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# Palonosetron and Granisetron for the Prevention of Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy: A Prospective Comparative Randomised Active Controlled Trial

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**Abstract**
**Background**: *Selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are reported to have potent antiemetic effects for postoperative nausea and vomiting (PONV). The purpose of this study was to prospectively evaluate the efficacy of Palonosetron and Granisetron for the prevention of PONV in patients undergoing laparoscopic cholecystectomy.*
**Methods**: *In this prospective, randomized observational study, 70 patients who were undergoing laparoscopic cholecystectomy under general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron (1.5 mg/kg,i.v.; n = 35), and granisetron group ( 0.05mg/kg i.v.; n = 35). The treatments were given before the end of surgery. The incidence of PONV, severity of nausea/vomiting, and the use of rescue antiemetic requirements during the first 48 h after surgery were evaluated.*
**Results**: *The overall incidence of PONV was 26.5 % for this series. The number of complete responders at 48 hr after the surgery was 20 (57 %) for granisetron, and 23 (65%) for palanosetron representing no statistical difference (P = 0.086).*
**Conclusions:** *Palanosetron is more effective in prevention of PONV in patients undergoing laproscopic cholecystectomy surgeries as compared to granisetron especially in 24-48 hr period postoperatively.*

## Introduction

Laparoscopic surgeries are the second most common cause of postoperative nausea and vomiting (PONV), a frequent and disturbing complication of surgery and anaesthesia [1]. The incidence of PONV after laproscopic surgery is around 25-30% but laparoscopic cholecystectomy is reported to be nearly 80 % [2] and can result in prolonged hospital stay and recovery times. Numerous antiemetics have been studied to prevent and treat PONV after laparoscopic abdominal surgery, including antihistamines, anticholinergics. However, these agents can cause undesirable side effects such as sedation, dry mouth, etc..Selective serotonin 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) 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. Most 5-HT3 receptor antagonist research has focused on granisetron, and the antiemetic efficacy of these compounds has been well established for the

prevention and treatment of chemotherapy-induced emesis, as well as for PONV.

Granisetron selectively blocks the 5-HT3 receptor with a relatively short half-life of 4 to 9 h Palonosetron is a second-generation 5-HT3receptor antagonist with an even higher receptor binding affinity, and a prolongedmean half-life of about 40 h [8]. We hypothesized that long acting palonosetron treatment would be more effective in lowering the incidence of PONV, compared to treatment with granisetron. The purpose of this study was to prospectively evaluate the efficacy of palonosetron and granisetronin the prevention of PONV in patients undergoing laparoscopic cholecystectomy

**Methods**

70 patients of age(18-60 year )of ASA grade 1& 2, patients were randomly assigned to receive palonosetron (n = 35) or granisetron (n = 35)using a random number table.

**Exclusion criteria**

Exclusion criteria were as follows: Allergy to any of the experimental drugs, opioid dependence, a history of PONV and motion sickness, use of antiemetic medication within 24 h prior to surgery, pregnancy.

**Study Protocol**

All patients received intravascular (iv) Fentanyl (1-2 mcg/kg) and glycopyrrolate (0.004 mg/kg) as premedication 1 hr before anesthesia induction. Palanosetron (1.5mcg/kg iv) or granisetron (1.5mcg/kg iv) was given 30 min before induction of anesthesia according to study group.In the operating room, the vital signs of the patient were continuously monitored using

Electrocardiogram, pulse oximetry, and measurement of noninvasive arterial pressure. Anesthesia was induced and maintained with Thiopentone sodium (6 mcg/kg) Succinylcholine (2 mg/kg) was administered to facilitate tracheal intubation. Airway was secured with appropriate size endotracheal tube.Anesthesia was maintained with sevoflurane (0.5-5 %) and nitric oxide (50 %) throughout surgery. Vecorunium(0.08mg/kg) was given for maintenance of anaesthesia. Nasogastric tube was inserted.

All patients were ventilated using an Drager anesthetic machine. After anesthesia induction, patients were mechanically ventilated with constant flow and I:E ratio of 1:2, and tidal volume (TV) set at 8 ml/kg of ideal body weight. Respiratory rate was adjusted to 8–20 breaths/min to maintain end-tidal carbon dioxide concentration (ETCO2) of 30–40 mmHg at 60 % inspired oxygen with air [9].

