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Evaluation of Palonosetron versus Ondansetron in Preventing Postoperative Nausea and Vomiting

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ABSTRACT
Postoperative nausea and vomiting (PONV) is a common and distressing complication of surgery under general anaesthesia. This randomized, double-blind study evaluated the relative efficacy of palonosetron and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 50) or ondansetron 8 mg (n = 50), intravenously, immediately before induction of general anaesthesia. The incidence of a complete response during 0-3 hour in the postoperative period was 70% with ondansetron and 92% with palonosetron, the incidence during 3-12 hour postoperatively was 60% with ondansetron and 92% with palonosetron. During 12-24 hour, the incidence was 54% and 90% and 24-48 hour the incidence was 50% and 88% respectively. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Keywords: *Antiemetics, anaesthesia, nausea, palonosetron, ondansetron, post-operative and vomiting.*

INTRODUCTION

Postoperative nausea and vomiting (PONV) is the most common complication of surgery and anaesthesia[1], leading to adverse consequences including patient dissatisfaction, unexpected hospital admission, and delayed recovery and return to work [2]. PONV is less commonly associated with more serious postsurgical complications such as wound dehiscence and surgical site bleeding [3]. The incidence of PONV can reach 80% in high-risk patients, underlining the importance of prevention and control by anaesthetists [4].

The complete knowledge about the risk factors responsible for PONV helps in designing the treatment regimens and interventions for its control. PONV poses a great challenge to the surgeon as well as anaesthesiologist as it causes a great discomfort, delay in discharge, increased readmissions to hospital, pulmonary complications and a delayed resumption of daily chores. Throughout the world, great amount of resources, time, capital and dedicated efforts are spent to find a better alternative for prevention of this irritating disturbance. [5],[6]

The advent of 5-HT3 antagonists in medical practice has provided a great relief to the physicians, oncologists and anaesthesiologists [7]. These pharmacological agents are as effective as

any other antiemetic drug but with a more safety and favourable side-effects profile as they lack the sedative, dysphonic and extra-pyramidal side effects of other commonly used antiemetics [8]. All the 5-HT3 antagonists like ondansetron, dolasetron, granisetron, azasetron, tropisetron and palonosetron have a favourable drug profile and a long duration of antiemetic action (4-48 hours). Ondansetron is being routinely used throughout the world, either alone or in combination with other drugs, for the prophylaxis of PONV in surgery mainly because of its lower cost. Among these agents, palonosetron has got a far higher receptor affinity and a much longer half-life which confer a prolonged duration of action [9]. The long duration of antiemetic effect is quite beneficial in preventing the problem of PONV.

The 5-hydroxytryptamine-3 (5-HT3) receptor antagonists are popular drugs for PONV prophylaxis because of their similar efficacy to droperidol or dexamethasone and their favourable side-effect profile.2 Palonosetron is a new, potent, selective 5-HT3receptor antagonist with a strong receptorbinding affinity and a long elimination halflife and, therefore, a long duration of efficacy [10],[11].

6 A study evaluating the efficacy and safety of palonosetron in preventing PONV found that a single 0.075 mg intravenous (i.v.) dose significantly decreased emetic episodes, nausea severity and rescuemedication use during the first 24 h after anaesthesia, in patients undergoing abdominal or gynaecological laparoscopic surgery [12]. It was also reported that palonosetron is as effective as ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy [13].

The present randomized, double-blind study was designed to evaluate the efficacy of palonosetron compared with ondansetron for preventing PONV in patients undergoing laparoscopic gynaecological surgery.

MATERIALS AND METHODS

The present study was approved by the ethical committee of the institution and a written consent was taken from the patients after explaining to them in detail about the implications of the anaesthetic and the surgical procedure. The selection criteria comprised of 100 ASA I/II patients between the age of 25 and 40 years who underwent laparoscopic cholecystectomyunder general anaesthesia, were enrolled for present study. All the patients underwent pre-anaesthetic assessment before enrolment.

