

Original Article

Prophylactic antiemetic effects of Midazolam, Ondansetron, and their combination after middle ear surgery

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ABSTRACT

Objective: The purpose of the present study was to evaluate the efficacy of midazolam-ondansetron combination in prevention of postoperative nausea and vomiting (PONV) after middle ear surgery and its comparison with using midazolam or ondansetron alone.

Methods: One hundred and forty patients were enrolled in four groups to receive midazolam 0.75 mg/kg in group M, ondansetron 4 mg in group O, midazolam 0.75 mg/kg and ondansetron 4 mg in group MO, and saline 0.9% in group S intravenously just before anesthesia. Assessment of nausea, vomiting, rescue antiemetic, and side effects of study drugs such as headache and dizziness was carried out postoperatively for 24 h.

Findings: The incidence of PONV was significantly smaller in group MO than group M and group O, while there was no significant difference between group M and group O during the first 24 h postoperatively. Requirement to the additional antiemetic was significantly more in group S (71.4%) compared to other groups, while in group MO (11.4%) was lower than group M (31.4%) and group O (34.3%).

Conclusion: Our study showed that prophylactic administration of midazolam 0.75 mg/kg combined with ondansetron 4 mg was more effective than using midazolam or ondansetron alone in prevention of PONV after middle ear surgery.

Keywords: Midazolam; middle ear surgery; Ondansetron; postoperative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common and distressing complications and are the main concern of 40–70% of patients after surgery.^[1,2] PONV does not only cause patient discomfort but also can lead to prolongation of stay in the postanesthesia care unit (PACU) and to serious complications including electrolyte imbalance, aspiration, increased bleeding, and wound dehiscence.^[3,4] Patients who suffer from PONV require additional healthcare

professional time and material resources.^[3] The incidence of PONV is approximately 25–30% in general surgery population and between 62% and 80% after middle ear surgery.^[5] Many factors such as the site and characteristics of the surgical procedure, the anesthetic technique, as well as the age, gender, weight of the patients, and vertigo history may influence PONV.^[6,7] The timing and the dose of the antiemetic agent to be used in the treatment are also important.^[8–16]

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Ondansetron is a 5-hydroxytryptamine 3 (5-HT₃) antagonist which usually recommended for prevention and treatment of nausea and vomiting during and after surgery.^[17] It works by blocking the action of serotonin, a natural substance, that may cause nausea and vomiting. Midazolam is in a class of medications called benzodiazepines. It has antiemetic effect by augmentation of the inhibitory effects of gamma amino butyric acid and adenosine-mediated inhibition of dopamine in the chemoreceptor trigger zone.^[12,18]

The efficacy of ondansetron or midazolam in prevention of PONV was investigated before.^[18] In a previous study, the incidence of PONV after using midazolam or ondansetron was 45%^[18] and 22%,^[5] respectively. Our hypothesis was that using the combination of midazolam with ondansetron probably reduces the incidence of PONV after middle ear surgery better than using each drug singly. There was not previous study about antiemetic effect of midazolam-ondansetron combination, so we design the present study to evaluate the effect of midazolam, ondansetron, and their combination in prevention of PONV after middle ear surgery in comparison with the placebo group.

METHODS

After obtaining institutional approval from Ethic Committee of university and informed consent from patients, 140 American Society of Anesthesiologist I or II patients, aged 18–62 years who were eligible to participate 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 four groups receiving midazolam 0.75 mg/kg (group M), ondansetron 4 mg (group O), combination of midazolam 0.75 mg/kg and ondansetron 4 mg (group MO), 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.^[17]

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 sodium thiopental 5 mg/kg, fentanyl 2 µg/kg, and atracurium 0.6 mg/kg. General anesthesia was maintained with 100–150 µg/kg/min propofol infusion and morphine 0.1 mg/kg for analgesia. 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.^[19,20] 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 diclofenac suppository 50 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.

