ORIGINAL RESEARCH PAPER

Anaesthesiology

COMPARATIVE EVALUATION OF SINGLE DOSE PALONOSETRON AND GRANISETRON IN MIDDLE EAR SURGERIES FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING.

KEY WORDS: Middle ear surgery, postoperative nausea and vomiting, Palonosetron, Granisetron.

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ABSTRACT

Background and aims: Palonosetron 5HT 3 antagonist have been evaluated in delayed chemotherapy induced nausea and vomiting but its antiemetic efficacy after middle ear surgery is less clear which is high risk for post operative nausea and vomiting.(PONV).This study aimed to evaluate whether Palonosetron conferred any advantage over Granisetron in terms of duration of prophylaxis and its effect on the incidence and severity of PONV in patients undergoing middle ear surgeries (MES) when used as single dose prophylactic antiemetic.

Methods: One hundred ASA I and II patients of either gender aged 18 to 60 were randomly assigned into group P (Palonosetron n=50) or group G(Granisetron n=50), by computerised randomisation. Analysis was done in terms of incidence and severity of nausea, vomiting and rescue antiemetic usage till 72 hours of surgery.

Results: During 72 hours, group P had more number of complete responders than in group G (56% vs. 34%). This difference was more significant after 24hours. 50% of patients in group G as against 28% in group required rescue antiemetic.

Conclusion: Single dose prophylactic Palonosetron 0.075 mg and 2.5 mg Granisetron conferred similar protection against postoperative nausea and vomiting for initial six hours postoperatively but Palonosetron was more effective than Granisetron for long term prophylaxis over 72 hours against PONV after MES without significant adverse effects.

INTRODUCTION:

Nausea and vomiting occurring postoperatively (PONV) is unpleasant outcome after middle ear surgeries (MES). Nausea occur in 20% of patients in PACU and 50% thereafter, with vomiting in 5% and 25% respectively.[1,2] Incidence of up to 80% has been reported after MES under general anaesthesia.[3,4,5] .5HT3 antagonists remains first choice for preventing PONV due to effectiveness, safety profile and fewer adverse effects[6,7].

There is less literature on Palonosetron stating its efficacy in MES which are highly emetogenic.This study was conducted with aim of assessing whether Palonosetron conferred any advantage over Granisetron in terms of duration of prophylaxis and its effect on incidence and severity of PONV after MES using single dose.

METHODS:

This was randomized, double blinded clinical control trial conducted at tertiary care institute after obtaining institutional ethics committee approval and written informed consent of patients. It was registered at clinical trial registry CTRI/2018/01/011305. It was conducted from 20/01/2016 to 23/10/2017.

Patients of age group 18 to 60 years with ASA grade I and II undergoing middle ear surgeries were included. Patients with history of allergy to study drug, who received medications including steroid, antiemetic or psychoactive drug in 24 hour of study initiation, history of nausea, vomiting & motion sickness, smoking, alcoholism or on antipsychotic drug, migraine, Meniere's disease, seizure or raised intracranial pressure, obesity (BMI ≥ 30), lower esophageal sphincter disorder, acid peptic disease, pregnant and breastfeeding mother and not willing to participate in study were excluded. All patients were examined and investigated according to institutional protocol.

Computer generated randomized sequencing was done and a separate anesthesiologist not involved in study was asked to load drug in 5 ml syringe and dilute it till 5 ml with saline as per randomization and labeled as study drug .

