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A Comparative Study to Ascertain the Efficacy of Palonosetron, Granisetron and Metoclopramide in Preventing Post-Operative Nausea and Vomiting in Patients Undergoing General Anaesthesia for Ear, Nose and Throat Surgeries

By Dr. Jasmine Kaur & Dr. Farah Husain

Introduction- Postoperative nausea and vomiting (PONV) can be a very distressing side effect following general anaesthesia. Patients and health care professionals report the avoidance of PONV is of equal or sometimes even greater concern than avoidance of postoperative pain.[1]It can result in increased morbidity, delay in hospital discharge and unexpected hospital re-admission, thereby increasing the total medical costs[2]. Moreover, PONV has been a major cause of decreased patient satisfaction[3]. There are several physiologic complications of nausea and vomiting that are of concern to the anaesthesiologist. Some of them being visceral wound dehiscence, electrolyte disorders, raised venous pressure leading to bleeding, rise in intraocular and intracranial tension and aspiration pneumonia especially in the sedated post-operative patient.

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Dr. Jasmine Kaur [α] & Dr. Farah Husain [σ]

I. Introduction

Postoperative nausea and vomiting (PONV) can be a very distressing side effect following general anaesthesia. Patients and health care professionals report the avoidance of PONV is of equal or sometimes even greater concern than avoidance of postoperative pain.[1]It can result in increased morbidity, delay in hospital discharge and unexpected hospital re-admission, thereby increasing the total medical costs[2]. Moreover, PONV has been a major cause of decreased patient satisfaction[3]. There are several physiologic complications of nausea and vomiting that are of concern to the anaesthesiologist. Some of them being visceral wound dehiscence, electrolyte disorders, raised venous pressure leading to bleeding, rise in intraocular and intracranial tension and aspiration pneumonia especially in the sedated post-operative patient.

PONV is influenced by multiple factors such as the patient itself, surgery and anaesthesia related factors and involves release of 5-hydroxytryptamine (5- HT) in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract (Figure 1). The 5-HT subtype3 (5-HT_3) receptors participates selectively in the emetic response. The risk and incidence of PONV increases with post-operative opioid use[3] but has been found to be decreased in smokers as compared to non-smokers[4]. On the other hand, its incidence increases in patients with history of motion sickness and after consumption of alcohol.

Certain surgical procedures like gynaecological, abdominal specially gastro intestinal, laparoscopic surgeries, ENT surgeries and ophthalmic surgeries are more likely to lead to PONV because of stimulation of vagal afferents during manipulation.[5]

