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ORIGINAL ARTICLE

A COMPARATIVE STUDY BETWEEN PALONOSETRON AND GRANISETRON TO PREVENT POSTOPERATIVE NAUSEA AND VOMITING AFTER MIDDLE EAR SURGERY

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ABSTARCT: BACKGROUND: The reported incidence of postoperative nausea and vomiting (PONV) following middle ear surgery is very high. Various treatment modalities have been tried by several workers with varying results. In this randomized double blind prospective clinical study, we investigated and compared the efficacy of palonosetron and granisetron to prevent postoperative nausea and vomiting after middle ear surgery. **MATERIAL AND METHODS:** Sixty patients (18-65 yrs. of age) undergoing elective middle ear surgery were randomly allocated one of the two groups containing 30 patients each. Group A received granisetron 2.5mg and Group B received palonosetron 75µg intravenously as a bolus 10 min before extubation. Peri-operative anesthetic care was standardized in all patients. The efficacy of study medication was assessed in terms of Complete Response (No emesis and no rescue antiemetic), incidence of emetic episodes and the incidence nausea in the postoperative study periods at 0-3 hours, 3-12 hours, 12-24 hours and 24-48 hours. **RESULT:** The incidence of a complete response (No PONV, No rescue medication) during 0-3 hour in the post-operative period was 86.6% with granisetron and 93.3% with palonosetron, the incidence during 3-12 hour postoperatively was 83.3% with granisetron and 93.3% with palonosetron. The corresponding incidence in 12-24 hour was 90% with palonosetron and 80%with granisetron group. During 24-48 hours, the incidence was 63.3% and 93.3% respectively ($p<0.05$). The incidences of adverse effects were statistically insignificant between the groups. **CONCLUSION:** Prophylactic therapy with palonosetron is more effective than granisetron for long term prevention of postoperative nausea and vomiting after middle ear surgery.

KEYWORDS: Palonosetron, Granisetron, Postoperative Nausea and Vomiting (PONV), Middle ear surgery.

INTRODUCTION: Post-operative nausea and vomiting (PONV) are frequent and unpleasant symptoms following general anaesthesia. Some patients view PONV as being more debilitating than operative procedure itself. This complication is not only unpleasant and aesthetically distressing to patient and their caregivers but when severe may be associated with dehydration, electrolyte imbalance, and delayed discharge particularly after day care surgery. Persistent PONV can cause tension on suture line, venous hypertension, increase bleeding under skin flaps, esophageal rupture and even expose patient to increase risk of pulmonary aspiration if airway reflexes are depressed due to residual anaesthetic dosage in body.[1] All the above factors will increase overall morbidity of patient, increase unplanned hospital admissions, increase medical complications, require more healthcare professional time, and unanticipated & longer hospital stay thus increasing direct cost of emesis & expanding total health care cost. This is why, we as a perioperative physicians need to anticipate, prevent and treat PONV especially in day care surgeries by prophylactic administration of antiemetics.

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The overall incidence of PONV is reported to be between 20-30%, but it can increase up to 80% in high risk patients.[2] Over the years, there has been considerable reduction in the incidence of PONV with the introduction of antiemetic prophylaxis like anti-cholinergics (Scopolamine), anti-histaminics (Diphenhydramine, cyclizine, promethazine, prochlorperazine), butyropheneones (Droperidol), and benzamide (Metoclopramide). However, these agents may cause undesirable adverse effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, extrapyramidal symptoms, and dysrhythmogenic effects such as prolong QT interval with droperidol.[3]

Granisetron is currently one of the commonly used drug for prevention of postoperative nausea and vomiting in adults. It is a highly selective and potent 5-HT_3 receptor antagonist.[4] It acts specifically at 5-HT_3 receptors on the vagal afferent nerves of the gut. Granisetron produces irreversible block of the 5-HT_3 receptors and it may account for the long duration of this drug. It has minimal side effects like headache, constipation and rare hypersensitivity reactions.[5,6] Palonosetron have emerged as alternative for postoperative nausea and vomiting in adults.

