ORIGINAL ARTICLE

A prospective, randomized, double-blind, comparative study of the efficacy of intravenous ondansetron and palonosetron for prevention of postoperative nausea and vomiting

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ABSTRACT

Background: Palonosetron is a second generation 5-Hydroxytryptamine-3 receptor antagonist with longer half-life and higher receptor binding affinity than Ondansetron.

Aims & objective: To assess the efficacy and safety profile of intravenous palonosetron cpompared to the ondansetron for prevention of post-operative nausea and vomiting (PONV) under general anesthesia.

Methodology: A prospective, randomized, placebo-controlled, double-blind study was conducted in 90 patients aged 20-60 years, undergoing major surgeries. Group I (n=30) received placebo injection; Group II (n=30) received inj. ondansetron 8 mg and Group III (n=30) received inj. palonosetron 0.075 mg IV. In the operating room, the study drugs were given IV in equal volume of 4ml, before inducing the patients. In postoperative period each patient was observed for retching, nausea and/or vomiting at 30 min; and then at 1, 2, 6, 12 and 24 hours. Any side effects intra-operatively and post-operatively were recorded.

Results: 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 with placebo was highly significant for ondansetron ($p < 0.05$), and highly significant for palonosetron ($p=0.009$). The difference in vomiting between Ondansetron and Palaonosetron was not significant but the incidence of nausea was significantly less common in the Palonosetron group than the Ondansetron group (16.7% vs. 43.4%, $p=0.006$).

Conclusion: We conclude that the second generation 5-HT3 antagonist, palonosetron is significantly more effective against PONV than ondansetron. It has a particularly more pronounced and prolonged effect on postoperative nausea.

Keywords: PONV; Ondansetron; Palonosetron; General anesthesia.

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INTRODUCTION

Despite having the better understanding knowledge about the pathophysiology of nausea and vomiting and use of more stable and effective anti-emetics like ondansetron, granisetron, the postoperative nausea / vomiting (PONV) continues to be the most disturbing complication following surgery and anesthesia.[1] The negative impact of PONV on patient's physical, metabolic and psychological condition not only delays discharge from or cause re-admission to hospital but also decreases the confidence level in future surgery and anesthesia.

The incidence of PONV increases with definite risk factors including female gender, non-smokers, motion sickness, type and duration of surgery and use of peri-operative opioids. In addition,[2-4] patient anxieties prior to surgery, type of anesthetic medications[5] and techniques also influence the incidence of PONV. With increased risk factors in a patient the chances of PONV may rise from 20% to 80%.

The role of $5HT_3$ receptors present in the central nervous system area namely at chemoreceptor trigger zone (CTZ), cerebral cortex, vestibular system and peripherally at gastrointestinal tract, have been established in the pathogenesis of PONV. The use of $5HT_3$ antagonists in the control of PONV proved to be beneficial by selectively blocking these receptors.

The $5HT_3$ antagonists like ondansetron, granisetron have been proved to be effective in preventing PONV even in the presence of several risk factors. Due to relative short duration of action (elimination half-life is less than 12 hours), most of them require repeated doses even during first 24 hours period. In spite of widely available anti-emetics not a single drug is 100% effective and combination therapy has its own side effect.[7-9]

Second generation $5HT_3$ antagonist, palonosetron was initially approved for prophylaxis of nausea and vomiting in cancer patients, as it improves the prevention of chemotherapy[7] induced nausea and vomiting and proved superior to ondansetron in these patients. Because of its unique chemical structure, greater binding affinity with additional allosteric site binding property[6] and a substantially longer half-life of almost 40 hours made palonosetron suitable for its use in prevention of PONV.

We designed this randomized double-blind study to compare the anti-emetic efficacy of new, long acting drug palonosetron with commonly used drug ondansetron in the presence of various risk factors of PONV.

METHODOLOGY

This prospective randomized, controlled, double-blind study was carried out at Department of Anesthesiology, GR Medical College, Gwalior (India), after getting approval from institutional ethical committee. Signed informed consent form was obtained from all the participants. 90 patients of ASA grade I and II of either sex, age group 20-60 years, scheduled for major elective surgeries under general anesthesia were enrolled in the study. Randomization of the patients was carried out by coded envelop technique among three study groups and drugs were loaded in identical syringes with the code by the personnel not participating in the study.

Group I (n=30) was the control group, and the patients in it received 4 ml of normal saline IV as placebo, Group II (n=30) patients received 4 ml of inj. ondansetron IV, and Group III (n=30) patients received inj. palonosetron 0.075 mg diluted to 4 ml with normal saline given slowly IV 10 min before induction.

