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PREOPERATIVE PALONOSETRON AND DEXAMETHASONE IN PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN MIDDLE EAR SURGERY: A PROSPECTIVE RANDOMISED DOUBLE BLIND CONTROLLED STUDY

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is one of the most frequent and most unpleasant adverse outcomes of surgery and general anesthesia. PONV is defined as nausea or vomiting occurring within 24 hours of surgery. The present study was undertaken to compare the efficacy of palonosetron and dexamethasone for prevention of postoperative nausea and vomiting in middle ear surgeries. **Materials and methods:** After approval from institutional ethical committee and written, informed consent from the patients, this prospective randomized double blind controlled study was conducted on 150 ASA grade I and II patients, aged 18-60 years scheduled for middle ear surgery. The patients were divided into three groups (50 patients each). Group N, D and P received Normal saline 1.5 ml (control), Dexamethasone 1.5 ml (6 mg) and Palonosetron 1.5 ml (0.075 mg) respectively. The drug was administered according to allocated group along with preanesthetic medication. Standard general anesthesia technique was used in all patients. The incidence of nausea and vomiting was noted during the period of 0-8 hours, 8-16 hours and 16-24 hours postoperatively. **Results:** Incidence of post operative nausea was less in group P as compared to group D and group N in duration of 0-8 hours (P=0.001), 8-16 hours (P=0.008), 16-24 hours (P=0.016). Also post operative vomiting was less in group P in duration of 0-8 hours (P=0.001). Rescue anti emetic required was less in group P as compare to group D and group N (P=0.003).**Conclusion:** Preoperative administration of palonosetron was more effective than dexamethasone in prevention of postoperative nausea and vomiting in middle ear surgery without any apparent side effects.

KEYWORDS: Dexamethasone, Middle ear surgery, Palonosetron, Postoperative nausea vomiting.

INTRODUCTION

During the last decade, life-threatening complications associated with anaesthesia have become rare. This safety record has encouraged anaesthesiologist to focus attention on minor morbidities. Besides post operative pain, the occurrence of postoperative nausea and vomiting (PONV) is the most frequent and most unpleasant adverse outcome of surgery and

general anaesthesia. PONV is defined as nausea or vomiting occurring within 24 hours of surgery. **(1)** PONV considerably increases health care costs due to delayed discharge from the recovery room, unanticipated hospital admission and greater demands on the time resources of the post care staff. These indirect costs usually far exceed the direct cost of antiemetics. The general incidence of nausea and vomiting is 50% and 30% respectively; in high risk patients, the PONV rate can be as high as 80%. **(1, 2, 3)**

The risk factors for PONV includes patient related factors like young age, female gender, obesity, non smoking status, history of motion sickness and history of PONV, anaesthesia related risk factors like use of inhalational anaesthetic agents and nitrous oxide, long duration of anaesthesia, perioperative use of opioids. Surgery related factors comprising long surgical procedures and few specific types of surgery (open gastrointestinal surgery, major gynaecologic surgery, laparoscopic surgery, breast surgery, craniotomy, eye and otorhinolaryngologic surgery) are all associated with increased risk of PONV.**(1, 4)**

The process for triggering nausea and emesis is complex because stimulation of vomiting center may come from several pathways and multiple neurotransmitters like serotonergic, dopaminergic, histaminergic, cholinergic and neurokininergic system. Besides the nucleus tractus solitarius and chemoreceptor trigger zone, two other pathways also have direct inputs to the vomiting center: vestibular apparatus and cerebral cortex. (5)

Dexamethasone is an inexpensive and effective antiemetic drug, with minimal adverse effects after a single-dose administration. The exact mechanism of antiemetic action of dexamethasone is not fully understood. There have been several suggestions, such as central or peripheral inhibition of the production or secretion of serotonin, central inhibition of the synthesis of prostaglandins, or changes in the permeability of the blood-brain barrier to serum proteins. **(6, 7)**

The introduction of 5-hydroxytrptamine subtype 3 ($5HT_3$) receptor antagonists like ondansetron represents a major improvement in the pharmacotherapy of chemotherapy and radiation therapy-induced nausea and vomiting. They have since being also proven to be highly effective in the prevention and treatment of postoperative nausea and vomiting

