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COMPARISON BETWEEN EFFICACY OF PALONOSETRON AND ONDANSETRON IN POSTOPERATIVE NAUSEA AND VOMITING IN MIDDLE EAR SURGERY: A RANDOMIZED DOUBLE BLIND STUDY.

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ABSTRACT

OBJECTIVE: Postoperative nausea and vomiting (PONV) is a common complication in patients after middle ear surgeries conducted under general anaesthesia. This prospective, randomized, double blind study study compares the effects of anti emetic drugs palonosetron and ondansetron on postoperative nausea and vomiting in patients undergoing middle ear surgeries under general anaesthesia. METHOD: Sixty ASA grade I-II patients between 20-50 years scheduled for tympanomastoid surgery under general anaesthesia were administered Ondansetron 4 mg (Group O) and Palonosetron 0.075 mg (group P) intravenously before induction of anaesthesia. Postoperative study period was divided into early (0-6 hours) and late (6-24 hours) period. The incidence of of nausea, vomiting and requirement of rescue antiemetic in patients of both groups was studied. PONV was evaluated on a four point scale. Statistical analysis was done using appropriate tests. Results are described as numbers (%) and mean+/- SD. p value <0.05 was taken to be significant. RESULTS: No statistical significance could be detected between mean PONV scores of group P and group O (0.930 vs 1.68) during early recovery phase. Number of patients showing complete response to drug in both groups were comparable in the first 6 hours ($p>0.05$), but were significantly more in group P between 6-24 hours ($p<0.05$). Number of patients having nausea and retching was significantly less in group P in the delayed recovery period (6-24 hrs). CONCLUSION: Intravenous palonosetron 0.075 mg has a comparable but prolonged prophylactic profile in preventing nausea and retching after middle ear surgery under general anaesthesia when compared to Ondansetron .

KEY WORDS: Postoperative nausea and vomiting, middle ear surgeries, Ondansetron, Palonosetron.

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INTRODUCTION

Post operative nausea and vomiting (PONV) is a common and distressing complication occurring after middle ear surgeries[1] .The deleterious effects in terms of clinical recovery and the economic implications in a busy tertiary care centre are manifold[2]. Nausea occurs in approximately 20% of patients in the recovery room and in 50% thereafter, with vomiting in 5% and 25% respectively [3]. An incidence of up to 80 % has been reported in literature in patients undergoing middle ear surgery under general anaesthesia, [4, 5, 6]. In Indian patients, the distressing effects of PONV are often underestimated and hence under treated. Although it is a debated issue whether prophylactic administration of antiemetics is justified preoperatively [7], some authors have advocated the liberal use of anti emetics in view of their low acquisition costs, excellent safety profile, mild and short lived side effects, and high impact on patient satisfaction [8]. Palonosetron and Ondansetron are both 5-HT3 receptor antagonists with good antiemetic efficacy. The higher receptor affinity and a much longer half-life (40 hours) of Palonosetron[9] as compared to Ondansetron (3-5 hours)[10] , provides the pharmacological basis for its long duration of action . The effect of Ondansetron alone as well as in combination with other drugs in middle ear surgeries has already been studied [6, 11]. Our study was conducted with the intention of assessing whether palonosetron conferred any advantages over ondansetron in terms of duration of prophylaxis and its effect on the incidence and severity of PONV in these patients when used as the sole antiemetic agent. The endpoints were evaluated by the following parameters: rate of complete response to the drug , episodes of nausea and emesis, and need for rescue antiemetic.PONV was defined as nausea or vomiting within 24 hours of surgery [12].

