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# Comparative Study of Ondansetron and Granisetron for Preventing Post-Operative Nausea and Vomiting in Laparoscopic Cholecystectomy under General Anaesthesia

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## ABSTRACT

**Introduction:** Post-operative nausea and vomiting (PONV) are commonly experienced unpleasant complications of general anesthesia following laparoscopic surgeries. The study was undertaken to compare the antiemetic efficacy of two different 5-hydroxytryptamine-3 receptor antagonists, Ondansetron and Granisetron when given prophylactically to patients undergoing laparoscopic cholecystectomy under general anesthesia.

**Methods:** A prospective, double-blind study was conducted in 60 patients aged 20-60 years ASA-PS I/II, weighing 40-80 kgs, undergoing elective laparoscopic cholecystectomy under general anaesthesia. Patients were divided into two groups: Group A (Ondansetron 4mg intravenously) and Group B (Granisetron 2mg intravenously) with 30 patients in each group. Both the drugs were diluted in normal saline to 10 ml and were given at the end of surgery before the reversal of the neuromuscular blockade. Episodes of nausea and vomiting were assessed at 6, 12, and 24 hours post-operatively. Collected data was applied with the appropriate test in Statistical Package for the Social Sciences (SPSS) and a p-value <0.05 was considered significant.

**Results:** Incidence of PONV was greater in Ondansetron group (53.33%) compared to Granisetron group (23.33%) (p=0.02). Demographic data were comparable in both groups (p>0.05). The episodes of retching and vomiting at different intervals were found to be higher in the Ondansetron group. However, it was statistically insignificant. The use of rescue anti-emetics was greater in group A (13.33%) compared to group B (3.33%) but the finding was not statistically significant (p=0.16).

**Conclusion:** The incidence of PONV was significantly high in the Ondansetron group than in the Granisetron group when given prophylactically in laparoscopic cholecystectomy.

***Key words***: *Cholecystectomy, Laparoscopic; Granisetron; Ondansetron; Post-Operative Nausea and Vomiting*

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## INTRODUCTION

Post-operative nausea and vomiting (PONV) is the most common distressing factor post-operatively.[1] Laparoscopic cholecystectomy (LC) is one of the most common surgery.[2] Laparoscopic surgeries are the second most common cause of PONV.[3] Incidence of PONV after surgery ranges from 20–30%.[4] PONV is experienced by 40-75% of patients .[5-9] PONV is attributed to pneumoperitoneum causing stimulation of mechanoreceptors in the gut and absorbed $CO_2$ stimulating nociceptors in the brain.

Consequences of PONV may be surgical (wound dehiscence, disruption of vascular anastomosis) or anesthetic (aspiration pneumonitis, dyselectrolytemia). Because of increased nursing care required, delayed discharges, and unexpected readmissions, PONV causes an increased financial burden. Thus, prophylactic antiemetic therapy is justified for patients undergoing LC. PONV prevention after laparoscopic surgeries is challenging. Thus, an effective prophylactic regimen is highly desirable for reducing patient discomfort and postoperative morbidity.

We conducted this study to compare the efficacy of intravenous Ondansetron and Granisetron in preventing PONV in patients after LC.

## METHODS

Asingle-centered, hospital-based, prospective, analytical, observational, comparative study was conducted in The Department of Anaesthesiology, Manipal Teaching Hospital after obtaining approval from Institutional Review Committee (MEMG/IRC/273/GA).

The incidence of PONV in laparoscopic cholecystectomy (LC) under general anaesthesia with the use of Ondansetron and Granisetron prophylactically according to Bhattarai et al. was 54% and 26% respectively.[10]

The sample size was calculated at a level of significance of 5% and power of 80% by using the following formula;

$$n = \{z_{1-\alpha}\sqrt{[2\bar{P}(1-\bar{P})]} + z_{1-\beta}\sqrt{[P_1(1-P_1)+P_2(1-P_2)]}\}^2/(P_1-P_2)^2$$

Where;

$P_1$= 54%= 0.54

$P_2$= 26%= 0.26

$\bar{P}$= ($P_1$+$P_2$)/2= (54+26)/2= 40%=0.4

Tabulated value of $z_{1-\alpha}$ at 95% Confidence Interval =1.96

$z_{1-\beta}$= 5%= 0.05

Putting the values in the above formula, the ideally required minimum sample size for the study comes out to be 23.91. So, for the sake of our convenience, we took a total sample size of 60 (30 in each group).

