Prophylactic administration of haloperidol plus midazolam reduces postoperative nausea and vomiting better than using each drug alone in patients undergoing middle ear surgery

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ABSTRACT

Aims: The efficacy of using midazolam or haloperidol for prevention of postoperative nausea and vomiting (PONV) has been investigated before. The main object of the present study was to evaluate the anti-emetic effects of combining administration of intravenous haloperidol with intravenous midazolam on PONV in patients underwent middle ear surgery in comparison with using each drug alone. **Methods:** Study design was randomized, double-blind, placebo-controlled. 80 patients, aged 18-60 years, scheduled for middle ear surgery in Kashani Hospital Medical Center under general anesthesia were enrolled in this randomized, double-blind, placebo-controlled study. Patients were divided into 4 groups of 20 each and received haloperidol 2 mg i.v. (Group H); midazolam 2 mg i.v. (Group M); haloperidol 2 mg plus midazolam 2 mg i.v. (Group HM); saline i.v. (Group C). The incidences of PONV and complete response were evaluated at 0-2 hours after arrival to the PACU and 2-24 hours after arrival to the ward in 4 groups. **Results:** Patients in group HM had significantly lower incidence of PONV compared with groups H, M, and C throughout 0-24 h ($P<00.5$). The HM group had the lowest incidence of PONV (0-2, 2-24, and 0-24 h) and the highest incidence of complete response. Postoperative anti-emetic requirement was significantly less in group HM compared with group M or H ($P<0.05$). **Conclusion:** Combine administration of haloperidol 2 mg plus midazolam 2 mg significantly reduced PONV better than using each drug alone in patients underwent middle ear surgery under general anesthesia.

Key words: *Anti-emetics, haloperidol, midazolam, otorhinolaryngologic surgical procedures, postoperative nausea and vomiting*

INTRODUCTION

Postoperative nausea and vomiting (PONV) is the most frequent adverse effect following anesthesia,[1] occurring in about 62% to 80% of patients candidate for middle ear surgery.[2,3] PONV, if untreated, can cause dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension and bleeding, esophageal rupture, and life threatening airway compromise.[4,5] Each vomiting episode can postpones discharge from the recovery room by about 20 minutes.[6]

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Haloperidol is a major tranquilizer with a D2-receptor antagonist effect, which has been used as an anti-emetic for prevention and treatment of PONV.[7-10] The majority of the previous reports investigated haloperidol as a sole drug for PONV, and combinations of haloperidol with other anti-emetics were infrequently assessed.[11]

Midazolam, a water-soluble benzodiazepine with an imidazole ring in its structure, has been described to be an effective drug for prevention and treatment of PONV in adult patients undergoing middle ear surgery and children undergoing strabismus surgery or tonsillectomy.[12-14] It is not clear that combining haloperidol with midazolam would provide superior prophylaxis against PONV than using haloperidol alone.

We assumed that prophylactic administration of haloperidol plus midazolam will provide more reduction in the incidence of PONV than either drug used alone or placebo. Therefore, we designed this randomized, double blind, placebo-controlled study to evaluate the anti-emetic effects of combining administration of intravenous haloperidol with intravenous midazolam on PONV in patients underwent middle ear surgery in comparison with using each drug alone.

METHODS

80 American Society of Anesthesiologists (ASA) physical status I-II patients, aged 18-60 years old, scheduled for middle ear surgery (tympanoplasty or mastoidectomy) gave written informed consent to participate in this double-blind, randomized, placebo-controlled study, which was approved by our institute Ethics Committee. The patients with gastrointestinal tract diseases, diabetes mellitus, difficult airway, psychiatric disorder, seizure disorder, Parkinson's disease, previous intolerance to the haloperidol administration, nausea and vomiting, obesity (body mass index more than 35 kg/m^2), a QTc interval more than 450 ms, and them receiving any anti-emetics within 24 hours before surgery were excluded from the study. Also, patients with allergies to metoclopramide, meperidine, or haloperidol, and those with a history of extrapyramidal syndrome or akathisia and pregnant patients didn't include into study.

