Original Article

A randomized study to compare palonosetron with ondansetron for prevention of postoperative nausea and vomiting following middle ear surgeries

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Abstract

Background and Aims: Postoperative nausea and vomiting (PONV) has multifactorial etiology. It is a commonly encountered morbidity after anesthesia specially following middle ear surgery. Various antiemetic medications have been tried with mixed responses. Palonosetron is a newer 5-hydroxytryptamine (5-HT_3) receptor antagonist marketed for PONV prophylaxis. This study was designed to compare the efficacy of palonosetron and ondansetron in preventing PONV after middle ear surgeries.

Material and Methods: One hundred patients of ASA class 1 or 2, aged 18 years and above, weighing between 40 and 90 kg scheduled for elective middle ear surgeries were randomly assigned into palonosetron group ($n = 50$) and ondansetron group ($n = 50$). Palonosetron was administered in dose of 1 mcg/kg maximum up to 75 mcg and ondansetron in dose of 0.1 mg/kg maximum up to 8 mg. Intraoperative monitoring of QTc interval was also done to see any significant change after the antiemetic administration. The incidence of nausea, vomiting, and side effects were recorded over 2, 12, and 24 hours postoperatively. All parameters were compared between the two groups as mean ± standard deviation and as count (%). Two sided P values of <0.05 were considered significant.

Results: The incidence of PONV ($P = 0.002$), nausea ($P = 0.0002$) and vomiting ($P = 0.006$) was significantly lower in palonosetron group than in ondansetron group in 2- to 12-hour period. QTc interval prolongation, a known side effect of ondansetron was not found in palonosetron group intraoperatively.

Conclusion: Palonosetron was found to be superior to ondansetron up to 12 hours after the surgery with no significant effect on QTc interval.

Keywords: Middle ear surgery, ondansetron, palonosetron, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is a major concern in the recovery period. Electrolyte abnormalities, dehydration, tension on suture lines, esophageal rupture, subcutaneous emphysema, pneumothorax, and aspiration of gastric contents in compromised patients are the main concerns with excessive PONV. It can also lead to delayed patient discharge from postanesthesia care unit and prolonged length of hospital stay. The etiology and consequences of PONV are multifactorial. High incidence of emesis is observed (62%–80%) after middle ear surgery when no prophylactic antiemetic is given.[1,2] Various antiemetic drugs are available which include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (promethazine, prochlorperazine, and metoclopramide), antihistaminic drugs (diphenhydramine and hydroxyzine), 5-HT_3 receptor antagonists (ondansetron, granisetron, and dolasetron), and steroids (dexamethasone). Because of the multifactorial

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etiology of PONV, no single drug is 100% effective. The 5-HT_3 receptor antagonists are commonly used because they are shown to be more effective in PONV prevention and treatment than other antiemetics with fewer side effects.[3] Among them, ondansetron, granisetron, and ramosetron are commonly used. Palonosetron has been reported to be effective against chemotherapy-induced nausea and vomiting[4,5] and PONV.[6,7] Palonosetron has more potent receptor affinity and a long plasma half-life.[8,9] Elimination half-life of ondansetron in adults is 3.8 ± 1 hours,[10] whereas the mean elimination half-life following single intravenous administration of palonosetron is approximately 40 hours[11] making the antiemetic effect to last even 48 hours after administration. Also, it is shown to be more effective than ondansetron against nausea and vomiting in patients using anticancer drugs.[7] However, comparison of palonosetron with other 5-HT_3 receptor antagonists are sparse especially after middle ear surgery.

So, the study was undertaken to compare the antiemetic effects of intravenous ondansetron and palonosetron in patients undergoing middle ear surgeries and test whether palonosetron has a better profile in terms of nausea score, vomiting score, and postoperative nausea and vomiting score compared with ondansetron.

Material and Methods

The study was carried out at our tertiary care hospital over a period of 8 months from October 2014 to May 2015 after obtaining institutional approval from the hospital's Institutional review board and Ethics Committee. One hundred patients of American Society of Anesthesiologists physical status I or II, nonsmokers, aged 18 years and above, and weighing between 40 and 90 kg, scheduled for elective middle ear exploratory surgeries in the ENT department of the hospital were selected as participants. Exclusion criteria included patients with body weight >90 kg; known hypersensitivity to serotonin antagonists; history of motion sickness; history of PONV; pregnant patients; lactating mothers; patients with ongoing gastrointestinal disease; disorder of any major organ function like liver, lung, heart, or bone marrow. Patients who received chemotherapy in last few weeks, who were on antiemetics, psychotomimetics, or steroids preoperatively were also excluded.

