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Study on Granisetron, Ondansetron and Palonosetron to Prevent Post-operative Nausea and Vomiting after Laparoscopic Surgeries

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Abstract

Introduction: Post-operative nausea and vomiting (POVN) is a common condition and causes much discomfort to the patient. It is not only unpleasant but also can have serious consequences like that of gastric content aspiration, rupture of esophagus, opening up of wounds, subcutaneous emphysema, or pneumothorax. *Aim of the Study:* To compare the anti-emetic effects of intravenous granisetron, ondansetron and palonosetron for prophylaxis of post-operative nausea and vomiting after laparoscopic surgeries under general anesthesia. *Materials and Methods:* This was a prospective, randomized, double-blinded, comparative study. A total of 75 patients were divided randomly into three groups each having 25 subjects. Group-A received ondansetron 8 mg, Group-B received Granisetron 2.5 mg and Group-C received Palonosetron 0.75 ug. Both male and female patients, ASA I–II with age ranging from 18–65 years and who underwent elective laparoscopic surgeries under general anesthesia were selected.The incidence of post-operative; nausea, retching and vomiting were studied. *Observations and Results:* Age, gender and weight were insignificant in all the 3 Groups. Groups-A/C was found to be statistically significant ($p < 0.05$) in 24–48 and also 12–24 hours. Retchingwas significantly less in Group-C when compared to other two groups. Incidence of vomiting was significantly less in Group-C when compared to Group-A and B. The p-value between Group–A and C was found to be statistically significant ($p < 0.05$) in 24–48 hours. *Conclusion:* Prophylactic therapy with palonosetron is more effective than prophylactic therapy with ondansetron and granisetron for the long-term prevention of PONV after laparoscopic surgery.

Keywords: Granisetron; Ondansetron; Palonosetron; PONV; Laparoscopic surgeries.

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Introduction

Pain and vomiting/emesis are common after anesthesia and surgery. They cause anxiety and distress to the patients. Post-operative nausea, retching and vomiting individually or in combination are identified as 'sickness' and each symptom is considered a separate entity. Post-operative nausea and vomiting (PONV) has been characterized as big little problem and is

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a frequent complication for both inpatients and outpatients undergoing virtually all types of surgical procedures. Earlier, in the 'Ether Era' the incidence of PONV was high and was about 75% to 80%. In the present scenario, it is comparatively less and is about 22% to 30% in adult patients.

According to the literature, incidence of PONV ranges from 25% to 55% in inpatients who have undergone surgery and 8% to 47% in outpatients.[1] It was observed that patients are concerned more about post-operative nausea and vomiting which can be quite distressing. PONV when severe and/or prolonged, can lead to wound dehiscence, bleeding from operative sites, venous hypertension, tears or rupture in the esophagus, if severe it may cause fracture in the ribs, herniation of stomach and also muscular fatigue. Persistent PONV is especially dangerous in post-operative neurosurgical cases where it can lead to raised intracranial pressure and also predispose to pulmonary aspiration. In the paediatric population, persistent vomiting can cause detrimental dehydration and electrolyte imbalance.[2]

Addressing the complications of PONV results in increased costto the patient, longer recovery time, extended bed occupancy in the hospital, added attention and time constraints for the nurses and physicians and also inconvenience to the family as a whole. Patients undergoing laparoscopic surgeries are more likely to encounter PONV. In laparascopic surgeries due to the presence of pneumo-peritoneum, the mechano receptors in the gut are stimulated much more, thereby leading to PONV.

The commonly used anti-emetic drugs like anti-histaminic, anti-cholinergics and dopamine receptor antagonists have clinically significant side effects, such as sedation, dry mouth, dysphoria and extra pyramidal symptoms. 5HT3 receptor antagonists are potent anti- emetics.[3] The present study was done to compare anti-emetic effects of intravenously administered granisetron, ondansetron and palonosetron for prophylactic PONV in patients undergoing laparoscopic surgeries under general anesthesia.

