Comparison of intravenous ondansetron and palonosetron in prevention of postoperative nausea and vomiting in patients posted for elective laparoscopic cholecystectomy

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Abstract
Introduction: PONV is a major complication after anaesthesia, present in 20-30% range¹. We compared efficacy and tolerance of ondansetron and palonosetron for PONV prophylaxis in patients posted for elective laparoscopic cholecystectomy.

Method: 60 patients of age 20-60 years, ASA I and II, scheduled for elective laparoscopic cholecystectomy were randomized double blindly to receive either 8 mg bolus IV ondansetron and 16 mg was added to the PCA mixture (O group), or 0.075 mg palonosetron only bolus dose (P group). Pregnancy, known hypersensitivity to both drugs, migraine, motion sickness were excluded. Chi square test and Fisher exact test were used for statistic evaluation. Microsoft excel and epi info version 3.4.3 were used. P value <.05 considered significant. PONV (0 no nausea, 1 nausea, 2 retching, 3 vomiting), rescue antiemetics and side effects were assessed in 24 hr postoperative period.

Result: Both groups were comparable in demographic parameters (age, sex, weight). Overall incidence of PONV did not differ significantly (p=.57) but patients, who needed rescue antiemetics were significantly less in group P than group O (P=<.05). Additionally side effects were also less in group P.

Conclusion: In patients undergoing elective laparoscopic cholecystectomy, use of palonosetron significantly reduced need of rescue antiemetics. Incidence of PONV and side effects were also less with P group.

Keywords: PONV, palonosetron, ondansetron.

Introduction
Postoperative nausea and vomiting, remains a significant problem in modern anaesthetic practice, occurs after both general and regional anaesthesia. The incidence of postoperative emesis in large studies has been reported to be in the 20-30% range.[¹] These factors prevent patients to return home at the end of the day, after surgery. Sometimes these factors necessitate readmission to the hospital.

The use of opioid-based intravenous-patient controlled analgesia (IV-PCA) for controlling postoperative pain has become widespread. Yet while IV-PCA is effective in controlling postoperative pain, continuous administration of opioid can cause or aggravate postoperative nausea and vomiting (PONV). PONV is the most common reason why patients choose to stop IV-PCA.
Thus there have been many studies on methods and drugs to prevent PONV. The 5-Hydroxytryptamine (5-HT₃) receptor antagonist is being commonly used because it is more effective in PONV prevention and treatment than other antiemetics and has few side effects[2]. Among 5-HT₃ receptor antagonists, ondansetron is the most widely used drug, granisetron and ramosetron are also used. Recently, palonosetron has been reported to be effective against chemotherapy-induced nausea and vomiting[3,4] and effective in the prevention of PONV[5,6].

Palonosetron is a newly developed 5-HT₃ receptor antagonist. Its receptor-affinity is more potent than other antagonists. Its plasma half-life is very long[7,8]. Also it is known to be more effective than ondansetron against nausea and vomiting in patients using anticancer drugs[4]. However, studies comparing the effects of preventing PONV between palonosetron and other 5-HT₃ receptor antagonists are sparse.

Thus we compared the effects of palonosetron and ondansetron in PONV prevention in patients who underwent laparoscopic cholecystectomy surgery and used IV-PCA after surgery.

Methodology
Data was randomly collected from 60 ASA I and II patients scheduled for laparoscopic cholecystectomy, aged between 20-60 years at GMC Kota, Rajasthan. These patients were randomly devided in Group P and Group O. The study was conducted over a period of two years.

Inclusion criteria
• ASA 1 and ASA 2 patients.
• 20-60 age group.

Exclusion criteria
• Documented hypersensitivity to any of the study drugs.
• Patients with history of migraine, motion sickness or previous PONV.
• Patients who are pregnant or menstruating.
• Patients who have taken antiemetic drugs within 24 hours before surgery.
• Patients with history of neurological or renal diseases.