In the operation theatre, standard monitors were attached including ECG, NIBP cuff, Pulse oxymeter. Intravenous ringer lactate was given 5 ml/ kg during induction of anaesthesia followed by 2 ml/ kg/ hr throughout surgery. Study drug which was prepared by the anesthesiologist not involved in patient care and study related follow up, was administered intravenously before induction so that patients of Group P received Palonosetron 0.075 mg[8,9] (**Themiset**-Themis Medicare, Strength 0.075 mg / 1.5 ml vial) **and** Granisetron 2.5 mg[10,11] was received by group G patients (**Granicip**-Cipla, Strength 1 mg/ml, 3 ml vial) ten minutes before induction of anaesthesia. All patients were premedicated with Injection Ranitidine 50 mg, Inj Fentanyl 2mcg/kg and Midazolam 0.03 mg/kg iv. After pre-oxygenation with 100% oxygen for three minutes, induction was done using 2 mg/kg of inj. Propofol i.v. and Injection Vecuronium Bromide 0.1mg/kg IV was used to facilitate intubation. Maintenance was done using oxygen: nitrous oxide (40%:60%) and Sevoflurane (1-3% dial flow concentration).Muscle relaxation was maintained by intermittent boluses of Vecuronium. After adequate local infiltration with 2%lignocaine and adrenaline surgeon proceeded with surgery and underlay technique for tympanic membrane graft placement was used. Diclofenac Sodium1.5 mg/kg IM was given after intubation and BD thereafter for postoperative analgesia. At the end of surgery, patients were extubated after reversal of neuromuscular blockade using injection Glycopyrrolate 8 mcg/kg + Neostigmine 0.05 mg/kg I.V. Adverse events such as bradycardia (HR<60 bpm), hypotension (fall in SBP by 20% from baseline or an absolute MAP<60 mmHg) or any other events during or within two hours after the procedure were noted and were treated accordingly using Inj Atropine 0.02mg/kg and fluid bolus and/or Inj Mephentermine. Patients were observed in PACU for two hours and thereafter in ward for nausea, vomiting, retching and its frequency.

Postoperative period was considered as starting from the time of extubation (Zero hours).All Patients were visited in ward at six, 24, 48 and 72 hour postoperatively to record the occurrence of nausea, retching and vomiting, vital parameters and any other side effect or adverse effect at the time of visit

or during the time interval between two visits by the investigator i.e. two-six hour, six-24 hour, 24-48 hour and 48-72 hour. Nausea was graded by using Visual Analogue Scale score where zero indicates no nausea and ten indicates severe nausea.

Incidence of emetic episodes were observed in two group of patients using PONV Score[12] in which **PONV Score zero is** No Nausea / Vomiting ,**PONV Score one –** Nausea alone, **PONV Score two –** Vomiting / Retching once and **PONV Score three is** Vomiting / Retching more than once in 30 minute interval. If nausea, vomiting occur, rescue medication (Injection Metoclopramide 10 mg) was given **for PONV score one and for PONV score one if the patient complain of nausea score ≥ five on VAS.** The total absence of nausea/ retching/ vomiting was considered as **complete response.**