This drug has unique 5-HT_3 receptor antagonist, has a greater binding affinity and longer half-life than older 5-HT_3 antagonists like ondansetron. We therefore conducted a prospective, randomized, double blind comparative study to compare the efficacy and adverse effects of injection granisetron 2.5mg with palonosetron 75µg to prevent postoperative nausea and vomiting in patients undergoing general anaesthesia for elective middle ear surgeries.

METHODS: After obtaining approval from the institutional ethics committee and written informed consent, we conducted a randomized double blind study in sixty ASA I or II patients aged 18–65 years, undergoing middle ear surgery (Tympanoplasty and Mastoidectomy) under general anaesthesia. Patients who had gastrointestinal disease, smokers, and had history of motion sickness and/or PONV and those who had taken antiemetic medication within last 24 hours were excluded from the study.

All patients were randomly assigned in two groups (30 patients each) —Group A received Granisetron (2.5mg), group B received Palonosetron (75µg). These drugs were administered intravenously towards the end of surgery and before reversal of anaesthesia in same volume, i.e. 5ml. A randomization list was prepared by a random number function in a computer spreadsheet and identical syringes containing each drug were prepared by personnel not involved in this study.

All patients were kept fasting after midnight and received no preanaesthetic medication. On the operation table, routine monitoring (ECG, pulse oximetry, NIBP,) were started and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO2) were recorded. An intravenous line was secured.

Anaesthesia was induced with midazolam 1mg, pentazocin 0.5mg kg-1 and thiopentone sodium 5mg kg-1 IV. Vecuronium bromide 0.8mg kg-1 was used to facilitate tracheal intubation.

Anaesthesia was maintained with 40: 60 mixture of oxygen and nitrous, 0.8 -1 MAC isoflurane. Controlled mechanical ventilation was adjusted to maintain ETCO2 pressure between 30-35mmHg. Muscle relaxation was achieved with vecuronium as required. The study drug was given 30min before the reversal of anaesthesia. At end of surgical procedure, all anaesthetic agents were discontinued and the patients were ventilated with 100% oxygen. Residual neuromuscular blockade was antagonized with neostigmine 0.5kg-1 and glycopyrrolate 0.1mg kg-1 body weight and the trachea was extubated when the patient became awake.

For postoperative analgesia, diclofenac transdermal patch was applied on body surface. All patients were observed postoperatively by resident doctors who were unaware of the study drug.

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Patients were transferred to postanaesthesia care unit and blood pressure, heart rate and oxygen saturation were monitored. All episodes of PONV (Nausea and vomiting) were recorded for 0-3 hour in postanaesthesia care unit and from 3-48 hour in postoperative ward (0–3, 3–12, 12–24, and 6–24 hrs).

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents from mouth. Complete response (Free from emesis) was defined as no PONV and no need for any rescue medication. Rescue medication was given to all patients who had demanded rescue for their nausea & for any episode of vomiting, injection metoclopramide 10mg was given intravenously. Rescue was not repeated till thirty minutes once given.

Statistical analysis was done using SPSS statistics package version 17 and are presented in a tabulated manner. Comparisons between groups were performed by using the Kruskal Wallis one way ANOVA by ranks or Fisher's exact test for small sample with a 5% risk or Mann - Whitney - Wilcoxon tests when normality tests failed or Chi-square test, as appropriate. The results were expressed in mean±SD and number (%).

