A Comparative Study Between Palonosetron and Granisetron to Prevent Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is commonly seen after laparoscopic surgery. In this randomized double blind prospective clinical study, we investigated and compared the efficacy of palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy.

Patients & Methods: Sixty female patients (18-65 yrs of age) undergoing elective laparoscopic cholecystectomy were randomly allocated one of the two groups containing 30 patients each. Group P received palonosetron 75 µg intravenously as a bolus before induction of anaesthesia. Group G received granisetron 2.5 mg intravenously as a bolus before induction.

Results: 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.

Conclusion: Prophylactic therapy with palonosetron is more effective than granisetron for long term prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy.

KEYWORDS: Palonosetron, Granisetron, Postoperative Nausea and Vomiting(PONV), Laparoscopic surgery.
Identical syringes containing study medications (2.5 ml) were prepared by the personal who were blinded to the computer generated randomization schedule. Patients were randomly allocated into two groups (n=30 each) to receive one of the following regimens: palonosetron 75µg in 2.5 ml (0.9% saline was added to make the desired volume) [group P] or granisetron 2.5 mg in 2.5 ml[group G]. The study medication were administered immediately before the induction of anaesthesia.

All patients were kept fasting after midnight and received midazolam 7.5 mg orally as premedication. On the operation table, routine monitoring (ECG, pulse oximetry, NIBP) were started and baseline vital parameters like heart rate(HR), blood pressure(systolic, diastolic and mean) and arterial oxygen saturation(SpO2) were recorded. An intravenous line was secured.

After preoxygenation for 3 minutes, induction of anaesthesia was done by fentanyl 2μg kg⁻¹ and thiopental 5mg kg⁻¹. Patients were intubated with appropriate size endotracheal tube after muscle relaxation with vecuronium bromide in a dose of 0.08mg kg⁻¹. Anaesthesia was maintained with 33% oxygen in nitrous oxide and sevoflurane 2%. Muscle relaxation was maintained by intermittent bolus doses of vecuronium bromide. The patients were mechanically ventilated to keep EtCO₂ between 35-40 mm Hg. A nasogastric tube was inserted to make the stomach empty of air and other contents. For laparoscopic surgical procedure, peritoneal cavity was insufflated with carbon dioxide to keep intra abdominal pressure <14 mmHg. At the end of surgical procedure, residual neuromuscular block was adequately reversed using intravenous glycopyrrolate and neostigmine and subsequently extubated. Before tracheal extubation, the nasogastric tube was suctioned and removed. For postoperative analgesia, diclofenac transdermal patch was applied on body surface. All patients were observed postoperatively by resident doctors who were unaware of the study drug. Patients were transferred to postanaesthesia care unit and blood pressure, heart rate and oxygen saturation were monitored. All episodes of PONV(nausea, retching and vomiting) were recorded for 0-3 hour in postoperative period and from 3-48 hour in postoperative ward.

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as the laboured, spastic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents from mouth. Complete response(free from emesis) was defined as no PONV and no need for any rescue medication. If there were two or more episodes of PONV during first 48 hours, rescue antiemetic (metoclopramide10 mg i.v.) was given.

Data were analyzed using computer statistical software system Graph Pad Instat Version 3.05 (Graph Pad software, San Diego, CA) and are presented in a tabulated manner. Comparisons between groups were performed by using the Kruskal Wallis one way ANOVA by ranks or Fisher’s exact test for small sample with a 5% risk or Mann – Whitney – Wilcoxon tests when normality tests failed or Chi-square test, as appropriate. The results were expressed in mean±SD and number(%).

RESULTS

The groups were comparable with respect to age, weight and duration of surgery [Table 1]. 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 [Table 2]. Thus a complete response during 24-48 hour in the postoperative period was significantly more patients who had received palonosetron than in those who had received granisetron (p<0.05) [Table 2].

| Table 1 | Patient’s characteristics and duration of surgery (Mean ± SD) |
| --- | --- | --- |
| Group G (n=30) | Group P (n=30) | P Value |
| Age (Years) | 42.3 ±4.32 | 43.4±6.46 | 0.47 |
| Weight (kg) | 52.24 ± 7.36 | 54.42 ± 8.22 | 0.55 |
| Duration of surgery (min) | 52.72 ± 6.62 | 55.82±8.44 | 0.62 |

| Table 2 | Incidence of Postoperative Nausea & Vomiting(PONV) |
| --- | --- | --- | --- |
| Postoperative period(hr) | Granisetron (n=30) | Palonosetron (n=30) | P Value |
| 0-3 hr | Complete Response 26(86.6%) | 27(90%) | 0.65 |
| | Nausea 4(13.3%) | 2(6.6%) | 0.67 |
| | Retching 1(3.3%) | 1(3.3%) | 1 |
| | Vomiting 2(6.6%) | 1(3.3%) | 0.42 |
| | Rescue Drug 0 | 0 | 1 |
| 3-24 hr | Complete Response 25(83.3%) | 27(90%) | 0.58 |
| | Nausea 4(13.3%) | 2(6.6%) | 0.72 |
| | Retching 1(3.3%) | 1(3.3%) | 1 |
| | Vomiting 3(10%) | 2(6.6%) | 0.68 |
| | Rescue Drug 0 | 0 | 1 |
| 24-48 hr | Complete Response 20(66.6%) | 27(90%) | 0.003 |
| | Nausea 6(20%) | 3(10%) | 0.09 |
| | Retching 2(6.6%) | 0 | 0.49 |
| | Vomiting 5(16.6%) | 2(6.6%) | 0.07 |
| | Rescue Drug 0 | 0 | 1 |
The commonly observed adverse effects were headache, dizziness and drowsiness but those were not clinically serious or significant. The incidence of adverse effects were statistically insignificant between the groups [Table 3].

