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COMPARATIVE STUDY OF ONDANSETRON,GRANISETRON AND RAMOSETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING

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ABSTRACT

Introduction: Nausea and vomiting have been associated with the use of general anesthetics for cardiac surgical procedures, with nausea, retching & vomiting as the most common postoperative complaints. The aim of the study is to compare the antiemetic effects of intravenous ondansetron, granisetron & ramosetron in a randomized double blind controlled manner for prevention of nausea and vomiting in early postoperative period in patients undergoing cardiac surgery.

Material & methods: Ninety patients undergoing cardiac surgery were randomly allocated into three equal groups, each receiving ondansetron, ,granisetron and ramosetron via intravenous route,before induction of anaesthesia . Anesthetic procedure was common to all patients. Emetic episodes in early postoperative period (first three hours) and delayed (upto 24 hours) were recorded and compared in different study groups.

Conclusion : Based on this study it can be concluded that in early postoperative period (first three hours) the three drugs ondansetron, granisetron and ramosetron are comparable to each other. If we consider the delayed postoperative period (upto 24 hours) ramosetron appears better than ondansetron .Effects of ramosetron and granisetron are comparable to each other.

Keywords: Post operative nausea & vomiting (PONV), cardiac surgery, ondansetron,granisetron and ramosetron

INTRODUCTION

Nausea, retching & vomiting are common postoperative complaints occurring after general anesthesia. [1] It is important to minimize vomiting and retching after cardiac surgery, to avoid potential cardiovascular complications and to improve patient comfort and assist in rapid recovery. [2] Patients with an increased risk of postoperative nausea and vomiting (PONV) are frequently given prophylactic treatment, often with a selective 5-hydroxytryptamine-3 (5HT3) antagonist. [3] These 5HT3 receptor antagonists produce less sedation, extrapyramidal reactions, adverse effects on vital signs or drug interactions with other anaesthetic medications. [4]

This study aims to compare the efficacy of intravenous ondansetron, granisetron & ramosetron in cardiac surgery patients in prevention of post operative nausea and vomiting

**OBJECTIVE: **

To assesses the incidence of post operative nausea and vomiting, up to 24hours, among patients undergoing cardiac surgery, with early tracheal extubation.

To compare and evaluate the efficacy of three drugs ondansetron , granisetron and ramosetron given before induction of anaesthesia on the incidence of postoperative nausea and vomiting in adults undergoing cardiac surgery.

To assess the requirement of rescue antiemetic.

METHODOLOGY: This is a prospective randomized double blind controlled study performed on 90 patients undergoing cardiac surgery at a high volume tertiary care cardiac centre.

After obtaining informed written consent, using computer generated random numbers, the patients were allocated into three groups of thirty each to receive ondansetron 0.1mg/kg(group A), granisetron 40mcg/kg(group B), ramosetron 0.3 mg (group C) before induction of anaesthesia

Patient's medical history, demographic information including, height, weight, age, tobacco use, alcohol use, and menstrual history, were obtained. All adult patients in the age group of 20 – 65 undergoing elective cardiac surgery at the institute were included in the study. Patients with history of motion sickness, history of post operative nausea vomiting , vestibular disease, body mass index>30 and those who received antiemetic within 24 hrs prior to surgery were excluded from the study .

The patients were prepared by overnight fasting of 8 hours and were administered tab alprazolam 0.5mg on the night before surgery. Study drugs were injected before induction of anesthesia. In order to eliminate bias blinding was done to the extent that the investigator was not aware of the type of study drug used. The study drug was prepared by single person in 5ml syringe and was diluted up to 5ml volume using distilled water. The investigator came to know the nature of drug only once the patient was observed for 24 hours.

Anesthesia was standardized with induction with inj fentanyl 10–15 µg kg^{-1} and inj midazolam 0.02–0.04 mg kg^{-1},inj vecuronium was administered to facilitate tracheal intubation. A gastric tube was inserted in all patients. The lungs were ventilated with an oxygen/air mixture (FI_{O2}0.5–0.6) with a tidal volume of 8–10 ml kg^{-1} to maintain normocapnia. Anaesthesia was maintained with isoflurane, fentanyl and midazolam. Total dose of fentanyl was 20µg $kg^{-1}$and midazolam was 0.15–0.2 mg kg^{-1}. After completion of surgery, patients were transferred to the ICU, where they were treated with warm air heaters to ensure normothermia. Inotropic drugs were continued when needed. Analgesia was provided by i.v. paracetamol 15mg/kg .Weaning from the ventilator and extubation were performed according to the institute's fast-track cardiac care protocol. During 1st 24 hrs after anaesthesia all episodes of nausea, retching and vomiting were recorded by personals who were unaware of the study drug. Rescue antiemetic was given in the form of metoclopramide 0.2mg/kg i.v. Nausea was defined as unpleasant sensation associated with the awareness of urge to vomit. Retching was defined as labored, rhythmic contraction of abdominal muscles without expulsion of gastric contents. Complete response was defined as no nausea, retching or vomiting and no need of rescue medication. The results were statistically analysed using one-way analysis of variance (ANOVA) or using chi-square test. P-values obtained using Chi-square test (Fisher's Exact Probability Test). P-value<0.05 is considered to be statistically significant.