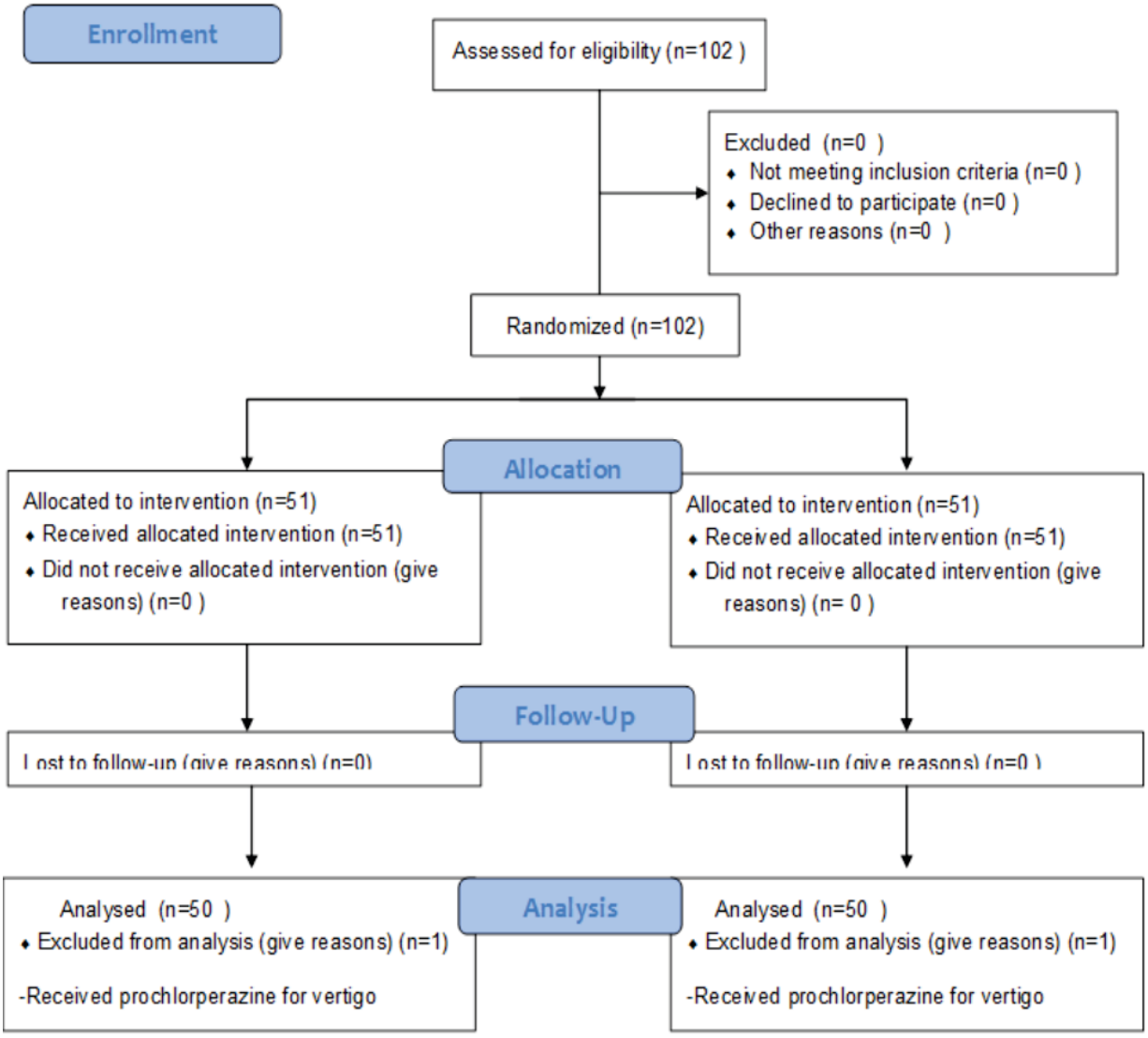
Sample size required to find a difference in proportion of postoperative nausea and vomiting between Palonosetron and Granisetron was found to be51 in each group with 80% power and level of significance at 5% with expected postoperative nausea and vomiting of 20% in Palonosetron and 40%in Granisetron group. Categorical variables were expressed in percentage and quantitative in mean ± SD. Fisher exact T test and Chi-square test were used as test of association between categorical variables and two groups. Statistical analysis was done using Epi Info 2007 software.

RESULTS:

Out of 102 patients posted for surgery, 100 patients i.e. 50 in each group were analyzed as one patient from each group received prochlorperazine for complaint of vertigo.

Demographic parameters of the patients including age, gender, BMI, ASA status were comparable. Also amount of fluid received, use of nitrous oxide and opioids were similar in both groups. Hemodynamic parameters throughout study period and duration of surgery were comparable (Table 1).

During observed period of 72 hours, numbers of complete responders were more in group P i.e. 56%rather than group G i.e. 34%.This was more significant statistically after 24 hours. During six to 24 hours period, 13 in group G versus two patients in group P suffered nausea and this difference was found to be statistically significant. Although none of them suffered from nausea (VAS score >five) requiring intervention. More number of patients have vomited once(PONV score of two) in group G during time interval of 24 to 48 hours and 48 to 72 hours and it was statistically significant although over all incidence of vomiting in both groups over period of 72 hours was comparable. None of the patients in both groups had PONV score of three. The number of patients requiring rescue anti-emetics at the end 72 hour were 14(28%) in group P as against 25(50%) in group G and this difference was significant statistically (p=0.024).