No premedication was given to the patients. Before surgery, the patients were informed about using visual analog scale (VAS), ranging from 0 (none) to 10 (worst possible pain), for evaluation of their pain. By using a computer-generated random number table, patients were randomly allocated into 1 of 4 groups (n=20 for each group): Group H receiving haloperidol 2 mg i.v.; group M receiving midazolam 2 mg i.v.; group HM receiving haloperidol 2 mg plus midazolam 2 mg i.v.; group C receiving saline i.v.. A nurse anesthetist prepared identical syringes containing either normal saline or the study medications for each subject. All medications were 3 ml in volume and were given IV 30 minutes before conclusion of surgery. The patients and investigator who collected all data were blinded to the group randomization.

After patients arrival to the operating room, non-invasive arterial blood pressure [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial blood pressure (MAP)], heart rate (HR), respiratory rate (RR), and Pulse Oximeter Oxygen Saturation (SpO2) level were monitored. Induction of anesthesia was done with 5 mg.kg^{-1} of thiopental sodium, 3 μg.kg^{-1} fentanyl and 0.6 mg.kg^{-1} of atracurium for facilitation of tracheal intubation. Morphine 1 mg.kg^{-1} was administered for intra-operative analgesia. Anesthesia was maintained with using 1.2% isoflurane and 50% nitrous oxide (which was replaced by air before closure of the middle ear cavity) in oxygen. At the end of the operation, residual neuromuscular blockade was reversed by i.v. neostigmine 0.04 mg.kg^{-1} and i.v. atropine 0.02 mg.kg^{-1}. After that, anesthetics were discontinued and extubation was done when airway reflexes had returned.

During study drugs injection, a standard lead II electrocardiogram at a paper speed of 25 mm/s and amplification of 0.1 mV/mm was recorded every 1 minute for 10 minutes. The QT intervals were measured manually from the onset of QRS complex to the end of T wave. Consequently, measured QT intervals were corrected for patients' heart rate by using a formula that published previously[15] and corrected QT interval (QTc) was obtained. Demographic data of patients (age, gender, weight), ASA physical status, types of operation, history of smoking, motion sickness, previous postoperative nausea and vomiting (PONV), phase of menstrual cycle (proliferative/luteal phase), duration of surgery (the time from beginning surgery till the closure of the last suture), duration of anesthesia (the time from induction of anesthesia till termination of anesthetic drug administration), extubation time (the time from discontinuation of anesthetics till extubation of trachea), post-anesthesia care unit (PACU) stay time (the time from arrival of patients to the PACU till discharge from it) were recorded.

The incidences of PONV and complete response, the severity of postoperative pain, the occurrence of postoperative extra-pyramidal side effects (EPS), arrhythmia, and headache were evaluated at 0-2 hours after arrival to the PACU and 2-24 hours after arrival to the ward in 4 groups. The subjectively-distasteful sensation accompanied with perception of the compulsion to vomit was defined as nausea. The strenuous, intermittent, rhythmic contraction of the respiratory muscles without throwing out of gastric contents was defined as retching. The vigorous expulsion of gastric contents from the mouth was defined as vomiting. If patients had nausea alone, it was graded into as tolerable or intolerable. If patients had intolerable nausea, ondansetron 4 mg IV was administered. We considered the incidence of both tolerable and intolerable nausea generally as nausea. Vomiting, vomiting with nausea, and retching were entirely regarded as vomiting. If patients had vomiting, the rescue anti-emetic (ondansetron 4 mg IV) was administered. If patients had no PONV throughout 24 hours, it was considered as a complete response.

By using VAS score, postoperative pain was evaluated at 0-2 h after arrival to the PACU and 2-24 h after transfer

to the ward. Meperidine 0.5 mg/kg was administered if the patients had VAS score of >4 cm and total dose of rescue analgesic was recorded. The level of sedation (1=awake; 2=drowsy, responds to verbal commands; 3=asleep, responds to touch or pain stimuli; and 4=does not respond) was evaluated at 5, 15, 30, 60, 120 minutes after an arrival to the PACU.

The sample size was estimated based on a power calculation, which showed that 20 patients per group were necessary to achieve 80% power to detect a 40% difference (from 60% to 20%) in the incidence of PONV between group C with group HM, with α=0.05. Data are presented as mean (SD), numbers or median.