Palonosetron is a second generation $5HT_3$ receptor antagonist newly approved for the prevention of PONV. It has a high affinity to $5HT_3$ receptor and at approximately 40 hours it has longest elimination half life. It seems to exhibit allosteric binding and positive co-operativity leading to persisting action beyond the receptor binding time. Palonosetron also exhibits anti nauseating property which is in contrast to other $5HT_3$ blockers. **(8, 9)** Several

studies have concluded that palonosetron is a better antiemetic than ondansetron in prevention of postoperative nausea and vomiting. **(10, 11)**

Middle ear surgeries are one of the surgeries associated with increased incidence of PONV. Studies directly comparing efficacy of palonosetron and dexamethasone are lacking.

Hence, we decided to conduct a study comparing the antiemetic efficacy of palonosetron and dexamethasone in middle ear surgery.

MATERIALS AND METHODS

After approval from the institutional ethical committee as well as written and well informed consent from patient and their relatives, 150 ASA grade I and II patients, aged 18-60 years scheduled for middle ear surgery were included in our study. Our study was carried out from March 2016 to January 2017 in M.B. Government Hospital affiliated to R.N.T. Medical College, Udaipur.

***Sample size*:**

Based on previous studies, we estimated that a reduction in the incidence of PONV by 30% in an intervention arm over the control group would be clinically significant. For the study to have a power of 80% with a α error of<0.05, we need to have 48 patients in each group. To compensate for the dropouts, we decided to include 50 patients in each group.

All patients in this study were subjected to detailed preanaesthetic evaluation which included: - present complaints, drug history, past history of surgical procedure under general anaesthesia, history of nausea, retching or vomiting within preceding 24 hours, any major medical illness and drug history. Routine investigations were carried out as per institutional protocol. Patients having history of nausea in the preceding 24 hours, drug allergy, neurological disease, hypertension, diabetes, PONV, motion sickness, digestive problems, treatment with antiemetics, obesity (BMI > 40), pregnancy or lactating mothers were excluded from the study.

In this prospective, randomized, double-blind and controlled study patients were randomly divided into 3 groups by using an opaque sealed envelope technique.

Group N: Patient received normal saline 1.5 ml in pre-anesthetic medication.

Group D: Patient received dexamethasone (6 mg) or 1.5 ml in pre-anesthetic medication as an antiemetic.

Group P: Patient received palonosetron (0.075 mg) or 1.5 ml in pre-anesthetic medication as an antiemetic

Preoperatively, patient was kept nil per orally (NPO) from mid night. In the operating room, standard monitoring (ECG, SPO_2 and NIBP) was applied. Patient was pre-medicated with inj. glycopyrrolate (0.004 mg/kg), inj. midazolam (20 mcg/kg) and inj. fentanyl (2µg/kg), inj.

palonosetron (0.075 mg) in group P and inj. dexamethasone (6 mg) in group D and normal saline in group N before induction.

After pre-oxygenation with oxygen and air for 5 minutes, anaesthesia was induced with thiopentone (3-5 mg /kg) and tracheal intubation was achieved with suxamethonium (1.5 -2 mg/kg). Intra-operative muscle relaxation was achieved with atracurium loading dose (0.5mg/kg) and maintained with 0.1 mg/kg intermittent doses. Mechanical ventilation was provided with oxygen and air mixture. Anaesthesia was maintained by using total intravenous anaesthesia through propofol infusion (50-200 mcg/kg/min). Nitrous oxide and inhalational anesthetic agent were avoided during anaesthesia. At the end of surgery, anaesthesia was discontinued and residual neuromuscular blockage was antagonized by giving neostigmine (0.05 mg/kg) mixed with glycopyrrolate (0.0 1mg/kg).

Patient was then kept in PACU. On fulfill the discharge criteria (Post anaesthetic Aldrete recovery score>9), the patient was shifted to ward.

The duty doctor was asked to document every episode of nausea and vomiting in the 24 hours study duration and administer inj. metoclopromide as rescue antiemetic on every episode of vomiting. No rescue antiemetic was given on incidence of nausea alone. The data was then collected and analysed.