Materials and Methods

This was a prospective, randomized, double-blinded, comparative study approved by the institution ethical committee. Informed consent was obtained from all the patients. The study group consisted of 75 ASA I–II male and female patients with age ranging from *18* to *65 years*. All the patients were posted for elective laparoscopic surgeries under general anesthesia and were randomly allotted to the groups, each containing twenty-five patients.

Exclusion Criteria

Patients with known gastrointestinal disease, smokers, patients with history of motion sickness, post-operative nausea and vomiting, pregnant women and menstruating women were excluded. Also those who had taken anti-emetic medication within past *24 hours* were excluded.

Using computer generated randomization technique these patients were divided into three groups each containing 25 individuals. Group-A received ondansetron 8 *mg*, Group-B received Granisetron 2.5 *mg* and Group-C received Palonosetron 0.75 *ug* along with premedication, immediately before induction of general anesthesia. Normal saline was added to bring the total injectable volume to 2.5 *ml* in each group. Two theatre assistants were used for group allotment of the patients and to prepare the study drugs. However, both were unaware of the study protocol and were uninvolved in any further evaluation of the patients.

All patients were kept nil orally after midnight. In the operation room, routine monitoring (ECG, pulse oximetry, NIBP) were attached and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO_2) were noted. An intravenous line was secured. All patients were premediated with inj. Glycopyrrolate 0.2 *mg*, inj. Midazolam 0.03 *mg/kg*, inj. Tramadol 2 *mg/kg* intravenously.

After pre-oxygenation for *3 minutes*, induction of anesthesia was done with inj. Thiopental 5 *mg/kg*. Patients were intubated with inj. Succinyl choline 2 *mg/kg* with appropriate size endotracheal tube. Anesthesia was maintained with 33% oxygen, nitrous oxide 67%. Muscle relaxation was maintained with inj. Vecuronium bromide and supplemented with Isoflurane. Mechanical ventilation was used to keep EtCO2 between 32–35 *mm Hg*. The stomach contents were emptied by a nasogastric tube. For the laparoscopic procedure, the peritoneal cavity was insufflated with carbondioxide. Intra-abdominal pressure was kept < 14 *mm Hg*. At the end of surgical procedure, residual neuromuscular block was adequately reversed using intravenous glycopyrrolate 1 *ug/kg* and neostigmine 0.05 *mg/kg* and then extubation was done. Before tracheal extubation, post-operative analgesia, injection diclofenac sodium-75 *mg* intramuscular was given

when pain score was > 4 Visual Analog Score (VAS). Resident doctors who were unaware of the study drug observed all the patients post-operatively and noted the findings. Patients were transferred to post-anesthesia care unit and vitals were monitored. All episodes of PONV (nausea, retching and vomiting) were recorded at intervals of 6, 12, 24 and *48 hours* in post-operative ward.

Nausea was defined as an unpleasant sensation with an urge to vomit. Retching was defined as the labored, spastic, rhythmic contraction of the respiratory muscles without the actual emesis. Complete response (free from emesis) was defined as no PONV and no need for any rescue medication. Injection metoclopramide 10 *mg* IV was given as rescue medication if they vomited more than twice. At the end of each time interval it was recorded, if the patient had vomiting or any sensation of nausea or retching.

The result was scored as nausea-1, retching-2, and vomiting-3 and statistical analysis was performed with the SPSS 17.0 for Windows Software. The normally distributed data were compared using Student's *t*-test. For comparison of skewed data, Mann-Whitney *u*-test was applied. Qualitative or categorical variables were described as frequencies and compared with Chi-square or Fisher's exact test whichever was applicable. *p* - values were corrected by the Bonferroni method and $p < 0.05$ was considered statistically significant.

Results

A total of 75 ASA grade I–II male and female patients, aged *18–65 years* were studied for PONV following elective laparoscopic surgeries under general anesthesia, (**Tables 1–7** and **Fig. 1**).

Table 1: Demographic data in study

Group	Age (in years)	Weight	Female	Male
A	28.72 ± 9.91	51.2 ± 5.5	18	7
B	30.5 ± 12.8	50.64 ± 5.39	17	8
C	30.1 ± 8.99	50.6 ± 5.28	18	7

All the groups are similar with regard to age, weight and gender.

