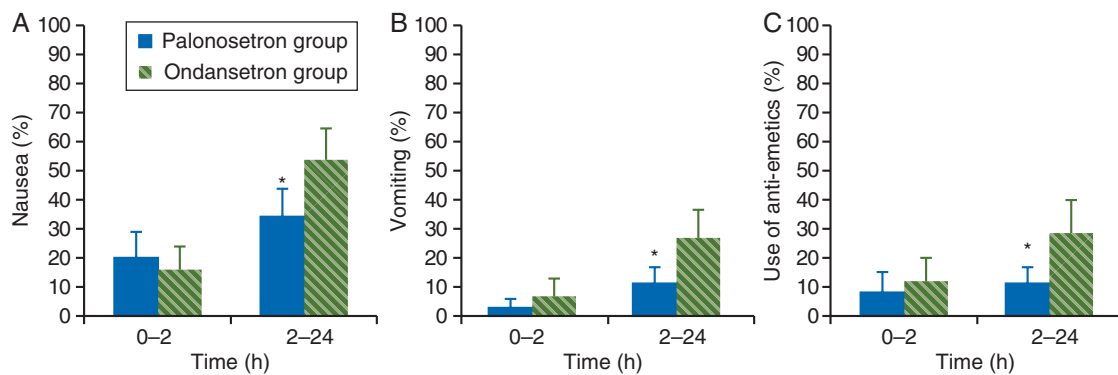


Fig 2 Incidence of (A) nausea and (B) vomiting, and (C) the use of anti-emetic in palonosetron and ondansetron groups during the 24 h post-operative period. For each group, the error bar indicates the value of the upper limit of the 95% confidence interval for the percentage of patients achieving the endpoint. * $P < 0.05$ compared with the ondansetron group.

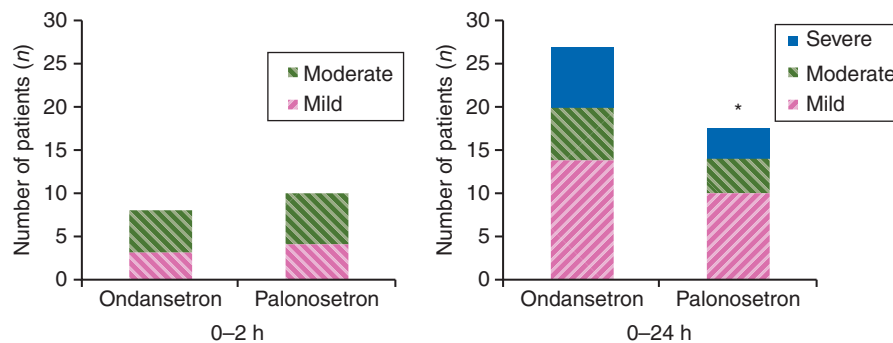


Fig 3 Severity of nausea during the 24 h postoperative period. * $P < 0.05$ compared with the ondansetron group.

Table 2 The severity of pain, cumulative fentanyl consumption, and rescue analgesic use. Values are mean (sd) or number (percentage)

| | Ondansetron (n=50) | Palonosetron (n=50) |
|---------------------------|--------------------|---------------------|
| Pain score | | |
| 0-2 h | 3.7 (1.7) | 3.5 (1.7) |
| 2-24 h | 2.2 (2.1) | 1.7 (1.6) |
| Fentanyl consumption (μg) | 195 (22.9) | 209 (25.3) |
| Rescue analgesic use | 5 (10%) | 5 (10%) |

Table 3 Reported side-effects. Values are number (%)

| | Ondansetron (n=50) | Palonosetron (n=50) |
|------------|--------------------|---------------------|
| Headache | 19 (38) | 18 (36) |
| Dizziness | 11 (22) | 7 (14) |
| Drowsiness | 6 (12) | 5 (10) |

target analgesic range longer than intermittent i.m. injection.¹² However, opioid-based PCA is inevitably accompanied by side-effects, and pain control is achieved at the expense of PONV. In general, PONV is the most common reason for dissatisfaction with opioid-based PCA. Because patients suffering from PONV often refuse to use a bolus dose for sufficient pain relief,¹³ the quality of pain control relies on the

prevention of PONV, especially in high-risk patients, such as those in this study.

The incidence of PONV reaches 10–78% depending on factors related to the operation, anaesthesia, and the patient.⁵ In particular, thyroidectomy is a surgery with a relatively higher PONV incidence of 60–84%.¹⁴ The main cause of PONV after thyroidectomy is not entirely clear, but it is thought to result from the age range and gender of patients (mostly middle-aged women) and strong vagal stimulation (surgical handling of neck structures).¹⁴ PONV could adversely affect patients who have received thyroidectomy, because vomiting could cause or exacerbate postoperative bleeding inside the surgery site. Such haemorrhage might compress

the trachea and lead to acute airway obstruction, which could necessitate tracheal intubation or re-operation to control the bleeding.¹⁵ Therefore, it is reasonable that appropriate PONV prophylaxis should be considered first rather than managing it after PONV is established.

