

Full Length Research Paper

A comparative study between palonosetron and ramosetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy

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Post operative nausea and vomiting (PONV) is common after laparoscopic surgery. Vomiting may create problems like electrolyte imbalance, dehydration and increased perception of pain. A number of pharmacological approaches (butyrophenones, antihistaminics, and dopamine receptor antagonists) have been tried for the prevention and treatment of PONV but undesirable adverse effects such as dryness of mouth, excessive sedation, hypertension, dysphoria, hallucinations and extra pyramidal symptoms have been noted. 5- hydroxytryptamine type3 (5HT₃) receptor antagonists are not only devoid of such side effects but also highly effective in prevention and treatment of PONV. Ramosetron is a highly selective and potent 5-HT₃ receptor antagonist. It is more potent and longer acting than previously developed 5-HT₃ receptor antagonists at equivalent doses. It is more effective than granisetron against cisplatin-induced emesis.

Keywords: Palonosetron, ramosetron, postoperative nausea, laparoscopic cholecystectomy, vomiting.

INTRODUCTION

Palonosetron, also a 5-HT₃ receptor antagonist, used for prevention of chemotherapy induced nausea and vomiting. This novel 5-HT₃ receptor antagonist has a greater binding affinity and longer half-life than older 5-HT₃ antagonists like ondansetron and granisetron. According to recent receptor binding studies, palonosetron is differentiated from other 5-HT₃ by its ability to interact with 5-HT₃ receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron (Rojas et al., 2008). Apart from that, this sort of receptor interaction may be associated with long lasting effects on receptor ligand binding and functional responses to serotonin (Gralla et al., 2003).

We designed this prospective randomized double blind trial to assess and compare the antiemetic efficacy of ramosetron and palonosetron to prevent PONV in patients undergoing laparoscopic cholecystectomy.

METHODS

The study protocol was approved by the ethical committee of Calcutta National Medical College, Kolkata and informed consent was obtained from the patients. Sixty ASA I –II female patients, aged 18-65 years, posted for elective laparoscopic cholecystectomy were randomly assigned to one of the two groups, containing thirty patients each. Group size of 30 patients were determined by power analysis based on standard deviation data from previously published reports. Patients who had gastrointestinal disease, those who had history of motion sickness and/or PONV, those who were pregnant or menstruating and those who had taken antiemetic medication within last 24 hours were excluded from the study.

Patients were then randomly allocated (using random table assignment) into two groups (n=30 each) to receive one of the following regimens: palonosetron 75µg in 2 ml (0.9% saline was added to make the desired volume) (group P) or ramosetron 0.3 mg in 2 ml (group R). These drugs were administered before the induction of

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Table 1. Patient's characteristic and duration of surgery (Mean \pm SD)

	Group R(n=30)	Group P(n=30)	P Value
Age (Years)	42.3 \pm 4.32	43.4 \pm 6.46	0.47
Weight (kg)	52.24 \pm 7.36	54.42 \pm 8.22	0.55
Duration of surgery(min)	54.4 \pm 6.62	53.46 \pm 8.26	0.65

anaesthesia. Identical syringes containing each drug were prepared by personal that was blinded to the randomization schedule.

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 2 μ g/kg and thiopental 5mg/kg. Patients were intubated with appropriate size endotracheal tube after muscle relaxation with vecuronium bromide in a dose of 0.08mg/kg. Anaesthesia was maintained with 33% oxygen in nitrous oxide and isoflurane 0.6%. 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 12 mmHg. At the end of surgical procedure, residual neuromuscular paralysis was 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 post anaesthesia care unit and blood pressure, heart rate and oxygen saturation were monitored. All episodes of PONV (nausea, retching and vomiting) were recorded in the following manner:

- 0-3 hour in postanaesthesia care unit
- 3-72 hour in postoperative ward

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as the labored, 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 72 hours, rescue antiemetic (metoclopramide 10 mg i.v.) was given.

Statistical Analysis

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. The results were expressed in mean (SD). Comparisons between groups were performed with the Kruskal Wallis one way ANOVA by ranks or Fisher's exact test for small sample with a 5% risk. Mann – Whitney – Wilcoxon tests were performed when normality tests failed or Chi-square test, as appropriate. The results were expressed in mean \pm SD and number (%).

RESULTS

The groups were comparable with respect to age, body-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 90% with ramosetron and 93.3% with palonosetron, the incidence during 3-24 hour postoperatively was 86.6% with ramosetron and 90% with palonosetron. During 24-48 hour, the incidence was 83.3% with ramosetron and 90% with palonosetron. During 48-72 hour, the incidence is 60% and 83.3% respectively (Table 2). Thus regarding complete response during 0-48 hour in the postoperative period, there was no significant difference between patients who had received ramosetron and those who had received palonosetron ($P > 0.05$) (Table 2). But during 48-72 hour, a complete response was significantly more in patients of group P than in patients of group R ($P < 0.05$) (Table 2). The commonly observed adverse effects were headache, dizziness and drowsiness but those were not clinically serious or significant. The incidences of adverse effects were statistically insignificant between the groups (Table 3).