Table 2: Incidence of nausea among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	3	3	7	11
B	1	2	4	6
C	1	1	1	3

The incidence of nausea was significantly less in Group-C as compared to Group-A and Group-B.

Table 3: Correlation of nausea in three groups in first *48 hours*

Group	Interval *p* - value	*p* - value
A/C	*0–6 hrs*	0.60
	6–12 hrs	0.60
	12–24 hrs	0.04*
	24–48 hrs	0.02*
A/B	*0–6 hrs*	0.60
	6–12 hrs	1.00
	12–24 hrs	0.49
	24–48 hrs	0.23
B/C	*0-6 hrs.*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.34
	24–48 hrs	0.46

The *p* – value between Groups-A and C was found to be statistically significant ($p < 0.05$) in *24–48 hours* and also *12–24 hours*. The *p* - value was statistically insignificant ($p > 0.05$) in all other cases.

Table 4: Incidence of retching among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	1	2	3	5
B	0	1	2	3
C	0	1	1	2

Table 5: Correlation of retching among the three groups in first *48 hours*

Group	Interval	*p* - value
A/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.60
	24–48 hrs	0.42
A/B	*0–6 hrs*	1.0
	6–12 hrs.	1.0
	12–24 hrs	1.0
	24–48 hrs	0.70
B/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	1.0
	24–48 hrs	1.0

The incidence of retching was significantly less in Group-C as compared to Group-A and Group-B. The *p* - values among all the groups were statisticallyinsignificant ($p > 0.05$).

Table 6: Incidence of vomiting among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	2	3	5	11
B	1	2	5	6
C	0	1	2	3

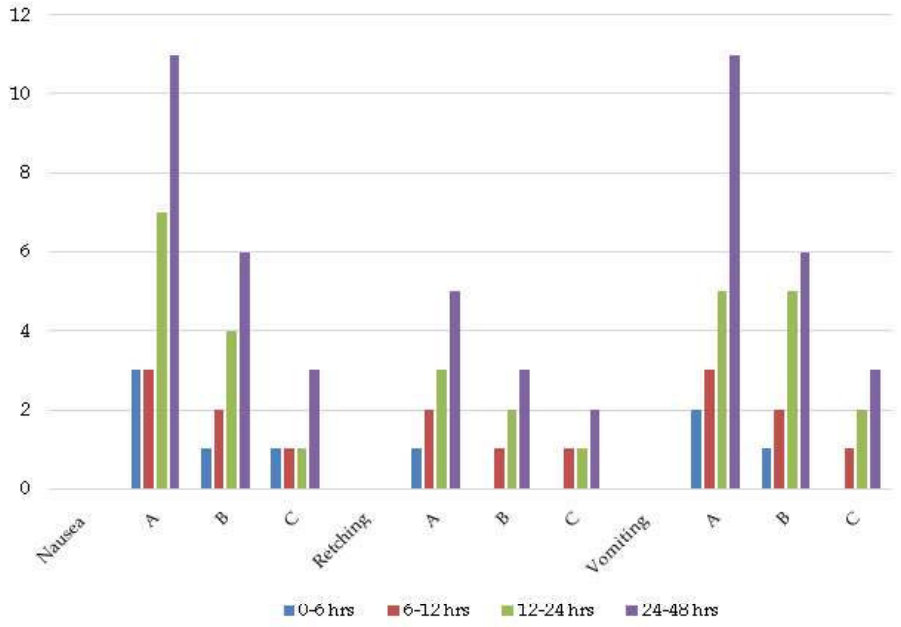

Fig. 1: Incidence of nausea, retching and vomiting in the three groups

(Pl. use **N-dash in Hrs Range)

Table 7: Correlation of vomiting among the three groups in first *48 hours*

Group	Interval	*p* - value
A/C	*0–6 hrs*	0.48
	6–12 hrs	0.60
	12–24 hrs	0.412
	24–48 hrs	0.02*
A/B	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	1.0
	24–48 hrs	0.13
B/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.417
	24–48 hrs	0.70

Incidence of vomiting was significantly less in Group-C when compared to Group A and B. The *p* - value between Group-A and C was statistically significant ($p < 0.05$) in 24–48 hours. The *p* - value was not statistically significant ($p > 0.05$) in all other cases.