Patients with difficulty in communicating, those prone to nausea, vomiting or motion sickness, patients on opioid analgesics or anti-emetics within 24 hours before anesthesia, requiring continuous gastric suction for 24 hours in postoperative period, patients having Mallampatti grade-II or above were excluded from study.

All the patients were kept nil orally overnight and allowed oral diazepam 10 mg and pantoprazole 40 mg (a proton pump inhibitor) before bed time at the night before surgery and early morning on the day of surgery as premedicant. In the operating room an IV line was secured and standard monitoring devices were applied. Study drugs were given by slow IV injection, 10 minutes before induction of anesthesia. After standard anesthesia induction with fentanyl 2 μg/kg, thiopentone sodium 3-5 mg/kg (propofol was avoided because of its anti-emetic property) and vecuronium 0.1 mg/kg, intubation was done with a cuffed endotracheal tube. Anesthesia was maintained with isoflurane in O_2 plus air mixture. Intermittent boluses of vecuronium were used for muscle relaxation and of fentanyl for analgesia. At the end of each surgical procedure residual effect of muscle relaxant was reversed with a combination of glycopyrrolate (10 μg/kg) and neostigmine (50 μg/kg). Inj. diclofenac sodium 75 mg was used intra-operatively and in the postoperative period for analgesia. After extubation and complete recovery, the patients were moved to postanesthesia care unit (PACU). In the PACU, every patient was watched and monitored for nausea, retching and vomiting at 30 min, 60 min, 2 hr, 6 hr, 12 hr and 24 hr. Any side-effects of the drugs or complications during the intra-operative and postoperative period were recorded and treated accordingly. All observed data are expressed as percetage and numbers. The incidence of nausea was assessed subjectively by intensity score, where 0=No nausea, 1=Mild nausea, 2=Moderate nausea and 3=Severe nausea.

Complete drug response (R) was considered as no PONV and if no use of rescue drugs to prevent or treat the PONV. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. Nausea was defined as the subjective unpleasant sensation associated with awareness of the urge to vomit.

The statistical observations of the categorical variables were evaluated by using Chi square and student's t-test for continuous variables and one-way analysis

of variance (ANOVA) for comparison of mean values among study groups. The observed side-effects were analyzed with Fisher's exact test. The observational results are expressed mainly as mean ± SD or number (%). $p < 0.05$ was considered significant.

RESULTS

The patient characteristics including the age, gender ratio, previous history of PONV or motion sickness were comparable and the differences were not statistically significant. In our study the mean age of the patient was 41.4±12.7 (range 20-60 years) in Group-I, 36.6±10.93 (range 20-60 years) in Group-II and 39±9.68 (range 20-60 years) in Group-III.

The male to female ratio was 1 in Group-I and Group-II and 1.3 in Group-III (56.6% vs. 43.3%).

In our study, the incidence of complete response to prevent vomiting (no vomiting, no rescue medications) for placebo and palonosetron were 56.6% and 86.6% (p-value=0.009 highly significant), and for placebo and ondansetron were 56.6% and 80% (p-value= 0.05 significant) respectively. Vomiting free patients in ondansetron group were 80% and in palonosetron group 86.6%, which was statistically not significant at the end of 24 hours (p-value= 0.11).

The overall incidence of nausea in the first 24 hours was much less in the palonosetron group than the ondansetron group (16.7% vs. 43.4%, p-value=0.006), but there was no observable significant difference between the Group-II and Group-III during the first 2 hours as far as both nausea and vomiting were concerned (Table 1).

Table 2: Significant adverse effects observed. Data presented as N(%)

	Placebo (n=30)	Ondansetron (n=30)	Palonosetron (n=30)
Headache	2(6.6)	4(13.3)	2 (6.6)
Dizziness	1(3.3)	0 (0)	1 (3.3)
Drowsiness	2(6.6)	1 (3.3)	0 (0)

The incidence of major adverse effects, e.g. headache, drowsiness and dizziness, was comparable between all the study groups (Table 2).

DISCUSSION

In this randomized, double-blind, phase three clinical study, we evaluated the response and efficacy of single IV dose of a new promising $5HT_3$ receptor antagonist, palonosetron and compared it with ondansetron for prevention of PONV.

