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A COMPARATIVE STUDY OF RAMOSETRON AND GRANISETRON FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC GYNECOLOGICAL SURGERIES UNDER GENERAL ANESTHESIA

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ABSTRACT

INTRODUCTION: Post-operative nausea and vomiting (PONV) is one of the most distressing and common complaint that patients have following general anesthesia. Laparoscopic gynecological surgery is associated with high incidence of post-operative nausea and vomiting. Granisetron is a selective competitive $5HT_3$ receptor agonist having both central and peripheral actions. Ramosetron is another $5HT_3$ receptor antagonist of newer generation with prolonged duration of action. This study compared the efficacy of prophylactic use of granisetron and ramosetron for prevention of PONV following laparoscopic gynecological surgery.

METHODS: In a prospective randomised study, 80 adult females received either granisetron(2.5mg) or ramosetron(0.3mg) (N=40 in each group) by the intravenous route at the end of the surgery. The treatment groups were similar in patient characteristics, surgical procedures and anesthetic management. Observation was done upto 48 hours post-operative.

RESULTS: Even though the incidence of nausea in the last 24 hours of observation was statistically significant in the ramosetron group vs granisetron (p=0.019) but the total response of 48 hours duration for both the groups were observed to be statistically insignificant (p=0.237).

CONCLUSION: In conclusion, prophylactic therapy with Ramosetron is equally effective as prophylactic therapy with Granisetron for the prevention of PONV in laparoscopic gynecological surgery.

KEYWORDS : postoperative nausea and vomiting (PONV), Granisetron, Ramosetron, laparoscopic gynaecological surgery

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most distressing and common complaint that patients have, following general anaesthesia. Kapur P.A described PONV as "the big little problem"[1] and considered it to be one of the major challenges faced by the anesthesiologists in their day to day practice. The phenomenon of PONV can lead to increase in the risk of wound dehiscence, bleeding from operative site, pulmonary aspiration of vomitus, esophageal tears (Mallory Weiss syndrome), muscle fatigue, fluid and electrolyte imbalance and also enhances psychological effects like anxiety and apprehension. In general, the incidence of emesis is highest in female patients of child bearing age and after certain surgical procedures including cholecystectomy, gynecological surgery and laparoscopy[2]. The highest incidence of post operative nausea and vomiting was reported in women undergoing laparoscopic ovum retrieval (54%) and the next highest occurred after laparoscopy (35%)[3]. A number of pharmacological agents like antihistaminic, phenothiazine derivatives, butyrophenones and dopamine receptor antagonists have been used as routine prophylaxis against PONV. However, these drugs have unwanted side effects like dysphoria, dry mouth, restlessness, tachycardia and extra pyramidal symptoms[2]. Recently introduced 5-HT_3 receptor antagonists are devoid of such side effects and have been proved highly efficacious in both preventing and treating PONV in gynecological surgery[4]. Granisetron is a selective competitive 5-HT_3 receptor antagonist, having both central and peripheral action, is in use as an anti emetic for a long time in gynecological surgery[4]. Ramosetron is another newer addition to selective 5-HT_3 receptor antagonist that have been proved to be an effective agent in preventing PONV in gynecological surgeries. This study was undertaken to evaluate and compare the efficacy of granisetron and ramosetron, given prophylactically, in preventing postoperative nausea and vomiting in the long term following laparoscopic gynecological surgery.

MATERIALS AND METHODS:

This comparative study was conducted with 80 female patients of 25-60 years of age who underwent laparoscopic gynaecological surgery under anesthesia. The study protocol was reviewed and approved by the hospital ethical committee and a written informed consent was obtained from each and every patient recruited in this study. Each group consists of 40 patients. Group A received i.v. Granisetron (2.5mg) and Group B received i.v. Ramosetron (0.3mg). The drugs were given at the end of surgery during skin closure. Subject exclusion criteria were unwilling patients, those with history of pulmonary, cardiovascular, metabolic, gastrointestinal disorders, motion sickness, previous PONV, pregnant and menstruating females as well as patients who have taken anti-emetic medication within 24hrs before the surgery and patients with history of allergy to study drugs.

