A COMPARATIVE STUDY OF GRANISETRON, RAMOSETRON AND PALONOSETRON AS ANTIEMETICS IN PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES

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ABSTRACT

BACKGROUND

Postoperative Nausea and Vomiting (PONV) are the most unpleasant side effects after surgery. The incidence of PONV after laparoscopic surgery is high (40-75%). The purpose of this study was to prospectively evaluate the efficacy of granisetron, ramosetron and palonosetron for the prevention of PONV in patients undergoing laparoscopic surgery.

METHODS

In this prospective, randomized observational study, 90 healthy patients who were undergoing abdominal laparoscopic surgery under general anaesthesia were enrolled. Patients were divided into three groups. Group A received Inj. granisetron (1 mg), group B received Inj. ramosetron (0.3 mg), and Group C received Inj. palonosetron (0.075 mg) intravenously five minutes before induction of anaesthesia. The incidence of nausea, vomiting, retching, rescue antiemetic requirements and complete response during the first 24 h after surgery were evaluated.

RESULTS

The number of complete responders during 0-4 h were 24 (80.00%) for Palonosetron, 23 (76.67%) for Ramosetron and 21 (70.00%) for Granisetron, which was statistically nonsignificant. During 4-12 h number of complete responders were 26 (86.67%) for Palonosetron, 25 (83.33%) for Ramosetron and 22 (73.33%) for Granisetron representing a significant difference ($p=0.021$) between Granisetron and Palonosetron, while Granisetron vs Ramosetron ($p=0.092$) and Ramosetron vs Palonosetron ($p=0.513$) showed non-significant differences. Similarly, during 12-24 h number of complete responders were 28 (93.00%) for Palonosetron, 26 (86.67%) for Ramosetron and 24 (80.00%) for Granisetron representing a significant difference ($p=0.011$) between Granisetron and Palonosetron. The incidence of PONV during 4-12 h and 12-24 h also showed a significant difference between Granisetron and Palonosetron.

CONCLUSIONS

The antiemetic effect of Palonosetron is better than Granisetron, whereas there was no significant difference in the antiemetic efficacy of Granisetron and Ramosetron as well as between Ramosetron and Palonosetron in patients undergoing laparoscopic surgery.

KEYWORDS

Granisetron, Palonosetron, Ramosetron, Postoperative Nausea and Vomiting, Complete Response.

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INTRODUCTION

Postoperative nausea and vomiting are the most unpleasant side effects after surgery. Overall incidence of PONV has been reported to be between 20% and 30%, but can increase upto 80% in high risk patients.^[1]

PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain.^[2] Prevention of

PONV in high-risk patients significantly improves postoperative ratings of well-being and satisfaction.^[3] While the experience of PONV is generally self-limited, postoperative vomiting/retching (POV) can lead to rare but serious medical complications, such as fluid and electrolyte disturbances, delayed hospital discharge, aspiration of gastric contents, suture dehiscence, oesophageal rupture, subcutaneous emphysema or pneumothorax.^{[4][5]}

The aetiology of PONV is usually multifactorial involving anaesthetic agents, the type of procedure and patient factors. Patient related factors are age, weight, gender and pre-existing disease, history of postoperative nausea and vomiting, anxiety and smoking. Numerous antiemetics have been studied to prevent and treat PONV after laparoscopic abdominal surgery including antihistamines, anticholinergics and benzamide.^[6-8]

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However, these agents can cause undesirable side effects such as sedation, dry mouth and hypotension.

Selective serotonin 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists have a well-established role in the prophylaxis and treatment of PONV due to their efficacy and fewer side effects compared to other antiemetics.^[9] Granisetron is one of the more selective 5HT₃ receptor antagonists than Ondansetron. The elimination half-life of Granisetron is 9 hours, which is 2.5 times longer than that of Ondansetron and thus requires less frequent dosing.^[10]

Ramosetron is also a selective serotonin receptor antagonist approved in Japan with affinity higher than that of the previously available drugs Ondansetron, Granisetron and Tropisetron.^[11] They have a little effect on the lower oesophageal sphincter pressure, oesophageal or gastric motility or small bowel transit time. Antiserotonins are generally well tolerated. Adverse effects reported are headaches, light headedness, dizziness, flushing at the intravenous site, transient increases in the plasma concentrations of liver transaminase enzymes, a warm epigastric sensation and constipation.^[12]

Palonosetron is first of second generation 5-HT₃ receptor antagonists for the treatment of PONV. This new agent has a higher receptor binding affinity and longer elimination half-life of about 40 hours.^[13] Recent receptor binding studies suggest that Palonosetron is further differentiated from other 5-HT₃ receptor antagonists by binding with 5-HT₃ receptor in an allosteric positively cooperative manner at sites different from those that bind with Ondansetron and Ramosetron.^[14]

Laparoscopic surgeries are the preferred surgical procedure these days. It has considerably decreased the surgical mortality, but the incidence of postoperative nausea and vomiting remains high and hence prophylactic antiemetics are indicated. Therefore, we designed a prospective randomized study to evaluate the efficacy of Granisetron, Ramosetron and Palonosetron as antiemetics for the prevention of postoperative nausea and vomiting in patients undergoing Laparoscopic surgeries.

