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Postoperative Nausea and Vomiting after Myringoplasty under Continuous Sedation Using Midazolam with or without Remifentanil

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Purpose: This prospective study evaluated the effects of continuous sedation using midazolam, with or without remifentanil, on postoperative nausea and vomiting (PONV) in patients undergoing myringoplasty. **Materials and Methods:** Sixty patients undergoing myringoplasty were sedated with midazolam in the presence of remifentanil (group MR), or after saline injection instead of remifentanil (group M). **Results:** Three patients (10%) in group M complained of nausea; two vomited. Four patients (13%) in group MR complained of nausea and vomited within 24 h after surgery. Rescue drugs were given to the six patients who vomited. No significant difference was detected between the two groups regarding the incidence or severity of nausea, incidence of vomiting, or need for rescue drugs. **Conclusion:** Midazolam-based continuous sedation can reduce PONV after myringoplasty. Compared with midazolam alone, midazolam with remifentanil produced no difference in the incidence or severity of nausea, incidence of vomiting, or need for rescue drugs.

Key Words: Midazolam, myringoplasty, PONV, remifentanil

INTRODUCTION

Postoperative nausea and vomiting (PONV), with an estimated incidence of 25-30%, are undesirable symptoms after general anesthesia and surgery.[1-3] In particular, middle ear surgery is associated with a high incidence of PONV, accounting for 62-80% of patients who undergo middle ear surgery experience PONV.[4-6] Many antiemetics, such as 5-HT_3 antagonists, dopamine receptor antagonists, and antihistamine drugs, have been studied for the prevention of PONV after middle ear surgery.

Midazolam, a rapid and short-acting benzodiazepine, has been widely used for the preoperative sedation or co-induction of anesthesia. The use of midazolam to prevent PONV is an off-label use of the drug. However, in several studies, midazolam has been reported to be effective for prophylaxis of PONV, when administered as a bolus before or after induction of anesthesia or as a continuous infusion

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postoperatively.[7-10] Unlugenc, et al.[10] reported that midazolam was effective for treating established PONV.

In a previous study, we indicated that midazolam-based continuous sedation for middle ear surgery had beneficial effects in overcoming pain and anxiety, and preventing PONV.[11] However, that study evaluated only the development of nausea but not its severity, the incidence and frequency of vomiting, or the need for rescue drugs. Furthermore, as midazolam has no analgesic effect, some patients were sedated using remifentanil in addition to midazolam, although opioids increase the incidence of PONV.

The present study evaluated the effects of continuous sedation, by using midazolam, with or without remifentanil, on PONV in patients undergoing myringoplasty.

MATERIALS AND METHODS

With approval from our institutional ethics committee and after obtaining written informed consent, 60 adult patients (ASA I or II) undergoing myringoplasty were included in this prospective randomized study. Exclusion criteria were age <20 years or >60 years, weight >100 kg, oral opening class IV Mallampati classification, history of chronic sedative use, known or suspected psychiatric disturbance, history of PONV or motion sickness, and any opioid or antiemetic medication taken within 24 hours before surgery. No premedication was used, and patients were informed before surgery that sedation would be performed for their myringoplasty. Patients were allocated to one of two groups randomized to receive remifentanil injection at loading and continuous doses of 0.5 μg kg^{-1} and 0.07 μg kg^{-1} min^{-1}, respectively, along with midazolam at loading and continuous doses of 0.04 mg kg^{-1} and 0.04 mg kg^{-1} h^{-1}, respectively, (group MR), or saline injection, instead of remifentanil, with the same doses of midazolam (group M).

Sedation

When the patients arrived in the operating room, noninvasive arterial pressure, heart rate, respiratory rate, pulse oximetry, and electrocardiography were monitored, and O_2 was administered at a rate of 5 L min^{-1} via a facemask. After an initial monitoring check, patients in group MR received an injection of remifentanil at a loading dose of 0.5 μg kg^{-1} and a continuous dose of 0.07 μg kg^{-1} min^{-1}. After 5 min, midazolam was injected at a loading dose of 0.04 mg kg^{-1} and a continuous dose of 0.04 mg kg^{-1} h^{-1}. In group M, patients received saline instead of remifentanil, followed by midazolam administration as in group MR. Myringoplasty was performed by an otolaryngologist who was blinded to the experimental groups.

Outcome measures of midazolam-based sedation

All patients were observed continuously for 2 hours in the recovery room and hourly in the ward. Symptoms of nausea or vomiting, including retching, were recorded. The severity of nausea was scored from 0 (no nausea) to 10 (most severe nausea) using a Visual Analog Scale (VAS). Rescue medication was given in cases of more than one episode of vomiting or at the patient's request.

Statistical analysis

An a priori power analysis was performed. A minimum of 30 patients in each treatment group was anticipated to provide an approximately 80% power for detecting a difference of 20% in the proportion of patients who were sedated using midazolam with remifentanil versus midazolam with saline at a significance level of 0.05. Numerical data were analyzed with the Mann-Whitney test and categorical data were analyzed using a Fisher's exact test. All statistical tests were one-sided, with statistical significance defined as $p<0.05$.

RESULTS

Patient demographics

There were no significant differences in age, gender, height, weight, or duration of anesthesia or surgery between the two groups (Table 1).