Table 3
Incidence of Adverse Effects

| Postoperative period (hr) | Granisetron (n=30) | Palonosetron (n=30) | P Value |
|--------------------------|--------------------|---------------------|---------|
| **0-3 hr**               |                    |                     |         |
| Headache                 | 2(6.6%)            | 3(10%)              | 0.67    |
| Dizziness                | 4(13.3%)           | 2(6.6%)             | 0.72    |
| Drowsiness               | 1(3.3%)            | 1(3.3%)             | 1       |
| **3-24 hr**              |                    |                     |         |
| Headache                 | 2(6.6%)            | 2(6.6%)             | 1       |
| Dizziness                | 3(10%)             | 2(6.6%)             | 0.68    |
| Drowsiness               | 1(3.3%)            | 1(3.3%)             | 1       |
| **24-48 hr**             |                    |                     |         |
| Headache                 | 0                  | 1(3.3%)             | 0.37    |
| Dizziness                | 0                  | 0                   | 1       |
| Drowsiness               | 0                  | 0                   | 1       |

DISCUSSION
Postoperative period is associated with variable incidence of nausea and vomiting depending on the duration of surgery, the type of anesthetic agents used (dose, inhalational drugs, opioids), smoking habit etc. 5-HT, receptor stimulation is the primary event in the initiation of vomiting reflex. These receptors are situated on the nerve terminal of the vagus nerve in the periphery and centrally on the chemoreceptor trigger zone (CTZ) of the area postrema. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT, receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT, receptors on vagus nerve afferent fibres.

The incidence of PONV after laparoscopic surgery is high (40-75%). The etiology of PONV after laparoscopic surgery is complex and is dependent on a variety of factors including age, obesity, a history of previous PONV, surgical procedure, anesthetic technique, and postoperative pain. In this study, however, both the groups were comparable with respect to patient demographics, types and duration of surgery and anesthesia and analgesics used postoperatively. Therefore the difference in a complete response (no PONV, no rescue medication) between the groups can be attributed to the study drug.

Granisetron is effective for the treatment of emesis induced by cancer chemotherapy. The precise mechanism of granisetron for the prevention of PONV remains unclear, but it has been suggested that granisetron may act on sites containing 5-HT, receptors with demonstrated antiemetic effects. Palonosetron is a unique 5-HT, receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting. It is a novel 5-HT, receptor antagonist with a greater binding affinity and longer biological half-life than older 5-HT, receptor antagonists. The exact mechanism of palonosetron in the prevention of PONV is unknown but palonosetron may act on the area postrema which contain a number of 5-HT, receptors. Therefore, the possible mechanism of this antiemetic for preventing PONV is similar to that of granisetron.

The effective dose of granisetron is 40-80µg kg⁻¹ for the treatment of cancer chemotherapy induced nausea and vomiting. The dose of granisetron 2.5 mg (approximately 45µg kg⁻¹) selected for this study was within its effective dose range (40-80µg kg⁻¹). However, the dose of palonosetron to be used for the prevention of PONV is not established but was extrapolated from the dose used in the clinical trials. Kovac LA and Colleagues demonstrated that palonosetron 75µg is the more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25µg and 50µg.

Our study demonstrate that the antiemetic efficacy of palonosetron is similar to that of granisetron for preventing PONV during the first 24 hours (0-24 hours) after laparoscopic surgery and that palonosetron is more effective than granisetron for getting a complete response (no PONV, no rescue medication) for 24-48 hours. This suggests that palonosetron has an antiemetic effect which lasts longer than granisetron. The exact reason for the difference in effectiveness between granisetron and palonosetron is not known but may be related to the half lives (granisetron 8-9 hrs versus palonosetron 40 hrs) and/or the binding affinities of 5-HT, receptor antagonists (palonosetron interacts with 5-HT, receptors in an allosteric, positive cooperative manner at sites different from that bind with granisetron).

We did not include a control group receiving placebo in our study. Aspinall and Goodman have suggested that if active drugs are available, placebo controlled trials may be unethical because PONV are very much distressing after laparoscopic surgery.

Adverse effects with a single therapeutic dose of granisetron or palonosetron were not clinically serious and there were no significant differences in the incidence of headache, dizziness and drowsiness between the groups. Thus both palonosetron and granisetron are devoid of clinically important side effects.

In conclusion prophylactic therapy with palonosetron is more effective than prophylactic therapy with granisetron for the long term prevention of PONV after laparoscopic surgery.
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