MATERIAL AND METHODS

After obtaining an approval from Institutional Ethical Committee, ninety patients aged 18-65 years of either sex with American Society of Anaesthesiology (ASA)-physical status I or II and scheduled for elective laparoscopic surgery were included in the study. An informed written consent was taken from each patient.

Exclusion Criteria

Patients with ASA III and above, patients with previous history of postoperative nausea and vomiting, history of motion sickness, history of gastroesophageal reflux disease, patient who has taken any antiemetic 24 hours prior to the surgery, patients with BMI > 30 kg/sqm, pregnant females, allergy to any of these drugs. Patients enrolled were randomly allocated to three groups (Group A, Group B and Group C) according to simple random sampling and each group consisted of thirty patients. Group A patients received Granisetron 1 mg IV, Group B patients received Ramosetron 0.3 mg IV, Group C patients received Palonosetron 0.075 mg IV.

Pre-anaesthetic check-up was done one day before surgery and it included detailed history, thorough physical examination (General and Systemic) and relevant

investigations. Demographic profile including age, sex, height and weight were recorded and BMI calculated. An informed written consent was taken from all patients at the time of preanaesthetic examination. All patients were prescribed tab Midazolam 7.5 and Pantoprazole 20 mg as a part of premedication night before surgery and were advised to stay NPO for at least 8 hours prior to surgery.

After arrival of patient in the preoperative room, an intravenous line was secured with 18G intravenous cannula on the dorsum of left hand and ringer lactate was started. Injection Ranitidine 50 mg IV was given in preoperative room. Thereafter, the patients were shifted to Operation Theatre. Monitors were attached and baseline pulse rate, blood pressure (systolic pressure, diastolic pressure and mean arterial pressure) oxygen saturation by pulse oximeter were recorded.

On table the patient received one of the study drugs five minutes before the induction by an anaesthetist not involved in the study. All the patients were pre-oxygenated for 3 minutes and induced with Propofol 2 mg/kg IV and intubation was facilitated with IV Rocuronium 0.6 mg/kg IV. Anaesthesia was maintained with 0.5-1% Halothane, 50% Nitrous oxide, 50% oxygen and neuromuscular blockade by incremental doses of Rocuronium whenever required. Blood pressure (Systolic blood pressure, diastolic blood pressure and mean arterial pressure), pulse rate, SPO₂, end-tidal carbon dioxide concentration (ETCO₂) and ECG changes were monitored throughout the surgery. Ventilation was controlled manually. A nasogastric tube was inserted to make the stomach empty of air and other contents. Patients received injection diclofenac 75 mg deep IM for postoperative analgesia before shifting them to postoperative ward and repeated after every 8 hours for 24 hours.

On completion of surgery, residual effect of muscle relaxant was reversed with Glycopyrrolate 0.01 mg/kg IV and Neostigmine 0.05 mg/kg IV in all patients. Before tracheal extubation, direct pharyngoscopy was performed and secretions were removed and nasogastric tube was aspirated. Subsequently, patients were extubated when extubation criteria was met and shifted to recovery room. Postoperatively, patients were advised to take rest and remain in the bed at least for the first 24 hours. Other emetogenic analgesics and drugs were avoided for 24 hours.

The number of episodes of nausea, retching and vomiting and the side effects like headache, dizziness, drowsiness, and myalgias were assessed postoperatively for 24 hours. The above findings were recorded in the following intervals: 0-4 hours, 4-12 hours and 12-24 hours in the postoperative period and statistical analysis was done accordingly. Complete response was defined as no nausea, retching or vomiting and no need for rescue antiemetic medication. Nausea was defined as subjectively unpleasant sensation associated with awareness of urge to vomit. Retching was defined as laboured spastic rhythmic contraction of the respiratory muscle without the expulsion of gastric contents. Rescue antiemetic was given in the form of injection Metoclopramide 0.15 mg/kg IV (10 mg).

