Palonosetron versus ondansetron for prevention of postoperative nausea and vomiting during middle ear surgery: a double-blind, randomized, comparative trial

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Objective
The aim of the study was to assess the efficacy and safety of palonosetron versus ondansetron for postoperative nausea and vomiting during middle ear surgery.

Patients and methods
This study was conducted on 60 patients, ASA I and II, ages ranging between 23 and 48 years, scheduled for middle ear surgery; they were randomly allocated into two equal groups: group 1 received ondansetron (4 mg) intravenously and group 2 received palonosetron (0.25 mg) intravenously. All medications were given over 30 s immediately before induction of general anesthesia. The duration of surgery, hemodynamic parameters, the severity and frequency of nausea, retching, and vomiting, time to recovery, and time to discharge of all patients were recorded. The patient's requests for rescue antiemetics and details of adverse events throughout the study were recorded.

Results
A total of 28 patients in group 2 and 22 patients in group 1 had complete response to antiemetic drugs. No patient in group 2 needed rescue antiemetic, whereas four patients in group 1 received ondansetron (4 mg) as rescue. With respect to the severity of nausea, group 2 showed significant decrease in nausea score in comparison with group 1. With respect to the complications, four patients in group 2 and one patient in group 1 developed headache. One patient in group 2 had diarrhea.

Conclusion
Palonosetron is a good antiemetic alternative during anesthesia with minimal side effects.

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

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Introduction

Besides postoperative pain, postoperative nausea and/or vomiting (PONV) is the most frequent and most unpleasant adverse outcome of surgery and general anesthesia. It occurs in 20–30% of patients [1]. Moreover, from the patient's point of view, the anesthetist is clearly responsible for this 'big little problem' during the early postoperative period [2].

Although many scientific clinical studies have been conducted in recent years to overcome this problem, a global panacea for its total prevention has not been found.

One of the approaches to manage PONV is the clinical use of serotonin (5-HT3) receptor antagonists, which represent a new antiemetic drug class with improved efficacy, prolonged action, and reduced side effects. 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema of the medulla oblongata [3].

Ondansetron was the first serotonin antagonist, and its introduction was a milestone in the prevention of nausea and vomiting. It was considerably more effective and had fewer side effects (no extrapyramidal symptoms or sedation) compared with other types of antiemetics [4].

Palonosetron is a selective serotonin subtype-3 (5-HT3) receptor antagonist with a strong binding affinity. It is used to prevent nausea and vomiting caused by cancer chemotherapy. In addition, it was granted FDA approval in March 2008 for the prevention of PONV during the period up to 24 h after surgery [5,6].

The aim of this study was to assess the efficacy and safety of palonosetron versus ondansetron for PONV during middle ear surgery (MES).

Patients and methods

This study was conducted in Benha University Hospital after its ethical committee approval and

patient's informed written consent. This prospective, randomized, double-blind comparative study was conducted on 60 patients, ASA I and II scheduled for MES (tympanoplasty or mastoidectomy). Patients with hypokalemia or hypomagnesemia, patients receiving diuretics or antiarrhythmic drugs, patients with prolonged QT interval syndrome, pregnant or lactating women, patients who had gastrointestinal diseases, those who had a history of motion sickness and those who had taken antiemetic within 24 h before surgery, and patients known to have hypersensitivity to one of the used drugs were excluded from the study.

Patients were randomly allocated by using a computer-generated random number table into two equal groups:

Group 1 (the ondansetron group) (30 patients) received ondansetron (4 mg) intravenously in 10 ml normal saline over 30 s immediately before induction of general anesthesia.

Group 2 (the palonosetron group) (30 patients) received palonosetron (Aloxi; MGI Pharma, Helsinn Healthcare) 0.25 mg intravenously in 10 ml normal saline over 30 s immediately before induction of general anesthesia.

All patients received general anesthesia, which was induced using propofol (2 mg/kg) intravenously, fentanyl (2 μg/kg). After good preoxygenation, endotracheal intubation was facilitated using rocuronium bromide (0.5 mg/kg). Anesthesia was maintained with isoflorane 1.5%; top up doses of rocuronium were used as required and reversed with neostigmine (0.04–0.08 mg/kg) and atropine (0.1–0.2 mg/kg). Following extubation, the patients were maintained on supplemental O_2 until awake in the recovery room. The duration of surgery (which is the time initiated from induction of general anesthesia until skin closure) was recorded. Hemodynamic parameters (heart rate, NIBP, and SpO_2) were recorded every 15 min throughout the procedure until the end of surgery and every 1 h for 6 h postoperatively.