Technique
The study was a prospective, randomized, double blinded one. Written informed consent was taken from all patients. Pre-anaesthetic medication was given with ranitidine 150 mg and tab alprazolam 0.5 mg, the night before and morning of surgery. SpO₂, NIBP, ECG monitors were attached. The baseline values were recorded. IV access was established. Patients were randomly allocated into two groups.

1) Those who receive ondansetron (8 mg) IV bolus before induction of anesthesia and 16 mg was added in IV PCA mixture and .(Group O)
2) Those who receive only bolus dose of IV Palonosetron (0.075 mg) before induction of anesthesia (Group-P)

All patients were kept in the NPO state for 8 h or longer. The patients did not receive premedication. General anesthesia was induced with propofol 1.5-2 mg/kg and fentanyl 1 µg/kg. Tracheal intubation was facilitated with rocuronium 0.8-1 mg/kg. Anesthesia was maintained with sevoflurane 1.5-3 vol% and O₂-N₂O 3 L/min (FiO₂ 0.5), and fentanyl 1-2 µg/kg/hr . Heart rate and blood pressure were kept in the 20% range of base-line before anesthesia. Mechanical ventilation was performed so that P\textsubscript{ET}CO\textsubscript{2} was 30-35 mmHg. When the surgery was over, pyridostigmine and glycopyrrolate were used for reversing muscle relaxation. The patient was extubated with the return of consciousness and the stabilization of spontaneous breathing. The patients were randomly assigned to the ondansetron group (n = 50) and the palonosetron group (n = 50). In the ondansetron group, ondansetron 8 mg (4 ml) was i.v. administered as a bolus injection immediately before anesthesia induction. Ondansetron 16 mg (8 ml) was added in IV-PCA and was continuously infused. In the palonosetron group, palonosetron 0.075 mg (4 ml) was i.v. administered immediately before anesthesia induction and normal saline 8 ml was
added to the IV-PCA. In both groups, fentanyl 600 µg and ketorolac 240 mg were diluted with normal saline 100 ml. The basal rate for IV-PCA was 2 ml/h, bolus injection was 2 ml, and the lockout time was set at 15 min. Both groups used identical syringes for bolus intravenous injection and the same type of IV-PCA machine. Fifteen min before the end of the surgery, continuous intravenous administration of fentanyl was discontinued and IV-PCA was infused. After the surgery, if the patient wanted additional analgesics, ketorolac 30 mg was given. Postoperatively all episodes of PONV experienced by the patient during the first 24 hours after anaesthesia, was recorded by direct questioning. These were assessed by a nausea and vomiting score. Rescue anti-emetic i.e. inj.metoclopramide was used if patient had nausea or vomiting.

**Statistical analysis**
At the end of the study, the data was compiled systematically and was subjected to statistical analysis using ‘Chi-square’ test and Microsoft excel and Epi info version 3.4.3.

**Results**

**Demographic data & Type of surgery**
The age, sex, weight of patients & type of surgery in the two groups (O and P) were comparable and there was no significant difference. (p value >0.05).

**Hemodynamic parameters**
Study period was from baseline to 24 hrs. (5 min., 15min., 30min., 1hr, 2hr, 12 hr,24 hr) in both groups O and P groups. Patients were hemodynamically stable in both groups. There was no statistically significant difference in mean pulse rate, Systolic BP & SPO2 throughout the study period (baseline to 24 hr) in both group.

**PONV and Adverse effects**
In Early (<1 hr) Period .In group O 19 out of 30 did not have any nausea. While in P 23 out of 30 did not have any nausea. P value (>0.05).In Late (1-24 hr) period, In group O 20 out of 30 did not have any nausea, while in P 27 out of 30 did not have any nausea. p value(>0.05) .In early study period (0-1 hr) 5 patients out of 30 showed adverse effects like headache and dizziness in group O. 1 patients out of 30 showed adverse effects like headache and dizziness in group P. In late study period (1-24 hr) 1 patients out of 30 showed adverse effects in group O. 0 patients out of 30 showed adverse effects like headache and dizziness in group P. There was no statistically significant difference in both group (p value>.05).

