

Comparing the preventive effect of midazolam and midazolam-dexamethasone on postoperative nausea and vomiting in elective middle ear surgery

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Abstract **Background:** Nausea and vomiting are common postoperative complications with incidence of 20–80% depends on the surgery type, anesthetic drugs, age, sex, etc. This complication may lead to patient discomfort, intraocular, and intracerebral pressures increase, sutures rupture, esophageal injury, and rarely death. Many studies reported that midazolam and dexamethasone alone can decrease postoperative nausea and vomiting (PONV), but their combination has never been studied yet. The aim of this study was to compare the effect of midazolam and midazolam-dexamethasone on PONV after middle ear surgery.

Materials and Methods: 66 ASA I and II patients aged 15–65 year scheduled for elective middle ear surgery under general anesthesia randomly divided into two groups. Immediately after induction of the anesthesia group one (M) received midazolam 0.075 mg/kg and group two (M+D) received combination of midazolam (0.075 mg/kg) plus dexamethasone (0.05 mg/kg). Then the severity of nausea was measured by visual analog scales 0–10 (VAS) in recovery room at 6, 12, and 24 h after surgery. Metoclopramid (0.1 mg/kg) was administrated I.V. slowly if nausea score was above 3 or patient had vomiting. The postoperative need for antiemetics and the duration of stay in recovery room were recorded. Values of $P < 0.05$ were considered statistically significant.

Results: There were no significant differences in age, gender, and weight between the two groups. There was no significant difference in the mean nausea scores between two groups except after 12 h postoperatively (1.39 ± 3.19 in M group vs. 0.42 ± 1.71 in M+D group). The mean vomiting frequency was significantly less in midazolam-dexamethasone group in the recovery room (0.9 ± 0.29 vs. 0 ± 0) and at 6–12 h (1.09 ± 2.41 vs. 0.3 ± 0.8), and 12–24 h (0.42 ± 1.32 vs. 0.03 ± 0.17) postoperatively. During the first 24 h postoperatively, the metoclopramid consumption was significantly less in combination therapy (6.48 ± 9.54) than in the midazolam group (12.9 ± 23.44) (Value < 0.5).

Conclusion: The combination of midazolam-dexametazone is more effective than midazolam alone in prevention of postoperative vomiting after middle ear surgery. Therefore, we recommend combination therapy for patients who are prone to PONV.

Key Words: Dexamethasone, midazolam, middle ear surgery, nausea, vomiting

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is a frequent and critical issue especially in the era of ambulatory surgery.^[1] This complication is more common in abdominal laparoscopic, gynecologic, and middle ear surgery and has been shown to have a relation to age, gender, drugs, hemodynamic changes, anesthetic techniques etc.^[2] This unpleasant experience is a leading cause of prolonged hospitalization and an anticipated hospital admission.^[3]

It has been shown that in ambulatory surgical patients one-third of delay in the time of discharge is due to PONV.^[4] PONV is an unpleasant experience that many patients remind it worse than pain^[5-7] and even most of patients claim that moderate pain, less conscious, and paying more expense is much better than suffering from PONV.^[6] In previous studies, the incidence of PONV was reported between 20–80% depends on the type of surgery and existence of risk factors. Although mortality is rare, PONV can result in serious complications and has been shown to be a cause of unhealing of surgical wounds, pain, esophageal injury, dehydration, hypokalemia, alkalosis, intraocular hemorrhage, increase ICP, myocardial ischemia and in rare conditions pneumonia aspiration and death^[2,7-9]

Drugs available for PONV prophylaxis are metochlopramide, ondansetron, dexamethasone, midazolam, antihistamines, and butirphenon.^[10-16] These agents may have side effects including dry mouth, hypotension, dysphoria, deep sedation, hallucination, tachycardia and extra pyramidal signs.^[5,10,17] As far as patients usually consider potential cost savings associated with drug therapy, the benefit from the use of more expensive drugs such as ondansetron and geranisetrone has been limited.^[14,18] For this reason, the challenge to use and introduce more cost-effective drugs with fewer side effects to prevent PONV is going on.^[14] Among these drugs, midazolam that is a short-acting drug with rapid onset of action in the benzodiazepine class has shown more safety and lack of serious side effects in PONV prophylaxis when used before or after induction of anesthesia.^[2,8,9,11,14,18] There are also some reports of antiemetic effect of midazolam in patients who were resistant to traditional antiemetics. Dexamethasone is also a well-established antiemetic in patient receiving cancer chemotherapy and is most effective for preventing PONV when it is administered immediately before induction of anesthesia rather than near the end of anesthesia.^[19]