CONSORT flow diagram

DISCUSSION:

This was double blind randomized clinical trial meant to asses efficacy of single dose of Palonosetron as against Granisetron, both being 5HT3 antagonist , in patients undergoing middle ear surgeries. Palonosetron was chosen as this 5HT3 antagonist has longer half life of 40 hours, causes 5HT3 receptor internalization and exhibits negative cooperativity with NK1 receptor[13]. This unique property makes it more effective agent against delayed chemotherapy induced nausea and vomiting for which other agents in group are ineffective. This given property can be utilized for prevention of PONV where longer duration prophylaxis is required as in cases of middle ear surgeries. Granisetron with half life of eight to nine hours is also effective in preventing PONV by causing irreversible blockade of 5HT3 receptor on vagal afferents from gut[11,12].

In our study, overall incidence of PONV was around 38 %, although number of risk factors suggested by Apfel's simplified risk score[14] was balanced between two groups.

Our study found palonosetron had better antiemetic efficacy as compared to Granisetron in preventing PONV in patients undergoing middle ear surgery over long term period of 72 hours. Although both drugs were comparable during immediate postoperative period of 6 hours, long term effect was better with palonosetron. Overall statistically significant difference in both groups was observed during period of six to 72 hours. Also headache and dizziness were commonly reported side effects which were not clinically serious and were comparable. However as there was no control group its attribution to study group cannot be commented upon.

In our study , during study period of 72hours ,56% patients in group P showed complete response as against 34%in group G which was statistically significant (p=0.0273)(Table 2,4). While number of complete responders was comparable in both groups during initial six hours, statistically significant difference in both groups was observed during six to 72 hours (Table 2,3). Number of complete responders in group P was 78% as against 54% in group G during six to 24 hours period. Further this number increased up to 94% in group P while it was70% in G during 24-48 hours and 96% in group P compared to 62% in group G during 48 - 72 hours and all this was statistically significant. These results were comparable to study done by Bhattachegee et al[11] where complete response of 90% in patients who received Palonosetron 0.075 mg was observed up to 48 hours and complete response as less as 63.3% in 24 to 48 hours was observed those who received Granisetron 2.5 mg. Similarly Singh et al[15] (2015) found significant number of complete responders in Palonosetron group as against Granisetron group during 24 to 48 hours. This suggests that antiemetic effect of palonosetron last longer than Granisetron and this difference may be related to half lives (Granisetron eight - nine hours compare to Palonosetron 40 hours) and/ or binding affinity of 5HT3 receptor antagonists.

Despite PONV prophylaxis, few patients developed PONV and required rescue antiemetic for PONV over zero-72 hour in 28% patients of group P as compared to 50%patients of group G. ($p < 0.024$).

We studied both drugs of same class targeting 5HT3 receptors which may not be effective in providing complete protection against PONV as multiple neurotransmitters including dopamine, neurokinin, histamine and serotonin are involved in physiology of PONV[16,17]. So these drugs may need to combine whenever indicated with some other class of drug to prevent PONV after middle ear surgery considering its high emetogenic potential.

We studied the efficacy of single dose inj. Palonosetron and Granisetron as a prophylactic antiemetic. Considering the known duration of action of Granisetron much less than Palonosetron, comparison of these two drugs by administering another dose of Granisetron to adjust the difference in duration of action needs further evaluation. Also we excluded the patients with some significant risk factors for PONV and tried to avoid the drugs having high emetogenic potential in postoperative period. Therefore our result may not be applicable to these patients.

Also we didn't take control group as it will be unethical to withhold antiemetic prophylaxis to patients undergoing highly emetogenic surgery.

Summary and conclusion:

From our observations and analyzed data we can conclude that prophylactic intravenous administration of single dose of 0.075 mg Palonosetron and 2.5 mg Granisetron conferred similar protection against postoperative nausea and vomiting for initial six hours postoperatively but Palonosetron was more effective than Granisetron for long term prophylaxis over 72 hours against PONV after middle ear surgery without any significant adverse effects.