Pneumoperitoneum was established with a closed Veress needle technique, and the intra-abdominal pressure was maintained at 12–14 mmHg. After CO2insufflation, patients were placed in the reverse Trendelenburg position at 20° and right up position. Laparoscopic cholecystectomy was performed through two ports of 10 mm and two ports of 5 mm in the standard position [9].

Nausea was defined as a subjectively unpleasant sensation associated with the urge to vomit. Incidences of vomiting included retching (defined as the labored, spastic, rhythmic contraction of the respiratory muscles without expulsion of the gastric contents) and actual vomiting (defined as the forceful expulsion of gastric contents from the mouth). A complete response to palonosetron and granisetron was defined as an absence of PONV and no need for further rescue antiemetic drugs. A rescue antiemetic (10 mg metoclopramide) was administered IV upon patient request, if two or more episodes of PONV occurred during the study period, if nausea intensity increased from moderate to severe (VAS > 5) and on vomiting.

The primary outcome was incidence of complete responders during the study period. Details of any other adverse effects such as headache and dizziness were also collected. All data were collected at 6, 24, and 48 h after surgery.

**Statistical Analyses**

Sample size was calculated using two proportions power analysis on the basis of the primary outcome measure. It was estimated that 30 patients per group would be required for the

power analysis (for a power of 80 % and a type 1 error of 5 %) to demonstrate a relative reduction of 25 % in complete response in each group 48 h after surgery. This calculation was based on previously published studies [10,11]. Student's t-test was used to compare the inter-group differences, and a chi-square test was used for categorical variables. P-values were corrected. Values are expressed as counts or the mean ± standard deviation. P-values < 0.05 were considered statistically significant.

**Results**

All patients underwent laparoscopic cholecystectomy under general anesthesia. All patients completed the study. Patient characteristics and basic operative data are presented in Table 1. A total of 75 patients were screened to assess their eligibility for this trial and 70 patients were enrolled in the study. The groups were comparable with respect to age, weight, duration of surgery, and ASA score. The overall incidence of PONV was 39 %. The incidence of nausea was highest during the 24-48hr (total incidence of 20 %) and decreased throughout the study period.number of complete responders at 48 hr after the surgery was 20 (57 %) for granisetron, and 23 (65%) for palanosetron representing no statistical difference

The differences between the groups were not statistically significant (P = 0.086, Table 2). All two groups were comparable across the time intervals examined.

The number of subjects in each of the two study groups experiencing at least one episode of vomiting within the three time intervals is shown in Table 2. More subjects suffered vomiting in the late phase (24-48 h) of postoperative period in the granisetron group compared with the palanosetron group, which had no vomiting during this period. However, this difference was not statistically significant.

The incidence of most of the common adverse events, such as headache and dizziness, was similar among the two groups, and no clinically significant treatment related adverse events were observed.

**Table 1**

| Characteristics | Palanosetron Group n=35 | Granisetron Group n=35 | P value |
|---|---|---|---|
| Age(years) | 51.5±16.3 | 52.5±15.7 | 0.42 |
| Height(cm) | 155.3±3.1 | 157.1±6.1 | 0.65 |
| Weight(kg) | 60.1±4.9 | 59.3±5.1 | 0.55 |
| Operation Time(min) | 100.2±34.1 | 99.4±25.3 | 0.46 |
| Anaesthesia Time | 128.1±47.5 | 123.5±35.1 | 0.63 |
| Fluid administered | 522.1±61.2 | 644±33.3 | 0.75 |
| ASA 1/2 | 23/12 | 24/11 | |

**Table 2**

| | Palanosetron Group n=35 | Granisetron Group n=35 | P Value |
|---|---|---|---|
| 0-6 hours | | | |
| Nausea | 2 | 3 | 0.5 |
| Vomiting | 1 | 1 | 1 |
| Rescue Drug | 1 | 1 | 1 |
| 6-24 hours | | | |
| Nausea | 2 | 4 | 0.336 |
| Vomiting | 0 | 1 | - |
| Rescue Drug | 0 | 1 | - |
| 24-48 hours | | | |
| Nausea | 5 | 13 | 0.053 |
| Vomiting | 2 | 7 | 0.075 |
| Rescue Drug | 1 | 7 | 0.027 |
| | | | |
| Complete Responders | 23(65%) | 20(57%) | 0.311 |