Differences among groups mean were compared 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. Repeated measure analysis of variance was used for analysis of continuous variables. Categorical variables were analyzed by Pearson chi-square test and by Fisher's exact test when the anticipated number was <5. Mann-Whitney *U*-test was used as appropriate. The difference in median sedation level among 4 groups was analyzed by the Kruskal-Wallis test. $P<0.05$ was set as statistically significant. All statistical analyses were performed using SPSS 16.0 for Windows statistical package.

RESULTS

80 patients were enrolled in the study. No patient was excluded from the study due to any problem. There was no difference in patient characteristics such as sex, ASA, age, weight, types of operation performed, history of PONV, motion sickness, smoking, phase of menstrual cycle, time to tracheal extubation, duration of PACU stay, durations of surgery and anesthesia among the 4 groups [Table 1]. There was no significant difference in extubation time or duration of PACU stay among 4 groups [Table 1].

When compared with the C group, the H, M, and HM groups had a lower incidence of PONV (0-24 h) [Table 2].

Table 1: Patients characteristics, extubation time, PACU stay time and surgical details in the four groups

Variable	Group H	Group M	Group HM	Group C
Age (yr)	38.7±15.8	29.05±12.9	33.1±13.3	37.3±14.1
Gender (F/M)	10/10	15/5	15/15	13/7
Weight (Kg)	66.8±13.8	65.6±10.8	67.9±12.5	61.8±13.5
ASA (I/II)	13/7	16/4	19/1	16/4
Smoker (Y/N)	5/15	2/18	2/181/19	
History of motion sickness (*n*)	3	0	1	2
Previous PONV (*n*)	3	1	3	3
Phase of MC (P/L, *n*)	6/4	6/9	9/6	6/7
Duration of surgery (min)	189.4±11.2	191.1±13.8	196.3±13.5	193.4±11.5
Duration of anesthesia (min)	214.0±14.3	221.9±23.1	218.0±11.0	221.0±12.5
Extubation time (min)	27.5±5.5	29.7±12.3	26.5±4.3	23.2±18.1
PACU stay time (min)	66.5±5.9	69.5±6.0	67.5±5.5	68.0±5.5
Type of operation performed (*n*)				
Tympanoplasty (T)	5	8	6	2
Mastoidectomy (M)	4	1	1	5
T + M	11	11	13	13

Group H – Haloperidol treated patients; Group M – Midazolam treated patients; Group HM – Haloperidol-midazolam treated patients; Group C – Control group; ASA – American society of anesthesiologists; PONV – Postoperative nausea and vomiting; MC – Menstrual cycle; P/L – Proliferative/luteal phase; PACU – Post-anesthesia care unit, Values are presented as mean±SD or number, There were no significant differences between four groups; *N*=20

Table 2: Incidences of postoperative nausea, vomiting and complete response in four groups

Variable	Group H	Group M	Group HM	Group C
0-2 h	6 (30)	9 (45)	3 (15)*†	10 (50)
2-24 h	6 (30)	4 (20)†	2 (10) †	10 (50)
0-24 h	12 (60)†	13 (65)†	5 (25)‡*†	20 (100)
Complete response	4 (20)	9 (45)	14 (70)‡†	4 (20)

Group H – Haloperidol treated patients; Group M – Midazolam treated patients; Group HM – Haloperidol-midazolam treated patients; Group C – Control group; Values are presented as number (%); *$P<0.05$ vs. group M; †$P<0.05$ vs. group C; ‡$P<0.05$ vs. group H. Comparison was done by using a series of 2×2 χ^2 test or Fisher's exact test, as appropriate, *N*=20

The HM group had the lowest incidence of PONV (0-2, 2-24, and 0-24 h) and the highest incidence of complete response [Table 2]. Patients in group HM had significantly lower incidence of PONV compared with groups H, M, and C throughout 0-24 h (P<00.5). No differences were found among the H and M groups [Table 2].

During anesthesia, the QTc interval after the administration of the test medication in 4 groups was not different from their pre-injection values. The mean values of QTc intervals in 4 groups during a 15-min observation period were below 450 ms (data not shown). The QTc intervals during the 15-min observation period were not significantly different among 4 groups.