Primary objective: Incidence of postoperative nausea and vomiting in the first 24 hours using three scoring systems (nausea score, postoperative vomiting score, and postoperative nausea and vomiting score) following the use of either of the two study drugs.

Secondary objective: Evaluation of QT interval change from intraoperative multipara monitor (Philips intellivue MP5) and postoperative ECG compared with the preoperative baseline ECG.

The preanesthetic regimen, anesthesia procedure, and surgical technique were kept standardized and uniform for all subjects. All the patients were allowed to take light and nonresidual diet in the evening of previous day of operation. All the patients were advised to remain fasting prior to surgery as per ASA Task Force guidelines for preoperative fasting. Intravenous (IV) fluid was started and the patients were premedicated with Inj. fentanyl 2 mcg/kg and patients were monitored throughout with routine monitoring and preoperative pulse rate, electrocardiogram (ECG), blood pressure (BP), and oxygen saturation were recorded.

One hundred patients were randomly divided into two groups of 50 each by computer-generated randomization list. Patients were blinded of allocated group and informed written consent was taken. The antiemetics used were palonosetron in Group A (n = 50): Inj. Palonosetron 1 mcg/kg (Themiset™, Themis Medicare) diluted up to 5 mL with normal saline solution and injected intravenously just before induction of anesthesia. In Group B (n = 50): Inj ondansetron 0.1 mg/kg (Emeset™, CiplaMed) maximum of 8 mg was injected intravenously at the time of skin closure.

Anesthesia was induced with Inj. Propofol (1%) 1.5-2 mg/kg given slow IV. Endotracheal intubation was facilitated by Inj. atracurium (0.5 mg/kg) IV and sevoflurane, air–oxygen mixture. Maintenance of anesthesia was done with intermittent positive pressure ventilation with 0.8–1.0 MAC of sevoflurane and intermittent boluses of Inj. Atracurium. Ventilation was adjusted to maintain end tidal carbon dioxide between 30-40 mmHg throughout the procedure. Paracetamol 15 mg/kg and diclofenac 1mg/kg were injected intravenously 20 minutes before completion of surgery (start of closure). Stomach decompression was done with an orogastric tube. Tracheal extubation and residual neuromuscular block was reversed with Inj. neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01 mg/kg. After tracheal extubation oxygen was administered at an FiO^2 of 1 for 5 minutes. Postoperative pain relief was achieved with injection paracetamol 15 mg/kg 8 hourly and injection diclofenac as rescue analgesic.

Pulse rate, ECG, BP, and oxygen saturation were monitored for 2 hours postoperatively. Intravenous fluids were infused postoperatively as per standard fasting guidelines till the patients were allowed to take orally.

The observations were recorded as per the following protocol on the proforma designed for the study which included:

1. Patient's demographic profile (age, weight, ASA physical status, type of surgery, duration of anesthesia, a proper history, and clinical examination)
2. Pulse rate, BP and oxygen saturation (SpO_2) were recorded prior to the induction
3. Intraoperative pulse rate, BP, and SpO_2 were recorded throughout the surgery and the mean was calculated
4. PONV were scored at 0, 2, 12, and 24 hours after completion of surgery [Table 1].

For the purpose of the study, an episode of PONV denotes a distinct spell of nausea, retching (an involuntary attempt to vomit but not actually productive of stomach contents), or vomiting (actual expulsion of stomach contents). Patients with complain of nausea, vomiting, or retching were administered injection prochlorperazine 12.5 mg as rescue antiemetic. Patients were monitored for adverse effects in PACU/recovery ward and this was recorded for 24 hours following surgery. A 12-lead ECG was repeated in the recovery to identify any QT changes in ECG in palonosetron group and preoperative ECG was used for comparison and intraoperatively also any QT prolongation was monitored using QT_c interval.