**Need of Rescue Antiemetic**
In group O;9 out of 30 patient needed rescue antiemetic and in group P, 2 out of 30 needed it in early study period (<1 hr). In group O,8 out of 30 patient needed rescue antiemetic and in group P 1 out of 30 needed it in late study period(1-24 hr). This result showed statistically significance. p value in early period was .04.in late period p value was .015. both these values were statistically significant.

<table>
<thead>
<tr>
<th>Table 1: Incidence of PONV &lt;1 HR</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>&lt; 1 hr</td>
</tr>
<tr>
<td>No Nausea=0</td>
</tr>
<tr>
<td>Nausea=1</td>
</tr>
<tr>
<td>Retching=2</td>
</tr>
<tr>
<td>Vomiting=3</td>
</tr>
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Figure 1: Incidence of PONV in <1 hour

![Graph showing incidence of PONV in <1 hour for both groups O and P.]

Table 2: PONV Score in 1-24 Hour

<table>
<thead>
<tr>
<th></th>
<th>Group O</th>
<th>Group P</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>1-24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Nausea=0</td>
<td>20</td>
<td>27</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Nausea=1</td>
<td>8</td>
<td>3</td>
<td>.18</td>
</tr>
<tr>
<td>Retching=2</td>
<td>1</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Vomiting=3</td>
<td>1</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Figure 2: Incidence of PONV in 1-24 Hour

![Graph showing incidence of PONV in 1-24 hour for both groups O and P.]

Table 3: Incidence of Adverse Effects In Both Groups

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Group O</th>
<th>Group P</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 hr</td>
<td>5</td>
<td>1</td>
<td>.19</td>
</tr>
<tr>
<td>1-24 hr</td>
<td>1</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>
Figure 3: Incidence of adverse effects in 24 Hours

![Incidence of adverse effects in 24 Hours](image)

Table 4: Need of Rescue Antiemetic I.V. Metoclopramide

<table>
<thead>
<tr>
<th></th>
<th>Group O</th>
<th>Group P</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 hr</td>
<td>9</td>
<td>2</td>
<td>.04</td>
</tr>
<tr>
<td>1-24 hr</td>
<td>8</td>
<td>1</td>
<td>.015</td>
</tr>
</tbody>
</table>

Figure 4: Need of rescue antiemetic I.V. Metoclopramide

![Need of rescue antiemetic I.V. Metoclopramide](image)

**Discussion**

Post operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. Pathophysiology, of PONV in middle ear surgeries being vestibular stimulation, increase in middle ear pressure, and presence of swallowed blood in adenotonsillectomy procedures. Apfel et al.\(^{[10]}\) stated that among patients receiving inhaled anesthesia, female, a history of PONV or motion sickness, non-smoker, and postoperatively using opioid were the more important risk factors of PONV, and each additional risk factor increased the PONV incidence rate to 21, 39, 61, and 79%.

The boundary of the present study was restricted to female non-smoker who used opioids for IV-PCA. These patients belonged to the high risk group since they had three of the risk factors listed by Apfel et al.\(^{[10]}\) and had laparoscopic surgery,
which is known for a high incidence of PONV. So they were expected to have a high PONV incidence rate[11,12]. Thus on an ethical reasons, the study did not include a control group.

Opioid-based IV-PCA is a safe method for managing postoperative pain with a high rate of satisfaction because the patient self-infuses additional doses when necessary and keeps the drug's plasma concentration stable[13]. However, postoperative opioid use had caused PONV in many studies[10]. When PONV occurs while using IV-PCA, patients do not infuse adequate doses for pain control[14]. Sometimes patients voluntarily stop PCA, so antiemetics are used for PONV prevention.

