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ANTIEMETIC EFFICACY OF PALONOSETRON COMPARED WITH THE COMBINATION OF ONDANSETRON AND DEXAMETHASONE FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC GYNAECOLOGICAL SURGERY

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Abstract

Background and aims: *For the prevention of PONV, we evaluated the efficacy of palonosetron compared with ondansetron along with dexamethasone in patients undergoing laparoscopic gynaecological surgery.*
Methods: *A total of 84 adults, posted for elective laparoscopic surgeries under general anaesthesia were included in the study. The patients were randomly allocated to two groups (n = 42 each). Immediately after induction, patients in the first group (group I) received 4 mg ondansetron with 8 mg dexamethasone, and patients in the second group (group II) received 0.075 mg palonosetron. Any incidences of nausea and/or vomiting, the requirement of rescue antiemetic, and side effects were recorded.*
Results: *In group I, 66.67% of the patients had an Apfel score of 2, and 33.33% of the patients had a score of 3. In group II, 85.71% of patients had an Apfel score of 2, and 14.29% of the patients had a score of 3. At 1, 4, and 8 hours, the incidence of PONV was comparable in both groups. At 24 hours there was a significant difference in the incidence of PONV in the group treated with ondansetron with dexamethasone combination (4/42) when compared to the palonosetron group (0/42). The overall incidence of PONV was significantly higher in group I (23.81%: ondansetron and dexamethasone combination) than in group II (7.14%: palonosetron). The need for rescue medication in group I was significantly high.*
Conclusion: *Palonosetron was more efficacious compared to the combination of ondansetron and dexamethasone for preventing PONV for laparoscopic gynaecological surgery.*

Keywords

postoperative nausea and vomiting (PONV) • palonosetron • ondansetron • dexamethasone

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications of anaesthesia. Though self-limiting most of the time, it does put the patient in a state of discomfort. The incidence of PONV after general anesthesia is up to 30% when inhalational anaesthetics are used with no prophylaxis [1]. However, the incidence of PONV can reach 80% in high-risk patients, underlining the importance of prevention and control by anaesthetists [2]. The need for an ideal antiemetic is yet to be a reality, and the search is still on. The Apfel scoring system is a validated and widely accepted risk stratification tool for PONV. The four risk factors included in the final simple sum score are female gender, prior history of motion sickness or PONV, nonsmoking, and the use of postoperative opioids. If no or only one risk factor is present, the incidence of PONV may vary between about 10% and 21%, whereas if at least two risk factors are present, it may rise to between 39% and 78%. However, there may be various other reasons for causing PONV, such as the use of inhalational agents during the surgery. Volatile anaesthetics are the leading cause of early postoperative vomiting [3].
Nausea is described as an unpleasant sensation referred to as a desire to vomit not associated with expulsive muscular movement. Vomiting is described as the forceful expulsion of even a small amount of upper gastrointestinal contents through the mouth. The neuroanatomical site controlling nausea and vomiting is an ill-defined region called the "vomiting centre" within the reticular formation in the brainstem [4, 5]. The primary afferent pathways involved

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in stimulating vomiting are the chemoreceptor trigger zone (CTZ), vagal mucosal pathway in the gastrointestinal system, neuronal pathways from the vestibular system, reflex afferent pathways from the cerebral cortex, and midbrain afferents. Stimulation of one of these afferent pathways can activate the sensation of vomiting via cholinergic (muscarinic), dopaminergic, histaminergic, or serotonergic receptors [6]. The primary event in the initiation of the vomiting reflex is the stimulation of the 5-hydroxytryptamine-3 (5-HT3) receptor. These receptors are situated on the nerve terminal of the vagus nerve in the periphery and centrally on the CTZ of the area postrema. 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 [7]. Efferent signals are directed to glossopharyngeal, hypoglossal, trigeminal, accessory, and spinal segmental nerves [5],

The 5-HT3 receptor antagonists are popular drugs for PONV prophylaxis with a reasonable side effect profile [2]. There have been many studies on drugs to be used for the prevention of PONV, but there is no single best agent for the same issue.

All the 5-HT3 antagonists—ondansetron, dolasetron, granisetron, azasetron, tropisetron, and palonosetron—have a favorable 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 daycare surgery mainly because of its lower cost. Among these agents, palonosetron has a far higher receptor affinity and a much longer half-life, which confer a prolonged duration of action. The extensive research in the prevention of PONV has established 0.075 mg as the minimum effective dose of palonosetron, and the same has been approved by the US Food and Drug Administration (FDA) for PONV prophylaxis [8].