Statistical analysis: Dependence of qualitative characters on groups was tested using Chi square test and difference between means of different quantitative data among groups was analyzed by ANOVA. The student t test was used for comparing intergroup differences. $p<0.05$ was considered as statistically significant. The analysis was performed using IBM SPSS version 2016.

RESULTS

Demographically all the groups were comparable ($p>0.05$). Duration of surgery and anaesthesia was also comparable in all the groups ($p=0.59$, $p=0.523$ respectively). All the three groups showed no statistical significant difference when the haemodynamic parameters (Pulse Rate, MAP, SpO2) were compared ($p>0.05$)

Table 1: Incidence of nausea

Duration (Hours)	Group N		Group D		Group P		p value
	No.	%	No.	%	No.	%	
0-8	19	38	12	24	3	6	0.001
8-16	8	16	3	6	0	0	0.008
16-24	4	8	0	0	0	0	0.016

The authors observed that the incidence of nausea was much less in palonosetron group as

compared to control and dexamethasone groups. This was statistically significant at duration of 0-8 hours and 8-16 hours. (Table 1). Infect none of the patients in group P and D had incidence of nausea after 8 and 16 hours of postoperative period respectively.

Table 2: Incidence of vomiting

Duration (Hours)	Group N(n=22)		Group D(n=12)		Group P(n=2)		p value
	No.	%	No.	%	No.	%	
0-8	17	34	10	20	2	4	0.001
8-16	3	6	2	4	0	0	0.235
16-24	2	4	0	0	0	0	0.132

We further observed that the incidence of emesis was also much less in palonosetron group as compared to control and dexamethasone groups (Table 2). Similar to nausea, the incidence of vomiting was zero in group P and D after 8 hours of postoperative period. There was statistically significant difference in incidence of vomiting in the three groups only at 0-8 hours of duration.

The groups were also compared by Bellville Score Scale (lack of nausea and vomiting=0, nausea =1, nausea with retching=2 and vomiting =3).

Comparison of PONV score in between groups showed that at 0-8 hours duration, group P had statistically significant lower PONV score when compared to group N and group D (p=0.00 and p=0.014 respectively) (Table 3). At duration of 8-16 hours, group P had low PONV score when compared to group N (p=0.019). Although there was no statistically significant difference between group N and group P as well as between group P and group D. There was no statistically significant difference among all three groups at 16-24 hours postoperative period.

In our study complete response was assumed when there was no episode of nausea and vomiting occurring in the duration of 24 hours. At 0-8 hours duration 90% (n=45), 56% (n=28) and 26% (n=13) patients in group P, group D and group N showed complete response respectively (p<0.001) (Fig 1). At 8-16 hours 100% (n=50), 90% (n=45) and 78% (n=39) patients in group P, group D and group N showed complete response respectively and that was also statistically significant (p=0.002). At 16-24 hours duration, 100% complete response was observed in group P and D where as it was 88% (n=44) in group N (p=0.002).

Requirement of rescue antiemetic on occurrence of vomiting in duration of 0-8 hours was 34% in group N, 20% in group D and 4% in group P and that was statistically significant (p=0.003).At duration of 8-16 hours and 16-24 hours duration, the requirement of rescue antiemetic in different groups was statistically insignificant(p>0.05) (Table 4)

Table 3: Bellville Score Scale

Duration	Group N (n=22)	Group D (n=12)	Group P (n=2)	P value		
				N vs D	N vs P	P vs D
0-8 hours	1.06	0.64	0.16	0.114	0.00	0.014
8-16 hours	0.28	0.14	0.02	0.310	0.019	0.176
16-24hours	0.16	0	0	0.07	0.07	NA*

*NA-Not applicable

Table 4: Requirement of rescue IV metoclopramide

Duration (hours)	Group N(n=22)		Group D(n=12)		Group P(n=2)		p Value
	No. of patients	**% of patients**	**No. of patients**	**% of patients**	**No. of patients**	**% of patients**	
0-8	17	34	10	20	2	4	0.003
8-16	3	6	2	4	0	0	0.245
16-24	2	4	0	0	0	0	0.133
0-24	22	44	12	24	2	4	0.000