Time to recovery (which was the time initiated from extubation until the patient transfer to postoperative care unit) and time to discharge to ward (which was the time initiated from patient arrival to postoperative care unit until patient discharge to ward based on the modified Aldrete score) were also recorded.

Ventilation parameters were tidal volume of 7 ml/kg, respiratory rate of 12/min, and peak inspiratory pressure of 30 cmH_2O. End-tidal CO_2 was maintained between 30 and 40 mmHg. Heart rate and mean blood pressure was maintained within 20% of the preoperative level. Standard monitors (ECG, SpO_2, end-tidal CO_2, and NIBP) were applied. The patients received lactated Ringer's solution at a rate of 10 ml/kg/h during anesthesia and 2 ml/kg/h after anesthesia until patients tolerated oral fluids.

At the end of the procedure, the severity and frequency of nausea, retching, and vomiting in all patients were recorded for 24 h.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit.

Retching was defined as the labored spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents.

Vomiting was defined as the forceful expulsion of gastric contents from the mouth.

The intensity of nausea was measured using a categorical verbal rating scale [7], in which 0 = nil, 1 = mild, 2 = moderate, and 3 = severe nausea. Vomiting and retching were graded as follows: 0 = no vomiting or retching and 1 = vomiting or retching.

Complete response, which was the primary outcome, was defined as percentage of patients who did not experience postoperative nausea, retching, and vomiting or who did not request rescue antiemetic. In addition, the patient's requests for rescue antiemetics were recorded for analysis. Details of adverse events throughout the study were recorded.

Statistical analysis

Sample size was calculated according to the primary outcome (patients with complete response). Statistical analysis was performed using SPSS version 16. Quantitative data were presented as mean and SD. Qualitative data were presented as number and percentages. Tests used were the Student's *t*-test for analysis of age, weight, duration of surgery, time to recovery, time to discharge, and nausea score and the χ^2-test for analysis of the rest of parameters. *P*-value less than 0.05 was considered significant. *P*-value less than 0.01 was considered highly significant.

Results

Demographic characteristics and operative details showed nonsignificant difference between groups with respect to age, sex, weight, duration of surgery, and type of surgery (Table 1).

Hemodynamic parameters showed nonsignificant difference between the groups (Figs 1–3).

Regarding patients with complete response (no nausea, retching, or vomiting), 28 patients in group 2 and 22 patients in group 1 had complete response to antiemetic drugs, which is statistically significant ($P < 0.05$). No patient in group 2 received rescue antiemetic, whereas four patients in group 1 received ondansetron (4 mg) as rescue, which is statistically significant ($P < 0.05$) (Table 2).

With respect to the severity of nausea, group 2 showed significant decrease in nausea score in comparison with group 1 (Fig. 4).

Time to recovery showed nonsignificant difference between groups, whereas time to discharge to ward showed a significant decrease in group 2 in comparison with group 1 ($P = 0.04$) (Table 3).

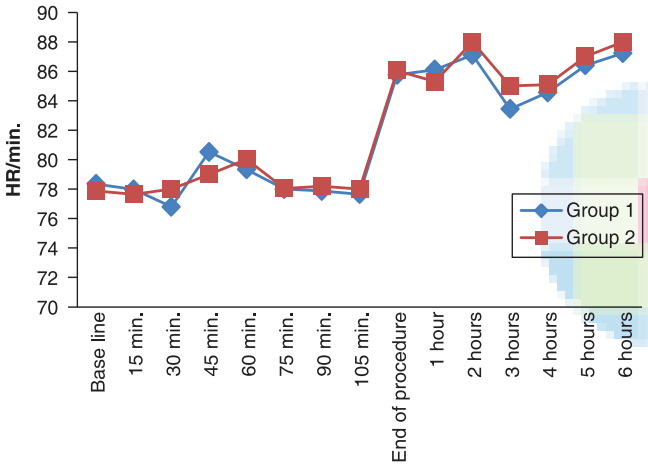
With respect to the complications, four patients in group 2 and one patient in group 1 developed headache. However, it was mild, transient, and did not need treatment. One patient in group 2 suffered from