The patient's satisfaction was rated on a 10-point scale from 0 to 10 where 0 represented "no satisfaction at all and 10 represented complete satisfaction."^[19] Complete response was defined as absence of nausea and vomiting during 24 h postoperatively.^[19] 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 $\alpha = 0.05$. The data was presented as mean \pm 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

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 >2 episodes in 30 min

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 (SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred forty patients were randomly allocated into four groups, and no patient was excluded. Patient characteristics, operation type, duration of surgery, duration of anesthesia, time to oral intake, extubation time, PACU time, and patient satisfaction are shown in Table 2. Time to oral intake was significantly higher in group S ($P < 0.001$) than to the other groups. PACU time was not significantly different between the four

groups [Table 2]. Postoperatively, 11 patients (31.4%) in group M, 12 patients (34.2%) in group O, 4 patients (11.4%) in group MO, and 25 patients (71.4%) in group S, received 0.15 mg/kg metoclopramide IV and there was significant difference between group MO and the other groups ($P < 0.001$). PONV was significantly less in those patients who received a combination of midazolam and ondansetron as compared to the other groups [Table 3]. Subsequently, 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. The overall patient satisfaction was significantly higher in the group MO compared the other groups [$P < 0.001$, Table 2].

VAS of nausea in group MO was significantly less than other groups ($P < 0.001$). There was no

Table 2: Demographic characteristics and para-clinical data of patients

Variable	Group M (n=35)	Group O (n=35)	Group MO (n=35)	Group S (n=35)	P
Age (years)	27.6±12.5	26.4±13.6	28.5±13.6	25.6±13.5	0.815
Sex (male/female)	23/12	26/9	21/14	29/6	0.167
Weight (kg)	72.7±9.61	70.0±9.6	71.5±8.8	69.4±8.5	0.424
ASA grade (1/2)	22/13	19/16	21/14	20/15	0.899
OP type					
Mastoidectomy	20	17	15	19	0.923
Tympanoplasty	9	10	11	10	
Mastoidectomy and tympanoplasty	6	8	9	6	
Duration of surgery (min)	138.5±9.2	135.1±12.9	136.4±12.7	132.3±13.4	0.188
Duration of anesthesia (min)	150.9±9.2	147.5±12.9	148.8±12.7	144.7±13.4	0.188
Time to oral intake (h)	3.2±0.9 [†]	3.4±1.0 [†]	2.3±0.6 [*]	6.3±1.5	<0.001
Extubation time (min)	13.8±2.6	14.0±2.8	14.3±2.9	13.6±2.6	0.759
PACU time (min)	53.5±5.3	54.6±5.3	52.9±5.2	51.2±5.2	0.057
Patient satisfaction	5.9±1.4 [†]	5.7±1.4 [†]	8.2±0.9 [*]	4.1±2.0	<0.001

Data are presented as mean±SD or number of patients. Group M received 0.75 mg/kg IV midazolam, Group O received 4 mg IV ondansetron, Group MO received 0.75 mg/kg IV midazolam and 4 mg IV ondansetron, Group S received saline 0.9%. ^{*} $P < 0.05$ versus the other groups, [†] $P < 0.05$ versus Group S. IV=Intravenous, SD=Standard deviation, ASA=American Society of Anesthesiologist, OP=Operation, PACU=Postanesthesia care unit

Table 3: The incidence of patients with PON, POV, PONV and requiring rescue antiemetic in four groups

Variable	Group M (n=35)	Group O (n=35)	Group MO (n=35)	Group S (n=35)	P
PONV 0-2 h					
0	24 (68.6) [†]	23 (65.7)	31 (88.6) [*]	10 (28.6)	<0.001
1	5 (14.3)	6 (17.1)	2 (5.7)	7 (20.0)	
2	5 (14.3)	6 (17.1)	1 (2.9)	14 (40.0)	
3	1 (2.9)	0 (0.0)	1 (2.9)	4 (11.4)	
PONV 2-24 h					
0	25 (71.4) [†]	24 (68.6)	32 (91.4) [*]	12 (34.3)	<0.001
1	5 (14.3)	6 (17.1)	2 (5.7)	7 (20.0)	
2	4 (11.4)	5 (14.3)	1 (2.9)	13 (37.1)	
3	1 (2.9)	0 (0.0)	0 (0.0)	3 (8.6)	
Rescue antiemetic	11 (31.4) [†]	12 (34.3) [†]	4 (11.4) [*]	25 (71.4)	<0.001