Incidence was less in group C (Palonosetron) when compared to group A and B.

Discussion

Nausea and vomiting following general anesthesia are a distressing problem for the patients and are frequently listed among the most important pre-operative concerns apart from pain. With changing trends of increased outpatient office based medical/ surgical environment, more emphasis is focused on the "the big little problem" of PONV following general anesthesia.

In spite of much advancement in the management of PONV with the invention of new drugs, multimodal approaches of management like administering multimodal approaches of management like administering multiple different anti-emetic medications, less emetogenic-anesthetic techniques, adequate intravenous hydration, adequate pain control etc., the incidence of post-operative nausea and vomiting remains still high, ranging from 25%–55% following inpatient surgery and 8%–47% following outpatient surgery.[4]

An effective anti-emetic that could be used to treat nausea and vomiting without extending recovery time and that remain effective for *48 hours* following treatment would be significant asset to the anesthesiologist's armamentarium, especially in settings like office based anesthesia where the patients is admitted for day care surgery and is discharged on the same day. Drugs acting for longer duration also have an advantage in surgeries where the incidence of post-operative nausea and vomiting is very high like laparoscopic surgery, middle ear surgery, tonsillectomy, laparotomy, strabismus surgery, orchidopexy, etc.[4,5]

Unfortunately, commonly used anti-emetic medications like antihistamines, anticholinergics, gastroprokinetic, butyrophenones cause undesirable side effects like sedation, dysphoria, restlessness and extrapyramidal symptoms. To overcome this later serotonin antagonists like ondansetron, tropisetron, dolasetron, granisetron and palonosetron were introduced for treatment of nausea and vomiting. They were primarily used in treating chemotherapy induced vomiting with minimal and clinically acceptable side effects. The most distressing and intolerable emesis induced by anti-malignant medication is better controlled with these 5HT antagonists and they proved to have a promising role in the field of oncology. Abundant research in oncology demonstrates the efficacy of these drugs. However, there were many reports in the literature about their role in prevention of post-operative nausea and vomiting.

Post-operative period has variable incidence of nausea and vomiting. PONV depends on the duration of surgery, the type of anesthetic agents used (dose, inhalational drugs, opioids), smoking habits, etc. Vomiting reflexes are initiated by 5-HT receptor stimulation. The vagus nerve terminals bear these receptors and they are also present centrally on the chemoreceptor trigger zone (CTZ) of the area postrema. Anesthetic agents initiate the vomiting reflex as they stimulate the central 5HT receptors on the CTZ. These agents also release serotonin from the enterochromaffin cells of the small intestine and cause stimulation of 5-HT receptors on afferent fibers of vagus nerve.[6]

The incidence of PONV after laparoscopic surgery is high (40–75%). The etiology of PONV after laparoscopic surgery is complex and is dependent on patient age, body weight, history of previous PONV, the type of surgical procedure and technique of administration of anesthesia. In the present study, however, all the groups were comparable with respect to patient demographics, anesthesia and analgesics used post-operatively. Therefore, the difference in a complete response (on PONV, no rescue medication) between the groups can be attributed to the study drug.