In this randomised control trial, we attempted to evaluate the efficacy of palonosetron compared with ondansetron along with dexamethasone for preventing PONV in patients undergoing laparoscopic gynaecological surgery.

Materials and method

This prospective randomised, double-blind study was performed at the North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, India, after obtaining the institutional ethical committee clearance. The subjects of this study were randomised into two groups by computer randomisation. The two groups were

Group I: O + D (ondansetron + dexamethasone), *n* = 42

Group II: P (palonosetron), *n* = 42

American Society of Anesthesiologists (ASA) classification 1 and 2 female patients age between 20 and 70 years posted for elective laparoscopic gynaecological surgery under general anaesthesia with a preoperative Apfel score of at least 2 were included in this study. Patients with any known allergy to the study drugs, pregnant women, body weight more than 30% above the ideal body weight, and/or a history of vomiting or retching within 24 hours before the operation or administration of antiemetics and steroids or within 24 hours before the operation were excluded from the study.

Premedication in each case was standardized in both groups to reduce bias. Tab alprazolam 0.5 mg and Tab ranitidine 150 mg were administered to all the patients. For induction, injection propofol (2 mg/kg IV) and fentanyl (2 µg/kg IV) were used in all cases. Injection vecuronium 0.1 mg/kg IV was administered for facilitation of endotracheal intubation with an appropriate size endotracheal tube. Anaesthesia maintained with isoflurane 1 to 2% and oxygen/air and intermittent boluses of injection vecuronium as per requirement. Injection paracetamol 1 g IV was administered over 20 minutes after induction in both groups.

Immediately after induction, group I received 4 mg of dexamethasone IV plus 4 mg of ondansetron IV, and group II received 0.075 mg of palonosetron IV.

On completion of the surgery, the neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg IV and glycopyrrolate 0.01 mg/kg IV. The fluid was given according to the precalculated formula. After extubation and recovery of anaesthesia, patients were observed in the postanaesthetic care unit (PACU) for 1 hour and then transferred to the ward. All patients received adequate standardized analgesia in the postoperative period and were also monitored for postoperative pain.

Anaesthetists who were not a part of the study and unaware of patient allocation by randomisation were instructed to prepare the drugs, and as both of the drugs used in this study were transparent, total dilution was made to 5 mL for both of the drugs used in both of the groups. Prepared drugs were handed over to the anaesthesiologists, who were unaware of the drug in the syringe involved in the laparoscopic gynaecological cases done under general anaesthesia.

The primary outcome was measured with the occurrence of PONV to a Visual Analogue Scale (VAS; 0, no nausea; 10, worst nausea) at 1, 4, 8, and 24 hours postoperatively. This monitoring was done by anesthesiologists blinded to the study.

If any patient retched and had the symptoms of vomiting, it was counted as vomiting. Side effects of palonosetron and ondansetron were also evaluated.

Sample size calculation

The sample size was calculated using Stata/MP 14.2 for Windows. Assuming 30% reduction (from previous studies), at a

significance level of 0.05 and power 80% with an allocation ratio of 1:1, the sample size of 84 (42 in each group) was required.

Results

A total of 84 patients were evaluated (n = 42, in each group). In both groups, demographic variables were comparable (p = .5078). The mean age in group I (O + D) was 30.90 ± 6.05 years; in group II (P), 30.07 ± 5.40 years.

Out of 84 cases of proposed laparoscopic gynaecological procedures, the majority of the procedures were diagnostic hysterolaparoscopy. In group I, 71.42% (30) and in group II, 76.19% procedures were diagnostic hysterolaparoscopy. Laparoscopic cystectomy comprised 16.66% in both groups. Other procedures are mentioned in Table 1. The distribution of different procedures between the two groups does not have a significant effect (p = .193) on the assessment of outcome.

The Apfel scores were calculated depending on the risk factors present. An Apfel score of more than 2 was included. In group I, 73.80% of the patients had an Apfel score of 2, and 26.20% of the patients had a score of 3. In group II, 76.19% of patients had an Apfel score of 2, and 23.81% of the patients had a score of 3 (Table 2). The distribution of subjects with Apfel scores of 2 and 3 was similar in both groups and was comparable.