MATERIALS AND METHODS

After approval from Institutional ethics committee, informed consent was taken from sixty patients with ASA Physical Status I & II, aged 20-50 years, with a BMI < 30kg/m^2 who were scheduled for elective tympanomastoid surgery under general anaesthesia. Exclusion criteria were patients with history of allergy or hypersensitivity to 5-HT3 antagonists, history of/or prolonged cardiac conduction/QTc interval on preoperative ECG, gastrointestinal liver or renal disease, patients who were menstruating, pregnant or lactating mothers, smokers, those who had history of motion sickness and/ or PONV, and those who had received antiemetic premedication in the past 24 hours. Patients were assigned by closed envelope randomization schedule to one of two groups - Group O (n=30) received Ondansetron single injection 4 mg IV (Cipla Ltd.Mumbai,India) and Group P (n=30) received Palanosetron 0.075 mg IV (Themis Medicare Ltd.,India)prior to induction. Before surgery, drugs were prepared in identical 2.5 ml syringes and coded by an anaesthesia assistant not involved in the surgery. Patients were fasted 6 hours preoperatively and after securing an intravenous line, were premedicated with intravenous ranitidine 50 mg and intravenous Midazolam 2 mg,and study drugs were administered by a blinded anaesthetist just prior to induction. Standard intraoperative monitoring included pulse oximetry, automated blood pressure measurement and electrocardiogram lead II (Schillers truescope-II, Hamburg Germany). Anaesthesia was induced in all patients with Propofol (**2** mg/kg).Neuromuscular relaxation was induced by an intravenous bolus of atracurium (0.5mg/kg). Following endotracheal intubation anaesthesia was maintained with N_2O/O_2 (2:1), atracurium bolus and sevoflurane 1.5-2.5% inspired concentration. Ventilation of the lungs was controlled (tidal volume of 10 ml kg^{-1} respiratory rate of 10 breaths min^{-1}) to maintain an end-tidal carbon dioxide partial pressure(PETCO2) in the range 35-45 mm Hg. At the end of surgery patients were extubated following antagonism of residual neuromuscular block with atropine (0.015 mg kg^{-1}) and neostigmine (0.05 mg kg-1). Inj. Diclofenac Sodium 75 mg was given intramuscularly for postoperative pain relief. Postoperatively, standard fasting guidelines

were followed. Patients were evaluated in the recovery room by an assistant who was ignorant about the coding and identity of the antiemetic drug given. When awake (judged by spontaneous eye opening, response to commands and the ability to verbal contact), patients were asked about any sensation of nausea, or episodes of retching and vomiting were noted. The evaluation on a scale of 0-3 (0=no nausea or vomiting, no rescue medication; 1=nausea; 2=retching; 3=vomiting) was made for two periods: in the recovery room (0-6hrs), and in the ward(6-24hrs). Inj. Metoclopramide (10mg i.v) was given for a score of 2 or more, or if the patient complained of severe nausea. The incidence of adverse events like headache, dizziness sedation was observed. Statistical analysis was done using students unpaired t-test for continuous variables expressed as mean+/- SD. PONV scores were analysed using Mann Whitney Rank Sum Test. Proportions were analysed using chi square test and Fischer Exact test. p value<0.05 was considered significant.

RESULTS

Both groups were comparable in terms of age, weight, ASA physical status and duration of surgery (table 1). The type and amount of drugs used in anaesthesia, and any intraoperative and postoperative haemodynamics which may have had an impact on PONV in these patients were also not significantly different. In the early recovery period (0-6 hrs), although mean PONV scores were lower in group P as compared to group O (0.930 vs 1.68) the difference was not found to be of statistical significance (Table 2). Similarly no significance could be detected between both groups in number of patients who showed a complete response to drug in groups P and O (80% vs 66%)and in the number of patients who had nausea and retching ($p>0.05$) (Table 2, figure 1). No patient had vomiting in both groups. Between 6-24 hrs postoperatively, the difference in PONV scores between group P and group O (1.03 vs 0.56) was significant ($p<0.05$). Also le patients in group P showed a higher complete response to the drug compared to group O (80% vs 50%, $p<0.05$) (Table 2,figure 2). The difference between number of patients having nausea and retching between both groups was also statistically significant ($p<0.05$). No patient had vomiting in both groups. Mean number of rescue analgesic doses in both groups during 0- 6 hours was similar. During late recovery phase mean number of doses was 1 in group O, while no rescue analgesic was required in group P patients. Analysis of gender subpopulation revealed that as compared to females, higher number of males in both groups showed complete response to drug in both early and late postoperative phases (Table 2). Females exhibited a greater tendency for nausea and retching. One patient in group O complained of dizziness and headache. No other clinical side effects of the drug were observed in group P.

Table1
Demographic characteristics

Variables	Group O n=30	Group P n=30	P value
Age(yrs)*	42.7±6.92	38.9±9.76	0.087
Sex M/F	15/15	15/15	
Weight(kg)*	49.03±8.04	48.7±7.95	0.08
ASA 1/2#	13/15	14/16	
Duration of surgery (min)*	98.66±22.31	98.9±22.82	0.968

Mean+/- SD #American Society of Anaesthesiologists Physical Status
Group O-Ondansetron Group P-Palonosetron

Table 2
PONV characteristics

Postoperative period(hr)	Group O n= 30	Group P N=30	P values
Recovery room(0-6hrs)			
PONV Score	1.68	0.93	0.06
Complete response	20(66%)	24(80%)	0.381
M/F	11/8	14/10	
Nausea	10(33.33%)	6(20%)	0.381
Retching	3(10%)	2(6.6%)	1.000
Vomiting	0	0	
Rescue drug	1	1	
Surgical ward(6-24 hrs)			
PONV Score	1.03	0.56	0.029*
Complete response	15(50%)	24(80%)	0.03*
M/F	10/8	13/11	
Nausea	14(40%)	5(16.66%)	0.026*
Retching	6(16.66%)	0	0.024*
Vomiting	0	0	
Rescue drug	1	0	

