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RESEARCH ARTICLE

A PLACEBO CONTROLLED STUDY OF PROPHYLACTIC ANTI EMETIC EFFECTS OF MIDAZOLAM AND ONDANSETRON FOR PREVENTING POST OPERATIVE NAUSEA AND VOMITING IN MIDDLE EAR SURGERY

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ABSTRACT

The present study evaluated the antiemetic effects of midazolam an ondansetron for preventing post operative nausea and vomiting in middle ear surgeries. **Material and Mehods:** After attaining approval by ethical committee of the institute, 105 patients were randomly divided into three groups (35 patients of ASA I and II physical status in each group). Group M received 0.05mg/kg of midazolam diluted in 5 ml of normal saline IV, Group O received 0.15mg/kg of ondansetron diluted in 5 ml of normal saline IV, Group S received 5ml of normal saline IV, immediately prior to the induction of general anesthesia. Observation for nausea, vomiting and retching were carried out at 0-2 h and 2- 24 h postoperatively. Nausea was recorded on 0 to 10 rating (VAS score). Score 0= no nausea, 1-3= mild nausea, 4-6=moderate nausea, 7-10 =severe nausea. **Results:** The incidence of nausea and vomiting was significantly less in Group M and Group O as compared to Group **Conclusion:** Our study showed that IV midazolam and ondansetron provides significant reduction in nausea and vomiting in patients undergoing middle ear surgery.

INTRODUCTION

Middle ear surgeries (Tympanoplasty and mastoidectomy) performed under general anesthesia is associated with high incidence of post operative nausea and vomiting(PONV), between 60 to 80 percent. Numerous antiemetics have been introduced in order to reduce PONV such as anticholinergics, phenothiazones, butyrophenones, 5HT3 antagonists,dopamine receptor antagonists. Many studies have been conducted that midazolam can be used as prophylaxis of PONV by administration before or after the induction of anesthesia. Midazolam has been used as an antiemetic in adults and children both as preventive and rescue medication. The possible mechanism for the antiemetic effect of benzodiazepine at the chemoreceptor trigger zone reducing synthesis, release, and postsynaptic effect of dopamine. Our study was conducted to evaluated and compare the efficacy of midazolam and ondansetron for PONV in patient undergoing middle ear surgery.

METHODS

After obtaining institutional approval from Ethic Committee of university and informed consent from patients, 105 American Society of Anesthesiologist I or II patients, aged 18–62 years who were participated in this double-blinded randomized clinical trial. These patients were scheduled for elective middle ear surgery, mastoidectomy, or tympanoplasty. Patients with previous history of motion sickness, antiemetic therapy within 24h preoperatively, patients on opioid treatment, smokers, and pregnant patients were not included. If anesthetic technique was changed, the patients were excluded from the study. Patients were randomized into three groups receiving midazolam 0.05 mg/kg (group M), ondansetron 0.15 mg/kg (group O), and saline 0.9% (group S) intravenously (IV) before induction of anesthesia. The randomization was done by using random allocation software. The study drugs were administered by an anesthesiologist blinded to data collection Before induction of anesthesia, the patients were informed on the using the visual analog scale (VAS) for nausea and pain evaluation. The monitoring was performed by continuous electrocardiogram, noninvasive blood pressure, pulse oximetry, and end-tidal carbon dioxide. Induction of anesthesia was done with propofpl 1-2 mg/kg, tramadol 1-2/kg, and atracurium 0.6 mg/kg. General anesthesia was maintained with 0_2 and N_2O with inhalational agent (isoflurane) and atracurium 0.1 mg/kg for muscle relaxant. Neuromuscular blockage was reversed with neostigmine 0.4 mg/kg and atropine 0.2 mg/kg and after that patients were extubated. PONV were evaluated using nausea-vomiting score at 0–2 h and 2–24 h (Table 1). Vomiting was defined as forceful expulsion of gastric contents from mouth or retching. Postoperative nausea and pain intensity were evaluated by using VAS at 0–2 and 2–24 h with 0 = no pain or PONV and 10 = the worst imaginable pain or PONV. Patients with a PONV score of 2 or more were given IV metoclopramide 0.15 mg/kg, and that dose was recorded. Time to the first oral intake was recorded. Patients with a pain score of 4 or more were given inj.diclofenac 75 mg and its dose was recorded. Length of staying in the recovery room was evaluated by using Modified Aldrete Score. Extubation time (defined since discontinuation of anesthetic drugs until removal of endotracheal tube) was also recorded. Consciousness was assessed based on Observer's Assessment of Alertness/Sedation scale at the time of evaluation of nausea and vomiting (where 1 = awake/alert, and 5 = deep sleep). The sample size was estimated based on a power calculation which showed that 35 patients per group were necessary to achieve

80% power to detect a 30% difference (from 50% to 20%) in the incidence of PONV between group O with group MO with α =0.05 The data was presented as mean ± standard deviation or numbers (%). Differences among groups for quantitative variables was analyzed by using one-way analysis of variance (ANOVA) and **post hoc** comparisons at various points in time by using Bonferroni's type I error rate correction for multiple tests of significance. Analysis of continuous variables was done by using repeated measure ANOVA. Categorical variables were analyzed by using Chi-square test. Mann–Whitney U-test and Kruskal–Wallis test were used as appropriate. **P** <0.05 was considered statistically significant. The analysis of data was performed by using SPSS 20.0 software for Windows.

Table 1. Nausea and vomiting score

Score	Nausea and vomiting degree
0	No nausea, no vomiting
1	Nausea present,no vomiting
2	Nausea present , vomiting present
3	Vomiting more than 2 episodes in 30 mins.