Table 1: Distribution of proposed procedures

Proposed procedure	Group 1	Group 2	Grand Total	P value
DHL (Diagnostic Hystero laparoscopy)	30	32	62	
Laparoscopic Cystectomy	7	7	14	
Laparoscopic Hysterectomy	1		1	
Laparoscopic Tubal Occlusion	3	2	5	0.193
Laparoscopy	1		1	
Total Laparoscopic Hysterectomy		1	1	
Total	**42**	**42**	**84**	

The PONV incidence at 1 hour was zero in both groups. At 4 hours group I had nausea in 1 patient (2.38%), and 1 patient (2.38%) had vomiting. Total PONV at 4 hours was 2 (4.76%) in group I. In group 2 there was no nausea or vomiting. At 8 hours group I had nausea in 1 patient (2.38%), and 1 patient (2.38%) had vomiting. Total PONV at 4 hours was 2 (4.76%) in group I (Table 3).

At 24 hours group 1 had nausea in 4 patients (9.52 %). Total PONV at 24 hours was 4 (9.52%) in group I. In group II there was no nausea or vomiting. The difference was found to be significant.

In the 24- to 48-hour segment, group I had nausea in 2 patients (4.76%). Total PONV at 24 to 48 hours was 2 (4.76%) in group I. In group II only 2 patients had nausea (4.76%), and 1 patient (2.38%) had vomiting. Total PONV was 3 (7.14%) in group II.

In total 8 (19.05%) patients had nausea and 2 (4.76%) patients had vomited in group I. Total incidence of PONV was 10 (23.81%). In group II, 2 (4.76%) patients had nausea, and 1 (2.38%) patients had vomiting. The total incidence of PONV in group II was 3 (7.14%). The incidence of PONV in group I was significantly higher than in group II (p = .0488), calculated by using the Mann-Whitney-Wilcoxon Test for 2 independent samples (Table 3).

The need for rescue medication in group I was 8 (19.05%); in group II none needed any rescue medication (p = .0093). Patients' satisfaction in both groups was comparable (Table 4).

Headache was the only drug-related complication noted in our study. In group I, 4 (9.52%) patients and in group II, 3 (7.14%) patients had a headache. Both groups were comparable in this regard.

Discussion

PONV, though an anticipated complication in laparoscopic gynaecological surgeries, is still a major issue for anaesthesiologists and patients. Despite prophylactic antiemetics, there may be a significant incidence of PONV, which may have various serious clinical consequences, such as patient dissatisfaction, delay in recovery, and wound dehiscence.

Table 2: Comparison of the Apfel scores between the groups

Apfel Score	Group 1		Group 2		Total	P value
2	31	73.80%	32	76.19%	63	
3	11	26.20%	10	23.81%	21	0.992
Total	**42**	**100.00%**	**42**	**100.00%**	**84**	

Table 3: Comparison of two groups in terms of PONV incidence

PONV Incidence	Group 1			Group 2			P value
	Nausea	Vomiting	Total PONV	Nausea	Vomiting	Total PONV	
At 1 hour	0	0	0	0	0	0	1.000
At 4 hr	1 (2.38%)	1 (2.38%)	2 (4.76%)	0	0	0	0.1548
At 8 hr	1 (2.38%)	1 (2.38%)	2 (4.76%)	0	0	0	0.1548
At 24 hr	4 (9.52%)	0	4 (9.52%)	0	0	0	0.0416#
At 24-48 hr	2 (4.76%)	0	2 (4.76%)	2 (4.76%)	1 (2.38%)	3 (7.14%)	0.6312
Total	**8 (19.05%)**	**2 (4.76%)**	**10 (23.81%)**	**2 (4.76%)**	**1 (2.38%)**	**3 (7.14%)**	**0.0488**

Table 4: Need for Rescue antiemetic in both the groups

Rescue antiemetic	Group 1	Group 2	P value
Yes	8 (19.05%)	0 (0%)	
No	34 (80.95%)	42 (100%)	**0.0093**
Total	**42**	**42**	

Palonosetron is a novel 5-HT3 receptor antagonist first approved for the prevention of chemotherapy-induced nausea and vomiting. It has a greater binding affinity and longer biological half-life than older 5-HT3 receptor antagonists [9].

Recently there have been studies comparing the effects of palonosetron and other 5-HT3 receptor antagonists on PONV prevention 10-12]. Park and Cho studied the use of ondansetron 8 mg and palonosetron 0.075 mg before anaesthesia induction on patients with two or more risk factors. Palonosetron (42.2%) was far better than ondansetron (66.7%) in PONV prevention for up to 24 hours [10].

