

## Original Research Article

## A Comparative Study of Granisetron and Palonosetron as Antiemetics for Prevention of Post Operative Nausea and Vomiting in Patients Undergoing Laparoscopic Surgeries

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### Abstract

Laparoscopic surgeries are associated with an appreciably high rate of post operative nausea and vomiting (PONV). This study was designed to compare the effectiveness of Granisetron with that of Palonosetron for prevention of PONV after laparoscopic surgery. **Methods:** In a randomized, prospective study, 50 adult patients of both sexes received Granisetron 2.5mg and Palonosetron 75mcg intravenously at the end of surgery. Perioperative anaesthetic care was standardized in all patients. Patients were then observed 24 hours after administration of the study drug. **Results:** A complete response (defined as no PONV and no need for another rescue antiemetic) was achieved in 76% of the patients given Granisetron and 84% of the patients given Palonosetron with ( $P < 0.05$ ). No significant difference observed in the recovery time from anesthesia between the two drugs and slight difference in the adverse events were observed between the two groups.

**Conclusion:** This study concludes that the prophylactic intravenous administration of Palonosetron is more effective drug than Granisetron for controlling postoperative nausea and vomiting with less incidence of side effects.

**Keywords:** Anaesthesia : PONV; laparoscopic surgery; Granisetron, Palonosetron.

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### Introduction

The most common and distressing symptoms, which follow anesthesia and surgery, are pain and emesis. The syndrome of nausea, retching and vomiting is known as 'sickness' and each part of it can be distinguished as a separate entity. PONV (post operative nausea and vomiting) has been characterized as big 'little problem' and has been a common complication for both inpatients and outpatients undergoing virtually all types of surgical procedures.

Post operative nausea and vomiting are the most unpleasant side effects after surgery. Overall incidence ranging from 18 -30 % [1] or as high as 70-80% in certain high risk population without prophylaxis. There are number of factors influencing the occurrence of PONV which includes patient factors (age, gender, obesity, anxiety, history of motion sickness or previous PONV and gastroparesis), operative procedures, anesthetic techniques (drugs for general anesthesia, regional anesthesia and monitored anesthesia care) and post-operative factors (pain, dizziness, ambulation, oral intake and opioids). Laparoscopic surgery is one condition, where risk of PONV is particularly pronounced. This increased risk of PONV is due to pneumo-peritoneum causing stimulation of mechanoreceptors in the gut [2]. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT<sub>3</sub> receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT<sub>3</sub> receptors on vagus nerve afferent fibers. Plenty of antiemetic drugs are available these days which include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (Promethazine, Prochlorperazine and Metaclopramide),

antihistaminic drugs (Diphenhydramine Hydroxizine), 5HT<sub>3</sub> receptor antagonists (Ondansetron, Granisetron, Dolasetron) and steroids (Dexamethasone). In spite of plenty of anti-emetic drugs available no single drug is 100% effective in prevention of PONV and combination therapy has got a lot of side effects [2]. Considerable progress has been made for better control of post operative nausea and vomiting in the recent years. The newer antiemetics like 5 – Hydroxytryptamine 3 receptor (5HT<sub>3</sub>) antagonists are potent therapeutic agents with fewer side effects. Granisetron is one of the more selective 5HT<sub>3</sub> receptor antagonist which has a elimination half life of 9 hours. It has lesser side effects unlike the contemporary antiemetics [3]. Palonosetron is the most recent 5HT<sub>3</sub> receptor antagonist first introduced for management of chemotherapy induced nausea and vomiting. Its half life is about 40 hours [4]. Laparoscopic surgeries are the preferred surgical procedure these days. It has considerably decreased the surgical mortality but the incidence of post operative nausea and vomiting remains high and hence prophylactic antiemetics are indicated. Patients receiving general anesthesia were 11 times more likely to experience PONV than those who received monitored anesthesia care, regional anesthesia or chronic pain block. The present study was undertaken to compare the antiemetic effects of IV Granisetron and Palonosetron for prophylaxis of postoperative nausea and vomiting in patients undergoing laparoscopic surgery.

### Aim & Objectives

This randomized prospective comparative study done to compare the effects of IV granisetron and palonosetron as antiemetics for prevention of post operative nausea and vomiting in patients undergoing laparoscopic surgeries.