The sample size was determined using the following equation:

$$N = (Z\alpha/2 + Z\beta)2 \times (p1\ (1\text{-}p1) + p2\ (1\text{-}p2))/(p1 - p2)2$$

where
n = sample size for each group
$Z\alpha/2$ = critical value of 95% confidence interval = 1.96
$Z\beta$ = critical value of 80% power = 0.84

The sample size was taken as 50 in each group based on the observed incidence of PONV during 24 hours as 40% and 67% with palonosetron and ondansetron, respectively.

Descriptive analysis of parametric parameters is expressed as means and standard deviation and as count (%). Ordinal data were expressed as median and range. Tables were used to illustrate relationship of variables and comparisons made using the Student's *t*-test and Wilcoxon test, a *P* value of <0.05 was reported as statistically significant.

Results

No statistically significant difference was observed in the two groups with respect to age, weight, ASA grading ($P > 0.07$) [Table 2] and duration of anesthesia. The preoperative pulse rate, BP (systolic and diastolic), and SpO_2 were also comparable in both the groups.

The overall PONV score during 0–2 and 12–24 hours were comparable between the two groups with *P* value >0.05. However, the PONV score during 2–12 hours was lower in Group A compared with Group B [Table 3]. Postoperative nausea scores during 0–2 and 12–24 hours were not statistically significantly different between the two groups. The postoperative nausea score during 2–12 hours was higher in Group B as compared with Group A and this was found to be statistically significant with a *P* value <0.05 [Table 4]. Between 2- and 12-hour postoperative period, nausea score of 0 was present in 72% of Group A patients and 32% in Group B patients with *P* value <0.05. In 2- to 12-hour period postoperative vomiting score of 0 was present in 94% of Group A patients and 72% of Group B patients and the difference was statistically significant,

Table 1: Scoring systems used for nausea, vomiting and post operative nausea and vomiting (PONV)

Score	Nausea Score	Vomiting score	PONV score
0	None	None	No nausea/vomiting/retching/no antiemetics given
1	Mild intermittent nausea	One vomit only	Nausea
2	Constant moderate nausea	Several vomits	Retching
3	Severe nausea	Repeated retching/vomiting	Vomiting

Table 2: American Society of Anesthesiologists grading between the two groups

ASA Grade	Group A		Group B		*P*
	Frequency	%	Frequency	%	
I	27	54	18	36	0.070
II	23	46	32	64	
Total	50	100	50	100	

Table 3: Post-operative nausea and vomiting score

Overall PONV score		Group A		Group B		*P*
		Frequency	%	Frequency	%	
0-2 h	0	37	74	36	72	0.82
	1	10	20	7	14	0.43
	2	0	0	3	6	0.24
	3	3	6	4	8	1
	Total	50	100	50	100	
2-12 h	0	35	70	17	34	<0.05
	1	12	24	17	34	0.27
	2	0	0	0	0	
	3	3	6	16	32	<0.05
	Total	50	100	50	100	
12-24 h	0	46	92	44	88	1
	1	4	8	5	10	1
	2	0	0	0	0	
	3	0	0	1	2	
	Total	50	100	50	100	

whereas for 0- to 2-hour and 12- and 24-hour period, it was not statistically significant [Table 5]. There was higher incidence of retching in Group B (14%) than in Group A in 2- to 12-hour period and this was statistically significant. Frequency of inj. prochlorperazine 12.5 mg was more in Group B than in Group A patients in 2- to 12-hour period with *P* value of 0.004 [Table 6]. There was, however, no statistical difference between the two groups. The frequency of adverse effects, such as dizziness, drowsiness, and constipation, was comparable in both the groups. No significant changes in QT_C interval [Table 7] was observed in the palonosetron group in the perioperative period.

Discussion

The reported incidence of nausea in the postoperative period is 22%–38% and the incidence of vomiting is 12%–26%.[11]

Table 4: Nausea score

Postoperative nausea score		Group A		Group B		*P*
		Frequency	%	Frequency	%	
0-2 h	0	41	82	35	70	0.16
	1	8	16	8	16	1
	2	1	2	7	14	0.06
	3	0	0	0	0	
	Total	50	100	50	100	
2-12 h	0	36	72	16	32	<0.001
	1	12	24	17	34	0.27
	2	2	4	17	34	<0.05
	3	0	0	0	0	
	Total	50	100	50	100	
12-24 h	0	44	88	44	88	1
	1	6	12	6	12	1
	2	0	0	0	0	
	3	0	0	0	0	
	Total	50	100	50	100	