Table 1: Demographic Parameters of Patients and duration of Surgery

Parameter	Group P(n=50)	Group G(n=50)	p value
Age (years) Range	18 – 58	18-58	0.7285
Mean(±SD)	31.86 ±12.23	29.70 ±10.87	
Sex			
Male n(%): Female n(%)	21(42%) :29(58%)	24(48%) :26(52%)	0.546
ASA Grade (I:II) n(%)	39(78%): 11(22%)	38(76%): 12(24%)	0.812
BMI (kg/m2) Range Mean(±SD)	18.02-26.66 22.13± 1.6347	17.3 –27.4 21.78± 2.05	0.354
Duration of surgery			
Range (Minutes) Mean ± SD (Minutes)	150-420 278.80 ± 55.3519	175-375 283.10 ±47.3792	0.454

Table: 2 Distribution of patients according to the PONV Score 0 (No nausea/vomiting)

Postoperative Period	Group P (n =50) n (%)	Group G (n =50) n (%)	p Value
0 – 2 Hours	38 (76%)	40 (80%)	0.6292
2 – 6 Hours	33 (66%)	34 (68%)	0.8316
6 – 24 Hours	39 (78%)	27 (54%)	0.0113
24 – 48 Hours	47 (94%)	35 (70%)	0.0017
48 – 72 hours	48 (96%)	32 (62%)	< 0.001
0 – 72 Hours	28(56%)	17(34%)	0.0273

Table: 3Distribution of patients according to incidence of nausea Vomiting, number of complete responders and use of rescue antiemetic

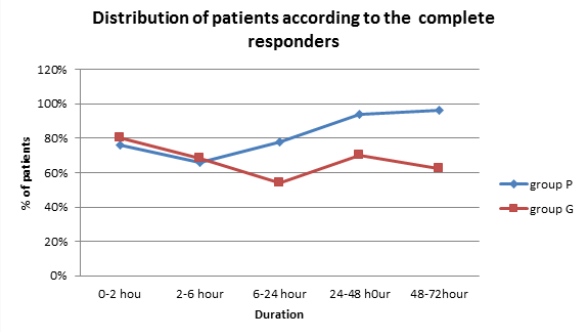
Postoperative time period	Parameter	Group P (n =50) n(%)	Group G (n =50) n(%)	p value
0–2 Hours	Nausea	9 (18 %)	7 (14%)	0.5854
	Vomiting/retching	3 (6 %)	3 (6%)	>0.99
	Complete responder	38 (76 %)	40 (80%)	0.6292
	Rescue anti-emetics	3 (6 %)	3 (6%)	>0.99
2-6 hours	Nausea	11(22%)	9(18%)	0.8026
	Vomiting/retching	6(12%)	7(14%)	0.7612
	Complete responder	33(66%)	34(68%)	0.8316
	Rescue anti-emetics	6(12%)	7(14%)	0.7612
6 -24 hours	Nausea	2(4%)	13(26%)	0.0020
	Vomiting/retching	9(18%)	10(20%)	0.7988

	Complete responder	39(78%)	27(54%)	0.0113
	Rescue anti-emetics	9(18%)	10(20%)	0.7988
24-48 hours	Nausea	1(2%)	3(6%)	0.3094
	Vomiting/retching	2(4%)	12(24%)	0.0039
	Complete responder	47(94%)	35(70%)	0.0017
	Rescue anti-emetics	2(4%)	12(24%)	0.0039
48-72 hours	Nausea	0(0%)	1(2%)	0.4173
	Vomiting/retching	2(4%)	17(34%)	<0.001
	Complete responder	48(96%)	32(64%)	<0.001
	Rescue anti-emetics	2(4%)	17(34%)	<0.001

Table: 4 Number of patient with nausea, vomiting/ retching, complete responders and use of rescue anti-emetics over 72 hour

Parameter	Group P (n=50)n(%)	Group G (n=50) n(%)	p value
Nausea only	8(16%)	**8(16%)**	> 0.99
Vomiting/retching	14(28%)	25(50%)	0.024
Complete responder	28(56%)	17(34%)	0.0273
Rescue anti-emetics	14(28%)	25(50%)	0.024

Graph 1



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