The time to the first anti-emetic demand was significantly more in group H, M, and HM compared with group C (P<0.05) [Table 3]. Postoperative anti-emetic requirement was significantly less in group H, M, and HM compared with group C (P<0.05) [Table 3]. This variable was also significantly less in group HM compared with group M or group H (P<0.05) [Table 3].

There was no significant difference in VAS scores and postoperative analgesic demand among 4 groups [Table 3]. Median sedation level was not significantly different among 4 groups [Table 4]. The incidence of adverse effects was not significantly different between 4 groups [Table 5]. There was no patient with extrapyramidal side effects, arrhythmias, or QTc prolongation in either group.

DISCUSSION

A great numbers of patients underwent surgery are at high risk for PONV and warrant using more than one anti-emetic for prophylaxis.[6] This is the first study to evaluate the anti-emetic effect of combined use of intravenous midazolam and haloperidol on PONV in patients underwent tympanoplasty or myringotomy. Our study showed that haloperidol 2 mg i.v. plus midazolam 2 mg i.v. produced a greater reduction in the incidence of PONV till 24 hours after middle ear surgery compared with using midazolam or haloperidol alone while it had no important side effects, such as QT prolongation, increasing severity of postoperative pain, level of sedation, and occurrence

Table 3: Postoperative analgesics and antiemetic use in four groups

Variable	Group H	Group M	Group HM	Group C
Postoperative analgesic requirement (mg)	0.05±0.02	1.3±5.6	1.4±5.4	0.0±0.0
Time to first antiemetic demand (hours)	2.3±2.2†	3.4±1.6†	12.1±3.4†	0.4±0.5
Postoperative antiemetic requirement (mg)	2.5±4.4†	2.0±4.1†	0.5±1.5†*‡	6.5±4.6
Visual analogue scale				
0-2 h	0.8±1.3	1.0±1.4	1.05±1.2	0.2±1.1
2-24 h	1.7±1.6	1.3±1.8	1.8±1.9	1.1±1.4
0-24 h	1.1±0.05	0.5±0.9	0.4±0.6	0.7±1.3

Group H – Haloperidol treated patients; Group M – Midazolam treated patients; Group HM – Haloperidol-midazolam treated patients; Group C – Control group; Values are presented as mean±SD; *P<0.05 vs. group MI †P<0.05 vs. group C; ‡P<0.05 vs. group H. There was no significant difference in VAS scores and postoperative analgesic requirement between four groups; N=20

Table 4: Median sedation level in different time intervals in four groups

Timing of measurement (minute after arrival to PACU)	Group H	Group M	Group HM	Group C
5	3	3	3	3
15	2.5	2	2	2
30	1	1.5	1	2
60	1	2	2	2
120	1	1	1	1

Group H – Haloperidol treated patients; Group M – Midazolam treated patients; Group HM – Haloperidol-midazolam treated patients; Group C – Control group; Values are presented as median; There was no significant difference between four groups; N=20

Table 5: Incidence of adverse effect in four groups

Variable	Group H	Group M	Group HM	Group C
Extrapyramidal side effects	0	0	0	0
Arrhythmia	0	0	0	0
Headache	0	2	2	2
QTc prolongation	0	0	0	0

Group H – Haloperidol treated patients; Group M – Midazolam treated patients; Group HM – Haloperidol-midazolam treated patients; Group C – Control group; Values are presented as median; There was no significant difference between four groups; N=20

of extrapyramidal symptoms. Also, administration of midazolam plus haloperidol significantly decreased postoperative anti-emetic requirement in comparison with using midazolam or haloperidol alone.

Middle ear surgery (tympanoplasty or mastoidectomy) is accompanied with high incidence of PONV. The previous studies showed that the incidence of PONV after middle ear surgery under general anesthesia was between 62% and 80%.[2,3,16] Our results showed that there was high incidence of nausea (50-100%, 2-24 hours after operation) during general anesthesia for middle ear surgery. Risk factors of PONV are age, female sex, obesity, history of motion sickness or previous PONV, smoking, menstruation, type of operative procedure, technique of anesthesia, and type of analgesic used for postoperative pain relief.[17,18] Using nitrous oxide during surgery is another risk factor in this regard because it increases middle ear pressure.[3]

In our study, all these factors were matched well among 4 groups. Before closure of tympanic membrane, nitrous oxide (N2O) was discontinued and replaces with air, so no pressure was produced in middle ear due to diffusion of N2O. Consequently, the differences in the incidence of nausea and vomiting between groups can be due to study drug used.