The patients with ASA III/IV status, psychiatric diseases, diabetes, history of drug abuse, chronic obstructive pulmonary disease, previous history of motion sickness and PONV, patients with history of systemic hypertension, endocrine or metabolic disorders, hepatic or renal disease, cardio-pulmonary dysfunction, patients with gastro-intestinal disorders, psychiatric diseases, and morbid obesity were excluded from study. Other exclusion criterions were pregnant and menstruating females, those who had taken antiemetic drugs within 24 hours before surgical procedures.

The total 100 patients were equally divided into two groups of 50 patients according to a computer-generated random table. Patients of group P were given injection palonosetron (0.075 mg), patients of group O were given injection ondansetron (4 mg), intravenously along with premedication, five minutes before induction of general anesthesia. The study drug preparation was done by an assistant who was unaware to the study protocol and was not involved in the study for any further evaluation of patients.

All patients were given tab alprazolam 0.25 mg and tab ranitidine 150 mg the night before surgery and were kept fasting for eight hours prior surgery. On arrival to operation-theater, routine monitoring of heart rate, systemic arterial blood pressure, pulse oximetry (SpO_2), electrocardiogram (ECG) was started. After securing intravenous line, infusion of lactate Ringer was started. Patients were premedicated with intravenous midazolam (0.05 mg kg^{-1}), fentanyl (2 μg kg^{-1}), and glycopyrrolate (0.2

mg) followed by study medication according to group allocation five minutes prior to induction of general anesthesia.

After pre-oxygenation, induction was done with propofol (2 mg kg^{-1}), and tracheal intubation was facilitated with vecuronium bromide 0.08 mg kg^{-1}. Anesthesia was maintained with isoflurane, N_2O (60%) in oxygen. All patients were mechanically ventilated to maintain the EtCO2 between 35-40 mm Hg. Additional analgesia during the surgery was achieved with fentanyl (25 µg). At the end of surgery, the residual neuromuscular blockade was antagonized with appropriate doses of neostigmine (0.05 mg kg^{-1}) and glycopyrrolate (0.01 mg kg^{-1}). Extubation was performed when respiration was adequate and patient was able to obey simple commands.

The baseline systemic arterial blood pressure, pulse rate, and SpO2 were recorded followed by after premedication, after induction and then at five min intervals till one hour and then at every 15 min till the end of surgery. They were monitored for any hypotension, hypertension, arrhythmias, hypoxemia, and bronchial spasm. Hemodynamic changes occurring during study period were managed with volume expansion, vasopressor or atropine, if required.

Postoperatively, nausea or emetic episode were recorded by the nursing staff without knowledge of which group of anti-emetic drug was given to the patients. The side effects like headache, dizziness, and drowsiness were also noted. Postoperatively, the patients were given intramuscular injection of diclofenac sodium (75 mg) for postoperative analgesia.

Nausea was defined as an urge to vomit, and vomiting was defined as the forceful expulsion of gastric contents from the mouth. Patients were asked about nausea and vomiting at 2, 4, 6, and 12 hours. Complete response was defined as no nausea, retching or vomiting, and no need of rescue antiemetic medication within 12 hours in postoperative period. If required, rescue anti-emetic metoclopramide 5 mg was given intramuscularly. The total number of complete responders was recorded.

The recorded data are systematically compiled in tabulated manner as mean ± SD and analyzed by Stat graphics Centurion, using one-way ANOVA and Chi-square test. Comparison between groups for postoperative nausea and vomiting score was performed by using the Kruskal Wallis test. $P < 0.05$ was considered as statistically significant.

RESULTS

The demographic profile of the patients for the present study with respect to age, body weight, ASA grading revealed no significant comparative difference between the two groups. Mean duration of surgery as well as mean duration of anaesthesia were comparable in both the groups and on statistical analysis revealed no significant difference (table .1).