RESULTS:

Total 90 patients observed during this period. Divided in 3 groups of 30 patients each , ondansetron (group A), granisetron (group B), ramosetron (group C) before induction of anaesthesia.

Clinical characteristics are tabulated as below:

Demographic Profile of patients

Table 1: **Distribution of age between three study groups.**

Parameters	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**		**Group Comparisons**		
	No. of patients (n)	% of patients	No. of patients (n)	% of patients	No. of patients (n)	% of patients	Group A vs Group B	Group A vs Group C	Group B vs Group C
Age (years)									
<30	6	20	7	23.3	5	16.6	0.148	0.462	0.444
30-39	6	20	13	43.3	9	30			
40-50	5	16.7	4	13.3	8	26.7			
≥50	13	43.3	6	20	8	26.7			

Table 2**: Distribution of sex between three study groups.**

Parameter	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**		**Between Group Comparisons**		
Sex	No. of patients (n)	% of patients	No. of patients (n)	% of patients	No. of patients (n)	% of patients	Group A vs Group B	Group A vs Group C	GroupB vs Group C
Male	11	36.7	13	43.3	13	43.3			
Female	19	63.3	17	56.7	17	56.7	0.598	0.598	0.999

Table 1 & 2 shows the distribution of age and sex is not statistically significant among three study groups.

Table 3**: Distribution of anthropometric parameters between three study groups.**

Parameters	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**		**Between Group Comparisons**		
	Mean	S.D	Mean	S.D	Mean	S.D	Group A vs Group B	Group A vs Group C	Group B vs Group C
Height (cm)	162.4	8.3	164.8	7.3	163.6	6.6	0.438	0.808	0.813
Weight (kg)	58.3	11.2	59.4	10.5	61.2	8.9	0.898	0.513	0.79
B.M.I(kg/m^2)	22	3.4	21.8	2.7	22.8	2.9	0.945	0.541	0.361

The distribution of anthropometric parameters was not statistically significant among three study groups**.**

Table 4 **: Inter-group comparison of duration of anesthesia and duration of surgery.**

Duration (Min)	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**		**Between Group Comparisons (P-values)**		
	Mean	S.D	Mean	S.D	Mean	S.D	Group A vs Group B	Group A vs Group C	Group B vs Group C
Duration of Anesthesia (Min)	193.5	46.1	191.3	26.9	189.7	41.6	0.453	0.36	0.985
Duration of Surgery (Min)	160.7	46.6	159	30.3	147.2	39.5	0.487	0.383	0.982

There is no statistically significant difference in the duration of surgery and anesthesia in the three study groups.

Table 5**: Comparison of early post operative nausea ,vomiting, retching and rescue antiemetic in Group A, B and C during 0-3 hr postoperatively.**

Parameters	**Group A (n=30) Ondansetron**		**Group B (n=30) Granisetron**		**Group C (n=30) Ramosetron**	
	0-3hrs		0-3hrs		0-3hrs	
	Number	%	Number	%	Number	%
Nausea	4	13.3	3	10.0	1	3.3
Vomiting	4	13.3	4	13.3	2	6.7

Retching	1	3.3	2	6.7	0	0.0
Rescue Antiemetic	4	13.3	4	13.3	1	3.3

Table 5a**: Statistical comparison of nausea, vomiting, retching and rescue antiemetic in Group A, B and C during early (0-3 hr) postoperative period.**

Parameters	**Group A vs Group B**		**Group A vs Group C**		**Group B vs Group C**	
	P value	Remarks	P value	Remarks	P value	Remarks
Nausea	0.688	NS	0.353	NS	0.612	NS
Vomiting	0.999	NS	0.671	NS	0.671	NS
Retching	0.554	NS	0.988	NS	0.492	NS
Rescue Antiemetic	0.999	NS	0.353	NS	0.353	NS

P-values are obtained using Chi-square test (Fisher's Exact Probability Test). P-value<0.05 is considered to be statistically significant. Table 5 shows the percentage of patients having nausea in the 0-3 hr postoperative period as 13% with Group A, 10% with Group B and 3.3% with Group C. The percentage of patients having vomiting in the 0-3 hr postoperative period was 13.3% with Group A, 13.3% with Group B and 6.7% with Group C. The percentage of patients who needed rescue antiemetic between 0-3 hr was13.3% in Group A, 13.3% in Group B and 3.3% in Group C. Table 5a shows that the difference between the three study groups with regards to nausea ,vomiting, retching and rescue antiemetic was not statistically significant during early 0-3 hr postoperative.