Each of the patients selected for the study was visited and examined on the day before surgery, was counselled and written informed consent was taken. A thorough pre-anaesthetic check-up was carried out and the baseline investigations were reviewed and recorded. All patients were instructed not to consume any solid food after midnight, but clear fluids were permitted up to two hours prior to the scheduled time of operation. All patients received tablet Alprazolam 0.5mg orally on the night before and another 0.5mg of the same drug in the morning of surgery to allay fear, anxiety and apprehension. The anaesthetic regimen and surgical procedure were standardized for all patients. After wheeling patients into the operating room, the standard monitors were attached. By using a computer generated random number table, the patients either granisetron or ramosetron for laparoscopic gynaecological surgery each day were chosen randomly. 40 patients were allotted in each group. Group A received i.v. Granisetron (2.5mg). Group B received i.v. Ramosetron (0.3mg). The study medications were prepared in identical 5ml syringe and diluted to 5 ml volume and administered intravenously over 30 seconds at the end of the surgery. In the operating room an intravenous cannula (18G) was inserted and provided with balanced salt solution at a rate which is titrated according to requirement. Standard monitors were attached and baseline parameters were duly noted. All the patients were pre-medicated with Midazolam (0.07mg/kg) intravenously (i.v.) 5 minutes before induction of anesthesia. Next the patients were given with i.v. fentanyl citrate (2µg/kg) and glycopyrrolate (0.01mg/kg). Ventilation was assisted with face mask (100% O_2) for 3 minutes. Anesthesia was induced with i.v. thiopentone (5mg/kg) followed by i.v. administration of succinylcholine (2mg/kg) to facilitate laryngoscopy and intubation. After intubation with a proper size cuffed endotracheal tube anaesthesia was maintained with nitrous oxide 66% and oxygen 33% on IPPV and titrated administration of halothane (0.5-2%) and intermittent non-depolarizing muscle relaxants i.v. Atracurium (0.05mg/kg) was used as and when necessary. Minute ventilation and respiratory rate was adjusted in such a way to keep $ETCO_2$ around 35mm of Hg. After intubation all patients were given a nasogastric tube placement in order to ensure baseline emptying of air and gastric contents from stomach, which was withdrawn subsequently. 75mg of diclofenac sodium was administered intramuscularly before surgical draping in order to prolong and improve analgesia in the peri-operative period. During operation, the abdomen was insufflated with carbon dioxide, maintaining an intra abdominal pressure (IAP) limit of 15mmHg. The following parameters were continuously monitored intra operatively – pulse rate, systolic and diastolic blood pressure and mean arterial pressure, E.C.G. in lead II, SpO_2, $ETCO_2$. Intravenous Ringer's lactate was used for intra operative and immediate fluid management for first 4 hours. Intravenously Granisetron and Ramosetron were administered at the completion of surgery during

skin closure. Residual neuromuscular blockade was reversed with i.v neostigmine (0.05mg/kg) and i.v. glycopyrrolate (0.01mg/kg). Extubation was done after clinical assessment of complete reversal. Patients were shifted to the recovery area where standard recovery criteria were fulfilled.

All patients were closely monitored in the post-anaesthesia care unit for the first 0-4 postoperative hours and thereafter in the ward for 4- 48 hours. All of them received supplemental oxygen (6L/min) by face mask in the postoperative period for first 2 hours. Number of episodes and severity of postoperative nausea and vomiting in both the study groups was assessed at 0-4 hours, 4-24 hours, and 24-48 hours intervals.

The severity of postoperative nausea and vomiting was assessed by the following score where 0 = complete response (no PONV, no rescue antiemetic required), 1= only nausea, 2 = nausea with retching,3 = vomiting ***Complete response*** of prophylactic antiemetic was defined as no symptoms related to emesis and no need for rescue antiemetic within the study period. ***Nausea*** was defined as a subjective unpleasant sensation associated with an extreme urge to vomit. ***Retching*** was defined as rhythmic, laboured, spasmodic respiratory movements against a closed glottis with contractions of the abdominal muscles without any expulsion of gastric contents. ***Vomiting*** was defined as the rapid and forceful evacuation of stomach contents up to and out of the mouth. ***Rescue antiemetic*** was administered to all those patients who vomited 2 or more times or complained of nausea and/or retching lasting for at least 15 minutes. The drug used as a rescue antiemetic was metoclopramide 10mg intravenously. Frequencies of rescue antiemetics in these 2 groups was assessed. Incidences of any other *adverse effects* were assessed.

All results were statistically analyzed. Plan for statistical analysis: All clinical dates were tabulated and presented as Mean ± Standard Deviation. Demographic parameters like age, bodyweight, and data like duration of anesthesia and surgery in between group A & B were compared using unpaired t test. Post-operative parameters like SpO_2, respiratory rate, and pulse rate, systolic and diastolic blood pressure and postoperative nausea and vomiting score were compared using the appropriate test. The number of patients showing complete response, the episodes and severity of post-operative nausea and vomiting and those requiring rescue medications in between groups A & B are recorded and compared using Chi-square test. A p-value <0.05 was considered statistically significant.