P<0.05

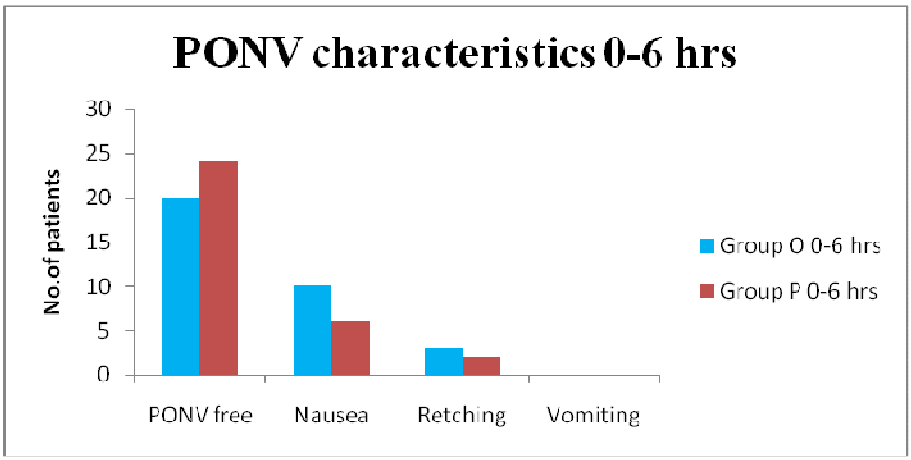

Figure 1
PONV characteristics 0-6 hrs

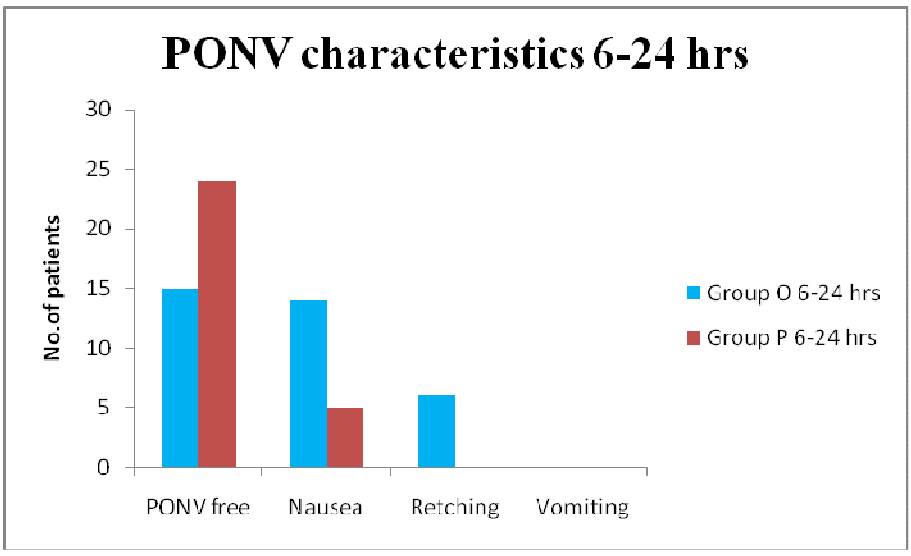

Figure 2
PONV characteristics 6-24 hrs

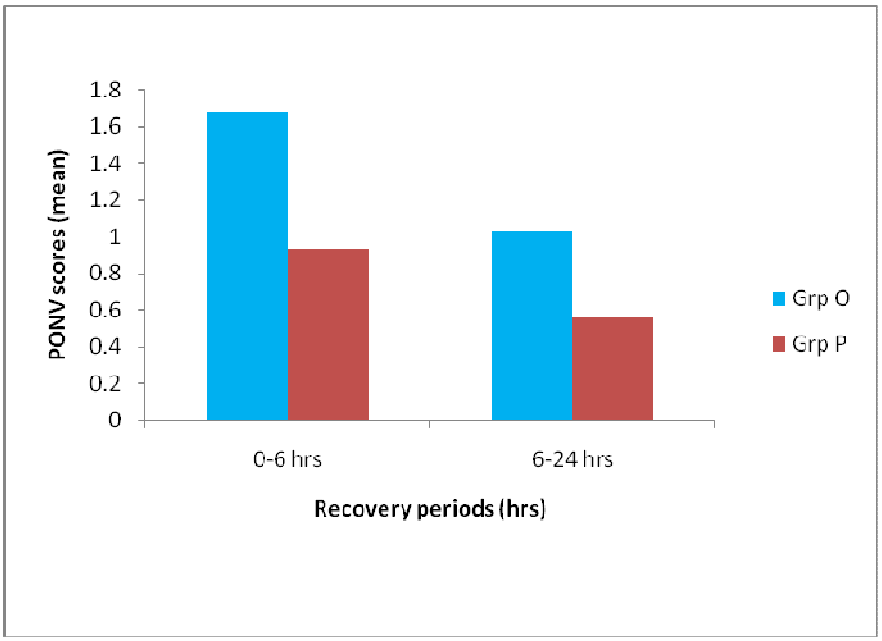

Figure 3
Mean PONV scores during both recovery phases

DISCUSSION

Our study tries to analyze another drug in the armamentarium of antiemetics to to deal with the underestimated issue of nausea and vomiting in postoperative patients. Although it seldom has long term or disastrous implications, it can be very unpleasant for the patient, sometimes more so than postoperative pain [13, 14, 15]. With the increasing emphasis on early discharge it becomes imperative that PONV be adequately controlled. The multifactorial aetiology of PONV involving surgical, anaesthetic and individual risk factors [2] make it difficult for a single drug approach to control it in the postoperative period. Even though patient predictive scores for PONV have been validated [12], other factors like duration and type of surgery and anaesthesia have also been implicated [1]. It has been reported that patients receiving general anaesthesia with volatile agents, nitrous oxide and opiods were 11 times more likely to experience PONV than in other other forms[16]. 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. The female gender is a validated high risk factor for the occurrence of PONV [12]. In our study also, more female patients had nausea and retching in both groups. Complete response to drug was seen more in the male subpopulation in both groups (Table 2). 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 after middle ear surgeries [17, 18].

Since the superior pharmacologic profile of ondansetron over metoclopramide has already been established in laparoscopic surgeries[19] we compared both drugs belonging to the same group. It has been recommended that in cases of breakthrough PONV, repeat antiemetic should be of a different class than the one used for prophylaxis [20]. This was why metoclopramide was used as a rescue analgesic. The requirement of rescue drug was similar in both groups in the early postoperative period but less in group P in the later period. 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-HT_3 receptor antagonists. Both the manner as well as the sites of binding of palonosetron with 5-HT_3 receptors is different from that of ondansetron[21]. The nature of this receptor binding may modify the functional responses to serotin[22]. The timing of administration of the antiemetic drug ondansetron has been long debated. Although the manufacturers recommend administration before induction, the relative short half life (3.5-4hrs) of the drug may decrease its antiemetic activity in surgical cases