### Materials and Methods

#### Source of Data

The study was conducted at NRI Medical College on patients admitted for elective Laparoscopic surgeries during 2018 to 2019

#### Method of Collection Of Data

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In this study, 60 patients in the age group of 20-50yrs, belonging to ASA grade I & II Scheduled for elective laparoscopic surgery under GA will be included. Patients were randomly divided into two groups of 30 each. Group 'G' – GRANISETRON group (n = 30) Group 'P' – PALONOSETRON group (n = 30)

#### Inclusion Criteria

1. Patients aged 20– 50 years
2. Either sex
3. ASA I – II
4. Patients posted for elective laparoscopic surgeries

#### Exclusion Criteria

1. Patients with previous history of post operative nausea and vomiting
2. History of motion sickness
3. History of gastroesophageal reflux disease
4. Patient who has taken any antiemetic 24 hours prior to the surgery
5. Obese patients
6. Pregnant females
7. Diabetic patients
8. ASA grade III or above
9. Emergency surgery
10. H/O Drug allergy
11. Full stomach
12. Extremes of age
13. Respiratory disease
14. Difficult airway.

#### Methods

##### Pre-Anesthetic assessment

On the day prior to surgery a thorough clinical examination of the patient was performed including General Physical Examination & systemic examination (Cardiovascular system, Respiratory system, Central nervous system, Gastro-intestinal system), H/O Drug allergy, Airway assessment was done by Mallampatti Grading. All patients were explained about the anesthesia technique & written informed consent was taken. Patients were kept NPO for 8hrs prior to surgery.

##### Lab Investigation

Routine investigation were done. (Hb%, Blood grouping, BT, CT, DC, Urine analysis, Serum creatinine, Fasting blood sugar, ECG)

No specific investigations required pertaining to the study.

##### Pre-Medication

All patients were given tablet diazepam 5mg orally at bed time on the previous night of surgery to allay anxiety and apprehension.

##### Technique of anaesthesia

60 patients aged between 20-50 yrs of either sex belonging to ASA grade I & II were randomly divided into 2 groups, each group consisted of 30 patients. Group G (Granisetron group) Group P (Palonosetron group). Anesthesia machine, circuits checked, resuscitation equipments were kept ready. On the day of surgery after confirmation of NPO status patients were shifted to operating room and routine monitoring devices pulse oximetry, NIBP, ECG monitors were attached, and baseline blood pressure, heart rate, ECG and O saturation values were recorded. Later capnography was attached after the intubation. Continuous monitoring of the vital parameters were done. An IV line was secured with an appropriate sized cannula in all patients and IV fluids were started. Prior to induction, injection Glycopyrolate 0.2mg administered IV, Inj Fentanyl 1.5 µg/kg IV. Surgery was allowed to commence. During surgery the patients were placed in trendelenburg position whenever required and positions of the patients was changed based on surgical requirement. A nasogastric tube was inserted to make the stomach empty of air and other contents, peritoneal cavity was insufflated with carbon dioxide to keep intra abdominal pressure. <12mmHg. Anaesthesia was continued with N<sub>2</sub>O(50%), O<sub>2</sub>(50%), isoflurane. Vecuronium top up doses, analgesics (Fentanyl 1.5mcg/kg) and IV fluids administered

based on the requirements. Patients received one of the study drugs at the end of surgery. Group I (Granisetron group) patients received IV granisetron 2.5 mg in 2.5 ml & Group II (palonosetron group) patients received IV palonosetron 75µg in 2.5 ml administered slow iv over period of 30 seconds. At the completion of surgery patients were made supine, when they had respiratory attempts residual neuromuscular block was reversed with inj glycopyrrolate 10 µg/kg and neostigmine 0.05mg/kg. Before tracheal extubation, the nasogastric tube was suctioned and removed. Recovery was assessed with Recovery time & extubation was done after thorough throat suction.

**Recovery Time (RT):** Recovery time in minutes was measured from the time Nitrous Oxide is switched off until the patient respond to simple verbal commands. After complete clinical recovery patients were shifted to post anesthesia care unit. The patients then were assessed with the help of clinical recovery score.