In our study, the dose selection was based on the recommendations of a previous study of single IV dose of 0.075 mg palonosetron.[11] US Food and Drug Administration (FDA) approved a single dose of palonosetron 0.075 mg for preventing PONV for up to first 24 hours after the surgery.[10-12] We evaluated effect of single dose of palonosetron in comparison with single IV dose of ondansetron 8 mg, as many other investigators suggested this as an optimum dose.

A stratified multicenter study[12] evaluated the dose response of the three different single IV doses of palonosetron and observed a linear trend in efficacy with increasing doses, with only the highest dose (0.075 mg) of palonosetron demonstrated a statistical significant

Table 1: Frequency of nausea and vomiting compared between placebo (Group -I), Ondansetron (Group-II) and Palonosetron (Group-III) and nausea and vomiting free patients.

	Group I N =30	Group II N = 30	Group III N = 30	p-value I, II	p-value I, III	p-value II, III
30 minutes.						
Nausea n (%)	10 (33.4)	8 (26.7)	3 (10)		0.02	0.09
Vomiting n (%)	5 (16.7)	4 (13.4)	2 (6.7)	0.5	0.22	0.38
				0.7		
60 minutes.						
Nausea n (%)	10 (33.4)	4 (13.3)	3 (10)	0.06	0.02	0.68
Vomiting n (%)	10 (33)	3 (10)	2 (6.7)	0.02	0.009	0.64
120 minutes.						
Nausea n (%)	17 (56.6)	3 (10)	5 (16.7)	0.0001	0.001	0.44
Vomiting n (%)	7 (24)	2 (6.7)	2 (6.7)	0.07	0.07	0.99
8 hours						
Nausea n (%)	25 (83.3)	5 (16.7)	5 (16.7)	0.0001	0.0001	0.99
Vomiting n (%)	6 (20)	1 (3.4)	2 (6.7)	0.04	0.12	0.55
24 hours						
Nausea n (%)	22 (73.3)	13 (43.3)	5 (16.7)	0.06	0.0001	0.006
Vomiting (n (%)	13 (43.3)	6 (20)	4 (13.4)	0.05	0.009	0.48
Nausea free n (%)	5(16.6)	11(36.6)	18(60)	0.07	0.0005	0.07
Vomiting free n (%)	9 (30)	15 (50)	21 (70)	0.11	0.001	0.11

treatment effect with complete drug response(no emesis, no rescue medication) was 43%. Another concurrent study described in the accompanying paper in the same issue of the journal showed the benefit of 0.075 mg IV doses of palonosetron in that complete drug response was 56% over first 24 hours and 70% for 24-72 hours post-operatively.[11]In our study during 0 to 24 hours postoperatively the complete drug response was 83.3% with palonosetron which was statistically significant. We also found that a single dose of 0.075 mg palonosetron produced a considerable decrease in the incidence and severity of nausea than ondansetron (16.7% Vs 43.3%, p=0.006) but there was no significant difference in the incidence of vomiting over 24 hours postoperatively. The findings of our study are also consistent with the findings of other previous studies,[8] which showed that palonosetron is better than ondansetron at least in prevention of nausea.

The safety profile of palonosetron was comparable to the drug ondansetron. Most $5HT_3$ antagonists exhibit side effects like headache, dizziness and drowsiness. In our study, the incidence of drowsiness and dizziness in palonosetron and ondansetron groups were 0% Vs 3.3% and 3.3% Vs 0% respectively, which was consistent with previous studies. We avoided use of N_2O so as to minimize the baseline risk factors for PONV during maintenance of general anesthesia. Side effect like headache was 6.6% in palonosetron group and 13.3% in ondansetron group which was consistent with findings of another earlier study,[13] which demonstrated a frequency of headache in 6.67% in palonosetron group and 20% in ondansetron group.

Limitations and Scope of Future Studies: In order to generalize such a study, one needs to include regional anesthesia procedures, including use of neuraxial opioids. We exclusively enrolled patients who had had only general anesthesia. Further studies are required on palonosetron in larger study samples and in a wide variety of surgical procedures, especially involving high risk for PONV cases. There is also a need for more studies to ascertain the equipotency of these drugs with various other dose options and routes of administration e.g. continuous IV infusion. There is a scope of further studies using a combination of anti-emetic drugs to get optimum management of PONV in different groups of patients including extreme age groups e.g. elderly and pediatric patients.

CONCLUSION-

We conclude that the second generation $5\text{-}HT_3$ antagonist, palonosetron is significantly more effective against PONV than ondansetron. It has a particularly more pronounced and prolonged effect on postoperative nausea.

Conflict of Interest: None.

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