Data Analysis

All the observations made in the study were recorded in specially prepared proforma. Observations at different time periods were compared for each parameter in the group and intergroup comparison was done. All the data was analysed

and subjected to statistical analysis for significance. Data are presented as Mean $\pm$ SD and proportions as appropriate. Non-parametric data was compared using the Chi-square test and parametric data was compared using student 't' test. A

significant difference is assumed with P less than 0.05. All analyses were performed using the Statistical Package for Social Science (SPSS for windows version 16, SPSS Inc., Chicago, IL).

	No. of Patients (%)			Group Comparison		
	Group A*	Group B	Group C	A vs B	A vs C	B vs C
Age (Years)	42.73 $\pm$ 9.16	41.80 $\pm$ 9.08	42.60 $\pm$ 9.46	0.693	0.956	0.739
Sex Male	18 (60.00)	17 (56.67)	14 (46.67)	0.634	0.062	0.162
Female	12 (40.00)	13 (43.33)	16 (53.33)			
ASA I	17 (56.67)	16 (53.33)	14 (46.67)	0.633	0.162	0.352
II	13 (43.33)	14 (46.67)	16 (53.33)			
Weight (kg)	64.10 $\pm$ 6.43	63.33 $\pm$ 6.16	65.40 $\pm$ 4.81	0.639	0.379	0.153
Height (cm)	153.77 $\pm$ 8.36	154.60 $\pm$ 7.62	157.47 $\pm$ 7.16	0.688	0.071	0.139
BMI (kg/m ²)	20.84 $\pm$ 1.79	20.47 $\pm$ 1.60	20.78 $\pm$ 1.45	0.401	0.884	0.437
Duration (min.) Anaesthesia	85.67 $\pm$ 7.51	83.83 $\pm$ 8.58	81.50 $\pm$ 9.30	0.382	0.061	0.317
Surgery	67.33 $\pm$ 7.63	65.17 $\pm$ 8.86	63.17 $\pm$ 9.42	0.314	0.071	0.401

Table 1: Patient's Characteristics and Duration of Surgery

*Group A = Granisetron, Group B = Ramosetron, Group C = Palonosetron.

The groups were comparable with respect to age, sex, ASA status, weight, height, BMI and duration of anaesthesia and surgery.

Parameters	Mean±SD		p-value
	Pre-operative	Post-operative	
Group A			
Heart rate (beats/min.)	89.50±10.08	87.27±9.89	0.389
Systolic BP (mmHg)	131.55±8.10	129.23±7.90	0.270
Diastolic BP (mmHg)	82.17±9.08	81.23±7.42	0.665
Mean AP (mmHg)	98.81±8.15	97.33±7.11	0.457
SPO2 (%)	99.14±1.06	99.43±0.97	0.241
Group B			
Heart rate (beats/min.)	81.62±6.75	83.00±7.41	0.458
Systolic BP (mmHg)	130.14±9.28	128.50±9.24	0.499
Diastolic BP (mmHg)	78.69±6.45	80.17±6.11	0.371
Mean AP (mmHg)	96.12±6.98	96.30±6.73	0.920
SPO2 (%)	99.53±0.73	99.30±0.79	0.241
Group C			
Heart rate (beats/min.)	82.10±8.39	84.47±7.15	0.251
Systolic BP (mmHg)	132.10±9.62	129.50±8.34	0.272
Diastolic BP (mmHg)	81.70±5.47	79.33±4.76	0.079
Mean AP (mmHg)	98.50±6.47	96.10±5.57	0.129
SPO2 (%)	99.80±0.48	99.67±0.61	0.351

Table 2: Comparison of pre- and post-operative clinical parameters

The difference between the preoperative and postoperative heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation was not significant across the three study groups.

Parameters	No. of Patients (%)			Group Comparison (P Values)		
	Group A*	Group B	Group C	A vs B	A vs C	B vs C
0-4 hrs.						
Nausea	7 (23.33)	5 (16.67)	4 (13.33)	0.24	0.07	0.51
Vomiting	5 (16.67)	4 (13.33)	3 (10.00)	0.51	0.17	0.46
Retching	4 (13.33)	3 (10.00)	2 (6.67)	0.46	0.12	0.39
Rescue antiemetic	5 (16.67)	4 (13.33)	3 (10.00)	0.51	0.46	0.46
Complete response	21 (70.00)	23 (76.67)	24 (80.00)	0.292	0.101	0.573
4-12 hrs.						
Nausea	6 (20.00)	4 (13.33)	2 (6.67)	0.21	0.01	0.12
Vomiting	4 (13.33)	2 (6.67)	1 (3.33)	0.12	0.01	0.28
Retching	4 (13.33)	2 (6.67)	1 (3.33)	0.12	0.01	0.28
Rescue antiemetic	4 (13.33)	2 (6.67)	1 (3.33)	0.12	0.01	0.28
Complete response	22 (73.33)	25 (83.33)	26 (86.67)	0.092	0.021	0.513
12-24 hrs.						
Nausea	5 (16.67)	3 (10.00)	2 (6.67)	0.17	0.01	0.39
Vomiting	3 (10.00)	1 (3.33)	0 (0.00)	0.06	0.00	0.07
Retching	2 (6.67)	1 (3.33)	0 (0.00)	0.28	0.01	0.07
Rescue antiemetic	3 (10.00)	1 (3.33)	0 (0.00)	0.06	0.00	0.07
Complete response	24 (80.00)	26 (86.67)	28 (93.33)	0.213	0.011	0.122