Table 1 Demographic characteristics and operative details

	Group 1	Group 2	Test	*P*-value
Age (years)	33.93 ± 7.93	34.16 ± 6.24	$t = 0.12$	0.9
Sex (male : female)	13 : 17	15 : 15	$\chi^2 = 0.26$	0.6
Weight (kg)	73.87 ± 13.89	75.03 ± 12.09	$t = 0.34$	0.73
Duration of surgery (min)	107.7 ± 11.8	109.6 ± 16.91	$t = 0.5$	0.61
Type of surgery [*n* (%)]				
Tympanoplasty	14 (46.6)	12 (40)	$\chi^2 = 0.27$	0.6
Mastoidectomy	16 (53.4)	18 (60)		

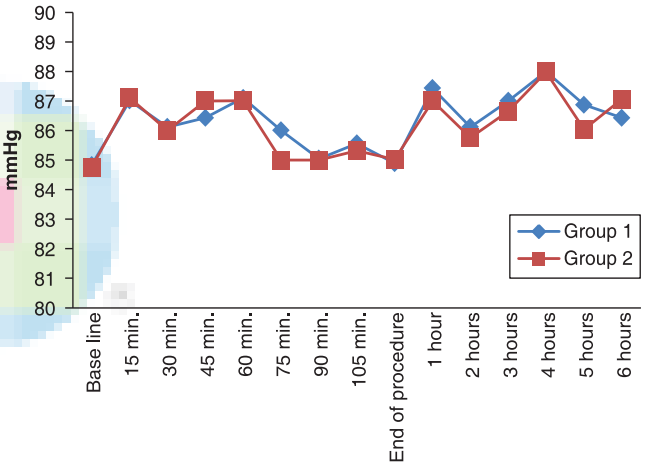
Data were represented as mean ± SD for age, weight, and duration of surgery and as numbers for sex and type of surgery.

Figure 1



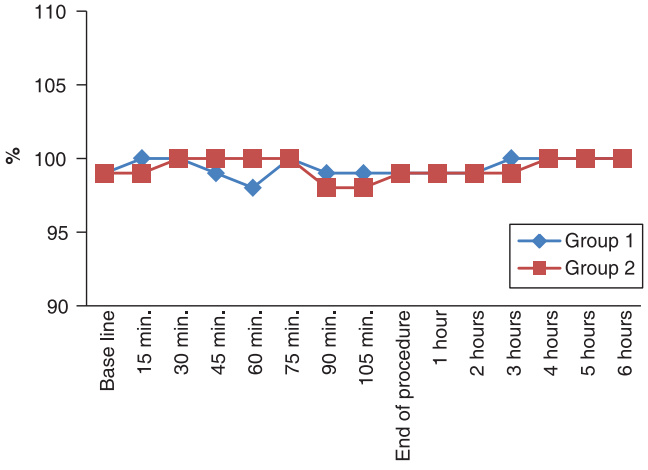
Heart rate (HR).

Figure 2



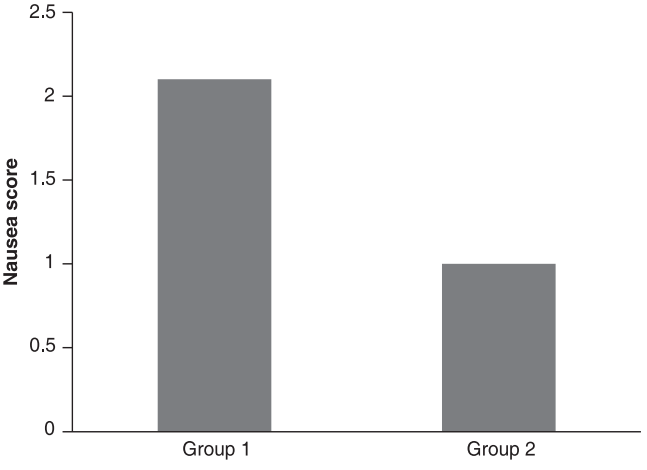
Mean arterial blood pressure.

Figure 3



O_2 saturation.

Figure 4



Mean postoperative nausea score in the studied groups.

Table 2 Comparison between groups with respect to nausea and vomiting

	Group 1	Group 2	χ^2	*P*-value
Complete response	22 (73.3)	28 (93.3)	4.32	0.037*
Nausea	5 (13.3)	2 (6.7)	1.45	0.22
Retching	1 (3.3)	0 (0)	1.01	0.32
Vomiting	2 (6.7)	0 (0)	2.67	0.1
Rescue	4 (13.3)	0 (0)	4.28	0.038*

Data were represented as [*n* (%)]; *Significant *P*-value.