Preoperatively, the baseline heart rate and systemic blood pressure were comparable among the three groups with no statistically significant difference. The heart rate and systemic blood pressure did not show any significant difference among the groups after intubation at 5 minutes, 15 minutes, and 45 minutes, and at the end of surgical procedures.

Table 1: Comparison of Demographic data between two groups

Parameter/variable	Group P	Group O
Age (years)	33.2±7.9	34.6±8.2
Body weight (Kgs)	54.4±7.3	58.9±7.8
ASA GradeI/II	21/29	26/24
Male/Female	22/28	30/20
Mean duration of Surgery	108.6±45.2 min	103.2±47.2 min
Mean duration of anaesthesia	130.7±32.6min	138.9±42.6min
Rescue dose of antiemetic	6.4mg	10.6mg

Values were expressed in Mean±S.D

The incidence of a complete response (no PONV, no rescue medication) during 0-3 hour in the postoperative period was 70% with ondansetron and 92% with palonosetron; the incidence during 3-12 hour postoperatively was 60% with ondansetron and 92% with palonosetron. During 12-24 hour, the incidence was 54% and 90% and 24-48 hour the incidence was 50% and 88% respectively. 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 ondansetron (table 2).

Table 2: Comparison of PONV in two groups

Post -operative period	Group P n(%)	Group O n(%)
0-3hours		
Complete response	46(92%)	35 (70%)
Nausea	2(4%)	10(22%)
Retching	1(2%)	3(6%)
Vomiting	1(2%)	6 (12%)
Rescue drug	0	
3-12 hours		0
Complete response	46 (92%)	30(60%)
Nausea	2(4%)	10(20%)
Retching	1(2%)	4(8%)
Vomiting	2(4%)	8(16%)
Rescue drug	0	3(2%)
12-24hours		
Complete response	45(90%)	27(54%)
Nausea	3(6%)	13(26%)
Retching	1(2%)	6(12%)
Vomiting	2(4%)	6(12%)
Rescue drug	0	5(10%)
24-48hours		
Complete response	44(88%)	25(50%)
Nausea	3 (6%)	13(26%)
Retching	1(2%)	5(10%)
Vomiting	2(4%)	8(16%)
Rescue drug	0	9(18%)

Value were expressed in number of patients and percentages

Incidence of nausea episode at 0-12 hours were observed in 10 patients (20%) of ondansetron group, two patients (4%). The difference among the groups was statistically highly significant. At 12-48 hours, thirteen (26%) of ondansetron group suffer from nausea as compared to only three patients (2.5%) in palonosetron group. The difference among the three groups was statistically significant.

Retching was observed in only one patient of palonosetron group and six patients of ondansetron group post operatively. The number of patients who had vomiting episodes in postoperative period was 16% in ondansetron group, 4% in palonosetron group respectively. The difference was significantly high.

It is very clearly evident that incidence of side effects are comparatively much lower in palonosetron group. The incidence of postoperative headache was significantly higher in the O group. The incidence of other side effects like pain, anxiety dizziness, constipation and myalgia were comparable (table 3).

Table 3: Comparison of side effects in both groups

Side effects	Group P N(%)	Group O N(%)
Pain	3(6%)	2(4%)
Anxiety	2(4%)	3(6%)
Head ache	3(6%)	6(12%)
Dizziness	2(4%)	2(4%)
Dry mouth	0	0
Sedation	1(2%)	2(4%)
Constipation	1(1%)	3(6%)
Myalgia	0	3(6%)

Value were expressed in number of patients and percentages

DISCUSSION

In the present day scenario, PONV still remains a big headache and nuisance for the surgeons and anaesthesiologists as well as an irritating discomfort for the patients almost equal in intensity to pain [14]. The delayed convalescence, hospital readmission, delayed return to work of ambulatory patients; postoperative surgical morbidities such as pulmonary aspiration, wound dehiscence, bleeding from the wound and metabolic derangement due to excessive emetic episodes are few of the adverse consequences of the PONV [15]. It is very difficult to predict the outcome in an individual patient as various other causes, besides the established risk factors, can influence the incidence of PONV. The present study was carried out mainly to see the comparative efficacy of the new and much promising long-acting 5-HT3 antagonist palonosetron against ondansetron in laparoscopic cholecystectomy.

