ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF GRANISETRON VERSUS PALONOSETRON TO PREVENT POSTOPERATIVE NAUSEA AND VOMITING AFTER OPEN CHOLECYSTECTOMY

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ABSTRACT: BACKGROUND: Postoperative nausea and vomiting (PONV) is commonly seen after abdominal surgery. In this randomized double blinded prospective clinical study, we investigated and compared the efficacy of palonosetron and granisetron to prevent postoperative nausea and vomiting after open cholecystectomy. **PATIENTS & METHODS:** Hundred female patients (20-65 years of age) undergoing open cholecystectomy were randomly allocated one of the two groups containing 50 patients each. Group A received Granisetron 45 µg/kg body weight intravenously as a bolus before induction of anaesthesia. Group B received Palonosetron 1.5 µg/kg body weight intravenously as a bolus before induction. **RESULTS:** Palonosetron during 25-48 hour post-operative period significantly reduced the incidence of nausea 6 (12%) and vomiting 3 (6%) as compared to Granisetron group where 15 (30%) patients had nausea and 10 (20%) had vomiting. Complete response (no PONV, no rescue medication) was significantly higher in patients who received Palonosetron 45 (90%) as compared to Granisetron 37 (74%) ($p < 0.05$). Statistical analysis of the observations done between the treatment groups were performed by using unpaired student 't' test and chi square 'X²' test. **CONCLUSION:** Prophylactic therapy with Palonosetron is more effective than Granisetron for long term prevention of postoperative nausea and vomiting after open cholecystectomy.

KEYWORDS: Palonosetron, Granisetron, Postoperative Nausea and Vomiting (PONV), open cholecystectomy.

INTRODUCTION: Post-operative nausea and vomiting (PONV) has been one of the most distressing accompaniments of surgery and anaesthesia. PONV has been called as the "big little problem".¹ It has also been reported that the avoidance of post-operative nausea and vomiting was of greater concern to patients than postoperative pain.²

Persistent retching and vomiting causes dehydration and electrolyte imbalance. It can also lead to tension on suture lines, venous congestion and increased bleeding under skin flaps resulting in muscular strain, incisional hernia, gastric herniation, and oesophageal tear.³ A number of pharmacological agents (antihistamines, butyro-phenones, dopamine receptor antagonists) have been tried for the prevention and treatment of PONV but undesirable side effects such as excessive sedation, hypertension, dry mouth, dysphoria, hallucinations and extra pyramidal symptoms have been noticed.² 5-hydroxytryptamine type 3(5HT₃) receptor antagonists are devoid of such side effects and are highly effective in prevention and treatment of PONV.

Granisetron, a selective 5HT₃ receptor antagonist is more potent and longer acting with elimination half-life (9 hours) 2.5 times longer than that of Ondansetron and thus requiring less frequent dosing.⁴ It acts specifically at 5-HT₃ receptors on the vagal afferent nerves of the gut and

ORIGINAL ARTICLE

produces irreversible block.⁴ It has minimal side effects like headache, constipation and rare hypersensitivity reactions. It is effective and well tolerated in patients refractory to antiemetic treatment, and those with hepatic or renal impairment and in children.⁵

Palonosetron, a highly selective 5-HT₃ receptor antagonist is used for preventing chemotherapy induced nausea and vomiting. This unique 5-HT₃ receptor antagonist has a greater binding affinity and longer half-life than older 5-HT₃ antagonists like ondansetron. Recent receptor binding studies suggest that palonosetron acts by interacting with 5-HT₃ receptors in an allosteric and positive cooperative manner at sites different from those that bind with ondansetron and granisetron.⁶ This receptor internalisation is associated with long lasting effects on receptor ligand binding and functional responses to serotonin.

We designed this prospective randomized double blinded trial to assess and compare the antiemetic efficacy of granisetron and palonosetron to prevent PONV in patients undergoing open cholecystectomy.

PATIENTS & METHODS: The study protocol was approved by the institutional ethical committee and informed consent was obtained from every patient. Hundred ASA I-II female patients, aged 20-65 years, undergoing open cholecystectomy were randomly assigned to one of the two groups, containing fifty patients each. Patients who had previous gastric surgery, bleeding disorder, history of smoking, motion sickness, vestibular disease and/ or pregnant or menstruating, paediatric patients and those who had taken antiemetic medication within last 48 hours were excluded from the study.

Patients were randomly allocated into two groups (n=50 each) to receive one of the following regimens: granisetron 45 µg/kg body weight intravenous [group A] or palonosetron 1.5 µg/kg body weight intravenous [group B], both diluted in 0.9% NS to make a total volume of 5ml. The study medications were administered immediately before the induction of anaesthesia.

All patients were kept fasting after midnight and were pre medicated with Inj. Glycopyrrolate 0.2 mg intramuscularly 30 minutes before surgery. On the operation table, multi parameter monitor was applied for monitoring heart rate, electrocardiogram, non-invasive blood pressure, saturation of peripheral oxygen and end tidal carbon dioxide. Baseline vitals were recorded. After venous cannulation all the patients were pre hydrated with 7 ml/kg ringer lactate solution.