Recent studies recommend the combination therapy with two or three agents in preventing PONV

in patients at risk. Among drugs available for combination therapy for PONV prophylaxis, the combination of dexamethasone-metoclopramid, ondansetron-dexamethasone, propofol-midazolam, and midazolam-ondansetron has been administrated. Taken together, these studies demonstrated that in prevention of PONV combination therapy is more effective than the use of monotherapy in patients at risk.^[20-24] With respect to the high incidence of nausea and vomiting after middle ear surgery, and no previous study to evaluate the preventive effect of midazolam-dexamethasone in combination on PONV, we aimed to compare the effect of midazolam alone and midazolam-dexamethasone in combination with PONV in candidates of middle ear surgery.

MATERIALS AND METHODS

In a double blinded clinical trial study following Institutional Research and Ethics Committee approval and written informed consent, 66 ASA I and II patients aged 15–65 year were enrolled in to this study. Individuals under 100 kg without history of motion sickness, postoperative nausea and vomiting, pregnancy, and hypersensitivity to midazolam and dexamethasone were included

Patients were scheduled for elective middle ear surgery requiring general anesthesia with orotracheal intubation and they were randomly divided into two groups.

All patients received a standardized general anesthesia involving preoxygenation and induction of anesthesia with fentanyl 2 µg/kg and thiopental sodium 5 mg/kg followed by atracurium 0.5 mg/kg for tracheal intubation. Patients randomly assigned to one of the two groups. Immediately after induction of anesthesia and intubation, group one received midazolam 0.075 mg/kg and group two received combination of midazolam 0.075 mg/kg plus dexamethasone 0.05 mg/kg, then anesthesia was maintained with nitrous oxide (50%) in oxygen (50%), isoflurane (0.5–2%), and morphine 0.1 mg/kg I.V.

All patients were monitored by electrocardiogram (ECG), capnogram, pulse oximetry, and noninvasive blood pressure monitoring.

At the end of the surgery neuromuscular blockage was reversed with neostigmine 0.4 mg/kg and atropine 0.02 mg/kg. Thereafter, patients were extubated and transferred to the recovery room.

In the recovery room and then at 6, 12, and 24 h postoperatively the severity of nausea was measured

and recorded by visual analogue scales (VAS) (Scores 0–10). The frequency of vomiting was also recorded at the same time intervals. Both VAS and vomiting after surgery is evaluated by another anesthesiologist. Metoclopramid 0.1 mg/kg was administrated I.V. slowly when nausea score was above 3 or patient had vomiting. The postoperative need for antiemetics and the duration of stay in recovery room were recorded. Criteria for recovery discharge obtained from the standard modified aldrete score.

All data were gathered by questionnaire and the statistical analyses were performed using the SPSS 10 statistical package programmer.

Demographic data (sex, age, and weight), nausea scores, and the frequency of postoperative vomiting were analyzed with Chi-square and *t*-test and a value of $P < 0.05$ were considered to be statistically significant.

RESULTS

Sixty six patients (31 male and 35 females) enrolled in to the study. Subject's characteristics are summarized in Table 1. There were no significant differences in age, gender, and weight between two groups. Similarly there was no significant difference in the mean of nausea scores between groups except after 12 h postoperatively (1.39 ± 3.19 vs. 0.42 ± 1.71) [Table 2].

The mean of vomiting frequency was significantly less in midazolam- dexamethasone group in recovery room (0.9 ± 0.29 vs. 0 ± 0) and at 6–12 h (1.09 ± 2.41 vs. 0.3 ± 0.8) and 12–24 h (0.42 ± 1.32 vs. 0.03 ± 0.17) postoperatively [Table 3].

The mean and standard deviations of postoperative metoclopramid consumption during the first 24 h in the midazolam-dexamethasone group was significantly less than that in midazolam group ($P < 0.05$) Table 4.

Duration of stay in recovery room was 67.87 ± 8.38 min in midazolam group and 61.36 ± 10.09 min in midazolam-dexamethasone group ($P = 0.003$).

DISCUSSION

This prospective randomized study showed that combination therapy with midazolam and dexamethasone prevents PONV more effectively than Midazolam alone. This effect was statistically significant for nausea after 12 h postoperatively. Moreover, the frequency of vomiting was significantly less in recovery room and after 6 h during the first postoperative day.