Postoperative period is associated with variable incidence of nausea and vomiting depending on the duration of surgery, the type of anaesthetic agents used (dose, inhalational drugs, opioids), smoking habit etc [16]. The incidence of PONV after laparoscopic surgery is high(40-75%). The aetiology 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, anaesthetic technique, and post-operative pain [17]. Several receptor types – including serotonin 5-HT3, dopamine D2, histamine H2, α2-adrenergic, muscarinic cholinergic,

neurokinin1 and GABA – are involved in the initiation and co-ordination of the vomiting reflex in patients with PONV [18].

In this study, both the groups were comparable with respect to patient demographics, types and duration of surgery and anaesthesia 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.

Kovac et al.[12] found that 0.075 mg palonosetron significantly reduced PONV in the first 24 h after anaesthesia, compared with placebo. In addition, Paventi et al. [19] compared the efficacy of 4 mg versus 8 mg ondansetron for the prevention of PONV after laparoscopic cholecystectomy and concluded that 8 mg was more effective than 4 mg. Based on previous studies we selected the dose of palonosetron as 0.075mg and ondansetron as 8mg.

5-HT_3receptor stimulation is the primary event in the initiation of vomiting reflex [20]. 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 [21]. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT_3receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT_3 receptors on vagus nerve afferent fibres [21].

The 5-HT3 antagonists exerts their antiemetic action by blocking the binding of serotonin to 5-HT3 receptors in the gut and the CTZ of area postrema which has got projections to the vomiting centre of lateral reticular formation of medulla oblongata [22]. Ondansetron was the first 5-HT3 receptor antagonist to be marketed and has frequently been used to control PONV [1]. Palonosetron – a second generation 5-HT3 antagonist – has unique structural, pharmacological and clinical properties that distinguish it from other 5- HT3 antagonists [2].

Palonosetron is a unique 5-HT_3 receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting. It is a novel 5-HT_3 receptor antagonist with a greater binding affinity and longer biological half-life than older 5-HT_3 receptor antagonists [23]. 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_3 receptors [24].

Our study demonstrate that the antiemetic efficacy of palonosetron is similar to that of ondansetron for preventing PONV during the first 24 hours (0-24 hours) after laparoscopic surgery and that palonosetron is more effective than ondansetron 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 ondansetron. The exact reason for the difference in effectiveness between ondansetron and palonosetron is not known but may be related to the half -lives. Moreover ondansetron has a shorter half-life of 3-5 hours, whereas palonosetron has a half-life of approximately 40 hours, which makes it more effective in preventing nausea and vomiting [25]. How the efficacy of different 5-HT3 receptor antagonists vary is still unclear but most probably these differences may involve multiple factors such as intrinsic differences in 5-HT3 receptor blocking activity, 5- HT3 receptor affinity and binding stability, and differences in autocrine activity of serotonin released from enterochromaffin cells to act on 5-HT3 or 5-HT4 receptors on EC cells [26].

Palonosetron 0.075 mg, i.v. improves the control of nausea and vomiting through the second and third postoperative days. Palonosetron undergoes a slow elimination phase which results in a long half-life of approximately 40 h, in contrast with the 3 – 5-h half-life of ondansetron [27],[28].

The 5-HT3 antagonists have an enviable safety profile, with most side-effects (e.g. headache, constipation, dizziness) being mild and transient [29] Palonosetron has a similar safety profile to other 5-HT3 antagonists [30]. Adverse effects with a single therapeutic dose of ondansetron or palonosetron were not clinically serious. Thus both palonosetron and ondansetron are devoid of clinically important side effects. Mild side effects are clinically comparable in two groups.

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

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