Emesis related to cancer chemotherapy responds well to Granisetron. The exact mechanism of action of granisetronis unclear, but it is proposed that granisertron may act on sites containing 5-HT receptors with demonstrated anti-emetic effects. Palonosetron is a unique 5-HT receptor antagonist and is widely used for the prevention of chemotherapy related nausea and vomiting. It has a greater binding affinity and longer biological half-life than older 5-HT receptor antagonists. The proposed mechanism of palonosetronis that it functions via the area postrema which contains many 5-HT receptors. Therefore, granisetron and palonosetron may have similar mechanisms to exert anti-emetic effect in preventing PONV.[7]

For chemotherapy related nausea and vomiting the effective dose of granisetron is 40–80 *ug*. A dose of granisetron 2.5 *mg* (approximately 45 *ug/kg*) was used in this study as the effective dose range is (40–80). However, the dose of palnonosetron for the prevention of PONV is not established but was extrapolated from the dose used in clinical trials. Kovac LA and colleagues demonstrated that palonosetron 75 *ug* is the more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25 *ug* and 50 *ug*.

In our study, we compared the anti-emetic efficiency of ondansetron, granisetron and palonosetron post-operatively for laparoscopic surgeries in first *48 hours*. Our study demonstrates that in the first *12 hours* anti-emetic efficiency of all three drugs (ondansetron, granisetron and palonosetron) is similar and the difference is statistically not significant.

Palonosetronis more effective than ondansetron and granisetron for getting complete response (no PONV, no rescue medication required) for *24–48 hours* and the p - value < 0.05) is statistically significant between ondansetron and palonosetron groups in *24 to 48 hours*.

This suggests that palonosetron has longer lasting anti-emetic effect as compared to the other two drugs. The variable effectiveness of these drugs could be related to their half-lives (ondansetron *3–4 hours*, granistron *8–9 hours*, versus palonosetron *40 hours*.) It could also be due to the binding affinities of 5-HT receptor antagonists as palonosetron interacts with 5-HT receptors in an allosteric, positive manner at sites different from those of ondansetron and granisetron.

Bhattacharya *et al*.[8] reported that granisetron is superior to ondansetron for prevention of PONV. They observed that incidence of PONV was less with granisetron when compared to ondansetron within first *6 hours* post-operatively in patients undergoing day care gynecological laparoscopy. These findings are in agreement with our study where incidence of PONV was less with ondansetron and granisetron in first *6 hours*.

Bhattacharjee *et al*.[5] reported that the incidence of PONV was less with palonosetron when compared with granisetron within *24–48 hours* in patients

undergoing laparoscopic cholecystectomy. These findings are similar to our observations.

Mehta *et al.*[9] compared ondansetron and granisetron for prevention of PONV following elective caesarean section and concluded that both the drugs had significantly reduced PONV. Our study correlates well with their study in early prevention of PONV with ondansetron and granisetron.

Tahir *et al.*[10] did study on palonosetron in the prevention and treatment of PONV and found that palonosetron is effective in preventing delayed period of PONV up to *24–72 hours*. Our study concurs with their study in the prevention of late period of PONV (*24–48 hours*) with palonosetron.

Sarbari *et al.*[11] studied the efficacy of Ramosetron, Palonosetron and Ondansetron for preventing post operative nausea and vomiting in female patients undergoing laparoscopic cholecystectomy, the incidence of post-operative nausea and vomiting was 34.5%, 62.1% and 65.5% respectively, representing a significant overall difference ($p = 0.034$) as well as between Ramosetron and Ondansetron ($p = 0.035$). Ramosetron was labeled to be a better prophylactic anti-emetic than Palonosetron or Ondansetron in female patients under general anesthesia.

We did not include a control group receiving placebo in our study. Aspinall and Goodman[12] have suggested that if active drugs are available then placebo controlled trials should not be done as it would be unethical because PONV cause much anxiety and distress to the patients.

Conclusion

We conclude that anti-emetic prophylaxis with 5-hydroxytryptamine subtype 3 (5-HT3) antagonists provides clinically effective prevention of post-operative nausea and vomiting. These drugs have statistically significant difference in their efficacy and duration of action. Palonosetron is a better drug for anti-emetic prophylaxis of PONV in patients undergoing laparoscopic surgery under general anesthesia as compared to ondansetron and granisetron as it has prolonged duration and minimal side effects. Prophylactic therapy with palonosetron is more effective than prophylactic therapy with ondansetron and granisetron for the long-term prevention of PONV after laparoscopic surgery.

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