EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 8
327-331
Year: 2019

COMPARISON OF ANTI-EMETIC EFFICACY OF PALONOSETRON VS ONDANSETRON FOR THE PREVENTION OF PONV

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Article Received on 27/05/2019 **Article Revised on 18/06/2019** **Article Accepted on 09/07/2019**

ABSTRACT

Background: Post operative nausea and vomiting (PONV) is a common problem following general anaesthesia The aetiology for PONV is multifactorial. Ondansetron is the first 5HT3 antagonist available commercially. Palonosetron is the most recently introduced member of this class. **Aim:** To evaluate the efficacy of palonosetron compared with ondansetron for preventing PONV in patients undergoing laparoscopic cholecystectomy surgeries. **Material and Methods:** In this randomized comparative study a total of 100 patients were enrolled and divided equally into two groups, group A (Ondensetron 8 mg) and group B (Palanosetron 0.075 mg). The occurrence of nausea and vomiting was noted. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. $P<0.05$ was considered statistically significant. **RESULTS:** There were no statistically significant differences between the two groups in terms of demographic characteristics There was no significant difference in episodes of vomiting between the two groups at 0 to 2 hrs, 2 to 6 hrs and 6 to 24 hrs. **CONCLUSION:** Both ondansetron and palonosetron are equally effective in the immediate post operative period but palonosetron is more effective over 24 hour period.

KEYWORDS: Ondansetron, Palonosetron, PONV, 5-HT_3 Receptor Antagonists.

1. INTRODUCTION

Post operative nausea and vomiting (PONV) is one of the commonest problems faced following general anaesthesia. It generally occurs in 20-30% of all patients and can be as high as up to 80% in high risk patients.[1, 2] The aetiology of PONV is multifactorial and it involves factors related to anaesthesia, surgery and patient related. Adverse effects of PONV include delayed recovery, extended hospital stays and delayed return to work.

There are a number of drugs that are used for the management of postoperative nausea vomiting (PONV). These drugs are generally antihistaminics, phenothiazine derivatives, anticholinergics and dopamine receptor antagonist with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia.[3,4,5]

Serotonin release stimulates the chemoreceptor trigger zone in the central nervous system, resulting in nausea and vomiting. Selective serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (5-HT_3RA) which are recently introduced do not have such side effects and they are highly effective and thus the first line therapies in prevention of PONV.[6,7]

Chemically 5-Hydroxytryptamine$_3$ (5-HT_3) antagonists are similar to serotonin in which there 3 substituted indole ring. As 5-HT_3 antagonists are more effective for the prevention and treatment of PONV than other antiemetics and have fewer side effect profile, therefore they are being commonly used. Ondansetron is the most commonly used drug amongst 5-HT_3 receptor antagonists, other drugs in this group include granisetron and ramosetron. More recently, palonosetron has been reported to be effective in the prevention of PONV.

First 5HT_3 antagonist available commercially is Ondansetron. It is used for chemotherapy induced nausea and vomiting. Now it is also being commonly used in the treatment of PONV. Short half life of Ondansetron is 3-5 hours.[8]

Most recently introduced member of this class of drugs in India is Palonosetron. Because of its unique chemical structure, the interaction pattern with the 5-HT_3 receptor

is different from earlier 5-HT_3 receptor antagonists with additional allosteric site binding property.[9] Differences in binding and effects on 5-HT_3 receptor function may be relevant to the unique beneficial actions of palonosetron.[7] The present study is a randomized double blind study designed to evaluate the efficacy of palonosetron compared with ondansetron for preventing PONV in patients undergoing laparoscopic cholecystectomy surgeries.

2. MATERIAL AND METHODS

We started a prospective, randomized and comparative study on 100 patients fulfilling grade I and grade II of American society of anaesthesiologists (ASA) classification, of either sex between the age group of 18 to 60 years, who were posted for elective laparoscopic cholecystectomy surgery under general anaesthesia at the department of anaesthesia, SRMS IMS, Bareilly, India from October 2016 to May 2017. This was done after getting approval from the ethical committee and obtaining written informed consent in local language. Exclusion criteria: patients who have received anti emetics, psychoactive medications or steroids within 24 hrs of the study initiation, patients with vomiting or retching in the 24 hours preceding the surgery, patients with vestibular pathology, patients with ongoing vomiting from gastrointestinal disease, patients who have received cancer chemotherapy within 4 weeks before the study entry, patients who have received emetogenic radiotherapy within 8 weeks before study entry, any history of motion sickness, pregnant and lactating patients and patients who did not give consent to participate in the study.

