Palonosetron in preventing postoperative nausea and vomiting in middle ear surgery: a randomized-controlled study

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Background
This study aimed to evaluate the efficacy of palonosetron, the 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, in preventing postoperative nausea and vomiting (PONV) after middle ear surgery.

Patients and methods
Sixty-two ASA I and II patients who had undergone middle ear surgery under general anesthesia were included in a double-blind, placebo-controlled study and were enrolled into two groups: palonosetron group (P) and placebo control group (C). Patients were administered 0.075 mg of palonosetron or isotonic saline, respectively. The incidence of PONV and requirement of rescue antiemetics were assessed. The severity of nausea was evaluated according to the visual analogue scale. Patients who had not experienced any attack of vomiting or received rescue drug were considered to have a complete response.

Results
The incidence of PONV was significantly lower in group P than that in the control group C during (0–4 h) *P*-value less than 0.001 and (4–24 h) 0.05 periods, and the incidence of complete response was 83.7% in group P and 6.5% in group C ($P<0.001$).

Conclusion
Palonosetron could provide effective prophylactic antiemetic control to prevent PONV after middle ear surgery under general anesthesia.

Keywords:
middle ear surgery, palonosetron, postoperative nausea and vomiting

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Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications after anesthesia and surgery with a relatively high incidence (60–80%) after middle ear surgery [1]. The annual cost of managing PONV in the USA is believed to approach a billion dollars [2].

A wide variety of prophylactic antiemetic regimens have been used for the prevention of PONV. Many of the traditional antiemetics produce undesirable side effects and have limited efficacy [3]. Therefore, the search for more ideal compounds has continued [4].

Palonosetron is a new 5-hydroxytryptamine-3 (5-HT3) receptor antagonist that can be distinguished from older 5-HT3 receptor antagonists (ondansetron, dolasetron, and granisetron) by its unique chemical structure, greater binding affinity ($pK_i = 10.45$), and considerably longer half-life ($\sim$40 h) [5].

The aim of our study was to evaluate the efficacy of palonosetron in prophylaxis against PONV in middle ear surgery.

Patients and methods

The protocol of this study was approved by the Ethics Committee of our institute. Written, informed consent was obtained from 62 patients (both men and women) who had undergone elective middle ear surgery, American Society of Anesthesiologist (ASA) physical status (I–II), age range (18–60), and BMI less than 35 kg/m^2 were enrolled in this study. Patients were excluded if they had received a prophylactic antiemetic within 24 h of surgery or were allergic to the study drugs.

According to a prospective double-blind, placebo-controlled protocol, both the patient and the nurse (collecting the data in the ward and by telephone after discharge) were blinded to which study group the patient belonged. Patients were allocated randomly to one of the two study groups, palonosetron group (P) ($n = 31$ patients) and control group (C) ($n = 31$ patients), by withdrawing a sealed envelope.

During preanesthetic assessment, all patients were educated about the nausea score used in our study (visual analogue scale, where 0 = no nausea and 10 = worst possible).

On arrival to the operating room, standard monitors were applied. General anesthesia was induced using propofol (2–2.5 mg/kg), atracurim besylate (0.5 mg/kg), and a bolus of remifentanil (0.1 mg/kg); then, the patients in group P received palonosetron (0.075 mg) (Emecad; Cadila Pharmaceuticals Ltd, Ahmedabad, India) 3 ml clear fluid intravenously slowly over 10 s [6], whereas the

patients in group C were injected with 3 ml of isotonic saline intravenously Anesthesia was maintained with sevoflurane 2–3%, combined with nitrous oxide (concentrate 50–60%). Remifentanil infusion was adjusted to maintain a target mean arterial blood pressure of 60 mmHg. At the time of emergence, all patients received tramadol 1 mg/kg intramuscularly and muscle relaxant was reversed with neostigmine (2.5 mg) and atropine (2 mg).