Table 1: Patients characteristic

	Midazolam (n=33)	Midazolam- dexamethasone (n=33)	P value
Gender (M/F)	(16/17)	(15/18)	0.8
Age	32.7 ± 10.2	34.8 ± 8.8	0.49
Weight	60.6 ± 11.1	63.1 ± 9.5	0.46

There are not any differences between two groups regard to demographic data

Table 2: Comparison of the postoperative nausea scores between two groups

Nausea score (VAS)	Midazolam	Midazolam- dexamethasone	P value
At recovery	0.88 ± 2.6	0.48 ± 1.2	0.22
0–6	3.15 ± 3.95	2.15 ± 3.49	0.14
6–12 h	2.24 ± 3.7	1.7 ± 3.3	0.3
12–24 h	1.39 ± 3.19	0.42 ± 1.71	0.049

Data are mean \pm SD

Table 3: Comparison of the mean vomiting frequency between two groups

Postoperative vomiting	Midazolam	Midazolam- dexamethasone	P value
At recovery	0.09 ± 0.29	0 ± 0	0.039
0–6	$0.85 \pm 1/8$	$0.6 \pm 1/2$	0.26
6–12 h	$1/0.9 \pm 2/41$	0.3 ± 0.8	0.04
12–24 h	0.42 ± 1.32	0.03 ± 0.17	0.047

Data are mean \pm SD

Table 4: Comparison of the mean of metoclopramide consumption in 24 h after surgery between two groups

Metoclopramide consumption	Midazolam	Midazolam- dexamethasone	P value
In the first 24 h	6.48 ± 9.54 mg	12.9 ± 23.44 mg	< 0.05

Moreover, in a group receiving combination therapy due to the lower incidence of nausea and vomiting duration of stay in recovery room was significantly shorter. In addition metoclopramid consumption was less in this group, but this difference was not significant.

Although the use of multidrug regimen for the better control of PONV has been proposed since many years ago^[25-29] It has been shown that combination of dexamethasone and granisetron has more beneficial effect than using each drug individually.^[4]

Kim and colleagues reported the same results in investigations of the influence of ondansetron and dexamethasone on PONV.^[26] They found the lower incidence of postoperative nausea and vomiting in combination therapy than using each drug individually. The incidence were declined from 52.1% to 23%.

Similarly, Midazolam that is benzodiazepine derivate has been used in preventing nausea and vomiting and its beneficial effect has been shown. Heidari and colleagues found that midazolam immediately after

induction of GA was effective in prevention of PONV.^[2] Sanjay and colleagues showed that midazolam in comparison with ondansetron had more efficacies in preventing PONV after cardiac surgery.^[29] In this study, the prevalence of nausea and vomiting with midazolam and ondansetron was 6% and 21%, retrospectively. Although Lee and his colleagues reported that there is no preference of ondansetron on midazolam in the prevention of nausea and vomiting.^[14] Furthermore, there is a report of the effectiveness of midazolam on persistent PONV.^[30]

After introduction of the beneficial effect of midazolam on prevention of PONV, more researches based on combination therapy with midazolam and agents from other therapeutic classes evaluated PONV. In one research done by Raid and his colleagues, it was shown that combination therapy with geranisetrone, ondansetron, midazolam, and dexamethasone in strabismus repair surgery in children aged between 4–12 years old was more beneficial than the use of each drug individually.^[31] In this study, anesthesia was induced with sevoflurane and the mixture of oxygen and nitrous oxide.

Eberhart and his colleagues showed that tropisetron and dexamethasone, both similarly reduced postoperative nausea and vomiting. This effect was more significant when combination of two drugs was used. In this study, the drugs were administered 1 to 2 h before induction of anesthesia in patients with moderate risk of PONV.^[32]

In our study, it was shown that the addition of dexamethasone to midazolam resulted in less postoperative nausea. This reduction was statistically significant after 12 h of surgery, but not significant at 0–12 h postoperatively. This probably may need a large number of patients to evaluate more precisely. In our research, in the midazolam-dexamethasone group, the mean frequency of postoperative vomiting was fewer compared to midazolam group in all time intervals. But during the first 6 h postoperatively this difference was not significant.

Our findings in this regard were similar to the observation of those of Raid and Eberhart^[32,33] Both of these studies were done on children aged between 4–12 years old who had a high incidence of PONV, following strabismus repair surgery and anesthesia were induced and maintained by sevoflurane.

Moreover, we found that the duration of stay in recovery room was longer in midazolam group compare to combination therapy group. This might be due to the higher incidence of vomiting that results in delayed

discharged from the recovery room.

From the results of this study, we conclude that in adults who are candidate of middle ear surgery the combination therapy with midazolam and dexamethasone prevents postoperative nausea and vomiting more than midazolam alone. Therefore, this combination therapy may be useful in cases that the incidence of PONV is high.

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