**Clinical Recovery Score (CRS):** The clinical recovery score was assessed at 0, 1, 2, 3 and 4 hours after patient's arrival in recovery room and assessments was done and appropriate recording were taken. The score consisted of simple questions to evaluate vigilance, cognition and orientation

##### Vigilance

Unconscious, not arousable — 0

Unconscious, arousable by nociceptive stimuli — 1

Unconscious, arousable by verbal stimuli — 2 Drowsy — 3

Awake, not attentive — 4 Awake, attentive — 5

##### Cognition

No understanding of simple orders — 0 Good understanding of simple orders — 1

##### Orientation

Confused — 0

Disturbed — 1 Well oriented — 2

##### Evaluation by patient of his/her condition

Uncomfortable — 1

Comfortable — 2

Excellent — 3

##### Clinical Recovery Score

11: Excellent recovery

9-10: Good Recovery

8: Fair recovery

<8: Poor recovery

In post anaesthesia care unit blood pressure and heart rate were recorded every 10 min for 30 min. Episodes of nausea and vomiting experienced by each patient were recorded by direct questioning. The number of patients who suffered nausea/vomiting were noted during the period's 0-4hrs, 4-12 hrs, and 12-24 hrs in the post operative period and statistical analysis was done accordingly. The side effects like headache, dizziness, hypersensitivity and constipation if any were assessed post operatively for 24 hours.

All patients were evaluated by using a PONV numeric scoring system. 0=No nausea/vomiting

1=Nausea alone

2 = Vomiting once

3=Vomiting twice or more times in 30 minute interval.

A rescue antiemetic Metaclopramide 10mg IV was given to all patients with PONV score=3.

Statistical analysis was done using student 't' test. A 'P' value of less than 0.05 will be considered to be significant.

##### Results and Observations

Total 60 patients were included in the study. Patient population were comparable across the two groups with respect to Age, Wt, Systolic BP, Diastolic BP, Heart rate. Statistical analysis was done by using student 't' test and rest of the study data have been categorically analyzed.

**Table 1:Age Distribution**

Range	Granisetron	Palonosetron
20-30	19 (76%)	18 (72%)
31-40	3 (12%)	4 (16%)
41-50	3 (12%)	3 (12%)

**Age, Weight Group:** Most of the patients in both groups belonged to age group 20-30. There was no statistically significant difference in the two groups. ( $P > 0.05$ ).

**Table 2: Sex Distribution**

Sex	Granisetron	Palonosetron
Male	5 (20%)	4 (17%)
Female	20 (80%)	19 (76%)

In our study females predominated males in granisetron group (20%) and palonosetron group (17%). But comparable in both groups

**Table 3:Weight Distribution**

Weight Range (in kgs)	Granisetron	Palonosetron
45-60	20 (80%)	18 (72%)
61-70	5 (20%)	7 (28%)
Mean weight $\pm$ SD	56.93 $\pm$ 10.62	50.86 $\pm$ 10.85

There was no significant weight difference between the two groups.

**Table 4:ASA Grade Wise**

Grade	Granisetron	Palonosetron
I	20 (80%)	20 (80%)
II	5 (20%)	5 (23%)

Both groups had almost similar numbers of ASA I and ASA II

**Table 5:Surgical Procedures Done**

Surgical Procedure	Granisetron	Palonosetron
Laparoscopic tubal occlusion (LTO)	16 (64%)	13 (52%)
Laparoscopic Appendectomy (LAPP)	2 (8%)	5 (20%)
Laparoscopic Cholecystectomy (LCHO)	4 (16%)	4 (16%)
Diagnostic Laparoscopy	3 (12%)	2 (8%)
Laparoscopic Hemiotomy	0 (0%)	1 (4%)

The above types of procedure were included in our study. LTO predominated in both groups than any other surgeries.

**Table 6:Comparison of Systolic BP, Diastolic BP, HR and SPO2 %**

Grade	Granisetron	Palonosetron
Mean Pulse	76.90 $\pm$ 1.5	82.73 $\pm$ 1.5
Mean SBP	131.46 $\pm$ 6.06	131.76 $\pm$ 6.23
Mean DBP	79.86 $\pm$ 11.25	82.13 $\pm$ 8.48
Mean SPO2 %	99.10 $\pm$ 0.76	99.17 $\pm$ 0.83

Systolic, Diastolic BP, Heart rate and oxygen saturation showed no statistically significant difference recorded in PACU between the study groups.