Postoperative analgesic protocol included tramadol intravenously (1 mg/kg) on demand (maximum/8 h), diclofenac sodium twice daily, and paracetamol (10 mg/kg) four times daily. All patients were discharged within 48 h of admission to our facility. Patients were followed up for 48 h by a nurse who was unaware of the study drug. Nausea, nausea score, emetic episode, rescue antiemetic drug requirements, complete response, patient satisfaction, and any complications were recorded at the following intervals: 0–4, 4–24, and 24–48. Nausea was defined as the subjective sensation of an urge to vomit in the absence of expulsive muscular movements [7]. Nausea was evaluated using the nausea visual analogue scale. Vomiting or emesis was defined as forcible expulsion through the mouth of the gastric contents [8], whereas retching was defined as an unproductive effort to vomit [7]. Retching and vomiting were collectively termed emetic episodes. Any attack of vomiting or nausea greater than score 5 was treated with rescue medication, metaclopramide 10 mg intravenously. Patients who did not respond to this initial treatment within 30 min were administered intravenous ondansetron (4 mg). If vomiting was still not controlled, patients were maintained on NPO as per the standard of care practices at our hospital. Patients who had neither emetic episodes nor rescue medication requirements were considered to have a complete response. The number of patients unable to be discharged or readmitted because of a severe attack of vomiting (persistent vomiting despite rescue regimen) was also recorded. All patients were interviewed 48 h after surgery to assess their satisfaction with the management of their PONV symptoms (using 100-point verbal rating scales, where 0 = poor and 100 = excellent). Adverse effects including headache, dizziness, myalgia, and constipation were recorded.

The primary outcome of this study was the incidence of PONV during the first 48 h postoperatively and the secondary outcomes were severity of nausea, need for rescue medication, adverse effects, and patient satisfaction.

Statistical analysis

On the basis of previous studies [1,9,10], the predicted incidence of PONV in this study was in the region of 70%. It was decided that a 30% reduction in the incidence of PONV in the P group would be clinically relevant. The α error was set at 0.05 (two sided) and the β error was set at 0.2 (power = 0.8). This analysis showed that 28 patients were necessary in each group. We assumed a dropout rate of 10%; thus, we increased the sample size to 31 patients per group. Statistical software package (Graph Pad In Stat, version 3.00 for Windows; Graph Pad Software Inc., San Diego, California, USA) was used for data analysis. Fisher's exact test, the unpaired *t*-test for parametric data, or the Mann–Whitney *U*-test for nonparametric data was used where appropriate. A *P*-value of less than 0.05 was considered statistically significant. Values were expressed as means (SD), median (IQR), or number (%).

Results

Sixty-two patients were enrolled in study; no patients were excluded. Patients' characteristics were comparable in the two groups (Table 1). During the periods between 0–4 h and 4–24 h, the incidence of nausea, emetic episodes, PONV, and the nausea score were significantly lower in group P compared with that in group C (Table 2). However, during a 24–48 h period, only the nausea score was significantly lower in group P (Table 2). The incidence of complete response was significantly higher in the patients in group P [26 patients (83.9%)] in comparison with group C [two patients (6.5%)] ($P<0.0001$). Patients in group P had higher satisfaction scores than those in group C ($P<0.0001$). There were no significant differences among both treatment groups in adverse effects (Table 3).

Discussion

PONV, defined as nausea and/or vomiting occurring within 24 h after surgery, affects between 20 and 30% of patients [11]; the incidence is further increased to 70–80% in high-risk patients [12]. The incidence of PONV after middle ear surgery without prophylactic antiemetic treatment is very frequent, varying from 62 to 80% [3,13]. The etiology of PONV is multifactorial; the main causes of PONV in this study likely included inhaled anesthetics, opioid analgesics, and vestibular stimulation caused by drilling and irrigating the bone adjacent to the inner ear. Traditional antiemetics, including anticholinergics (e.g. scopolamine), phenothiazines (e.g. promethazine), butyrophenones (e.g. droperidol), and benzamide (e.g. metoclopramide), are used for the prevention of PONV.

Palononsetron has been newly approved for the prevention of PONV since March 2008. It was compared with most 5-HT3 group drugs and versus placebo in high-risk surgeries. Palonosetron proved to be more effective than prophylactic therapy with granisetron for the long-term prevention of PONV after laparoscopic surgery [14]. Palonosetron also proved to be more effective than ondansetron for high-risk patients receiving fentanyl-based patient-controlled

Table 1 Demographic data and patient characteristics

Data	Group P ($n=31$)	Group C ($n=31$)
Age (years)	35.1 (8.8)	34.9 (8.8)
Sex (male/female) (*n*)	20/11	18/13
BMI (kg/m^2)	25.0 (3.6)	24.3 (3.8)
ASA class I/II	14/17	16/15
History of PONV	3 (9.7%)	4 (12.9%)
Smoking history	10 (32.3%)	13 (41.9%)
Motion sickness	1 (3.2%)	1 (3.2%)
Duration of surgery	123 (37)	129 (41)

Values are presented as mean (SD), or *n* (%).
PONV, postoperative nausea and vomiting.