RESULT: There was no significant difference in the age, sex distribution of the patients of both the groups, and duration of anesthesia or operation between two groups (Table 1). The incidence of a complete response (No PONV, no rescue medication) during 0-3 hour in the postoperative period was 86.6% with granisetron and 93.3% with palonosetron, the incidence during 3-12 hour postoperatively was 83.3% with granisetron and 93.3% with palonosetron. The corresponding incidence in 12-24 hour was 90% with palonosetron and 80%with granisetron group. During 24-48 hour, the incidence was 63.3% with granisetron and 93.3% with palonosetron (Table 2). Thus regarding complete response during 0-24 hour in the postoperative period, there was no significant difference between patients who had received granisetron and those who had received palonosetron (P>0.05) (Table 2). But during 24-48hour, a complete response was significantly more in patients of group B than in patients of group A (P<0.05) (Table 2). The commonly observed adverse effects were headache and dizziness but those were not clinically serious or significant. The incidences of adverse effects were statistically insignificant between the groups (Table 3)

Variables Mean±SD	**Group A**	**Group B**	**P value**
Age(y) ± SD	34.10±8.372	32.53±6.668	0.426
Weight(kg) ± SD	54.73±4.906	53.87±4.754	0.490
SEX M/F	18/12	21/9	0.897
ASA (I/II)	27/3	26/4	0.688
SURGERY			
Tympanoplasty	8	10	0.788
Mastoidectomy	22	20	0.899
Duration of surgery (min)	154.7 ± 63.4	151.7 ± 64.09	0.922
Duration of anaesthesia (min)	184.44 ± 65.8	181.5 ± 66.55	0.965
Values are expressed as mean ± SD; * Significance (p<0.05)			

Table 1: Patient demographic data and operative characteristics

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Parameter	Group A (n=30)	Group B (n=30)	P Value
0-3hr			
Complete response	26(86.63)	28(93.3%)	0.578
Nausea	2(6.7%)	2(6.7%)	1
Emetic episode	5(16.7%)	2(6.7%)	0.288
Rescue antiemetics	5(16.7%)	2(6.7%)	0.288
3-12hr			
Complete response	25(83.3%)	28(93.3%)	0.13
Nausea	4(13.3%)	2(6.7%)	0.67
Emetic episode	3(10%)	1(3.3%)	0.55
Rescue antiemetics	2(3.3%)	1(3.3%)	0.45
12-24hr			
Complete response	24(80%)	27(90%)	0.27
Nausea	3(6.7%)	1(3.3%)	0.55
Emetic episode	3(10%)	1(3.3%)	0.55
Rescue antiemetics	2(6.7%)	1(3.3%)	0.45
24-48hr			
Complete response	19(63.3%)	28(93.3%)	0.002
Nausea	8(13.3%)	1(3.3%)	0.04
Emetic episode	5(10%)	2(6.7%)	0.07
Rescue antiemetics	1(3.3%)	1(3.3%)	1.00

Table 2: Incidence of Postoperative Nausea & Vomiting (PONV)

Adverse event	Group A (n=30)	Group B (n=30)	P value
Headache	2(6.7%)	2(6.7%)	1.00
Dizziness	1(3.3%)	2(6.7%)	0.554
Drowsiness and general weakness	0	0	

Table 3: Incidence of adverse events

DISCUSSION: The incidence of PONV after middle ear surgery without prophylactic antiemetic treatment is very frequent, varying from 62 to 80%.[7] The etiology of PONV is multifactorial; the main causes of PONV in this study likely included inhaled anaesthetics', opioid analgesics, and vestibular stimulation caused by drilling and irrigating the bone adjacent to the inner ear.