Non-Probability (Convenience) sampling technique was used for undertaking the study. Sixty ASA I and II adult patients, aged 20-60, scheduled for LC under general anesthesia were included in the study after written informed consent was obtained.

Patients with a history of drug allergy or documented hypersensitivity to any of the drugs used in the study, history of other gastrointestinal diseases, vomiting or retching within 24 hours before the operation, history of motion sickness and/or migraine, administration of antiemetic or psychoactive medication within last 24 hours, patient converted to open cholecystectomy, history of severe/unstable cardiovascular, respiratory, metabolic, endocrine or neurologic disease, impaired renal or hepatic function were excluded from the study.

A pre-anesthetic evaluation was done for all patients and standard institutional preoperative advice was offered. All laparoscopic surgeries were carried out under GA by an anaesthesiologist unaware of the prophylactic treatment given. All cases were kept nil per oral (NPO) from midnight before surgery and premedicated with Tablet Ranitidine 150 mg HS on the night before operation and 6 am on

the day of surgery with sips of water.

Patients were randomly allocated into two groups (n= 30 each) using a computer-generated random number table. Study medication was prepared by a PG trainee who was not related to the study, in two identical syringes which had Inj. Ondansetron 4mg or Inj. Granisetron 2mg, each being diluted to 10 mL in normal saline and given to patients at the end of the surgery before reversing the neuromuscular blockade.

In the preoperative room, an IV line was secured and maintenance fluid was given according to the Holliday and Segar formula.[11] In the operation theatre routine monitoring devices like pulse oximetry, non-invasive Blood Pressure (NIBP), ECG monitors were attached; and baseline blood pressure, heart rate, and $O_2$ saturation values were recorded. Later capnography was attached after the intubation. The anesthetic regimen and surgical procedures were standardized for all patients.

The standard general anesthetic technique was administered to all the patients. Patients were premedicated with Inj. Midazolam 0.02mg/ kg, Inj. Fentanyl 1.5µg/kg & induced by Inj. Propofol at the dose of 1.5 to 2.5 mg/kg body weight. Tracheal intubation was done by appropriate size endotracheal tube facilitated by Succinylcholine 1.5-2mg/kg and muscle relaxation was maintained with Vecuronium 100µg per kg body weight. A nasogastric tube was placed for emptying the gastric contents. Anesthesia was maintained by $O_2$ and Isoflurane (1 to 2%). Intermittent doses of Vecuronium were given to maintain adequate muscle relaxation. Ventilation was controlled mechanically and adjusted to keep the end-tidal carbon dioxide ($ETCO_2$) at 30-35 mm of Hg throughout the surgery. Intraoperative HR, BP, $SpO_2$, ECG were monitored.

During laparoscopic surgery, the abdomen was insufflated with $CO_2$ at a pressure of 10 to 12 mm Hg. After the completion of the surgery, the abdomen was deflated by the surgeon. At the end of the surgery, Group A patients received 4mg Ondansetron, and Group B patients received 2mg Granisetron, both diluted to 10ml in normal saline, administered as slow IV injection over 30 seconds before the reversal of residual neuromuscular blockade. After the surgery was over, the residual neuromuscular block was adequately reversed using Inj. Neostigmine (0.05mg/kg) and Inj. Glycopyrrolate (0.01mg/kg). The nasogastric tube was suctioned & removed and subsequently, the trachea was extubated once the extubation criterion was met. Episodes of PONV were determined and noted in the first 24 hours after operation at different time intervals of 6, 12, and 24 hours. At the end of each interval, a blinded investigator inquired and recorded about the number of episodes of nausea and/or vomiting and the need for antiemetic rescue medication. Nausea was defined as an unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as the involuntary, labored, spastic, rhythmic contraction of the respiratory muscles but without the expulsion of gastric contents.[12] Vomiting was defined as the forceful expulsion of gastric contents from the mouth.

Complete response (free from emesis) was defined as no PONV and no need for any rescue medication.