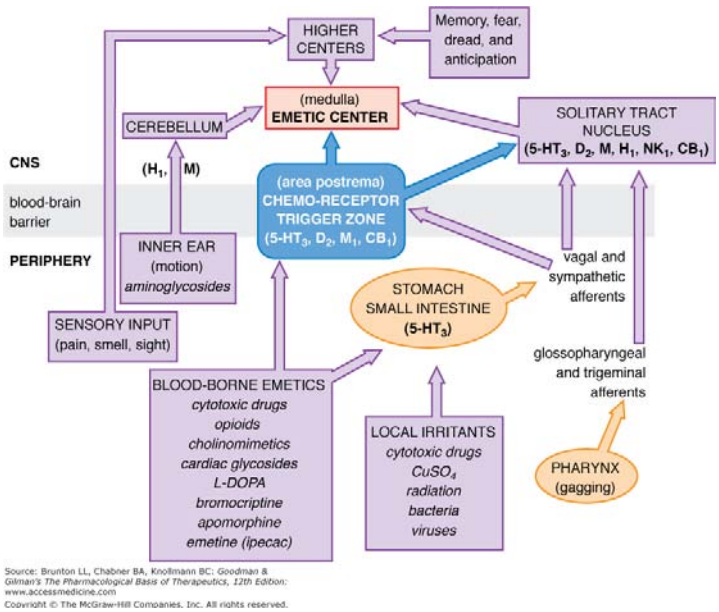

Figure 1

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Advances in PONV prophylaxis over recent years include use of non-pharmacological measures to reduce baseline risk, a change to less emetogenic anaesthetic techniques and the use of newer antiemetic drugs. However, the use of antiemetics, either alone or in combination, remains the mainstay in PONV management. Drugs used include metoclopramide, haloperidol, dexamethasone and the selective 5-HT_3receptor antagonists. The last group is now a first lineoption because of its effectiveness and general lack of adverse drug reactions.[6] Most clinical researches with the 5-HT_3 receptor antagonists have used ondansetron, and its antiemetic efficacy is well established in chemotherapy- induced emesis and in the treatment and prevention of PONV. However, several alternatives to ondansetrone.g. granisetron, tropisetron, dolasetron, ramosetronare also available now. Palonosetron, approved by the Drugs Controller General of India on 25.04.2009, is the most recently introduced member in this class of drug. Its interaction pattern with the 5-HT_3 receptor is different from earlier 5-HT_3 receptor antagonists, enabling a higher binding affinity and longer half-life.

We compared the antiemetic effectiveness of intravenous Palonosetron, administered as a single pre-induction dose, in ear, nose and throat surgeries during the first 48 postoperative hours with another 5-HT_3 receptor antagonist Granisetron and a commonly used Dopamine agonist, Metoclopramide.

Palonosetron is a novel $5HT_3$ receptor antagonist, first approved for the prevention of chemotherapy induced nausea and vomiting. It has greater binding affinity and longer biological half- life than older $5HT_3$ receptor antagonists.[8] It has been suggested that $5HT_3$ receptors are found in the gut and in areas of central nervous system associated with the regulation of nausea and vomiting; being abundant in the CTZ which has projections to the vomiting centre located in the lateral reticular formation of medulla oblongata[5]. Palonosetron has been compared with placebo for the prevention of PONV in patients undergoing open abdominal and gynaecological surgery[8]. Comparison with other antiemetic drugs and in other types of surgery is still limited. Drowsiness, headache cardiac rhythm disturbances are a few side effects.

Granisetron is a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT1; 5-HT1A; 5-HT1B/C; 5-HT2; for α1-, α2-, or β-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; picrotoxin or opioid receptors. The differences between these drugs could stem from differences in pharmacokinetics or receptor binding profiles.

Metoclopramide has been available for about 40 years, is cheap, and is widely used for treatment and prevention of nausea and vomiting. Metoclopramide has multiple sites of action. It is a prokinetic drug that acts by increasing the tone of the lower oesophageal sphincter. It also has an anti-dopaminergic action on the chemoreceptor trigger zone and at higher doses has an anti-serotonergic activity.[9,10]

II. Patients and Methods

After obtaining approval from the institutional ethical committee, written informed consent was taken from the patient one day prior to the scheduled surgery. A total of 90 adult patients of ASA I and II group, having one or both risk factors for PONV-prior history of PONV, Non-smoker, female gender, use of opioids in peri-operative period, scheduled to undergo Ear, Nose or Throat operations under general anaesthesia were selected and randomised in a double blind manner by computer generated algorithm. Patients were to receive either Inj. Palonosetron 0.075mg iv (Group P, n=30), Inj. Granisetron 1 mg (Group G, n=30) or Inj. Metoclopramide 10 mg iv (Group M, n =30) 15 minutes before induction of anaesthesia. Saline solution was added to bring the total volume of all the drugs to 5 ml.

Exclusion Criteria:

- Patients within ability to understand or cooperate with the study procedures as determined by the investigator
- Pregnant women
- Nursing or planning to become pregnant women
- Cancer patient who had chemotherapy within 4 weeks prior to study entry
- Any kind of emetogenic radiotherapy taken within 8 weeks prior to study entry
- Consumption of any investigational drugs within 30 days before study entry
- Consumption of any drug with potential antiemetic efficacy within 24 hours prior to anaesthetic procedures
- Any vomiting, retching, or nausea in the 24 hours preceding the administration of anaesthesia,
- Body Mass Index (BMI) >40
- Suspected / current history of alcohol abuse or drug abuse known hypersensitivity/ contraindication to 5-HT3 antagonist or study drug excipients
- Epileptic patients
- Patients receiving other drugs which are likely to cause extrapyramidal reactions were excluded from the study.