Table 3: Comparison of postoperative nausea, vomiting, retching, rescue antiemetic and complete response in study groups

*Group A = Granisetron, Group B = Ramosetron, Group C = Palonosetron

During 0-4 hrs. postoperatively, the intragroup comparison showed non-significant differences for all these parameters between the three groups.

During 4-12 hrs. postoperatively, the intragroup comparison showed significant difference for nausea ($p=0.01$), vomiting ($p=0.01$), retching ($p=0.01$), rescue antiemetic ($p=0.01$) and complete response ($p=0.021$) between groups A and C. While in Groups A and B and Groups B and C, all the parameters showed non-significant differences.

During 12-24 hrs. postoperatively, the intragroup comparison showed significant differences for nausea ($p=0.01$), vomiting ($p=0.00$), retching ($p=0.01$), rescue antiemetic ($p=0.00$) and complete response C ($p=0.011$) between Group A and Group C, while Group A and B and Group B and C all the parameters showed non-significant differences.

DISCUSSION

Postoperative Nausea and Vomiting (PONV) continues to be one of the most common complaints following surgery, occurring in more than 30% of surgeries or as high as 70% to 80% in certain high risk population without prophylaxis. PONV is also one of most common reasons for patient's poor satisfaction during postoperative period.

The incidence of PONV after laparoscopic surgery is high (40-75%). Pneumoperitoneum probably stimulates the mechanoreceptors in the gut and this increases the risk of PONV. Pneumoperitoneum induced intestinal ischemia may release serotonin and other neurotransmitters, which could lead to PONV. But Kim et al. found that lowering the pneumoperitoneum pressure to 8 mmHg does not reduce the incidence of PONV.^[15]

Despite advances in antiemetic therapy in the last decade, PONV is still found to be relatively high. The quest for more effective antiemetic drugs without sedative or extrapyramidal side-effects has led to the development of relatively new class of drugs 5-hydroxytryptamine antagonists. These agents also known as 'setrons,' are widely regarded as the most efficacious antiemetic available today.

Their actions involve both central and peripheral mechanisms. Centrally, they bind competitively and selectively to serotonin receptors in the Chemoreceptor Trigger Zone (CTZ) of the central nervous system. Peripherally, they block the receptors in the gastrointestinal tract, which prevents the action of serotonin and inhibits emetic symptoms (Bunce KT).^[16]

The need for the drugs with improved performance within this group arose on account of relatively less potency and shorter duration of action, besides detectable binding to other 5-hydroxytryptamine receptors by Ondansetron. Granisetron is a potent and highly selective 5-HT₃ receptor antagonist that has little or no affinity for other serotonin (5-HT) receptors. Ramosetron is a relatively recent drug and has a longer and more potent efficacy than previously developed 5HT₃ antagonists. There are several reports that Ramosetron was as effective as or even more effective than the older 5-HT₃ receptor for the prevention of PONV during 0-24 h after anaesthesia (Kim SI, et al).^[17] Furthermore, the antiemetic effect of Ramosetron can last up to 48 hours (Fujii Y et al).^[18] The differences in effectiveness between the older 5-HT₃ receptor antagonist and Ramosetron may be related to the

longer elimination half-life and higher receptor affinity ($pK_i=8.5$) of Ramosetron. Palonosetron is the latest 5-HT₃ antagonist. Its unique properties have led to it being described as the first of a second generation of 5-HT₃ antagonists. Recent receptor binding studies suggest that Palonosetron is further differentiated from other 5-HT₃ by interacting with 5-HT₃ receptors in an allosteric, positively cooperative manner at sites different from those that bind with Ondansetron and Granisetron. Palonosetron shows avid binding to the 5-HT₃ receptor with a pK_i of 10.4, which far exceeds the other 5-HT₃ antagonists (Muchatuta NA, Paech MJ).^[19] Palonosetron has the longest elimination half-life of 40 hours (Ho KY, Gan TJ).^[20]

Granisetron is highly specific 5HT₃ antagonist with a half-life that is about twice as long as that of Ondansetron. The FDA-approved dose for the prevention of PONV is 1 mg. This is based on a dose range study from Wilson and Associates, in which 0.1, 1.0 and 3.0 mg were associated with risk ratios for postoperative vomiting of 0.94 (Not significant), 0.56 and 0.66.