We have standardized the factors that may play a role in the development or attenuation of PONV. We have also standardized the anaesthetic technique for all the patients. There was no statistical difference between the two groups with respect to their demographic profile such as age, weight, height, sex, duration of anaesthesia and surgery, NRS for pain, and ASA status. We can, therefore, presume that the difference in effects between the two groups can be attributed to the drugs administered. Various drugs has been used to prevent PONV namely antihistamines.[8] phenothiazine derivatives, anticholinergic.[5] dopamine receptor antagonist.[9] and 5-HT3 antagonists. The 5-HT3 receptor antagonists are now a first line option because of effectiveness, more safety and favourable side-effects profile.[10,11] as they lack the sedative, dysphoric and extra-pyramidal side effects of other drugs.[12]

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Granisetron is a selective 5 hydroxytryptamine receptor antagonist (5HT3 RA). Granisetron is shown to be effective in preventing chemotherapy induced nausea & vomiting.[7,12] Later it's antiemetic efficacy was also tested in postoperative nausea and vomiting and was found to be effective in preventing PONV. Palonosetron is a selective serotonin subtype 5-HT_3 receptor antagonist with a strong binding affinity for the receptor.[13] it has been found to have a longer duration of action when compared to granisetron.

Fujii et al also carried out a study in 1999.[14] and concluded that granisetron 40μg/kg was an effective dose for prevention of emesis in patients undergoing thyroidectomy and increasing dose to 100μg/kg provided no further benefit. Kovac et al.[15] have concluded that a single 0.075mg intravenous dose of palonosetron significantly reduced emesis, intensity of nausea and the use of rescue anti-emetics in addition to delaying emesis and treatment failure. Keith A, Candiotti et.[16] al also confirmed that 0.075mg of palonosetron was effective antiemetic dose in a study conducted in out patients. So Granisetron 2.5mg (Approximately 45μg kg.[1]) and 0.075mg of Palonosetron is selected in the present clinical trial, as it has been found to have best treatment effect.

Our study demonstrated that palonosetron was statistically similar to granisetron for most of the end points during the first 24 hours, including Complete Response, emesis and nausea rates, and requirement of rescue anti-emetics after middle ear surgery. However, during 24-48hrs. we found that palonosetron is more effective than granisetron for getting a complete response (No PONV, no rescue medication). The results of this study are in accordance with results of Dhurjoti Prosad Bhattacharjee et al.[17] who compared Palonosetron and granisetron in preventing PONV after laparoscopic cholecystectomy under general anaesthesia in female patients. They found complete response of 90% each in patients who received palonosetron 0.075mg between 0 to 3hrs, 3 to 24 hrs, 24 to 48 hrs. and complete response of 86.6, 83.3% and 63.3% in those who received granisetron 2.5mg. These findings are comparable with findings of our study, where complete response (No PONV and rescue medication) for those patients who received granisetron 2.5mg were 86.6%, 83.3%, 80% and 63.3% between 0 to 3hrs, 3 to 12hrs, 12 to 24 hrs. and 24 to 48 hrs. Respectively and those patients who received Palonosetron 0.075mg were 93.3%, 93.3% 90% and 93.3% between 0 to 3hrs, 3 to 12hrs, 12 to 24 hrs. and 24 to 48 hrs. Respectively.

This suggests that palonosetron has an antiemetic effect which lasts longer than granisetron. The exact reason for the difference in effectiveness between granisetron and palonosetron is not known but may be related to the half-lives (Granistron 8-9hrs. versus palonosetron 40 hrs.) and/or the binding affinities of 5-HT3 receptor antagonists (Palonosetron interacts with 5-HT3 receptors in an allosteric, positive cooperative manner at sites different from that bind with granisetron).[18]

Adverse effects observed in this study were not clinically serious and did not differ in incidence between the groups. Headache was found in 2 of the 30 patients in both groups. Dizziness was found in 2 of the 30 patients in patients who received preoperative granisetron and in one patient who received palonosetron.

We had not taken any placebo group for comparison in our study as from multiple studies done earlier it was clear that granisetron is definitely better antiemetic as compared to placebo. Again, risk of postoperative nausea and vomiting is very high in patients undergoing middle ear surgeries and it would have been unethical to expose patients to such risk by not providing antiemetic prophylaxis.

CONCLUSION: In conclusion prophylactic therapy with palonosetron is more effective than prophylactic therapy with granisetron for the long term prevention of PONV after Middle ear surgery.

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