Table 5: Postoperative vomiting score

Postoperative vomiting score		Group A		Group B		*P*
		Frequency	%	Frequency	%	
0-2 h	0	47	94	45	90	0.72
	1	2	4	5	10	0.44
	2	1	2	0	0	1
	3	0	0	0	0	
	Total	50	100	50	100	
2-12 h	0	47	94	36	72	<0.05
	1	3	6	8	16	0.2
	2	0	0	6	12	0.03
	3	0	0	0	0	
	Total	50	100	50	100	
12-24 h	0	50	100	49	98	1
	1	0	0	1	2	1
	2	0	0	0	0	
	3	0	0	0	0	
	Total	50	100	50	100	

In susceptible individuals, the incidence of PONV can be as high as 60%–70%.[12] Apfel *et al.*[2] identified four risk factors (female gender, history of PONV and motion sickness, nonsmoker, and predicted opioid use) that form the basis for the Apfel scoring system. Each risk factor increases the likelihood of PONV by 18%–22%. Identification of baseline risk using the Apfel criteria is important, since an increase in risk factors increases the number of subsequent therapies required. These receptors are situated on the nerve terminals of the vagus nerve in the periphery and centrally on the chemoreceptor trigger zone (CTZ) located in the area postrema. The vomiting reflex is set into motion by anesthetic agents via stimulation of the central $5\text{-}HT_3$ receptors on the CTZ and peripherally of the $5\text{-}HT_3$ receptors on vagus nerve afferent fibers by releasing serotonin from the enterochromaffin cells of the small intestine.[13,14] The recently introduced palonosetron is a potent $5\text{-}HT_3$ receptor antagonist and unique structurally, pharmacologically, and clinically. It has a greater binding affinity and longer half-life than older $5\text{-}HT_3$ antagonists like ondansetron.[6] Palonosetron also interacts with $5\text{-}HT_3$ receptors in an allosteric, positively cooperative manner at different sites than ondansetron and granisetron.[15]

The overall PONV score and nausea score during 0–2 and 12–24 hours were comparable between the two groups in our study. However, the PONV score and nausea score during 2–12 hours was higher in ondansetron group compared with palonosetron group with 35 patients (70%)

Table 6: Rescue antiemetic used

Rescue antiemetic used		Group A		Group B		*P*
		Frequency	%	Frequency	%	
0-2 h	No	45	90	42	84	0.37
	Yes	5	10	8	16	
	Total	50	100	50	100	
2-12 h	No	42	84	29	58	<0.05
	Yes	8	16	21	42	
	Total	50	100	50	100	
12-24 h	No	49	98	46	92	0.36
	Yes	1	2	4	8	
	Total	50	100	50	100	

Table 7: Comparison of QTc interval

QTC interval	Group A		Calculated from baseline	
	n	Mean±SD	Mean difference	*P*
0 h	50	429.28±18.60		
1 h	50	433.82±21.21	4.54±16.98	0.065
2 h	42	432.74±21.83	4.50±14.84	0.056
3 h	24	429.37±25.36	3.75±15.43	0.246
4 h	4	449.0±57.0	24.50±28.12	0.180
5 h				
Post op	50	431.30±19.97	431.30±13.24	0.286