PONV after midazolam-based sedation with or without remifentanil

Three patients (10%) in group M complained of nausea

Table 1. Patient Demographics and Clinical Profiles

	Group M	Group MR
Number of patients	30	30
Male/Female	9/21	12/18
Age (yrs)	45.2±8.2	43.9±9.1
Height (cm)	158.2±6.1	160.1±7.8
Weight (kg)	59.1±9.0	62.1±9.8
Anesthesia time (min)	68.6±21.4	72.9±23.3
Surgical time (min)	47.6±19.9	49.6±20.6

Data are shown as means±SD. No significant difference was observed between the groups.

within 24 hours after surgery, and their severity scores were 5, 7, and 8, as compared with an overall average severity score of 0.67 for group M. Two of these three patients vomited once and three times, respectively. Four patients (13%) in group MR complained of nausea within 24 hours after surgery; their severity scores were 6, 8, 9, and 9, as compared with an overall average severity score of 1.07 for group MR. These four patients vomited one, two, two, and four times, respectively.

Rescue drugs were given to the six patients who vomited. The two patients who vomited once requested the rescue drugs, and the remaining four received rescue drugs according to the study protocol. There was no significant difference between the two groups with respect to incidence or severity of nausea, incidence or frequency of vomiting, or need for rescue drugs (Table 2).

DISCUSSION

PONV is one of the most common postoperative complaints and can occur after general, regional, and local anesthesia. The chemoreceptor trigger zone (CTZ) and the emetic center are associated with agonistic and antagonistic actions of various anesthetic-related agents and stimuli.[12] Middle ear surgery is associated with a high risk for PONV, because the operation may stimulate the vestibular labyrinth, which is innervated by the vestibular portion of cranial nerve VIII (vestibulocochlear), which in turn activates the CTZ in the area postrema.[12] CTZ manipulation leads to the activation of the parvocellular reticular formation, which is thought to be the emetic center, eventually resulting in emesis. Additionally, the sensory nerves to the auricle, external auditory meatus, tympanic membrane, middle ear cleft, and inner ear are provided by cranial nerves V (trigeminal), VII (facial), VIII (vestibulocochlear), IV (glossopharyngeal), and X (vagus). Stimulation of these parasympathetic nerves during surgical manipulations may induce PONV.[13]

Table 2. Postoperative Nausea and Vomiting (PONV) after Sedation

	Group M	Group MR
Incidence of PONV	3/30	4/30
Severity of nausea	0.67±2.07	1.07±2.80
Frequency of vomiting	0.13±0.57	0.30±0.88
Need for rescue drugs	2/30	4/30

Data are shown as means±SD. No significant difference was observed between the groups.

Previous studies have shown that middle ear surgery is associated with an incidence of PONV as high as 62-80% in patients under general anesthesia.[4-6] In cases of middle ear surgery under local anesthesia, Yung[14] found that the most common discomforts reported were noise during surgery and anxiety, followed by dizziness and pain. In our previous study, we also showed high anxiety and pain scores in patients who underwent surgery under local anesthesia.[11] Additionally, 42% of the patients suffered from PONV. However, the majority of patients who were sedated with midazolam overcame anxiety and pain satisfactorily. Furthermore, we found in the present study that continuous midazolam-based sedation was highly effective for reducing PONV after myringoplasty. Midazolam itself has an antiemetic effect, although the mechanism of the antiemetic action of midazolam has not been fully elucidated. Midazolam is thought to decrease dopamine input at the CTZ[15] and decrease adenosine reuptake.[16] This leads to an adenosine-mediated reduction in synthesis, release, and postsynaptic action of dopamine at the CTZ.[15] Midazolam may also decrease dopaminergic neuronal activity and 5-HT_3 release by binding to gamma-aminobutyric acid receptors.[17] As a result, midazolam-based continuous sedation can reduce PONV after myringoplasty.

In our previous study, we reported that the patients who were sedated using midazolam with remifentanil showed lower pain scores and higher satisfaction scores than those sedated using midazolam with saline.[11] However, intraoperative use of opioids is a well-known risk factor for PONV.[18,19] Opioids stimulate the CTZ in the area postrema of the medulla, possibly through δ-receptors, thereby leading to nausea and vomiting.[20] Thus, we expected that group MR would have a higher incidence of PONV than group M. However, the incidence and severity of nausea, incidence and frequency of vomiting, and need for rescue drugs were only slightly and insignificantly higher in group MR than in group M. The similar results between the groups may be attributable to an interaction between midazolam and remifentanil in the CTZ.

Another important observation in the present study was that patients felt extremely nauseous (average VAS score, 7.4) and the majority (86%) vomited eventually after PONV developed, despite the low rate of PONV (12%). Therefore, postoperative use of another antiemetic should be considered. Further studies are needed regarding the incidence and severity of nausea and incidence of vomiting after myringoplasty.

In conclusion, midazolam-based continuous sedation can reduce PONV after myringoplasty. Compared with patients receiving midazolam alone, patients receiving midazolam with remifentanil, which is a well-known risk factor for PONV, showed no difference in the incidence or severity of nausea, incidence or frequency of vomiting, or need for rescue drugs.

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