According to Fujii et al., Ramosetron is effective in preventing PONV after gynaecological surgery and Ramosetron 0.3 mg is an effective dose for preventing PONV. In addition, the manufacturer's recommended dose is 0.3 mg IV once a day.^{[21],[22]} Therefore, Ramosetron at the 0.3 mg dose was chosen for our study.

Based on the studies of Candiotti et al., the minimum effective dose of Palonosetron in the prophylaxis of PONV is 0.075 mg and this has been approved by the Food Drug Agency (FDA).^[23] They used Palonosetron 0.025 mg, 0.05 mg and 0.075 mg groups and the incidence of early emesis was lower in the Palonosetron 0.075 mg group compared with placebo. So in our study, we decided to use Palonosetron 0.075 mg.

Aspinall and Goodman suggested that if active drugs are available, placebo-controlled trials are unethical because PONV is a very disturbing and distressing event that can occur after laparoscopic surgery. So our study did not have a control group receiving placebo.^[24]

The percentage of patients who had nausea in 0-4 hours postoperative period was 23.33% with Granisetron, 16.67% with Ramosetron and 13.33% with Palonosetron which was statistically nonsignificant. The percentage of patients who had vomiting in 0-4 hours was 16.67% with Granisetron, 13.33% with Ramosetron and 10.00% with Palonosetron which was statistically nonsignificant. There was no statistically significant difference between the three groups with regard to complete response and need of rescue antiemetic during 0-4 hours postoperatively. Our results were similar to study conducted by Lee WS et al., who found that there were no significant differences in the overall incidence of postoperative nausea and vomiting and complete responders for Palonosetron, Granisetron and Ramosetron group.^[25]

The percentage of patients who had nausea between 4-12 hours of the study period was 20.00% with Granisetron, 13.33% with Ramosetron and 6.67% with Palonosetron. Similarly, the percentage of patients who had nausea between 12-24 hours of the study period was 16.67% with Granisetron, 10.00% with Ramosetron and 6.67% with Palonosetron. Significant reduction in nausea was observed with Palonosetron as compared to Granisetron during 4-24 hours postoperatively.

Likewise, the percentage of patients who had vomiting between 4-12 hours of the study period was 13.33% with

Granisetron, 6.67% with Ramosetron and 3.33% with Palonosetron. Similarly, the percentage of patients who had vomiting between 12-24 hours of the study period was 10.00% with Granisetron, 3.33% with Ramosetron and 0.00% with Palonosetron. A significant reduction in vomiting was observed with Palonosetron as compared to Granisetron during 4-24 hours postoperatively. Our results are in accordance with Gupta K et al., who reported that Palonosetron is better drug for antiemetic prophylaxis of PONV in patients undergoing laparoscopic cholecystectomy under general anaesthesia as compared to Ondansetron and Granisetron due to its prolonged duration and minimal side effects.^[26]

No statistically significant difference was seen between Palonosetron and Ramosetron and between Granisetron and Ramosetron regarding prevention of nausea, vomiting, retching, need of rescue antiemetic and complete response during 24 hours postoperatively. Our results were similar to Park SK, who found that the incidence of PONV between the Ramosetron group and the Palonosetron group did not demonstrate a difference during the 0-48 hour time period.^[27] Our study results were comparable to Fuji Y et al., who found no difference between Granisetron and Ramosetron for prevention of PONV for a period of 0-24 hours after anaesthesia.^[28]

There was statistically significant difference regarding complete response during 4-24 hours postoperatively between Palonosetron and Granisetron. Complete response was superior with Palonosetron as compared to Granisetron. The use of rescue antiemetic was also less in Palonosetron group as compared to Granisetron group during 4-24 hours.

Adverse effects with a single therapeutic dose of Granisetron, Ramosetron and Palonosetron were not clinically serious and there were no statistically significant differences in the incidence of headache, dizziness, drowsiness and myalgias between the groups.

CONCLUSION

In conclusion, our study demonstrated that the antiemetic effect of Palonosetron is better than Granisetron, whereas there was no significant difference in the antiemetics efficacy of Granisetron and Ramosetron as well as between Ramosetron and Palonosetron in patients undergoing laparoscopic surgery.

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