complaining of PONV in ondansetron group compared with 17 patients (34%) in palonosetron group (*P*-value <0.05 for PONV score, nausea score, and vomiting score). The comparable PONV and nausea score between 12 and 24 hours observed in our study may be due to the decrease in the number of risk factors for PONV that the patient was exposed to during that period such as washout of anesthetic agents and metabolism of opioids used in PACU/recovery room, absence of surgical stimuli, and use of nonemetogenic drugs like paracetamol and diclofenac for pain relief. One more reason may be the use of prochlorperazine 12.5 mg as rescue analgesic (29 in ondansetron group and in 13 patients in the palonosetron group). Probably, following administration of prochlorperazine, the PONV scores became comparable in both the groups in the 12- to 24-hour time zone. Moon *et al*. in 2012[16] reported in their study on thyroidectomies that the incidence of PONV during the 24-hour postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%), which correlated well with our study. No differences were observed between the groups in their study also during the first 2 hours postoperatively as in our study. In our study, the frequency of vomiting in ondansetron group was higher than the palonosetron group (28% vs 6%) during 2- to 12-hour follow-up and no vomiting episodes occurred in 94% of patients in palonosetron group, while it did not occur in 72% of patients in ondansetron group in 2- to 12-hour period and the difference was found to be statistically significant. However, same findings were not observed during the 0- to 2-hour and 12- to 24-hour follow-up periods except in the incidence of nausea, which was 68% in ondansetron group vs 28% in palonosetron group. As far as retching was concerned, it was not present in any patient in palonosetron group, whereas in ondansetron, it was observed in 14% subjects. The reason for the difference in effectiveness between the two drugs is believed to be related to the half-lives (ondansetron 3–5 vs palonosetron 40 hours) and the binding affinities to 5-HT_3 receptors. Both the manner as well as the sites of binding of palonosetron with 5-HT_3 receptors is different from that of ondansetron. In a similar study by Rao *et al*.,[17] palonosetron was found to be superior than ondansetron in middle ear surgeries. However, they used a fixed and low dose of ondansetron and that too before induction of anesthesia. We injected ondansetron at the end of the surgery in view of its shorter half-life and we used a per kg body weight dosing (maximum 8 mg). The timing of administration of the antiemetic drug ondansetron has been long debated. The manufacturers recommend administration before induction, the relative short half-life (3.5-4 hours) of ondansetron may decrease its antiemetic activity in surgical cases lasting more than 2 hours. Our mean surgical duration being around two and a half hours, and the fact that Palonosetron has a longer half-life; hence, it was administered at the time of induction and Ondansetron at the time of skin closure. The significant difference in PONV characteristics in both groups in later recovery period indicates the superior efficacy of palonosetron in long-term prophylaxis. Palonosetron was similarly evaluated and found to be favorable for prevention of PONV in middle ear surgeries by Mohamed and Michel[18] in a double-blind placebo-controlled study. Basu A *et al*.[19] compared palonosetron, granisetron, and ondansetron in middle ear surgeries. They found a single dose of palanosetron is a superior antiemetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in prevention of PONV during the first 24-hour period. Sun *et al*. observed that ondansetron (4 mg IV) was more effective in reducing the need for rescue antiemetics in the recovery room when administered at the end versus prior to the start of otolaryngologic surgery.[20] The sustained antinausea effect of palonosetron in late recovery period as compared with those in ondansetron group is of importance as this prolonged antinausea property of palonosetron assumes particular significance in day-surgery patients and for those who wish to return to their normal activities early. The frequency of adverse effects, such as headache, drowsiness, constipation, etc., was not statistically significant between the two groups confirming the fact that palonosteron has similar safety profile to other 5-HT_3 antagonists except for headache which was more in ondansetron group (26%) than palonosetron group (8%), and none of the adverse effects were clinically serious and resolved on its own during follow-up period. However we feel that in the setting of general anesthesia, it is presumptuous to attribute complaints of headache, dizziness, and sedation in the postoperative period to any particular drug.

5-HT_3 antagonists are known to prolong QT_C interval and predispose to arrhythmias.[21] We measured the QT_C duration in palonosetron group and no significant change in preoperative and postoperative QT_C interval was noted. None of the 50 patients in the palonosetron group showed ECG changes after administration of the drug that correlates with the study conducted by Kim *et al*., who studied the effect of Palonosetron on the QTc interval in patients undergoing sevoflurane anesthesia.[22]

The cost effectiveness of therapy is one of the primary considerations in PONV prophylaxis. The decision about whether or not to use PONV prophylaxis or to just treat patients with established symptoms depends on the efficacy of the drug, baseline risk for PONV, adverse effects of the antiemetics, and drug acquisition costs. Probable single dosing of palonosetron due to its long duration of action and better potency is more reasonable than multiple doses required with ondansetron.

Conclusion

Postoperative nausea and vomiting is an undesirable manifestation of the recovery period. Following middle ear surgery, the incidence can be as high as 80%. In our study, palonosetron was found to be superior to ondansetron for PONV prophylaxis after middle ear surgery. It has similar safety profile and longer duration of action than ondansetron. Palonosetron with its single dose regimen can reduce the need for multiple injections in postoperative period as with Ondansetron and can prove to be cost effective in the long run.

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Conflicts of interest
There are no conflicts of interest.

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