Park and Cho compared palonosetron with ondansetron in preventing PONV after gynaecological laparoscopic surgery. The incidence of PONV (first 24 hours) was significantly lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). Palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV [10].

In a randomised control study, Sharma and Shankaranarayana compared palonosetron with dexamethasone versus ondansetron with dexamethasone in laparoscopic hysterectomies. They concluded that the combination of palonosetron with dexamethasone is more effective in treating early, delayed, and long-term PONV compared to ondansetron with dexamethasone in patients undergoing elective laparoscopic hysterectomies under general anesthesia [11].

Kim et al compared palonosetron with ondansetron for prevention of PONV in patients receiving intravenous patient-controlled analgesia (IV-PCA) after gynaecological laparoscopic surgery. The incidences of nausea, vomiting, and side effects were recorded at the 2nd, 24th, 48th, and 72nd hours postoperatively. There were no significant differences between the groups in the incidence of PONV during the 72nd hour after the surgery. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs 4%, p = .025). The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynaecological laparoscopic surgery and receiving opioid-based IV-PCA [12].

Shadangi et al compared intravenous palonosetron to ondansetron for the prevention of PONV under general anaesthesia. In the postoperative period each patient was observed for retching, nausea, and/or vomiting at 30 minutes, then at 1, 2, 6, 12, and 24 hours. The number of patients, who remained vomiting-free in the first 24 hours after surgery was 56.6%, 80%, and 86% in the placebo, ondansetron, and palonosetron groups, respectively. The difference in vomiting between ondansetron and palonosetron was not significant, but the incidence of nausea was significantly less common in the palonosetron group than in the ondansetron group (16.7% vs 43.4%, p = .006). The authors concluded that palonosetron is significantly more effective against PONV than ondansetron [13].

Candiotti et al did a randomised, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing PONV. Patients with more than two PONV risk factors were randomised to receive one of three doses of IV palonosetron (0.025, 0.050, or 0.075 mg) or placebo immediately before induction of anaesthesia. A single 0.075 mg IV dose of palonosetron significantly increased the complete response (CR) rate (no emetic episodes and no rescue medication) from 0 to 24 hours and decreased nausea severity; furthermore,

patients experienced significantly less interference in their postoperative function due to PONV [14].

Bajwa et al conducted a prospective double-blind study, in which patients were randomly divided into two groups of 30, each in a double-blind manner. Group I received 8 mg of injection ondansetron IV, and group II received injection palonosetron 0.075 mg IV 5 minutes before the induction of anaesthesia. Twenty percent and 13.33% of the patients in group I had nausea and vomiting episodes postoperatively, as compared to 6.67% and 3.33%, respectively, in group II, which was statistically significant ($p < 0.05$). The authors concluded that palonosetron is a comparatively better drug to prevent PONV in patients undergoing daycare surgical procedures as compared to ondansetron [8].

Various other studies also confirm that palonosetron is more efficacious when compared with various other antiemetics such as granisetron or other first-generation 5-HT3 blockers or placebo in various laparoscopic and nonlaparoscopic surgeries [15-18].

In our study the distribution of cases in both groups was comparable. In both groups diagnostic hysterolaparoscopy was the most commonly done procedure. The Apfel scores preoperatively were also comparable in both groups. In our study we found that the antiemetic efficacy of ondansetron and dexamethasone is similar to palonosetron for up to 24 hours. At 24 hours there was a significant difference in the incidence of PONV in the group treated with ondansetron with dexamethasone when compared to palonosetron (9.52% vs 0%, respectively; $p = .0416$). In calculating the total incidence of PONV in both groups, group I had a significant incidence of PONV when compared to group II. The need for rescue medication was also significantly higher in group I. However, after rescue medication, most cases of nausea subsided; hence there was no significant difference in satisfaction of the patients in both groups. There were no complications noted except headache, which too was comparable in both groups.

Placebo groups were not considered appropriate in this study, as PONV is a distressing symptom, and it is unethical to let patients go through it when anticipated the same. However, the cost-effectiveness of palonosetron is in question when compared to the combination of ondansetron and dexamethasone for the prevention of PONV until 24 hours. According to our observations, dexamethasone may have an additive effect on ondansetron and thus have a prolonged effect on PONV when used as a combination.

Conclusion

Palonosetron is more effective in the prevention of PONV after gynaecological laparoscopic surgeries when compared to ondansetron and dexamethasone.

Conflict of interest: None

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