Table 6 **: Comparison of post operative nausea, vomiting, retching and rescue antiemetic in Group A, B and C during delayed (3-24 hrs) postoperative period.**

Parameters	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**	
	Number	%	Number	%	Number	%
Nausea	6	20.0	3	10.0	1	3.3
Vomiting	7	23.3	3	10.0	2	6.7
Retching	1	3.3	1	3.3	0	0.0
Rescue Antiemetic	7	23.3	3	10.0	2	6.7

Table 6a**: Statistical comparison of post operative nausea, vomiting, retching and rescue antiemetic in Group A, B and C during delayed (3-24 hrs) postoperative period.**

Parameters	**GroupA vs Group B**		**Group A vs Group C**		**Group B vs Group C**	
	P value	Remarks	P value	Remarks	P value	Remarks
Nausea	0.472	NS	0.044	Significant	0.612	NS
Vomiting	0.299	NS	0.045	Significant	0.987	NS
Retching	0.999	NS	0.987	NS	0.907	NS
Rescue Antiemetic	0.313	NS	0.045	Significant	0.987	NS

Table 6 shows that during delayed (3-24 hrs) postoperative period the percentage of nausea was 20% with Group A, 10% with Group B and only 3.3% with Group C. The percentage of patients having vomiting during delayed (3-24 hrs) postoperative period was 23.3% with Group A, 10% with Group B and 6.7% with Group C. The percentage of patients who needed rescue antiemetic was 23.3% in Group A, 10% in Group B and 6.7% in Group C. Table 6a shows that there was statistically significant difference between Group A and Group C with regards to nausea, vomiting and need of rescue antiemetic. The difference between Group C versus Group B and Group A versus Group B was not statistically significant with regards to nausea, vomiting, retching and rescue antiemetic during delayed (3-24 hrs) postoperative period.

Table 7**: Intergroup comparison of complete response (no nausea, no vomiting, no retching) during delayed (3-24 hrs) postoperative period between three groups.**

Parameters	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**	
	Number	%	Number	%	Number	%
Complete Response	24	80.0	25	83.3	28	93.3

Table7a**: Statistical comparison of complete response during early (0-3 hr) postoperative period between three groups.**

Parameters	**Group A vs Group B**		**Group A vs Group C**		**Group B vs Group C**	
	P value	Remarks	P value	Remarks	P value	Remarks
Complete Response	0.739	NS	0.254	NS	0.424	NS

Table 7 shows that the complete response during early (0-3 hr) postoperative period was 80% in Group A, 83.3% in Group B, 93.3% in Group C.The results were statistically non significant (table 7a)

Table 8 **: Inter group comparison of complete response(no nausea,no vomiting, no retching) during delayed (3-24 hrs) postoperative period.**

Parameters	**Group A Ondansetron**		**Group B Granisetron**		**Group C Ramosetron**	
	Number	%	Number	%	Number	%
Complete Response	21	70.0	27	90.0	28	93.3

Table 8a: Statistical comparison of complete response during delayed (3-24 hrs) postoperative period.

Parameters	**Group A vs Group B 3-24Hrs**		**Group A vs Group C 3-24Hrs**		**Group B vs Group C 3-24Hrs**	
	P value	Remarks	P value	Remarks	P value	Remarks

Complete Response	0.104	NS	0.042	Significant	0.987	NS

Table 8 shows that the complete response during delayed (3-24 hrs) postoperative period was 70% in Group A, 90% in Group B and 93.3% in Group C. The results were statistically significant (Table 8a) between Group A and Group C.