All patients were pre-oxygenated for 3 minutes with 100% oxygen. Premedication was done by using Inj. Glycopyrrolate 0.2 mg iv, Inj. midazolam 1 mg iv and Inj. fentanyl 2 microgram/kg iv. Patients were induced with was Inj Thiopentone sodium (4-7 mg/kg) iv. Injection Vecuronium 0.1 mg/kg iv was used to facilitate Endotracheal intubation. Anaesthesia was maintained with O_2 + N_2O + Isoflurane. Muscle relaxant used for

maintenance was Inj. Vecuronium bromide 0.02 mg/kg iv. In the intra-operative period, multimodal analgesia was achieved with Injection Paracetamol 1gm iv.At the completion of surgery, once patients had regained attempts of spontaneous breathing, they were given reversal with Inj. neostigmine 0.05 mg/kgand Inj. Glycopyrrolate 0.01 mg/kg.

After completion of surgery, patients were shifted to post-operative anaesthesia care unit where pain was controlled by Inj. Diclofenac sodium 75 mg IM 8 hourly or on patient demand and monitored for the incidence of nausea and vomiting according to Visual Analogue Scale (0-no nausea, 10- worst nausea) at 0-2 hrs, 2-6 hrs, 6-12 hrs, 12-24 hrs, 24-48 hrs, incidence of adverse effects in all the three groups, use of rescue antiemetic in the three groups and for patient satisfaction to the given drugs in all the three groups. Rescue Antiemetic was given when one episode of PONV occurred or at VAS >5 and the patient requested treatment. A complete response was defined as the absence of PONV and no use of rescue antiemetics. Inj. Palonosetron 0.075 mg was used as a rescue antiemetic in Group M and Inj. Metoclopramide 10 mg IV was used as a rescue antiemetic in Group P & Group G.

III. Statistical Analysis

Statistical analysis was performed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The statistical observations of the categorical variables were evaluated by using Chi square test and Independent student t test. The observed side effects and risk factors were analysed with Fisher's exact test. The observational results are expressed mainly Mean + SD or number (%)

A P value$<$0.05 was considered statistically significant.

IV. Results

The study groups were comparable demographically. There was no significant difference in the duration of surgery among groups (Table 1& Graph 1). The intraoperative hemodynamic parameters were also comparable.

Incidence of Nausea in Post-operative Period

Group P was found to have much less nausea as compared to the other groups ($p<0.05$) as per Table2.

Incidence of Vomiting in Post-operative Period

As there was no significant difference in incidence of vomiting in any of the three groups in 48 hours post- operative period as shown in Table 3, the drugs are comparable in their efficacy to prevent vomiting.

Subjective Assessment of Patient's Satisfaction

There was a significant difference in the satisfaction rate in Group P as compared to Group M (Graph 2).

Use of Rescue Medication in Post-operative period

There was no significant difference while comparing the need of rescue anti-emetic in Palonosetron and Granisetron group but a statistically significant p value (p value <0.05) was obtained while comparing Metoclopramide with Palonosetron ($p = 0.009$) and Granisetron ($p= 0.024$) as depicted in Table 4 and Graph 3.

Side Effects Profile: On comparison of side effects among three groups, in Group P, 3 patients complained of headache in 48 hours while 2 patients complained of headache in Group G and 1 patient in Metoclopramide Group implying no significant difference in side effects among the three groups. Similarly, after comparison of other side effects of 5HT3 antagonists like dizziness, constipation and myalgia there was no significant difference in the incidence of side effects in the three groups. All events were of mild severity and settled spontaneously without separate treatment. There was no instance of corrected QT interval prolongation ($QT_C > 450$ milliseconds) in either of the study groups. (Graph IV)

V. Discussion

Postoperative nausea and vomiting (PONV) is a common complication following surgery under general anaesthesia. Incidence of PONV is 30-40% in normal population undergoing general anaesthesia while the incidence touches a peak of 75-80% in certain high risk groups[2]. The postoperative period is associated with variable incidence of nausea and vomiting depending on the duration of surgery, the type of anaesthetic agents used (dose, inhalational drugs, opioids), smoking habit etc[4]. $5HT_3$ receptor stimulation is the primary event in the initiation of vomiting reflex[16]. Anaesthetic agents trigger this reflex by stimulating the central chemoreceptor trigger zone (CTZ) and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5 HT_3 receptors on the vagus afferent fibres[7]. Our objective was to compare two different groups of antiemetics, in a high-risk group of patients undergoing ear, nose and throat surgeries.