Observations:

Table 1: Demographic data

	Groups			
	Group A	Group B		
Parameter	**Mean ± Std. Deviation**	**Mean ± Std. Deviation**	**p value**	**Significance**
Age (years)	32.05 ± 8.4	32.6 ± 8.89	0.777	Not Significant
Body Weight (kgs)	54.2 ± 5.71	54.57 ± 6.1	0.772	Not Significant

In our study, both the groups were comparable with regards to age (years) and body weight(kg) (P>0.05)

Table 2: Duration of Anaesthesia and Surgery of 2 groups

	Group			
	Group A	Group B		
Parameter	**Mean ± Std. Deviation**	**Mean ± Std. Deviation**	**p value**	**Significance**
Duration of Anaesthesia (minutes)	95.37 ± 20.08	94.88 ± 18.31	0.908	Not Significant
Duration of Surgery (minutes)	77.62 ± 20.22	78 ± 18.6	0.931	Not Significant

The differences between the mean duration of anesthesia and surgery amongst patients of group A and B were negligible and found to be statistically insignificant (P>0.05)

Table 3: Incidence of Nausea in post operative period

	Group				
NAUSEA	**Group A**	**Group B**	**Total**	**p value**	**Significance**
0 to 4 Hours	6(15)	4(10)	10(12.5)	0.499	Not Significant
4 to 24 Hours	5(12.5)	4(10)	9(11.2)	0.723	Not Significant
24 to 48 Hours	11(27.5)	3(7.5)	14(17.5)	0.019	Significant
Total 48 Hours	16(40)	11(27.5)	27(33.8)	0.237	Not Significant

This table shows the comparison of the incidence of nausea, between the groups A and B during the post operative period (0-48 hours) where the incidence of nausea was significant only in the last 24 hours (P=0.019) but in the total span it was found to be non-significant (P=0.234).

Figure 1: Bar diagram showing the incidence of nausea in post operative period

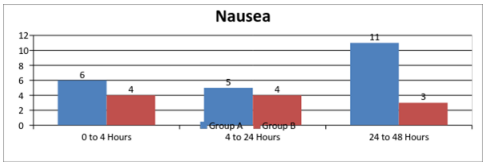

Table 4 : Incidence of vomiting in the post-operative period in 2 groups

	Group				
Vomiting	**Group A**	**Group B**	**Total**	**p value**	**Significance**
0 to 4 Hours	3(7.5)	2(5)	5(6.2)	0.644	Not Significant
4 to 24 Hours	3(7.5)	3(7.5)	6(7.5)	1.000	Not Significant
24 to 48 Hours	7(17.5)	2(5)	9(11.2)	0.077	Not Significant
Vomiting (48 hours)	11(27.5)	7(17.5)	18(22.5)	0.284	Not Significant

Table 5 shows the comparison of incidence of vomiting between the groups A and B in the post operative period where the difference between them was calculated to be non-significant in the entire 48 hours span(P=0.28)

Figure 2:Bar diagram showing of incidence of vomiting in the post operative period

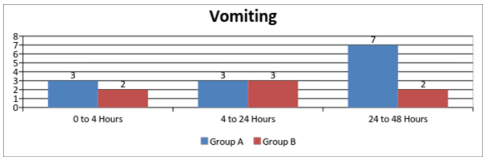

Table 5 : The complete response in the post operative period (48 hours) in 2 groups

	Group				
Complete Response	**Group A**	**Group B**	**Total**	**p value**	**Significance**
0 to 4 Hours	34(85)	36(90)	70(87.5)	0.499	Not Significant
4 to 24 Hours	35(87.5)	36(90)	71(88.8)	0.723	Not Significant
24 to 48 Hours	29(72.5)	37(92.5)	66(82.5)	0.019	Significant
Complete Response (48 Hours)	24(60)	29(72.5)	53(66.2)	0.237	Not Significant

This table compares the Complete Response to antiemetics among the patients of group A and B during the post operative period where the differences between the two groups was significant in last 24 hours but the differences in the total period of 48 pours was not statistically significant (p=0.237)

DISCUSSION

Postoperative nausea and vomiting (PONV) is a well-established entity, which has the potential to increase perioperative complications and morbidity. Kapur PA [1] has variously described PONV as the "big little problem", the "final therapeutic challenge" as well as the "big big problem" of ambulatory surgery.