DISCUSSION

Persistent nausea and vomiting may result in dehydration, electrolyte imbalance, tension on suture line, venous hypertension, increased bleeding under skin flaps and can expose the subject to an increased risk of pulmonary aspiration of vomitus, if airway reflexes are depressed from the residual effects of anaesthesia and analgesic drugs.**(12)**

The timing of prophylactic antiemetic administration is also important. Considering the fact that Palonosetron has longer half life (approximately 40 hours) and the effect of dexamethasone lasts for 48-72 hours despite

elimination half life of 3 hours both the drugs were administered before induction of anaesthesia in the present study. Singh T et al and Eidi M et al had also administered antiemetics before induction in their study.**(13,14)**

Apfel et al reported that use of inhalational anaesthetic and nitrous oxide should be considered as a leading cause of early PONV. These were avoided in our study.**(15)**

FDA has approved 0.075mg as the minimum effective dose of palonosetron for PONV prophylaxis.**(16)** Hence we decided to use 0.075mg for this study. Chakarvarty N et al and Singh T et alccalso used 0.075 mg of palonosetron in their study.**(10,13)**

Individual clinical studies have found that dexamethasone is an effective antiemetic prophylaxis at a dose of 5-8 mg .Hence 6 mg of dexamethasone was chosen as the dose in our study.**(14,17)** Isik B et al and Eidi M et al administered 5 mg and 8 mg dexamethasone in their study respectively. **(14,17)**

Demographic data (age, sex and weight), duration of surgery and anaesthesia, ASA grade and vitals parameters were comparable among all three groups.

Episodes of nausea, vomiting and PONV score were recorded at duration of 0-8, 8-16, and 16-24 hours of post-operative periods in all the three groups.

The authors observed that the incidence of nausea was much less in palanosetron group as compared to control and dexamethasone groups at duration of 0-8 hours, 8-16 hours and 16-24 hours which was statistically significant. (p=0.001, p=0.008, p=0.016).

Similarly the incidence of emesis was much less in palanosetron group as compared to control and dexamethasone groups during initial 8 hours of study(p=0.001).

The PONV Score was statistically significantly lower in palanosetron group when compared to dexamethasone and control group.

90% patients in palanosetron group showed complete response during initial 8 hours which further increased to 100% in remaining study period. The incidence of complete response was much less in dexamethasone group especially in initial 8 hours of postoperative period. . Study by Chakarvarty[10] had also showed 90% complete response in palonosetron group at 24 hours of duration. **(10)**

It has been recommended that in cases of breakthrough PONV, repeat antiemetic should be of a different class than the one used for prophylaxis. So metoclopramide was used as a rescue antiemetic.

Only few (4%) patients in palanosetron group required rescue antiemetic as compared to dexamethasone and control group (20% and 34% respectively) during first 8 hours of postoperative period. Study by Nupur Chakravarty et al had

showed that only 3.3% patients in palonosetron group at 0-6 hours duration required rescue antiemetic dose and after 6 hours none of the patient required rescue antiemetic.**(10)**

Addition of palonosetron to antiemetic prophylaxis also reduced the requirement of antiemetic medication and was associated with greater patient satisfaction.

Tahir S et al had compared the effects of palonosetron and dexamethasone on postoperative nausea and vomiting in adult patients undergoing laparoscopic abdominal surgery**. (18)** The incidence of nausea and vomiting was maximal during the first six hours postoperatively and the complete control of postoperative nausea and vomiting for first 24 hours was achieved in 80% patients of palonosetron group and 60% patients of dexamethasone group. They also observed that the use of rescue medication was about 50% less in palonosetron group than dexamethasone group. They had concluded that palonosetron was more effective antiemetic than dexamethasone. Their findings support our observation.