**Table 7:Incidence of Nausea**

Duration	Granisetron (n=25)	Palonosetron (n=25)
0-4hr	**4 (16%)	**2 (8%)
4-12hr	*2 (8%)	*1 (4%)
12-24hr	1 (4%)	0 (0%)

**Nausea:** Occurrence of nausea in granisetron group and Palonosetron group showed that incidence of nausea in 0-4 hours were 4 cases (16%) in Granisetron group as compared to 2 cases (8%) in Palonosetron group ( $P < 0.01$ ). Incidence of nausea in 4-12 hours were 2 cases (8%) in Granisetron group as compared to 1 case (4%) in Palonosetron group ( $P < 0.05$ ).

Incidence of nausea in 12-24 hours was only 1 case (4%) in Granisetron group as compared to 0 cases (0%) in Palonosetron group. The incidence of nausea was maximum during the first four hours and it was more in the Granisetron group.

**Table 8:Incidence of Vomiting**

Duration	Granisetron (n =25)	Palonosetron(n=25)
0-4 hr	**4 (16%)	**2 (8%)
4-12 hr	*3 (12%)	*1 (4%)
12-24 hr	0 (0%)	0

Incidence of vomiting episodes in granisetron group were 4 cases (16%) as compared to 2 cases (8%) in palonosetron group in 0-4 hours ( $P < 0.01$ ). In 4-12 hours granisetron group had 3 cases (12%) of incidence of vomiting as compared to 1 case (4%) in palonosetron

group ( $P < 0.05$ ). Again the incidence of vomiting was maximum during first four hours and no patient in any group vomited from 12 hours onwards.

**Table 9: Comparison of Rescue Antiemetic**

Anesthetic Sequelae	Granisetron (n=25)	Palonosetron(n=25)
Rescue antiemetic	7 (28 %)	3 (12%)

Need for rescue antiemetic is more in Granisetron group compared to palonosetron group.

**Table 10: Clinical Recovery Score (CRS) and Recovery Time (RT) (Mean  $\pm$ SD)**

Time Interval	Granisetron
0 hour	5.16
1 Hour	7.03
2 hour	8.33
3 Hour	8.83
4 Hour	10.33
Recovery time (Minutes)	5.67 $\pm$ 0.23

There was no significant difference in CRS and RT between the two groups

**Table 10: Comparison of Side Effects**

Side effects	Granisetron(n =25)	Palonosetron(n =25)
Headache	*5(20%)	*4 (16 %)
Constipation	*3(12%)	*2 (8%)
Dizziness	*3 ( 12%)	*2 (8 %)

Occurrence of side effects like headache, constipation and dizziness in granisetron group are 5(20%),3(12%),3(12%) respectively compared to 4 (16%), 2(8%),2 (8 %) in palonosetron group. The number of patients who suffered side effects were more in granisetron group.

#### Discussion

Postoperative nausea and vomiting (PONV) is of multifactorial origin. The incidence of PONV after anaesthesia, despite the advances in antiemetic therapy in the last decades is still found to be relatively high. Gold et al noted that the three most common causes for admission following day care surgery are pain, bleeding and intractable vomiting[5]. Factors affecting PONV include patient related factors (age, sex, phase of the menstrual cycle), anaesthesia related factors (use of volatile anesthetic agents, N<sub>2</sub>O, Opioid) and surgery related factors. Female gender has been associated with higher incidence of PONV compared to male patients. On an average, female patients suffer three times more often from PONV than men. Our study was aimed at comparing the antiemetic efficacy of Granisetron and Palonosetron in preventing PONV in laparoscopic surgery. In our study the factors that would have contributed to nausea and vomiting may be laparoscopic surgery, use of Halothane, use of Fentanyl etc. Use of facemask, use of Nitrous Oxide may or may not have contributed to nausea and vomiting. Laparoscopic surgery was chosen because of high incidence of PONV associated with it. Naguib et al demonstrated that the incidence of PONV after laparoscopic surgeries in their placebo group was remarkably high (72%)[6]. We have conducted studies on 50 patients of ASA I and II with demographic data in terms of age, weight, which were similar in the two groups. There was no significant difference in Granisetron and Palonosetron ( $P < 0.05$ ) in terms of Age and Weight. Study done by Pearman[7] shows that postoperative nausea and vomiting is more common in young age group and obese patients. Incidence of nausea in our study group was 28% in Granisetron group, 12% in Palonosetron group. Present study shows highly significant difference in first 0-4hr ( $P < 0.05$ ). While in 4-12hrs incidence of nausea shows marginally significant difference. After 12-24hrs, there was no significant difference in nauseating episodes. Study done by Pueyo[8] observed that nausea and vomiting is more common in first 6 hours post operatively. Same results are seen in the study done by Fujii[9]. Vomiting in the present study group was 28% in Granisetron, 12% in the Palonosetron group. In our study group incidence of vomiting was highly significant in first 4hrs ( $P < 0.01$ ). Present study showed that Palonosetron is better than Granisetron for preventing PONV. The incidence of a complete response (no PONV,