Table 2 Incidence of postoperative nausea and vomiting and number of patients who required rescue medication

	Group P ($n=31$)	Group C ($n=31$)	*P*-value
During 0–4 h			
Vomiting	2 (6.4%)	16 (51.6%)	<0.001*
Nausea	4 (12.9%)	20 (64.5%)	<0.001*
PONV	5 (16.1%)	27 (87.1%)	<0.001*
Number of patients who received rescue drug	3 (9.7%)	20 (64.5%)	<0.001*
Maximum nausea score	0 (0–0)	3 (0–7.75)	<0.001*
During 4–24 h			
Vomiting	0 (0.0%)	4 (12.9%)	0.113
Nausea	1 (3.2%)	10 (32.3%)	0.006*
PONV	1 (3.2%)	11 (35.4%)	0.003*
Number of patients who received rescue drug	0 (0.0%)	6 (19.3%)	0.024*
Maximum nausea score	0 (0–0)	0 (0–3)	0.0043*
During 24–48 h			
Vomiting	0 (0.0%)	1 (3.2%)	1.000
Nausea	0 (0.0%)	5 (16.1%)	0.052
PONV	0 (0.0%)	5 (16.1%)	0.052
Number of patients who received rescue drug	0 (0.0%)	5 (16.1%)	0.052
Maximum nausea score	0 (0–0)	0 (0–0)	0.0334*

Values are presented as mean (SD), median (interquartile range) or *n* (%).
PONV, postoperative nausea and vomiting.
*Statistically significant at $P<0.05$.

analgesia after thyroidectomy, especially 2–24 h after surgery [15].

To our knowledge, the current study was the first to compare it against placebo in middle ear surgery. This study showed that palonosetron was more effective than placebo in decreasing the incidence of nausea and vomiting, and reducing the severity of nausea. The incidence of PONV was 16.1 versus 87.1% during the 0 to 4-h period, 3.2 versus 35.4% during the 4 to 24-h period, and 0 versus 16.1% during the 24 to 48-h period. Twenty-six (83.9%) patients achieved a complete response in the palonosetron group compared with only two patients (6.5%) in the control group.

In middle ear surgeries, granisetron has been shown to reduce the incidence of PONV to 17 versus 63% for the placebo group during the first 24 h postoperatively [16]. However, the study duration was limited only to 24 h as the half-life of granistron is 8–9 h. Ondansetron was reported to reduce both the proportion of patients with PONV from 53 to 20% ($P<0.05$) and of those who required droperidol rescue drug from 53 to 17% ($P<0.05$) [1]. Fujii *et al.* [13] concluded that, during the first 24 h after anesthesia (0–24 h), a complete response was achieved in 90% of patients who received ramosetron and in 86% of patients who received granisetron, whereas in the second 24 h after anesthesia (24–48 h), a complete response was achieved in 90 and 66% of patients, respectively. Oshima *et al.* [17] found that on prophylaxis with tandospirone (30 mg), a complete response was achieved in 67% of their patients.

One of the most prominent results was the effect of palonosetron on the nausea score, which was statistically significant throughout the study period. This finding is supported by the result of Kovac *et al.* [11], who studied

Table 3 Incidence of complications, number of patients with a complete response, and patient satisfaction score

	Group P ($n=31$)	Group C ($n=31$)	*P*-value
Headache	3 (9.7%)	5 (16.1%)	0.711
Dizziness	2 (6.4%)	1 (3.2%)	1.000
Constipation	2 (6.4%)	2 (6.4%)	–
Myalgia	3 (9.7%)	6 (19.3%)	0.472
Number of patients delayed to discharge	0 (0.0%)	2 (6.4%)	0.491
Number of patients readmitted	0 (0.0%)	0 (0.0%)	–
Complete response	26 (83.9%)	2 (6.5%)	<0.001*
Patient satisfaction score	90.2 (12.5)	52.4 (24.8)	<0.001*

Values are presented as mean (SD), or *n* (%).
*Significant difference.

the effect of palonosetron in patients undergoing elective gynecological or breast surgery.

In conclusion, palonosetron could provide effective prophylactic antiemetic control to prevent PONV after middle ear surgery under general anesthesia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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