On comparison of overall incidence of nausea among the three groups at 0-48 hrs, Palonosetron was found to be most efficacious in this study. The incidence of nausea was only 33.33% in palonosetron group as compared to 60% in Granisetron group and 90% in Metoclopramide group which was found to be statistically significant ($p<0.05$). But there was no difference in the overall incidence of vomiting per se between the three groups.

In a similar study done by Bhattacharjee et al[11], they reported that prophylactic therapy with palonosetron is more effective than granisetron for prevention of PONV after laparoscopic cholecystectomy during the 24-48hour post-operative period, though not in the first 24 hours and both are devoid of clinically important side effects as established in our study.

Oksuz et al[12]did a similar study and evaluated the effectiveness of Metoclopramide, Ondansetron and Granisetron in the prevention of nausea and vomiting after laparoscopic cholecystectomy. They found that the drugs had similar antiemetic effect in the first 3hour post-operative period but during 4-24 hour, Granisetron resulted in a significantly lower incidence of PONV than metoclopramide and ondansetron, whereas metoclopramide was ineffective.

Similar results were obtained by K. Gupta et al[13] They did a prospective randomised study to compare Palonosetron, Ondansetron and Granisetron for antiemetic prophylaxis of postoperative nausea and vomiting and found that Palonosetron was comparatively highly effective than Granisetron to prevent the PONV after anaesthesia due to its prolonged duration of action.

Fujii et al[14] also found similar results in their study while comparing Granisetron, droperidol and metoclopramide in the treatment of established nausea and vomiting after breast surgery. They found that 88% of patients were emesis free in Granisetron group whereas only 56% patient were emesis free in Metoclopramide group, p value = 0.025.

In a randomised controlled trial in middle ear surgeries by Basu et al[15], a single dose of Palonosetron was found to be a superior anti-emetic to Granisetron or Ondansetron in complete prevention of postoperative nausea and vomiting during the first 24 hours period.

Inj. Metoclopramide 10mg iv was used as rescue antiemetic in Group P and Group G. In Group P 13.4% patients received rescue antiemetic while in Group G, 16.7% patients received rescue antiemetic. Inj. Palonosetron 0.075 mg was used as rescue antiemetic in Group M. 43.4% patients received rescue antiemetic in Group M. There is no significant difference while comparing Palonosetron and Granisetron group but a statistically significant p value (p value <0.05) was obtained while comparing Metoclopramide with Palonosetron ($p = 0.009$) and Granisetron ($p= 0.024$) which suggests that they are superior in preventing PONV than metoclopramide.

After completion of 48 hours of post-operative period, we asked the patients about the satisfaction to the given drug in all the three groups. In group P, 60% patients were satisfied, in Group G 50% patients were satisfied and in Group M, 36.7% were satisfied from the given drug and p value is< 0.05 when Group P was compared with Group M and while comparing Group G with Group M. It shows there is a significant difference in patient satisfaction when Group M was compared to rest of the groups with maximum satisfaction rate in Group P, implying that Palonosetron has better control in preventing PONV than Granisetron and Metoclopramide.

VI. Conclusion

Palonosetron, the newer 5 HT3 antagonist is more efficacious than Granisetron and Metoclopramide especially after 24 hours of surgery with more satisfaction score and less incidence of nausea and vomiting. So, if easily available, palonosetron may be considered more routinely in patients undergoing high risk surgeries for PONV.

Since our study was on smaller group of patients, to ascertain an overall potency of the newer drugs, a larger study population needs to be considered. Complications related to surgery such as stimulation of stapes leading to severe post-operative nausea were not considered while evaluating the data.