Then our study drugs were injected by an anaesthesiologist who was not involved in the study. Group A received Inj. Granisetron hydrochloride 45 µg/kg body weight intravenous and Group B received Inj. Palonosetron hydrochloride 1.5 µg/kg body weight intravenous, both diluted in 0.9% NS to make a total volume of 5ml.

After 3 minutes, patients were given Inj. Midazolam 0.04 mg/kg body weight and Inj. Fentanyl 2µg/kg body weight intravenous. After pre oxygenation for 5 minutes, patients were induced with Inj. Propofol 2 mg/kg body weight intravenous over 30-60 seconds. Tracheal intubation was done with Inj. Vecuronium 0.1mg/kg body weight using a Murphy endotracheal tube of appropriate size. After checking the position of endotracheal tube and securing it, anaesthesia was maintained with 60% nitrous oxide, 40% oxygen and 1.5 – 2% isoflurane. Incremental doses of Inj. Vecuronium 0.04 mg/kg body weight were given intra operatively.

With controlled mechanical ventilation, end tidal carbon dioxide was maintained between 30-35 mmHg. If the surgery was prolonged for more than 40 minutes then Inj. Fentanyl 1µg/kg body weight was repeated. Isoflurane was discontinued 5 min before the end of surgery and nitrous oxide

ORIGINAL ARTICLE

was stopped just before reversing the neuromuscular blockade with Inj. Neostigmine 0.05 mg/kg body weight and Inj. Glycopyrrolate 0.01 mg/kg body weight intravenous when the patient was on spontaneous respiration.

After oropharyngeal suctioning extubation was done and 100% oxygen was given using face mask till recovery of the patient. Patients were sent to recovery room in fully conscious state with vital signs within normal limits and airway reflexes intact. Diclofenac 100 mg suppository was kept at the end of surgery and if needed rescue analgesia in the form of opioids was given.

Postoperatively patients were monitored by resident doctors, who were unaware of the study drug for any nausea, retching or vomiting, for 48 hours by the visual analogue scale. Nausea was measured by 11 point numerical visual analogue scale. 0 = no nausea, 10 = worst nausea. A score of more than 5 was considered severe and a score of 4 or less was considered as minimal nausea. 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 was defined as no nausea or retching or vomiting and no need of rescue medication in the post-operative period up to 48 hours. Total number of episodes of vomiting was counted and those with two or more episodes of vomiting were given Inj. Metoclopramide 10mg intravenous as rescue antiemetic.

Post operatively any other adverse events like headache, dizziness, muscular pain and itching were also recorded. Patient satisfaction score was recorded at the end of the 48 hours from 1-5 with 5 being very satisfied and 1 being very dissatisfied. All the results were recorded and analyzed statistically. Statistical analysis of the observations done between the treatment groups were performed by using unpaired student 't' test and chi square 'X²' test. $p > 0.05$ was taken as insignificant.

STATISTICS: Student 't' test was used to compare the mean values of age, weight, duration of surgery and preoperative, intraoperative and postoperative vitals between two groups. Chi Square test (X²) was used to compare nausea, retching and vomiting, number of patients receiving rescue antiemetic, rescue pain relief, incidence of complete response, patient satisfaction score and complete response. All statistical analysis was done using SPSS for windows.

RESULTS: The two groups were comparable with respect to age, weight, ASA grade and duration of surgery. The incidence of nausea and vomiting during 24-48 hour postoperative period was significantly less in patients who received Palonosetron as compared with Granisetron [Table 1]. The incidence of complete response and patient satisfaction score during 0-48 hour in the postoperative period was significantly more in patients who had received Palonosetron than in those who had received Granisetron ($p < 0.05$) The commonly observed adverse effects were headache, dizziness and drowsiness but those were neither clinically serious nor statistically significant between the two groups. [Table 2].

DISCUSSION: Postoperative period is usually associated with variable incidence of nausea and vomiting depending upon the duration of surgery, the type of anesthetic agents used (dose, inhalational agents, opioids), smoking habit etc.⁷ 5-HT₃ receptor stimulation is the primary event in the initiation of vomiting reflex.⁸

ORIGINAL ARTICLE

These receptors are situated on the nerve terminal of the vagus in the periphery and on the chemoreceptor trigger zone (CTZ) of the area postrema centrally.² Anesthetic 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 vagus nerve afferent fibres.²

The incidence of PONV noted in adults is 25% ranging from 5-57% in literature. The incidence in day care surgeries is nearly the same varying from 8-45%.⁹ The etiology of PONV after open surgery is complex and is dependent on a variety of factors including age, obesity, and a history of previous PONV, surgical procedure, anesthetic technique, and post-operative pain.¹⁰ Factors particularly implicated in open cholecystectomy leading to PONV are pressure on stomach and gut, pain and pharyngeal stimulation. Among neural factors there are vagal reflexes elicited by irritation of parasympathetic nerve endings in the abdomen.² Also the hypotension occurring in some cases can lead to brain stem ischaemia, which activates the vomiting centre in the medulla and gastrointestinal ischaemia, releasing emetogenic substances such as serotonin which induce nausea and vomiting.