Subjects were screened on the basis of the above inclusion/exclusion criteria, total 100 patients were included in the study and divided into two groups equally, group A (n=50) received a single injection of ondansetron 8 mg I.V. and group B (n=50) received a single dose of palonosetron 0.075 mg I.V. just before induction of anaesthesia. A standardized anaesthetic regimen was followed in our study. All were kept nil per oral for 8 hours and were premedicated with Tab Pantoprazole 40 mg and Tab Alprazolam 0.25mg on the night before the surgery. Informed written consent for participation in the study was taken from all the patients. General Anaesthesia was induced with Fentanyl 2mcg/kg and Propofol 2 mg/kg and tracheal intubation facilitated with Vecuronium 0.1mg/kg. The anaesthesia was maintained on 1.0% – 1.5% Isoflurane & N_2O in 50% O_2. Intravenous fluids were given to the patients intraoperatively as needed. After intubation, bilateral air entry was checked, tube fixed and then connected to mechanical ventilator support with an adequate tidal volume of 6-8 ml/kg and respiratory rate 12 breaths/min. At the completion of surgery patients received Neostigmine 0.05mg/kg and Glycopyrollate 0.01mg/kg for reversal of neuro muscular blockade. The duration of surgery in all patients was noted. The occurrence of nausea and vomiting was monitored immediately at the end of surgery at 0-2 hrs and 2-6 hrs and 6-24 hrs post-op. Metoclopramide 10 mg I.V. was used as a rescue antiemetic when 2 episodes of vomiting have occurred or VDS more than 2 or if the patient requests for it. Complete response to antiemetic prophylaxis defined as the absence of nausea and vomiting and no need for rescue antiemetic during the observation period of 24hrs. Side effects like headache, constipation, diarrhoea, dizziness, fatigue, abdominal pain, insomnia if any, were recorded.

Statistical testing was conducted with the statistical package for the social sciencesystem version SPSS 23.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. $P<0.05$ was considered statistically significant.

3. RESULTS

Table. 1: Demographic profile.

Variables	Ondansetron (Mean±SD)	Palonosetron (Mean±SD)	P value
Age (years)	39.90 ± 13.24	40.36 ± 10.89	0.850
Weight (kg)	66.22 ± 12.59	67.32 ± 10.33	0.634
Duration of surgery (mins)	81.50 ± 17.76	81.30 ± 21.08	0.759
Duration of Anaesthesia (mins)	102.60 ± 18.25	100.40 ± 22.06	0.588
	N=50	N=50	
Sex (M/F)	25/25	24/26	0.841
ASA grade (I/II)	20/30	29/21	0.072

There were no statistically significant differences between the two groups in terms of demographic characteristics namely age, sex, weight, ASA status, duration of anaesthesia and surgery, as shown in Table 1.

The hemodynamic data were noted both during the intraoperative and postoperative periods at regular intervals, no any major changes were observed in either group. ($p>0.05$) The mean duration of surgery and anaesthesia were also comparable between the two groups. ($p=0.759$ and 0.588 respectively).

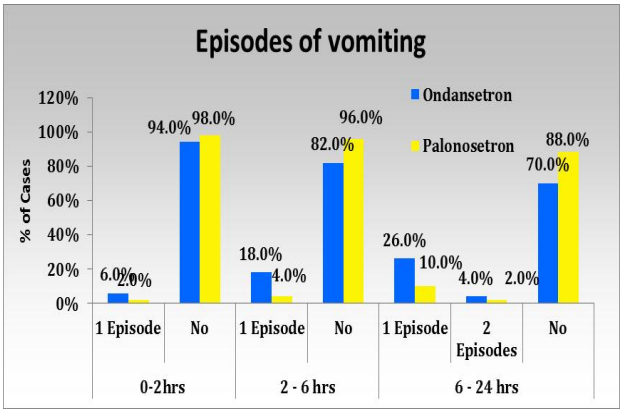

Figure. 1: Bar diagram showing episodes of vomiting between two groups.

There was no significant difference in episodes of vomiting between the two groups at 0 to 2 hrs, 2 to 6 hrs and 6 to 24 hrs, as shown in Figure 1.

Table. 2: Complete response to prophylactic anti-emetic therapy.

Complete Response (24hrs)	No. of patients	%	P Value
Ondansetron	0	0%	<0.001
Palonosetron	20	40%	

None of the patients in ondansetron group while 40% in palonosetron group showed complete response to the study drug ($p < 0.001$), which is statistically significant, as shown in Table 2.

4. DISCUSSION

Common sequelae of general anaesthesia and a leading cause of delayed discharge of unanticipated hospital admission after ambulatory surgical procedure are Postoperative nausea and vomiting (PONV).[10] This is very frequent in abdominal surgeries leading to recommendation of routine prophylactic administration of antiemetics.The etiology of nausea and vomiting after abdominal surgeries under general anaesthesia is multifactorial in origin. Age, type of surgery, anaesthetic procedure and duration of surgery may influence PONV.[11]

PONV continues to be a ―BIG LITTLE problem[12] for surgical patients in spite of significant advances in general anaesthesia. Incidence of PONV is 20-25%.In addition to patient dissatisfaction, PONV may have other adverse consequences such as delayed recovery, unexpected extended hospital stayand delayed return to work.[13]

PONV may lead to significant morbidity from dehydration, electrolyte imbalance, and aspiration of vomiting. Surgical complication like wound dehiscence and bleeding beneath skin flaps may follow severe PONV.