Data are presented as n (%) of patients. Group M received 0.75 mg/kg IV midazolam; Group O received 4 mg IV ondansetron; Group MO received 0.75 mg/kg IV midazolam and 4 mg IV ondansetron; Group S received saline 0.9%. ^{*} $P < 0.05$ versus the other groups, [†] $P < 0.05$ versus Group S. SD=Standard deviation, PONV=Postoperative nausea and vomiting, 0=No nausea, no vomiting, 1=With nausea, no vomiting, 2=With nausea, with vomiting, 3=Vomiting more than 2, IV=Intravenous, POV=Postoperative vomiting, PON=Postoperative nausea

significant difference between VAS of pain in four groups [Table 4]. No significant difference was found between groups in terms of side effects such as dizziness and headache [Table 5].

DISCUSSION

In the present study, we aimed to compare the antiemetic effect of the combination of midazolam-ondansetron with midazolam and ondansetron single and 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 MO than 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 in group MO compared with group M or group O.

The use of 5-HT₃ receptor antagonists is popular as the drugs have shown good efficacy in preventing PONV.^[3,21-26] 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.^[27] 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.^[28] Tramèr *et al.*^[29,30]

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.*^[31] 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.*^[32] 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.*^[33] 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.^[33]

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.

Table 4: Severity of postoperative nausea and pain in four groups

Variable	Group M (n=35)	Group O (n=35)	Group MO (n=35)	Group S (n=35)	P
VAS of nausea 0-2 h	2.6±0.5	2.6±0.9	1.3±0.5*	3.3±0.7	<0.001
VAS of nausea 2-24 h	2.1±0.7	2.1±1.1	1.0±0.0*	3.1±0.6	<0.001
VAS of pain 0-2 h	2.5±1.1	2.6±1.3	2.4±1.1	2.3±1.1	0.721
VAS of pain 2-24 h	1.7±0.7	1.5±0.7	1.6±0.7	1.9±0.7	0.189

Data are presented as mean±SD. Group M received 0.75 mg/kg IV midazolam; Group O received 4 mg IV ondansetron; Group MO received 0.75 mg/kg IV midazolam and 4 mg IV ondansetron; Group S received saline 0.9%. *P<0.05 versus the other groups. SD=Standard deviation, VAS=Visual analog scale, IV=Intravenous

Table 5: The incidence of postoperative adverse effects in four groups

Variable	Group M (n=35)	Group O (n=35)	Group MO (n=35)	Group S (n=35)	P
No complication	29 (82.9)	32 (91.4)	33 (94.3)	30 (85.7)	0.794
Dizziness	3 (8.9)	2 (5.7)	1 (2.9)	3 (8.6)	
Headache	3 (8.9)	1 (2.9)	1 (2.9)	2 (5.7)	

Data are presented as n (%). Group M received 0.75 mg/kg IV midazolam; Group O received 4 mg IV ondansetron; Group MO received 0.75 mg/kg IV midazolam and 4 mg IV ondansetron; Group S received saline 0.9%. IV=Intravenous

In conclusion, our study showed that the prophylactic antiemetic effect of the combination of 0.75 mg/kg midazolam with 4 mg ondansetron was superior to using midazolam or ondansetron singly in the first 24 h after operation. Further studies using this combination in the other surgeries with high incidence of PONV is recommended.

AUTHORS' CONTRIBUTIONS

MRS has planned the study and finalized it; AH, MC, MN, and MRS did the statistical analysis and prepared the first version of manuscript for publishing. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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