There are many previous studies regarding use of midazolam for prophylaxis and treatment of PONV.[12-13,19-21] In a study, performed by Splinter *et al*.,[13,14] it was shown that administration of midazolam 0.05 mg/kg after an induction of anesthesia significantly decreased the incidence of PONV similar to the same dose of droperidol in children underwent strabism surgery. Bauer and colleagues[19] showed that midazolam 0.04 mg/kg, when administered preoperatively, effectively reduced the incidence of PONV while increased patients' satisfaction. Safavi *et al*.[20] showed that midazolam 35 μg/kg, when administered intravenously 30 minutes before termination of surgery, was more effective in decreasing the incidence of PONV than midazolam premedication with a dose of 35 μg/kg. Jung and colleagues[12] showed that midazolam 0.075 mg/kg administered after an induction of anesthesia was effective for reducing PONV after middle ear surgery.

The mechanism, which midazolam acts as anti-emetic effect, has not been completely known. Midazolam reduces dopamine input at the chemoreceptor trigger zone (CRTZ)[22] and consequently decreases adenosine reuptake.[23] This effect decrease synthesis, release and postsynaptic effect of dopamine at CRTZ that mediated by adenosine. Adenosine, also, decrease dopaminergic neuronal activity and 5-HT3 release by binding to the gamma-aminobutyric acid (GABA) receptor.[24]

Haloperidol, that is a tranquilizer with a mechanism similar to droperidol, has prophylactic effect on PONV.[8-10] The anti-emetic effect of haloperidol was due to its central effect at dopamine D2 receptors.[25-27] It was shown that haloperidol well-tolerated when given prophylactically[28] or therapeutically[29] in postoperative periods. In our study, haloperidol decreased the incidence of PONV 2-24 hours after surgery although it remained relatively frequent (30%). We administered haloperidol in dose of 2 mg that were not reported to cause extrapyramidal effects.

Extrapyramidal side effects are infrequent in small dose.[29,30] Tornetta and colleagues[30] showed that larger doses of haloperidol (> 2 mg to 4 mg) didn't reduce incidence of PONV further. It was presumed that combination of haloperidol with the other drugs with anti-emetic effect will reduce the incidence of PONV further.

As our results showed, using midazolam in combination with haloperidol decreased the incidence of PONV at 0-2 and 2-24 hours from 30% in group receiving haloperidol and 20-45% in group receiving midazolam to 10-15% in group receiving both drugs. It is possible that when we use two anti-emetics with different mechanisms of action, only their anti-emetic effects are increased.[31,32] Haloperidol anti-emetic effect is through its antagonism of the D2-receptors in the CTRZ of medulla while midazolam is an anti-emetic because it reduces dopamine input at the CRTZ.[25,22] The long effect of haloperidol can be related to the long half life of haloperidol that is about 18 hours.[5]

The adverse effects that were observed in our study were not serious, and there was no significant difference among 4 groups. We had no case of an excessive sedation or extrapyramidal symptoms in any of the groups.

A limitation of our study was that we did not evaluate the severity of nausea by VAS score that is a more sensitive method for this purpose.

There are still many questions regarding the use of small dose of haloperidol in combination with midazolam for PONV prophylaxis that must be answered. For example, the proper dose of this combination has not been investigated. Also, the optimum timing of administration of combined use of two drugs has not been clearly explained.

CONCLUSION

Our study showed that intravenous administration of 2 mg haloperidol plus 2 mg midazolam significantly reduced PONV better than using each drug alone in patients underwent middle ear surgery under general anesthesia.

The results of our study didn't show significant adverse effect such as over-sedation or the QTc effect (if any) due to study drug administration. It is necessary to perform additional studies to determine the timing and safety of using combination therapy with different dosing.

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Authors' Contributions: MRS has planned the study and finalized it; AH and FM and GK have planned the study and finalized it too; MRS and AH did the evaluation statistical analysis and prepared the first version of article. All authors read and approved the article.

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