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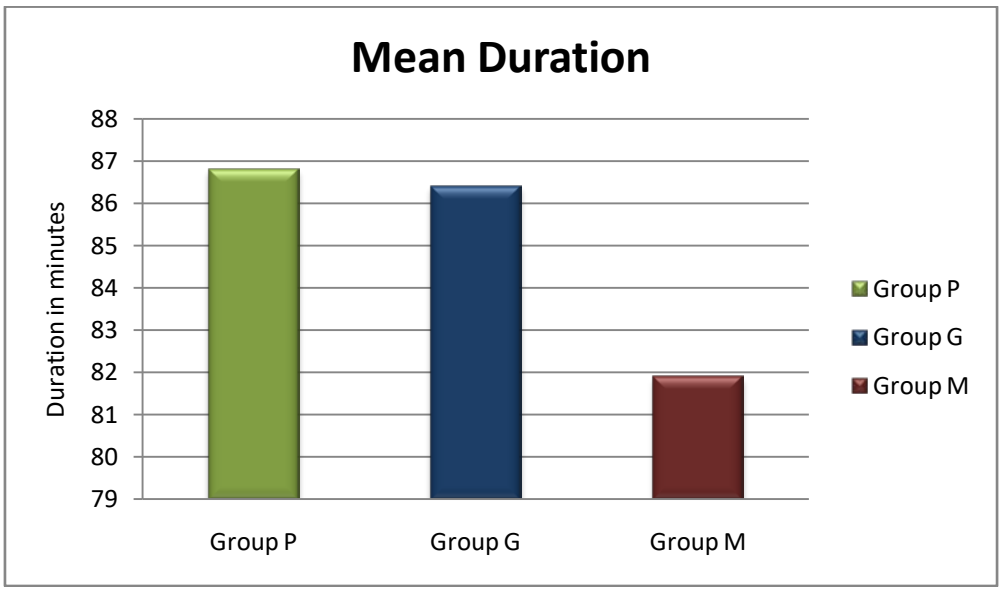
Table 1: Demographic data

	Group P	Group G	Group M
Age (yrs)	33.73 ± 12.65	32.62 ± 12.33	29.96 ± 12.22
Gender (M:F)	17 : 13	16 : 14	17 : 13
Weight (kgs)	50.06 ± 14.43	51.16 ± 7.18	50.03 ± 6.09
Duration of Surgery (min)	86.8 ± 11.2	86.46 ± 11.09	81.96 ± 11.6



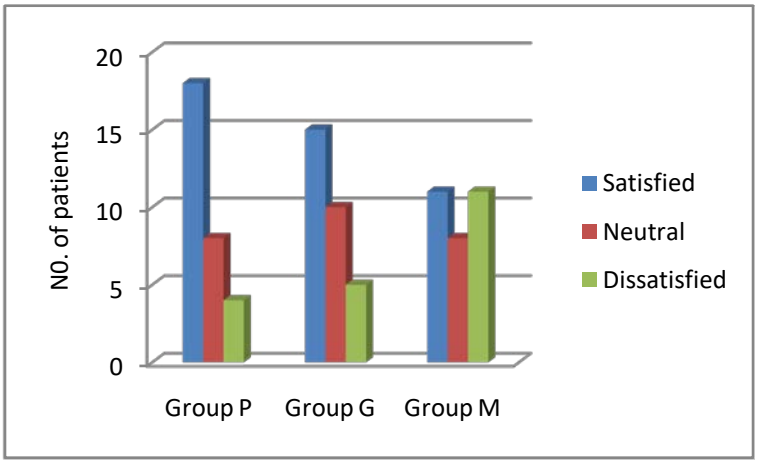
Graph 1: Mean duration of Surgery

Table 2: Incidence of Nausea in Post-operative Period

Time (hr)	GROUP P	GROUP G	GROUP M	GROUP P VS GROUP G	GROUP G VS GROUP M	GROUP P VS GROUP M
0-2	1	1	2	p= 1	p= 0.553	P= 0.553
2-6	2	3	2	p = 0.640	p = 0.640	P = 1
6-12	2	2	5	p = 1	p = 0.227	P = 0.227
12-24	3	4	7	p = 0.687	p = 0.316	**p = 0.165**
24-48	2	8	11	**p = 0.037**	p = 0.405	**p = 0.014**