Ahmed M. et al had compared palonosetron and ondansetron for prevention of postoperative nausea and vomiting in middle ear surgery and found a much lower incidence of nausea and vomiting in palonosetron group. Further they found the palonosetron group did not require any rescue anti emetic. **(19)**

Eidi M et al had compared preoperative ondansetron and dexamethasone in prevention of post tympanoplasty nausea vomiting. They observed that ondansetron and dexamethason were more effective than placebo group. Moreover they found that the incidence rate and intensity of PONV in the dexamethasone group was less than in ondansetron group after 8 hours of postoperative period. **(14)**

Isik B.et al compared antiemetic effect of ondansetron and dexamethasone on middle ear surgery. They found fewer incidences of postoperative nausea and vomiting in ondansetron group when compared to dexamethasone group. **(17)**

The differences in the incidence of PONV varied in the different studies. This seems to be associated with use of different anaesthesia techniques, different patient population and different types of surgery.

There were no severe adverse effects in any group of patients. Headache dizziness and constipation occurred in few patients but were not statistically significant in our study. In particular; there were no wound infections or healing delays in patients receiving dexamethasone.

CONCLUSION:

Based on this study it is concluded that preoperatively administration of palonosetron was more effective than dexamethsone in prevention of postoperative nausea and vomiting

in middle ear surgery without any apparant side effects.

LIMITATIONS

The patients with co morbidities were excluded, so the results of this study should not be generalized to other patients with severe underlying disease. Further studies should consider this limitation.

CONFLICT OF INTEREST

None

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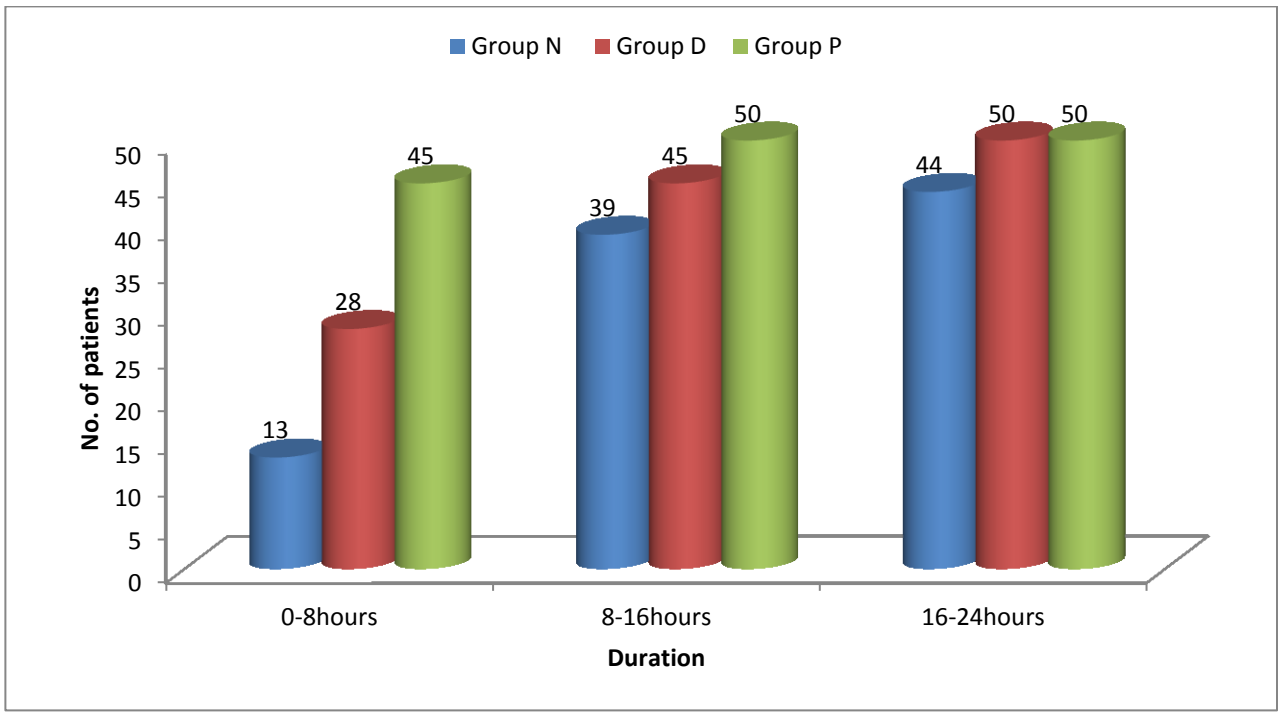

Fig1: Complete response in different time intervals