**Table 3**

| Authors | Prospective Study | Number of Patients | Year of study | Type of PONV | Complete responders (incidence%) |
|---|---|---|---|---|---|
| Yun. et al. | No | 98 | 2010 | Az,on | 35-51 |
| Ryu et al. | No | 120 | 2010 | On,Ra | 23-40 |
| Fujii et al. | Yes | 120 | 1999 | Ra,Gr | 87-90 |
| Swaika et al | Yes | 87 | 2011 | Ra ,Pa | 38-66 |
| Current Study | Yes | 70 | 2016 | Pa,Gr | 57-65 |

## Discussion

There were no statistically significant differences in the number of complete responses between the two groups. A variety of 5-HT3 antagonists have been used to manage PONV [12]. It is generally accepted that all 5-HT3 antagonists have a similar mechanism of action (selective or competitive binding to 5-HT3 receptors) as well as comparable efficacy and safety profiles [5,10].

The reported incidence of PONV is 30 to 80 % within the first 24 h after laparoscopic surgery when no prophylactic antiemetic is administered [5,3,13]. The present study reports an overall incidence of 33.3 %within the first 48 h post-surgery, without any statistical difference between the two groups. The high incidence during the first 24 h of surgery may be explained by the central action of carbon dioxide (CO2), stretching of the peritoneum and diaphragm, and increased blood pressure in the peritoneal cavity after CO2 insufflation during laparoscopic surgery, as previously reported by Ryu et al[3]. All these factors are considered to provoke nausea and vomiting by reducing the blood flow and releasing emetogenic substances, including serotonin [14, 15].

Granisetron produces irreversible block of the 5-HT3 receptors, and it may account for the long duration of this drug. [9,10] Palonosetron shows avid binding to the 5HT3 receptor which far exceeds than the other 5HT3 antagonists and has the longest elimination half-life of 40 h. We did not choose a placebo group as a control group in our study because the patients we chose were having a 40% risk of developing PONV and denial of effective antiemetic treatment was unjustified and unethical. Fuji et al. observed that during the 24 h after recovery from anesthesia, the frequencies of postoperative retching and vomiting in patients who had received granisetron were lower than those who had received placebo and the severity of postoperative vomiting was reduced with the administration of granisetron.[11]

Candiotti et al. demonstrated that palonosetron 75 μg is more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25 μg and 50 μg in the 0–48 h period.[12] Kovac et al. also found that palonos-etron 75 μg was more effective than placebo in the 72 h postoperative period in female patients undergoing elective gynecological and breast surgery.[13]

In our study, we randomized all the patients into two groups; Granisetron) and Palonosetron to avoid results getting affected by demographic factors (age, sex, weight, and duration of surgery). There is no statistically significant difference in the patients inboth the groups with relation to above factors.

Our study thus demonstrates that the antiemetic efficacy of palonosetron is similar to granisetron in the first 24 h after laparoscopic surgeries. However, in the 24–72 h period, palonosetron is significantly better in its antiemetic efficacy thangranisetron. This suggests that palonosetron has an antiemetic effect which lasts longer than granisetron.

The exact reason for the difference in effectiveness is not known but may be related to the half-lives (granisetron8–9 h vs. palonosetron 40 h) and/or binding affinities of 5-HT3 receptor antagonists (palonosetron interacting with 5-HT3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron).[16,17]

The major limitations of the current study are: (1) We compared the efficacy of palonosetron and

granisetron at their known optimal doses, not at equipotent doses, and (2) this was not a double-blinded study.

We did not administer equipotent doses of the compounds as they were unknown at the time of commencement of the study. Investigations on a larger scale are needed to assess the equipotency of palonosetron and granisetron.

## Conclusion

Thus, palonosetron is more effective in the prevention of PONV in patients undergoing elective laparoscopic surgeries under general anesthesia as compared to granisetron, especially in the 24–72 h period postoperatively. The least PONV score was also observed with palonosetron in the 24–72 h period postoperatively.

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