lasting more than two hours. Our mean surgical duration being less than two hours, and the fact that palonosetron has a longer half life was why we administered both the drugs before induction. The incidence of complete response to ondansetron as a sole antiemetic in the early postoperative period in our study is 66 %, a finding that agrees with other studies [11]. The comparable PONV characteristics in both groups in the early postoperative phase, followed by a significant difference in response in the later recovery period serve to accentuate the efficacy of palonosetron in long term prophylaxis. It is also arguable that considering the short half life of ondansetron, this significant difference in complete response to drug in the late postoperative period may not have been seen had ondansetron been given towards the end of surgery.

The sustained anti nausea effect of palonosetron in late recovery period in group P patients (16.66%) as compared to those in group O(40%) is of importance as this prolonged anti nausea property of palonosetron assumes particular significance in day-surgery patients and for those who wish to return to their normal activities early. This property of the drug has been reported in other studies [23]. We did not observe active vomiting in any case in our study. The anti-vomiting effect of 5 HT3 antagonists is said to be greater than the anti-nausea effect with 25% overall risk reduction for PONV [24, 25]. Adverse effects with single prophylactic doses of both drugs were minimal and not clinically serious with one patient reporting dizziness after ondansetron. However we feel that in the setting of general anaesthesia, it is presumptuous to attribute complaints of headache, dizziness and sedation in the postoperative period to any particular drug. Joslyn [26] reported that the rationale behind the administration of ondansetron prior to the induction of anaesthesia was that a more accurate assessment of adverse events such as complaints of injection site reactions, dizziness or light headedness as well as changes in hemodynamic parameters.

CONCLUSION

Prophylactic therapy with a single dose of intravenous palonosetron 0.075 mg is comparable in its antiemetic action with ondansetron 4 mg in the early recovery phase post operatively. Its utility lies in its ability to maintain a sustained antinausea action upto 24 hours, which is of potential value because PONV often presents late or after discharge [23]. However optimum control of PONV requires a multi-modal approach such as less emetogenic anaesthetic techniques, balanced analgesia, appropriate intravenous hydration, and the use of pharmacotherapy.

CONFLICT OF INTEREST

None

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