Nowadays several gynaecologic procedures are done laparoscopically. PONV is a significant problem in these patients as they include multiple high risk factors for PONV such as female sex, non smokers, use of

volatile anaesthetics, use of N_2O, use of intra and post-operative use of opioids as well as duration of surgery more than 30 minutes.

5-HT_3 receptor antagonists are the preferred anti emetics because they are effective in prevention of PONV with fewer side effects. Granisetron which achieves its antiemetic property by acting on the 5-HT_3 receptors in the chemo-receptor trigger zone (CTZ)[5] has been found to be very effective by Wilson et al[6] for prevention of PONV. Moreover, Granisetron has been reported to be more efficacious and longer acting than Ondansetron by Dipasri et al[7] for prevention of nausea and vomiting in early postoperative period in patients undergoing day-care laparoscopic tubal ligation.

Ramosetron has been found to act through the same 5-HT_3 receptors and exhibited more potent and sustained antagonistic activities against 5-HT_3 receptors than the existing 5-HT_3 receptor antagonists[8]. It is also effective for the treatment of cisplatin-induced emesis. The exact mechanism of Ramosetron for prevention of PONV is unknown but may act at the area prostrema and nucleus tractus solitarius, which contain a large number of 5-HT_3 receptors. The affinities of 5-HT_3 receptor antagonist was compared to be Granisetron 1 vs. Ramosetron 41[9,10] and the elimination half-life was Granisetron 3.1±1.2 hrs versus Ramosetron 5.8±1.2 hrs[11.] In this present study, comparison and evaluation has been done ***between the efficacy of Granisetron and Ramosetron group*** for prevention of PONV following laparoscopic gynaecological surgery for a span of 48 hours.

The major deficiency in our study design was the failure to include a control group receiving placebo. It has been previously demonstrated that Granisetron is a better anti-emetic than placebo for preventing PONV in major gynecologic surgery. Aspinall and Goodman[12] have also suggested placebo controlled trial are unethical if active drugs are available because PONV are common and distressing symptoms against which there is an effective treatment. Therefore, a control group was not included in the study.

In our study, the incidence of nausea in 0-4 hour and 4-24 hour interval for Granisetron group were 15% and 12.5% respectively, while the incidences for nausea in the same time interval for Ramosetron group were 10% and 10% respectively. It was seen that in the last 24 hrs of the study period of 48 hours, 27.5% patients of the Granisetron group and only 7.5% patients from the Ramosetron group, ***complained of nausea.*** The differences between the study groups were found to be statistically significant (p=0.019) only in the last 24 hours but if the total span of 48 hours is considered the differences between the two groups were found to be insignificant (p=0.237).

It was noted in the study that 7.5% of Granisetron group and 5% of Ramosetron group vomited in the 0-4 hour interval and incidence of vomiting in the next 4-24 hour interval was 7.5% for both groups and finally 17.5% (7 out of 40) patients of the Granisetron group and only 5% (2 out of 40) patients from the Ramosetron group, ***vomited*** at the end of the study period of last 24 hours**.** The differences were found to be statistically insignificant (p=0.077) in the span of 48 hrs.

The ***complete response was noted*** in 72.5% patients of the Granisetron group and the response was 92.5% in patients who received Ramosetron. Statistical analysis suggested the difference between the Granisetron and the Ramosetron group was found to be statistically significant (p=0.019) only in the last 24 hours but in total 48 hours post operative span this difference was not statistically significant. Our findings were corroborated by a study conducted by Won Suk Lee et al[13] where comparison of palanosetron, granisetron, ramosetron for prevention of postoperative nausea and vomiting after laparoscopic gynaecological surgery was conducted and they concluded that two drugs granisetron and ramosetron were found to be equally effective in 48 hours post operative time span.

Incidence of adverse effects like ***headache***, was reported by 2 patients in both the Granisetron group and Ramosetron group. ***Dizziness*** was reported by 2 in the Granisetron group, however only 1 patient from the Ramosetron, no one in 2 groups was found to be ***sedated***. One patient from each group had ***postoperative shivering***, whereas there was no incidence of any hypersensitivity reaction or extra pyramidal symptoms in any of the treatment groups. The differences of the adverse events between the study groups were found to be statistically non-significant (p>0.05). None of the side effects needed treatment. Thus, Ramosetron, like Granisetron, is devoid of clinically important side effects and the findings corroborated with the previous studies.

In conclusion, prophylactic therapy with Ramosetron is equally effective as prophylactic therapy with Granisetron for the prevention of PONV in laparoscopic gynecological surgery.

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