DISCUSSION

Postoperative nausea and vomiting (PONV) are common sequelae of general anaesthesia and a leading cause of postoperative discomfort after cardiac surgical procedures.[5] The complex act of vomiting involves coordination of the respiratory, gastrointestinal, and abdominal musculature and is controlled by the emetic center. [6,7] The area situated in the lateral reticular formation close to the tractus solitarius in the brain stem is thought to be the emetic center.[6,7] Stimuli from several areas within the central nervous system can affect the emetic center. These include afferents from the pharynx, gastrointestinal tract and mediastinum, as well as afferents from the higher cortical centers (including the visual center and the vestibular portion of the eighth cranial nerve) and the chemoreceptor trigger zone (CTZ) in the area prostrema. The area prostrema of the brain is rich in dopamine, opioid, and serotonin or 5-hydroxytryptamine (5HT3) receptors.[6] The four major neuro transmitter systems appear to play important roles in mediating the emetic response viz.

dopaminergic, histaminic (H1), cholinergic, muscarinic and 5HT3.[6] As there are four different types of receptors, there are at least four sites of action of the antiemetic drugs. Antiemetic agents may have actions at more than one receptor, but they tend to have a more prominent action at one or two receptors.[6,7]

Previously the standard practice was to sedate patients after cardiac surgery and to ventilate the lungs for a period of 12-
16 h after operation..A lengthy period of sedation and artificial ventilation

reduced the incidence of postoperative emesis. But recently the trend has been to extubate the trachea much earlier after surgery and have become increasingly aware of the problem of PONV.[8]
Using a moderate dose of fentanyl, and extubating the trachea within the first 6–8 h after cardiac surgery, the incidence of postoperative retching or vomiting was very high despite the use of hyoscine as premedication. The overall incidence of nausea and vomiting was therefore of a similar order to that after other types of major surgery.[9]

A large number of pharmacological and non pharmacological methods have been developed.[10] The non–traditional antiemetics include ephedrine, propofol and corticosteroids. Non pharmacological methods are complementary and alternative medicine (CAM) which includes acupuncture, acupressure, transcutaneous accupoint electrical stimulation, ginger, ephedera based compounds and aromatherapy Phenothiazines,butyrophenones (droperidol) and metoclopramide are associated with extrapyramidal side effects.Pharmacological agents like anticholinergics and antihistamines cause sedation and tachycardia. Phenothiazines,butyrophenones (droperidol) and metoclopramide are associated with extrapyramidal side effects Phenothiazines,butyrophenones (droperidol) and metoclopramide are associated with extrapyramidal side effects.[12]
The introduction of 5HT3 receptor antagonist in 1990s was heralded as a major advance in the treatment of PONV because of the absence of adverse effects that were observed with commonly

used traditional antiemetics.[7,13] The 5HT3 receptor antagonists produced no sedation, extrapyramidal reactions, adverse effects on vital signs or laboratory tests or drug interactions with

other anaesthetic medications.[4] 5HT3 receptor antagonists are routinely used nowadays to prevent PONV following cardiac surgery.

C.R. Grebenik et al has shown that using a moderate dose of fentanyl, and extubating the trachea within the first 6–8 h after cardiac surgery, the incidence of nausea was approximately 37% and that of postoperative retching or vomiting approximately 47%, despite the use of hyoscine as premedication.[14]In the above mentioned study, PONV appeared to be about 1.5–2 times more common in women.[14] Lerman has suggested that the incidence of PONV is approximately 2–3 times greater in women than in men.[15] In our study no statistically significant difference was seen. While obesity has been reported to increase PONV[16], in contrast with other studies, we did not find any correlation between body mass index and nausea and vomiting in our study.

Gigilo et al in their study to prevent nausea and vomiting following cancer chemotherapy concluded that both ondansetron and granisetron have similar antiemetic efficacy but dose of granisetron is much less than ondansetron.[17] It has been reported that using low dose granisetron

0.1 mg is effective in the treatment of PONV.**[18]** Naguib M et al showed no statistical differences between ondansetron, tropisetron and granisetron groups in lowering incidence of PONV, but concluded that ondansetron, when given prophylactically resulted in a significantly lower incidence of PONV than metoclopramide. **[19]** Wilson AJ et al concluded that granisetron is effective in the prevention of PONV and increasing the dose from 1 mg to 3 mg did not confer any additional advantage with 1 mg being the optimum dose.**[20]** Fujii Y et al showed that prophylactic therapy with ramosetron was more effective than granisetron for preventing postoperative nausea and vomiting during 0–48 hr after anesthesia.**[21]**

Our study is in accordance with studies of Noda et al.**[22]** & Koizumi et al **[23]** in which ramosetron and granisetron were found to have similar effectiveness for the prevention of postoperative nausea and vomiting.Ramosteron has been shown to have statistically significant complete response during delayed (3-24 hrs) postoperative period over ondansetron in our study**.**

Conclusion

Based on this study it can be concluded that during early (0-3 hr) postoperative period the three drugs ondansetron, granisetron and ramosetron are comparable to each other. During delayed (3-24 hrs) ramosetron appers better than ondansetron in prevention of PONV in cardiac surgery. Effect of ramosetron and granisetron appears comparable to each other. Further studies with larger patient numbers may be required to validate the findings of this study.

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