PONV was evaluated on a five-point ordinal scale:

0 = None
1 = Nausea
2 = Retching
3 = Vomiting
4 = Severe Vomiting (> 2episodes)

Any adverse reactions of the drug-like headache, dizziness, or hypersensitivity if any were noted in the 24 hours study period.

The number of episodes of emesis and nausea was recorded. Repeated vomiting within a 1-2 minutes period was recorded as single emesis. The severity of each nausea and vomiting were further assessed as:

a) Nausea was measured using an 11-point visual numerical scale with;

0 = No Nausea.
10 = Nausea as bad as can be.

A score of > 5 = Severe
5 = moderate
< 5 = minimal
The severe and moderate score was considered major nausea.
b) Vomiting was measured as
> 2 = Severe
2 = Moderate
< 2 = Mild
Moderate and severe nausea, retching, and vomiting were managed with rescue antiemetic. Rescue antiemetic consisted of 10mg metoclopramide IV and was given even for a single episode of vomiting. If the vomiting was not controlled, the dose was repeated at a 4-hours interval following the initial dose.
Post-operative pain was managed with non-opioid analgesics. Standard analgesia was maintained with injection Ketorolac 30mg eight-hourly alternating with injection Paracetamol infusion 1gm (1%) eight-hourly for the first 24 hours postoperatively.
Statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 25.0 for Windows). Continuous/qualitative variables were reported as mean ± standard deviation and were analyzed using independent Student's T-test. Categorical/quantitative variables were reported as numbers/percentages and were analyzed using the Chi-square test. A $p < 0.05$ was considered statistically significant.

## RESULTS

A total of 60 patients were enrolled in the study. The demographic features of the patients enrolled in the study were comparable (Table 1). The incidence of PONV in group A was 53.33% and that in Group B was 23.33% with a p-value of 0.02 as presented in Table 2. The incidence of PONV of the two groups at different time intervals are shown in Table 3. The episodes of retching and vomiting at different intervals were found to be higher in the Ondansetron group than in the Granisetron group. However, it was statistically insignificant. The use of rescue anti-emetic was greater in Group A (13.33%) compared to Group B (3.33%) but the finding was statistically insignificant (p=0.16).

***Table 1: Comparison of age, sex, and weight between two groups (n =60)***

| Demographic Variables | | | |
|---|---|---|---|
| | **Group A** | **Group B** | **p-value** |
| Age (Years) | 43.9 ± 10.40 | 41.03 ± 11.34 | 0.31 |
| Sex (M/F) | 7/23 | 10/20 | 0.39 |
| Weight (Kg) | 62.1 ±11.66 | 58.03 ±9.05 | 0.34 |

***Table 2: Incidence of PONV in two groups (n =60)***

| **Group** | **PONV** | | **p-value** |
|---|---|---|---|
| | **Absent** | **Present** | |
| Group A | 14 (46.67%) | 16 (53.33%) | 0.02 |
| Group B | 23 (76.67%) | 7 (23.33%) | |

## DISCUSSION

The incidence of PONV after general anesthesia, despite the advances in antiemetic therapy, is still found to be high. Nausea and vomiting are the most frequently reported complaints after laparoscopic surgeries.[13,14] Patient concerns regarding PONV are often greater than their concern for postoperative pain.[15] The cause of PONV is attributed to pneumoperitoneum, which causes stimulation of mechanoreceptors in the gut and the absorbed $CO_2$ stimulating the nociceptors in the brain. Iitomi et al. show a 3.2 times greater risk of PONV in laparoscopy cholecystectomy than open cholecystectomy.[16] The occurrence of PONV also depends upon other factors like patient characteristics, duration of surgery, and the anesthetic technique used.
Aspinall and Goodman, have suggested a placebo-controlled trial is unethical as we have effective anti-emetic drugs available and PONV after laparoscopic surgeries can

be distressing.[17] A control group was not included in this study. Total 60 cases were randomized, 30 in each group.