no rescue medication) during 0-3 hour in the postoperative period was 86.6% with granisetron and 90% with palonosetron, the incidence during 3-24 hour postoperatively was 83.3% with granisetron and 90% with palonosetron. During 24-48 hour, the incidence was 66.6% and 90% respectively ( $p < 0.05$ ). The incidence of adverse effects were statistically insignificant between the groups. Janknegt[10] studied that if Ondansetron is given at the induction time, it is ineffective in preventing PONV. So we administered study drug half an hour before end of the surgery. This makes the drugs to be effective postoperatively for longer time. Sinha[11] concluded the same results in his study. Our study shows no statistically significant difference in the baseline values of hemodynamic variables between the two groups before, during or after giving study drug. Study drugs granisetron and Palonosetron was given the end of the surgery, before extubation. In PACU we have recorded the SBP, DBP and HR over a period of 30min at regular interval. According to our study there was no haemodynamic alteration between these results. Study conducted by Dev[12] also shows the same results. There is no haemodynamic alteration seen in PR, SBP and DBP during study period. Kumar et al[13] in their clinical trial on recovery score and recovery time showed slightly lower clinical recovery scores with metoclopramide group compared to ondansetron which may be attributed to its established unpleasant sedative pharmacological activity. They did not notice any significant difference in the overall incidence of drowsiness or sedation in both the groups. They further stated that ondansetron does not affect patients vigilance, cognition or orientation and concluded that ondansetron (4 mg) and metoclopramide (10 mg) do not affect the cognitive aspects following major gynaecological surgery. In our study on the clinical recovery score and the recovery time we observed slightly lower clinical recovery score in the Granisetron group compared to Palonosetron and there was not much of significant difference in the recovery time. Incidence of side effects was significant in our study groups. Incidence of headache was 20% in Granisetron group while it was 16% in Palonosetron group shows statistically significant difference ( $P < 0.05$ ). Incidence of constipation and dizziness also shows significant difference in Granisetron and Palonosetron groups ( $P < 0.05$ ). The use of rescue antiemetic in Granisetron group which was about 7(28%) whereas in Palonosetron group about 3(12%) of the patients received rescue antiemetic. Updated guidelines for managing postoperative nausea and vomiting were recently announced at the 2006 Annual Meeting of American Society of Anaesthesiologists in Chicago, Illinois, USA. Evaluating the current medical literature, they recommended the use of antiemetics, with an emphasis on the

use of the 5HT<sub>3</sub> receptor antagonists. The guidelines also suggest a potential benefit of combination prophylaxis. Overall the panel recommended, —Prophylactic therapy with combination, three or more interventions, in patients at high risk for PONV[14]. So we have studied the effect of Granisetron 2.5 mg i.v. versus palonosetron 75µg i.v, administered to the patients, who had undergone laparoscopic surgery under general anesthesia.

### Conclusion

This study concludes that the prophylactic intravenous administration of Palonosetron is more effective drug than Granisetron for controlling postoperative nausea and vomiting with fewer incidences of side effects. Safety profile is more with Palonosetron and it is more potent than Granisetron. So we observed minimal emetic and nauseating episodes in postoperative period in patients who had received i.v. Palonosetron in comparison to i.v. Granisetron, undergoing laparoscopic surgery under general anesthesia. Even though there was slightly higher clinical recovery score in the patients who had received intravenous Palonosetron compared to patients who had received intravenous Granisetron, there was no significant difference in the recovery time from anesthesia between the two drugs.

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