Although the precise aetiology of PONV is unknown, various risk factors have been identified for PONV, which include female gender, non-smoker status, history of PONV or motion sickness, use of perioperative opioids, use of volatile anaesthetics, duration of surgery, duration of anaesthesia, and type of surgery. In this study, these risk factors were similar in the two groups. Therefore, the difference in PONV incidence between the groups can be attributed to the study drug.

The newest class of antiemetics used for the prevention and treatment of PONV are the serotonin receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron).

We conducted a study to compare the efficacy of ondansetron (Group A) and palonosetron (Group B) during laparoscopic surgery to prevent PONV.

Ondansetron is a potent, highly selective 5-HT_3receptor antagonist. The mechanisms of action of ondansetron are both central and peripheral. It blocks the 5-HT_3in the area postrema, nucleus tractus solitarius (NTS) and adjacent areas in the brain, which are related to nausea and vomiting. Also, it blocks 5-HT_3receptors in the mucosal vagal afferents in the gastrointestinal tract.

Palonosetron is a - second generation 5HT_3receptor binding agent newly approved by FDA for the prevention of PONV since March 2008. It has the highest binding affinity to the 5-HT_3receptor and at approximately 40 hours, has the longest elimination half life. Unlike the representatives of the first generation with competitive inhibition of the 5-HT_3receptor, palonosetron seems to exhibit allosteric binding and positive cooperativity leading to effects persisting beyond the mere receptor binding time.

Paventiet al[14] 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.

A study by Candiotti et al[7] comparing three different doses of palonosetron with placebo in elective laparoscopic abdominal and gynaecological surgery, a single 0.075mg i.v. dose of palonosetron significantly increased the complete response rate (no emetic episodes and no rescue medication) compared with placebo during the 0–24 hr postoperative period, but not during the 24–72 hr postoperative interval.

The doses of drugs used in the present study were based on the optimal dose for prophylaxis of PONV in these studies; thus, 0.075 mg palonosetron and 8 mg ondansetron were chosen.

We did not include a control group receiving placebo in our study, since placebo controlled trials may be considered unethical in view of the distressing implications of PONV.

It has been reported that patients receiving general anaesthesia with volatile agents, nitrous oxide and opioids were 11 times more likely to experience PONV than in other forms.[15] In our study as our purpose was to compare the efficacy of two drugs under similar surgical and anaesthetic conditions, we did not avoid any of these agents. Also, there were no significant differences in patient's age, sex distribution, weight, ASA status, Baseline HR, SPO_2, SBP and DBP. Thus both the groups were comparable with respect to their demographic and baseline hemodynamic profile In our study, 94% patients who received ondansetron didn't have any vomiting in the first 2 hrs postoperatively compared to 98% patients who received palonosetron. 82% patients and 70% patients in ondansetron group didn't have vomiting between 2-6hrs and 6-24hr period respectively compared to 96% and 88% in palonosetron group. This was statistically insignificant (p=0.617 for 0-2hrs, p=0.051 for 2-6hrs, p=0.086 for 6-24hrs). This result was not comparable to the result found in study by Moon YE[16] and Singh et al[17] where there was a statistically significant difference in the overall incidence of vomiting (p=0.044). Patients showing complete response (patients who had no nausea and vomiting and no need for rescue antiemetic during 24 hrs observation period) were significantly higher in Palonosetron group i.e 40% while 0% in Ondansetron group (p<0.001) [Table 5]. This is comparable with previous studies done by Nupur Chakravarty[19], Shadangi BK[20] and Taninder Singh.[17]

This suggests that palonosetron has an antiemetic effect which lasts longer than ondansetron. The exact reason for the difference in effectiveness between the two drugs is believed to be related to the half lives (ondansetron 3-5 hrs versus palonosetron 40 hrs) and/or the binding affinities of $5\text{-}HT_3$ receptor antagonists. Both the manner as well as the site of binding of palonosetron with $5\text{-}HT_3$receptors is different from that of ondansetron. The nature of this receptor binding may modify the functional responses to serotonin thus affecting the efficacy of drug. The PONV characteristics in both groups in the early post operative phase is comparable, but a significant difference in response in the later recovery period serves to accentuate the efficacy of palonosetron in long term prophylaxis. The $5\text{-}HT_3$antagonists have an enviable safety profile, with most side-effects (e.g. headache, constipation, dizziness) being mild and transient.

5. CONCLUSION

When palonosetron 0.075 mg was administered before induction of general anaesthesia, the severity of nausea was significantly less compared to 8mg of ondansetron during 2-6hrs and 6-24 hours of post operative period. However, it was comparable in the 0-2 hours of post operative period. As far as vomiting is concerned, patients receiving palonosetron had less incidence of vomiting than ondansetron group but the difference was not statistically significant during 0-2, 2-6 and 6-24 hours.

Also, the complete response of the drug was significantly higher with Palonosetron in 24 hours of post operative period. Thus we conclude that both ondansetron and palonosetron are equally effective in the immediate post operative period but palonosetron is more effective over 24 hour period.

Key Message: Both ondansetron and palonosetron are equally effective in the immediate post operative period but palonosetron is more effective over 24 hour period.

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