Many types of 5-HT₃ receptor antagonists are being currently used to prevent PONV. It affects the receptors of 5-HT₃ in the mucous membrane of the stomach and the central chemoreceptor trigger zone and suppresses nausea and vomiting. Among them, ondansetron is the most widely used type [15].

Palonosetron is a second generation serotonin 5-HT₃ receptor antagonist. Unlike other antagonists, it has unique structural, pharmacological, clinical characteristics. Other antagonists directly compete with serotonin, but palonosetron has an indirect effect by its allosteric binding with 5-HT₃ receptors[16]. Also it suppresses the response induced by substance P, has negative cooperativity with neurokinin-1 receptors by cross-talk, and creates an antiemetic effect[17]. These explain strong receptor-affinity of palonosetron and its long plasma half-life.

In high-risk groups for PONV such as in the present study, combination treatments such as TIVA with propofol and other drugs are recommended[18]. However, the present study aimed at comparing the effects of two drugs, so combination preventive methods could not be used. Instead, extensive literature was reviewed to find and use the method that best prevents PONV [5,6,9,19-21]. There have been many studies on optimal dose and usage of ondansetron. Generally an iv. injection of 8 mg is suggested as appropriate[19]. There are reports that when using opioid-based IV-PCA, adding ondansetron decreases PONV[20,21]. Palonosetron 0.075 mg is reported to be more effective in PONV prevention than 0.025 mg and 0.050 mg [5,6]. The findings of the studies above were collated so that in the present study, ondansetron 8 mg was infused as a bolus and 16 mg was added to IV-PCA and continuously infused. Palonosetron 0.075 mg was infused as a bolus.

Recently there have been studies comparing the effects of palonosetron and other 5-HT₃ receptor antagonists on PONV prevention [22-24]. Park and Cho [22] studied the use of ondansetron 8 mg and palonosetron 0.075 mg before anesthesia induction on patients with two or more risk factors. Palonosetron (42.2%) was far better than ondansetron (66.7%) in PONV prevention up to 24 h. Moon et al. [21] compared the effects of ondansetron and palonosetron in PONV prevention in high-risk patients with three or more risk factors. Similar to the present study, ondansetron was added to IV-PCA. As a result, palonosetron was far more effective than ondansetron in PONV prevention for 2-24 h (42% vs. 62%). However, in the present study the PONV incidence rates were similar in the palonosetron group and the ondansetron group( P value 0.31). But fewer patients needed rescue antiemetics in group P than in groups O (3 vs. 13 patients, respectively; (p < 0.01) during 0-48 h postoperatively.

In the present study, the method used in the ondansetron group (which used 8 mg as i.v. bolus and continuous iv. infusion of 16 mg addition in IV-PCA) was noteworthy in its remarkable effect in PONV prevention.

Palonosetron, as a 5-HT₃ receptor antagonist, also has side-effects such as headache, dizziness, and drowsiness. In the present study the two groups showed no difference in the incidence of side-effects. Recently the US FDA has warned against the use of ondansetron, which like droperidol, can cause severe heart complications such as QTc
interval prolongation. But palonosetron is not known to have such severe side effects\(^7\).

For ethical reasons, this study did not include a control group using placebos for high-risk patients for PONV. Thus the present study is limited in the sense that it could not define the base incidence rate for PONV in this particular procedure. Another limitation of the present study is that equipotent doses of the two drugs were not used; instead optimal doses were used for comparisons. For further study, these limitations need to be addressed and many other methods should be used with a large patient size.

**Conclusion**

PONV is multifactorial and combination of drugs with different mechanisms of action is more effective. Patients at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. It is also found that combinations act synergistically Overall incidence of PONV and adverse effects were less with combination of drugs. Need of antiemetic was significantly less with Palonosetron (p value<.05) in elective laproscopic cholecystectomy.

**References**