Table 3: Incidence of Vomiting in Post-operative Period

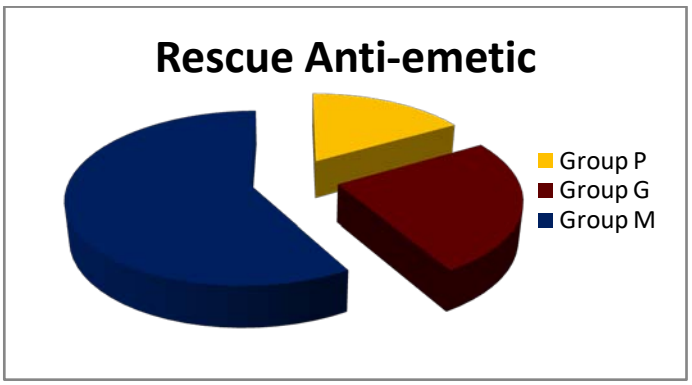
Time (hr)	Group P	Group G	Group M	Group P VS Group G	Group G VS Group M	Group P VS Group M
0-2	0	0	0	p= 0	p= 0	p= 0
2-6	0	0	1	p = 0	P = 0.313	p = 0.313
6-12	0	1	1	p = 0.313	p = 1	P = 0.313
12-24	1	1	2	p = 1	p = 0.55	p = 0.55
24-48	2	3	5	p = 0.64	p =0.44	P = 0.22



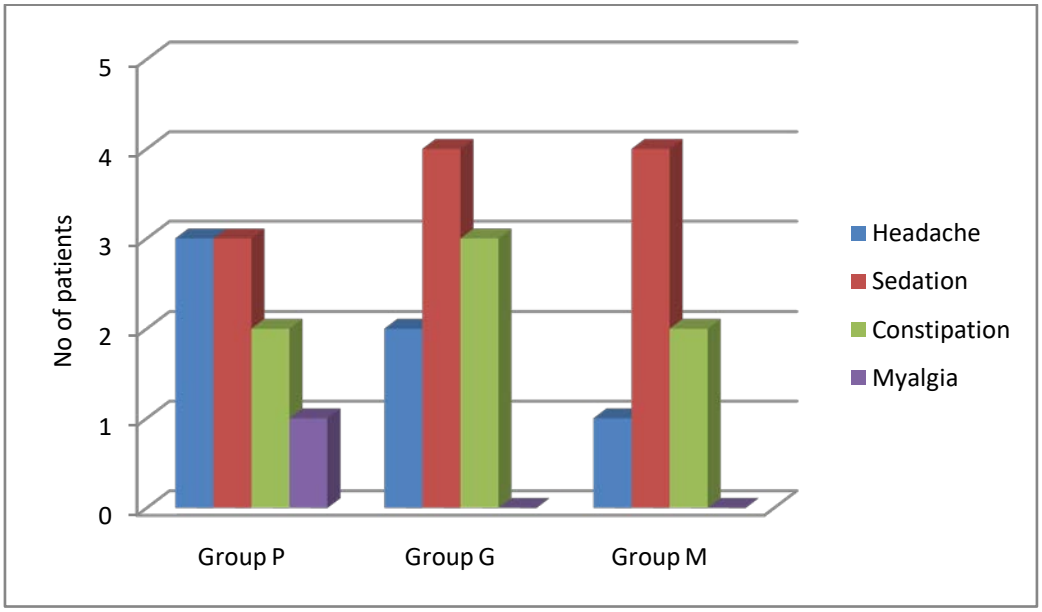
Graph 2: Subjective Assessment of Patient's Satisfaction

Table 4: Use of Rescue Medication in Post-operative period

	Group P	Group G	Group M	Group P VS Group G	Group G VS Group M	Group P VS Group M
No of patient receiving rescue medication	4(13.4%)	5(16.8%)	13(43.4%)	P = 0.717	**P = 0.024**	**P = 0.009**



Graph 3: Need for rescue anti-emetic in the three groups



Graph 4: Side effect profile