Table 3 Time to recovery and time to discharge

	Group 1	Group 2	*t*-test	*P*-value
Time to recovery (min)	14.7 ± 4.5	13.8 ± 5.1	0.72	0.47
Time to discharge to ward (min)	42.3 ± 10.9	37.1 ± 8.5	2.06	0.04*

Data were represented as [*n* (%)]; *Significant *P*-value.

diarrhea, which was also mild, transient, and required no treatment.

Discussion

Nausea and vomiting are the second most common complaints reported (pain is the most common) [8]. After the landmark 1992 review from Watcha and White [9], PONV became the more commonly used clinical term, and, in 1999, PONV became a medical subject heading in the National Library of Medicine [10]. Prevention of PONV significantly improves patient outcome [11]. Although PONV is generally self-limited, it may lead to rare but serious complications, such as aspiration of gastric contents, suture dehiscence, esophageal rupture, subcutaneous emphysema, or pneumothorax [12,13]. It also may prolong hospital stay time [14].

The incidence of PONV among patients undergoing MES or stapedectomy is frequently high. The etiology of PONV after MES performed under general anesthesia is not known, but it is probably multifactorial [15]. Several factors including age, sex, and obesity, history of motion sickness and/or previous PONV, menstruation, surgical procedure, anesthetic technique, and postoperative pain are considered to affect the incidence of PONV [16]. These factors were either well balanced between groups or excluded in the present study; therefore, the difference in complete response (no nausea, no rescue antiemetic) between the groups may be attributed to the differences in the antiemetic study drugs administered.

In the present study, study drugs were injected immediately before induction of general anesthesia depending on data provided by Gross *et al.* [17] who compared between early versus late intravenous administration of a single prophylactic dose of tropisetron and found that it has no impact on the incidence of PONV during the first 48 h after tonsillectomy and/or adenoidectomy in children.

The hemodynamic variables throughout the study were not allowed to decrease less than 20% of the preoperative level. In addition, there was no hypoxemia or hypercapnia throughout the study period, as these are risk factors to induce PONV. This is in agreement with the study by Golembiewski *et al.* [18] who reported that, in high-risk patients for PONV, it is important to reduce the patient's risk by ensuring good intravenous hydration, avoiding hypotension, and providing effective analgesia. In addition, Maharaj *et al.* [19] found that preoperative correction of intravascular volume deficits effectively reduces PONV in high-risk patients and recommended the preoperative administration of 2 ml/kg of compound sodium lactate for every hour of fasting to patients with an increased PONV risk.

Ondansetron (4 mg) was used in the present study for prevention of PONV. Several studies have demonstrated that ondansetron (4 mg) is as effective as 8 mg [20–22]. In addition, Tramer *et al.* [23] compared intravenous ondansetron 1, 4, or 8 mg with placebo in 2812 male and female patients in three different studies. The combined results showed that ondansetron (4 mg) was the optimal dose for treating established PONV.

The recommended dosage of palonosetron is 0.25 mg administered as intravenous single dose. This dose was recommended by Siddiqui and Scott [24]. They found that intravenous palonosetron (0.25 mg) was more effective than intravenous ondansetron (32 mg) in producing a complete response (no emesis, no use of rescue medication) during acute (0–24 h) or delayed (24–120 h) phases, and it was similar to intravenous dolasetron (100 mg) during acute phase but more effective during delayed phase.

In addition, recently approved by the FDA, palonosetron (0.25 mg) intravenously is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy [25].

In the present study, we compared palonosetron versus ondansetron for prevention of PONV during MES, and we recommended palonosetron as a good antiemetic alternative during the postoperative period with minimal adverse effects. This study is in agreement with the study by Yang and Scott [26] who documented that intravenous palonosetron is

indicated for the prevention of PONV in the first 24 h following surgery and found that intravenous palonosetron was noninferior to intravenous ondansetron (with statistically greater efficacy than ondansetron) or dolasetron, and they recommended that intravenous palonosetron is a useful alternative to currently recommended agents in PONV prevention. In addition, Rubenstein [25] documented the superiority of palonosetron over ondansetron and dolasetron in the prevention of both acute and delayed chemotherapy-induced nausea and vomiting. In addition, our results agreed with those of Siddiqui and Scott [24] who documented that intravenous palonosetron was generally well tolerated in clinical trials, with few adverse events being treatment related.

Conclusion

Palonosetron is a good antiemetic alternative during anesthesia with minimal side effects.

Acknowledgements

Conflicts of interest

None declared.

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