In this study, however, both the groups were comparable with respect to patient demographics, types and duration of surgery, anesthesia and analgesics used postoperatively. Haemodynamic (pulse rate, systolic blood pressure, diastolic blood pressure, SPO₂, EtCO₂ and respiratory rate) parameters during preoperative, intraoperative and postoperative period among the two groups were also comparable. 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-HT₃ receptors with demonstrated antiemetic effects.¹¹ Palonosetron is a unique 5-HT₃ receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting. It is a novel 5-HT₃ receptor antagonist with a greater binding affinity and longer biological half-life than older 5-HT₃ receptor antagonists.⁶ 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-HT₃ receptors.⁸ 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 for the treatment of cancer chemotherapy induced nausea and vomiting.¹² The dose of granisetron 45µg/kg 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 doses used in the clinical trials.^{13,14} Various studies were done to determine the optimally effective dose of palonosetron for controlling postoperative nausea and vomiting and it was found that palonosetron 1.5µg/kg body weight (appx.0.075mg) was appropriate. Same dose of palonosetron was used in our study.

In a study, Kovac et al¹⁴ had concluded that a single 0.075mg intravenous dose of palonosetron has significantly reduced emesis, intensity of nausea and the use of rescue anti-emetics in addition to delaying emesis and treatment failure.

Our study demonstrates that during 0-3 hours post-operative period, the antiemetic efficacy of granisetron and palonosetron was similar. In next 4-24 hours, the incidence of nausea and retching was clinically less and that of vomiting was significantly less with palonosetron 0.075mg as compared to granisetron.

ORIGINAL ARTICLE

Palonosetron significantly reduced nausea 7 (14%) and vomiting 3 (6%) as compared to granisetron groups where 14 (28%) patients had nausea and 9 (18%) had vomiting. During 25-48 hour post-operative period, palonosetron significantly reduced nausea 6 (12%) and vomiting 3 (6%) as compared to granisetron groups where 15 (30%) patients had nausea and 10 (20%) had vomiting. Similar results with 0.075mg palonosetron were concluded by Kovac et al¹⁴ in a study conducted on three different doses of palonosetron vs placebo in gynaecological surgeries. Candiotti et al also confirmed that 0.075mg of palonosetron was effective antiemetic dose.¹³

The number of patients requiring rescue antiemetic was higher in group A 11(22%) as compared to only 4 (8%) patients in group B which is statistically significant ($p<0.05$). In group A 37 (74%) patients had complete response. Thirteen (26%) patient had major nausea, retching and vomiting. Rescue antiemetic was given in eleven patients. In group B, 45 (90%) patients had complete response, five (10%) patients had major nausea, retching and vomiting and four patients required rescue antiemetic. Thus complete response during postoperative period was statistically significant ($p<0.05$) in palonosetron group than in granisetron group. The results of our study are in accordance with the study conducted by Bhattacharjee et al¹⁵ where antiemetic efficacy of palonosetron 75 µg was compared with granisetron 2.5mg in laparoscopic cholecystectomy and complete response during 24-48 hour, was 66.6% and 90% respectively.

Patient satisfaction score was generated with respect to satisfaction with the study drug. For statistical purposes patients having satisfaction score of 4 and 5 were taken as satisfied. Patients having satisfaction score of 1, 2 and 3 were taken as not satisfied. In group A 35 (70%) and in group B 44 (88%) patients were satisfied respectively. The difference among the two groups with regard to satisfaction of the patients was statistically significant. ($p<0.05$)

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-HT₃ receptor antagonists (palonosetron interacts with 5-HT₃ receptors in an allosteric, positive cooperative manner at sites different from that bind with granisetron).⁶

Adverse effects with a single therapeutic dose of granisetron or palonosetron were not clinically serious and there were no statistically significant differences in the incidence of headache, dizziness and drowsiness between the groups.¹⁶

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

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ORIGINAL ARTICLE

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DURATION 0-3 HOURS	GROUP A	GROUP B	SIGNIFICANCE
NAUSEA	10(20%)	6(12%)	NS
RETCHING	5(10%)	3(6%)	NS
VOMITING	5(10%)	3(6%)	NS
4-24 HOURS			
NAUSEA	14(28%)	7(14%)	NS
RETCHING	8(16%)	3(6%)	NS
VOMITING	9(18%)	3(6%)	S
25-48HOURS			
NAUSEA	15(30%)	6(12%)	S
RETCHING	9(18%)	4(8%)	NS
VOMITING	10(20%)	3(6%)	S

Table 1: Incidence of Postoperative Nausea & Vomiting (PONV) in 0-48 Hours

ORIGINAL ARTICLE

PARAMETERS	GROUP A	GROUP B	SIGNIFICANCE
RESCUE ANTIEMETIC	11(22%)	4(8%)	S
PAIN RELIEF	16(32%)	13(26%)	NS
COMPLETE RESPONSE	37(74%)	45(90%)	S
ADVERSE EFFECTS	9(18%)	6(12%)	NS
SATISFACTION SCORE	35(70%)	44(88%)	S

Table 2: RESULTS AND ANALYSIS

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