DISCUSSION

Postoperative period is associated with variable incidence of nausea and vomiting depending on factors like anaesthetic agents administered (dose, inhalational drugs, opioids), duration of surgery, smoking habit etc (Lerman, 1992). 5-HT₃ receptors are situated on the nerve terminal of the vagus nerve on the periphery and centrally on the chemoreceptor trigger zone (CTZ) of the

Table 2. Incidence of Postoperative Nausea & Vomiting (PONV)

Postoperative period (hr)	Ramosetron (n=30)	Palonosetron (n=30)	P Value
0-3 hr			
Complete Response	27(90%)	28(93.3%)	0.67
Nausea	3(10%)	2(6.6%)	0.65
Retching	1(3.3%)	1(3.3%)	1
Vomiting	2(6.6%)	1(3.3%)	0.45
Rescue Drug	0	0	1
3-24 hr			
Complete Response	26(86.6%)	27(90%)	0.57
Nausea	4(13.3%)	3(10%)	0.69
Retching	1(3.3%)	1(3.3%)	1
Vomiting	3(10%)	2(6.6%)	0.62
Rescue Drug	0	0	1
24-48 hr			
Complete Response	25(83.3%)	27(90%)	0.23
Nausea	4(13.3%)	2(6.6%)	0.19
Retching	2(6.6%)	1(3.3%)	0.49
Vomiting	4(13.3%)	2(6.6%)	0.17
Rescue Drug	0	0	1
48-72 hr			
Complete Response	18(60%)	25(83.3%)	0.004
Nausea	10(36.6%)	4(13.3%)	0.06
Retching	2(6.6%)	1(3.3%)	0.49
Vomiting	3(10%)	2(6.6%)	0.17
Rescue Drug	0	0	1

Table 3. Incidence of Adverse Effects

Postoperative period (hr)	Ramosetron (n=30)	Palonosetron (n=30)	P Value
0-3 hr			
Headache	3(10%)	2(6.6%)	0.62
Dizziness	4(13.3%)	3(10%)	0.76
Drowsiness	1(3.3%)	1(3.3%)	1
3-24 hr			
Headache	2(6.6%)	3(10%)	0.57
Dizziness	3(10%)	2(6.6%)	0.52
Drowsiness	1(3.3%)	1(3.3%)	1
24-48 hr			
Headache	0	1(3.3%)	0.43
Dizziness	0	0	1
Drowsiness	0	0	1
48-72 hr			
Headache	0	0	1
Dizziness	0	0	1
Drowsiness	0	0	1

area postrema³. 5-HT₃ receptor stimulation is one of the primary events in the initiation of vomiting reflex⁹. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT₃ receptors on the CTZ and

also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT₃ receptors on the vagus nerve afferent fibers (Watcha and White, 1992).

After laparoscopic surgery, the incidence of PONV is as high as 40-75%. The etiology of PONV after laparoscopic surgery is dependent on a variety of factors including age, obesity, history of previous PONV, anesthetic technique, and post operative pain (Janknegt et al., 1999). In this study, however, both the groups were comparable with respect to patient demographics, types 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 drugs.

Ramosetron is a highly potent 5-HT₃ receptor antagonist with relatively high pharmacological bioavailability and it is effective for the treatment of cisplatin induced emesis (Noda et al., 1994). The exact mechanism of ramosetron in the prevention of PONV is yet to be known but ramosetron may act on the area postrema as well as the nucleus tractus solitarius, both of which containing a number of 5-HT₃ receptors (Kamoto et al., 1993). Palonosetron is another 5-HT₃ receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting. It is a novel 5-HT₃ receptor antagonist with not only a greater binding affinity, but also a longer biological half-life than older 5-HT₃ receptor antagonists⁶. The exact mechanism of palonosetron to prevent PONV is unknown too but palonosetron also may act on the area postrema which contain a number of 5-HT₃ receptors (Gralla et al., 2003). Therefore the possible mechanism regarding the antiemetic effects of both the drugs to prevent PONV is apparently similar.

The effective dose of ramosetron to be used for the prevention of PONV is not established but is extrapolated from the dose used in the clinical trials. These investigations demonstrated that ramosetron 0.3 mg is effective for the prevention or treatment of cisplatin induced emesis (Fujihara et al., 1996). Fujii Y and colleagues (Fujii et al., 1999) conducted a comparative study between granisetron and ramosetron and they found that 0.3 mg ramosetron is effective in preventing PONV after gynecologic surgery (Fujii et al., 1999). The same dose (0.3 mg) of ramosetron is used in the present clinical trial and has been found to be effective for prevention of PONV. Kovac LA and colleagues (Kovac et al., 2008) demonstrated that palonosetron 75 µg is more effective dose for prevention of PONV after major gynecological and laparoscopic surgery than 25 µg and 50 µg (Kovac et al., 2008). So 75 µg of palonosetron is selected in the present clinical trial and it has been found that palonosetron in a bolus dose of 75 µg had an excellent antiemetic efficacy.

Our study demonstrate that the antiemetic efficacy of ramosetron is similar to that of palonosetron for preventing PONV during the first 24 hours (0-24 hours) after laparoscopic surgery and there is no significant difference between the two drugs to get a complete response (no PONV, no rescue medication) for 24-48

hours. During 48-72 hours, palonosetron is more effective than ramosetron for getting complete response (no PONV, no rescue medication). This suggests that antiemetic efficacy of palonosetron lasts longer than ramosetron. The exact reason for the difference in effectiveness between ramosetron and palonosetron is not known but may be related to the difference in elimination half lives (ramosetron 9 hrs versus palonosetron 30.8-36.8 hrs in Japanese and 33.7-54.1 hrs in US healthy subjects) (Kim et al., 2009 ; Stoltz et al., 2004).

We did not include a control group receiving placebo in our study. Aspinall and Goodman (Aspinall and Goodmann, 1995) have also suggested that placebo controlled trials may be unethical if active drugs are available as incidence of PONV is high after laparoscopic surgery (Aspinall and Goodmann, 1995). Therefore a control group was not included in this study.

Adverse effects with a single bolus dose of ramosetron or palonosetron were not clinically serious (Fujii et al., 1999; Kovac et al., 2008) and there were no significant differences in the incidence of headache, dizziness and drowsiness between the groups. Thus both ramosetron and palonosetron are devoid of clinically important side effects.

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

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