Incidence of PONV in Ondansetron group was 53.33% in this study. Similar incidence was found in study done by Bhattarai et al (54%) and Ommid et al (52%).[10,18] Study done by Bhattacharya et al found the incidence of PONV in Ondansetron group was 10%.[19] This difference in incidence in PONV might be because they conducted study in day care gynaecological laparoscopy and shorter duration of surgery. Study done by Gupta et al incidence of PONV was 70% which is higher in incidence to this study this might be due to drug given at the time of induction instead of at the end of surgery that was done in this study.[20]

Incidence of PONV in Granisetron group was 23.33% in this study. In the study done by Ommid et al, incidence of PONV was 29%[18] and that in study by Bhattarai et al was 26%.[10] The results were similar to this study. Study done by Bhattacharya et al found the incidence of PONV in Granisetron group to be 7%.[19] This difference in incidence in PONV might be due to the different type of surgeries studied and in the duration of. In study done by Gupta et al, incidence of PONV was 45% in Granisetron group which is higher in incidence to this study.[20] This might be due to drug given at the beginning instead of at the end of surgery.

In this study, 23.33% patients in Granisetron group as compared to 53.33% in Ondansetron group have PONV; the difference in incidence was statistically significant. In the study done by Ommiad et al the result were similar to this study.[18] But Bhattacharya et al found incidence of PONV to be 10% in patients in Granisetron group as compared to 20% in Ondansetron group.[19]

The timing of prophylactic administration of antiemetic has been found to have a significant effect on its efficacy in preventing severe PONV.[14,21] Tang et al, found a higher percentage of satisfied patients (90% vs 67%) when ondansetron was administered near the end of surgery.[14] It is stated that this makes the drug to be effective for longer duration.

Similar results were found in study done by Janknegt and Sinha.[22,23] So, we decided to administer study drugs just prior to reversal of the patient towards the end of surgery.

Incidence of nausea in first six hours in Ondansetron group was 7 (23.33%) and in Granisetron group was 3 (10%) but difference in incidence of nausea between two groups was statistically not significant. Ommid et al found similar result in first 6 hours of postoperative period; in Ondansetron group 11 (22%) experienced nausea and 7 (14%) in Granisetron group experienced nausea.[18] There were no cases of retching and vomiting episodes in both the groups in our study in the first six hours. There were three patients in ondansetron group who experienced vomiting in 6-12 hours but it was statistically insignificant. In the next twelve hours though the episodes of retching and vomiting were higher in ondansetron group than in granisetron group it was statistically insignificant.

No any adverse effects were seen in our study, even though ondansetron is said to be associated with a higher incidence and severity of certain CNS side effects compared with other serotonin receptor antagonists.[24]

Limitation of our study is that we have not considered duration of surgery. Incidence of PONV is less in smokers than in non-smokers.[25] However, we did not consider the history of smoking while collecting data. So, this is limitation of our study.

## CONCLUSION

In conclusion, for patients undergoing laparoscopic cholecystectomy (LC), prophylactic use of antiemetics should be considered. Preoperative antiemetic prophylaxis with serotonin receptor antagonists reduces the incidence of PONV, requirements of rescue antiemetics, and postoperative nausea scores after LC.

This study concluded that prophylactic use of Granisetron is more effective than Ondansetron for the prevention of PONV following LC in the first 24 hours.

***Table 3: Incidence of PONV in two groups in different time intervals (n=60)***

| Nausea and vomiting in different periods | Group A | Group B | p-value |
|---|---|---|---|
| 0-6 Hours | | | |
| No Nausea Vomiting | 23 (75.67%) | 27 (90%) | 0.17 |
| Nausea | 7 (23.33%) | 3 (10%) | 0.17 |
| Retching or Vomiting | 0 | 0 | |
| 6-12 Hours | | | |
| No Nausea Vomiting | 21(70%) | 27 (90%) | 0.06 |
| Nausea | 6 (20%) | 3 (10%) | 0.28 |
| Retching or Vomiting | 3(10%) | 0 | 0.08 |
| 12-24 Hours | | | |
| No Nausea Vomiting | 25 (83.34%) | 29 (96.67%) | 0.09 |
| Nausea | 4 (13.33%) | 1 (3.33%) | 0.16 |
| Retching or Vomiting | 1 (3.33%) | 0 | 0.31 |

***Table 4: Requirement of rescue antiemetic (n=60)***

| Group | Rescue antiemetic use | p-value |
|---|---|---|
| Group A | 4 (13.33%) | 0.16 |
| Group B | 1(33.33%) | |

## CONFLICT OF INTEREST
None

## SOURCES OF FUNDING
None

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