Various 5-HT₃ antagonists have been used to prevent PONV, and most clinical studies have been implemented with ondansetron. Ondansetron inhibits emetic symptoms by binding with the 5-HT₃ receptor located in the central chemoreceptor trigger zone and the gastrointestinal tracts,¹⁶ and has been extensively used to prevent PONV. While some studies have reported that adding ondansetron to PCA lessens PONV,⁷ other studies have not shown particular advantages.⁸ In particular, the effect in patients using fentanyl-based PCA seems to be unsatisfactory. The incidence of PONV in high-risk patients who receive PCA consisting of fentanyl and ondansetron is as high as 60%,^{9,17} which is similar to the results of this study.

Palonosetron is a second-generation 5-HT₃ antagonist with unique pharmacodynamic characteristics. Palonosetron is an allosteric 5-HT₃ receptor antagonist, whereas the previously developed 5-HT₃ antagonists compete directly with serotonin.¹⁸ Allosteric binding creates a conformational change in the serotonin receptor so that serotonin binding is indirectly inhibited.¹⁸ Consequently, palonosetron has higher affinity with 5-HT₃ receptors, which ultimately leads to greater potency and longer duration of action in comparison with standard 5-HT₃ antagonists.¹⁹ Palonosetron also inhibits responses induced by substance P, the dominant mediator of delayed emesis after chemotherapy, through differential inhibition of 5-HT₃/neurokinin-1 receptor cross-talk.²⁰ These pharmacological characteristics could decrease the need for combination therapy generally required for PONV prevention in high-risk patients. Although the combination of dexamethasone and an older 5-HT₃ antagonist is more effective than the 5-HT₃ antagonist alone,²¹ the combination of dexamethasone with palonosetron had an effect similar to that of palonosetron alone in high-risk patients.²² Moreover, palonosetron does not prolong the QTc interval, in contrast to older 5-HT₃ antagonists.¹⁹

In this study, palonosetron was more effective than ondansetron, especially 2–24 h after surgery. This finding concurs with the results of previous studies showing that palonosetron works better than ondansetron in delayed nausea and vomiting in patients receiving chemotherapy.^{23,24} The dose of palonosetron required to prevent PONV is lower than the dose used to prevent nausea and vomiting caused by chemotherapy. A single injection of 0.075 mg is now the US Food and Drug Administration-approved dose for preventing PONV for up to 24 h after surgery.²⁵

Many studies have been conducted on the dose and use of ondansetron for preventing PONV. Whereas a few clinical studies recommend either 4 or 8 mg of ondansetron, a meta-analysis suggested that 8 mg i.v. was optimal.²⁶ Also, mixing ondansetron with the PCA solution was suggested

for the prevention of PCA-related PONV. Adding ondansetron to PCA is more effective than a single dose of ramosetron, although the latter is the more persistent 5-HT₃ antagonist.²⁷ Based on the results of previous studies, we injected 8 mg of ondansetron at the end of surgery and added 16 mg to the PCA in order to achieve the maximal effect. Nevertheless, a single injection of palonosetron was superior to this combination of ondansetron.

The typical side-effects of 5-HT₃ antagonists include headache, dizziness, and drowsiness. In this study, the incidence of dizziness and drowsiness was similar in both groups, which corresponds to the results of previous studies. In contrast, the incidence of headache was considerably higher than in other studies. Most of these patients complained of headache in the posterior area. It is possible that this occipital headache is due to occipital nerve neuropathy resulting from the hyperextension of the neck required to secure a better field of vision during thyroid surgery. Another study reported a 47.5% possibility of suffering from headaches that are more than moderate.²⁸

Several limitations of our study should be noted. First, the baseline incidence of PONV was not measured because we did not include a placebo group, owing to our judgement that withholding preventive anti-emetics in high-risk patients would not be ethically justified. Secondly, we compared the efficacy of palonosetron and ondansetron based on the currently known optimal dose because their equipotent doses were known neither at the beginning of the study nor at the study's conclusion. In this study, ondansetron was continuously infused, whereas palonosetron was injected once as a bolus. Palonosetron is generally injected once a day because it has a longer half-life than older 5-HT₃ antagonists. The different injection methods might have caused pharmacokinetic differences. However, this should not have affected our conclusion that palonosetron is superior to ondansetron, considering the fact that the continuous infusion of ondansetron would have produced a steady plasma concentration of ondansetron. Nonetheless, further studies are required to ascertain the equipotencies of these drugs. Thirdly, before starting this study, we anticipated that there would be about a 30% difference between the two drugs. However, the actual difference in total PONV was only 20% (42% in palonosetron vs 62% in ondansetron, $P=0.045$). Although the absolute risk reduction of 20% is lower than anticipated, the acquisition of a relative risk reduction of 32% in this study could be deemed clinically significant, considering that the relative reduction rate of 30–40% is considered clinically relevant in general PONV research.²⁹ However, further studies are required to study palonosetron in more patients at more diverse surgical settings.

In conclusion, palonosetron was superior to ondansetron in high-risk patients receiving fentanyl-based i.v. PCA between 2 and 24 h after thyroidectomy. Palonosetron can be considered a promising anti-emetic drug for this subset of patients using opioid-based PCA.

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Declaration of interest

None declared.

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