RESULTS

One hundred five patients were randomly allocated into three groups, and no patient was excluded. Patient characteristics including age, weight, height, sex, BMI, duration of surgery were comparable among all the groups (Table 2).

Table 2. Patients demographic data

	Group M	Group O	Group S	P value
Age(years)	28±9	30±7	31±8	0.60
Sex(M/F)	20/15	18/17	21/16	0.90
Weight(kg)	68+10	62+13	63+12	0.25
Height(cm)	173+6	175+8	171+7	0.30
Durations(mins)	130.5	146.8	135.6	0.50
BMI(kg/m^2)	22.7+3	21.8+4	23+2.1	0.25

P value less than 0.05 is considered statistically significant.

Postoperatively, 10 patients (28%) in group M, 8 patients (22.8%) in group O, 26 patients (74.2%) in group S, received 0.15 mg/kg metoclopramide IV and there was significant difference between group M,O and the group S. (P < 0.001). PONV was significantly less in those patients who received midazolam and ondansetron as compared to the other group (Table 3).

Table 3. incidence of patients with PONV and rescue antiemetics in three groups

Variable	Group m (n=35)	Group o (n=35)	Group s (n=35)	P value
PONV (0-2hrs)				
0	25(71.4)	24(68.6)	12(34.2)	<0.001
1	5(14.3)	6(17.1)	8(22)	
2	5(14.3)	5(14.3)	12(34.2)	
3	0(0.0)	0(0.0)	3(8)	
PONV(2-24 hrs)				
0	26(74.28)	28(80.0)	17(48.51)	<0.001
1	4(11.4)	4(11.4)	7(20.0)	
2	4(11.4)	3(8.6)	8(22)	
3	1(2.9)	0	3(8.6)	
Rescue antiemetics	10	8	26	<0.001

Data are presented as (%) of patients. PONV =Postoperative Nausea and Vomiting, 0=NO Nausea, No Vomiting, 1=With Nausea, No Vomiting, 2=With Nausea, With Vomiting, 3=Vomiting >2.

Moreover, the difference was not significant between group M and group O. However, PONV in both of them were significantly less as compared to group S (Table 3). There was no significant difference between group M with group O in this respect. VAS of nausea in groups M and O was significantly less than other groups (**P** < 0.001). There was no significant difference between VAS of pain in four groups. No significant difference was found between groups in terms of side effects such as dizziness and headache.

DISCUSSION

In the present study, we aimed to compare the antiemetic effect of midazolam and ondansetron with placebo group. We evaluated the incidence of nausea and vomiting and their severity in the first 24 h and the number of patients with nausea and vomiting who used additional antiemetic between 0–2 and 2–24 h. We measured postoperative pain based on VAS which could effect on the incidence of PONV, and there was no significant difference in pain intensity between groups. In this study, we found the incidence of PONV was significantly smaller in group M and group O and there was no significant difference between group M and group O. Need to the additional antiemetic was significantly lower with group M and group O. The use of 5-HT3 receptor antagonists is popular as the drugs have shown good efficacy in preventing PONV (Honkavaara, 1996; Russell and Kenny, 1992; Naguib *et al.,* 1996; Steinbrook *et al.,* 1996; Steinbrook *et al.,* 1998; Philip *et al.,* 2000). These drugs act by two mechanisms: First, by blocking the 5-HT3 receptors in the area postrema and nucleus tractus solitarius; and second, by blocking peripherally afferent vagal impulses originating from 5-HT3 receptors in the mucosa of the gastrointestinal tract (Gyermek, 1996). It has been reported that after prophylactic administration of 4 mg ondansetron in radical mastoidectomy, nausea, and vomiting occurred at the rate of 33% while they occurred at the rate of 81.5% after placebo (Sadhasivam *et al.,* 1999). Tramèr *et al*. (1999) found that the anti-vomiting efficacy of ondansetron was consistently better than the anti-nausea efficacy. In this study, patients who received ondansetron showed a higher incidence of nausea than those who received midazolam in the first 24 h; however, this difference was not significant. Midazolam is a short-acting drug in the benzodiazepine class. Splinter *et al*. (1994) observed that administering midazolam 0.05 mg/kg after induction of anesthesia had antiemetic effects that were similar to the same dose of droperidol in children undergoing strabismus surgery. Bauer *et al*. (2004) found that preoperative IV midazolam 0.04 mg/kg was an effective way to reduce the frequency of PONV and increased patient satisfaction. Recently, Splinter *et al*. (1995) demonstrated that midazolam used in sub-hypnotic dose was as effective as ondansetron in treating PONV without untoward sedative effects. The results of the above studies are comparable with the results of our study. Midazolam antiemetic effect is triggered by glycine mimetic inhibitory effect, augmentation of the inhibitory effect of gamma-amino-butyric acid, augmentation of adenosinergic effects, inhibition of dopamine release, and augmentation of adenosine-mediated inhibition of dopamine in the chemoreceptor trigger zone (Splinter *et al.,* 1995). One of the clinical effects of midazolam is sedation. It was probable that the using midazolam prolonged sedation time in the recovery room. Our study showed that midazolam did not prolong PACU and extubation time. It was due to using sub-hypnotic dose midazolam for prevention of PONV. It was presumed from the results of our study that the more efficacy

of using midazolam-ondansetron combination in comparison with using each drug singly originates from the synergistic effect of two drugs. In conclusion, our study showed that the prophylactic antiemetic effect of 0.05 mg/kg midazolam with 0.15/kg mg ondansetron was superior to placebo in the first 24 h after operation without increasing recovery time and sedation. In comparison with midazolam, ondansetron did not provide superior benefit.

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