Antiemetic Efficacy of Low-Dose Midazolam in Patients Undergoing Thyroidectomy

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Abstract

Objective. Postoperative nausea and vomiting are distressing and frequent adverse events of anesthesia and surgery, with a high incidence following thyroidectomy. The aim of this study was to evaluate the efficacy of low-dose midazolam for preventing postoperative nausea and vomiting in patients undergoing thyroidectomy.

Study Design. Prospective, randomized, double-blind, placebo-controlled study.

Setting. University-affiliated hospital.

Subjects and Methods. Ninety patients, 30 men and 60 nonpregnant women, received intravenously placebo or midazolam at 2 different doses (50 and 75 µg/kg; n = 30 of each) immediately after induction of anesthesia. A standard general anesthetic technique, including sevoflurane and air in oxygen, was used. Postoperatively, during the first 24 hours after anesthesia, all episodes of nausea and vomiting were recorded and safety assessment were performed.

Results. The treatment groups were comparable with regard to patient demographics. The incidence of postoperative vomiting was 17% with midazolam 50 µg/kg (P = .042) and 13% with midazolam 75 µg/kg (P = .019), compared with placebo (40%). No difference in the incidence of postoperative nausea was found among the 3 groups. No clinically important adverse events, such as extrapyramidal signs, were found in any of the groups. None of the patients experienced drowsiness or excessive sedation.

Conclusion. Midazolam 50 µg/kg is as effective as midazolam 75 µg/kg for preventing postoperative vomiting, but not postoperative nausea, during the first 24 hours after anesthesia in patients undergoing thyroidectomy.

Keywords

complications, vomiting, antiemetics, midazolam, thyroidectomy

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Postoperative nausea and vomiting (PONV) are distressing and frequent adverse events of anesthesia and surgery, with a high incidence following thyroidectomy.1,2 The reported incidence of PONV varies from 63% to 84% in patients undergoing thyroidectomy.1,3 PONV decrease patient satisfaction4 and increase the risk of postoperative bleeding,5 which produces hematoma in the neck with the potential for airway obstruction. These effects justify the use of prophylactic antiemetics in patients undergoing thyroidectomy.

Numerous antiemetics have been studied for the prevention and treatment of PONV after thyroidectomy. These drugs include butyrophenones, benzamides, antihistamines, corticosteroids, propofol, and serotonin receptor antagonists.2,6-9 Among them, serotonin receptor antagonists are the most effective antiemetics in patients undergoing thyroidectomy.8,9 However, several investigations have criticized antiemetic therapy with serotonin receptor antagonists because of their high costs.10,11

Midazolam is a short-acting benzodiazepine with a rapid onset of action that is used for induction of general anesthesia and preoperative sedation.12 Previously, midazolam 50 to 75 µg/kg was reported to be effective for preventing PONV in adults undergoing middle ear surgery without delaying emergency from anesthesia or excessive sedation13,14 and in children undergoing strabismus surgery without prolonged length of postoperative stay.15 However, there have been no reports that have evaluated the antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. This prospective, randomized, double-blind, placebo-controlled study was performed to evaluate the efficacy of low-dose midazolam for preventing PONV after thyroidectomy.

Methods

After obtaining approval from our institutional review board (UAJH210401) and informed consent from the study participants, we enrolled 90 American Society of Anesthesiologists physical status I-II patients, 30 men and 60 nonpregnant...
women, aged 32 to 58 years, undergoing general anesthesia for elective partial or total thyroidectomy for Graves disease. All patients were in a physiologically euthyroid state. Patients who had gastrointestinal disorders, those who had a history of motion sickness and/or previous PONV, those who were menstruating, and those who had received antiemetic medication within 24 hours before surgery were excluded.

Using a computer-generated list of random numbers, patients were assigned to 1 of 3 treatment groups (n = 30 of each): placebo, midazolam 50 µg/kg, or midazolam 75 µg/kg. Study drugs were administered intravenously (IV) immediately after induction of anesthesia by a surgeon. Blinding the investigators, study drugs were administered using identical syringes prepared by personnel not involved in the study. The dose of midazolam was chosen because of previous reports that midazolam 50 to 75 µg/kg decreases the incidence of PONV after middle ear surgery or strabismus surgery.13-15

No patients were given preanesthetic medication. Anesthesia was induced with propofol 2 mg/kg IV and fentanyl 2 µg/kg; vecuronium 0.1 mg/kg IV was used to facilitate tracheal intubation. After tracheal intubation, anesthesia was maintained with sevoflurane 1.0% to 3.0% (inspired concentration) and air in a face mask. Partial pressure of end-tidal CO2 was controlled and adjusted to maintain partial pressure of end-tidal CO2 at 35 to 40 mm Hg throughout surgery, as measured by an anesthetic/respiratory gas analyzer (Ultima; Datex-Ohmeda, Helsinki, Finland). Muscle relaxation was achieved with vecuronium, as required. For reversal of muscle relaxation, atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were administered IV, and the trachea was extubated when the patient was awake. Masopharyngeal temperature was monitored and maintained at 36.0°C to 37.0°C using a warming pad.

At 24 hours postoperatively, an investigator (M.I.), who was blinded to treatment assignment, asked the patients whether nausea or vomiting had occurred during the first 0 to 24 hours after anesthesia, with only 2 possible answers (yes or no). Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit.4 Vomiting was defined as the forceful expulsion of gastric contents from the mouth.4 For the purpose of data collection, retching (defined as vomiting without the expulsion of gastric contents)4 was considered vomiting. If the patients had nausea and vomiting, they were categorized as having experienced vomiting. If 2 or more episodes of vomiting were recorded, metoclopramide 10 mg was administered IV as a rescue medication. Indomethacin 50 mg as an analgesic was administered rectally on request for intolerable pain. The investigator interviewed patients and recorded the details of any adverse effects throughout the study, as well as any spontaneous complaints.

Before beginning the study, a power analysis indicated that 30 patients per group would be required to detect a 35% difference in the incidence of PONV with a power (1 - β) of 0.8 (α = .05). Statistical analyses of data among the groups were performed by analysis of variance with Bonferroni correction for multiple comparisons, χ2 test, Fisher exact probability test, or Mann-Whitney test, where appropriate. A P value of <.05 was significant. Values were mean ± SD or number (%).

## Results

No patients were excluded from the study according to the exclusion criteria. The treatment groups were comparable with regard to patient demographics (Table 1). The incidence of postoperative vomiting was 17% with midazolam 50 µg/kg (P = .042) and 13% with midazolam 75 µg/kg (P = .019), compared with placebo (40%). No difference in the incidence of postoperative nausea was found among the 3 groups. Five patients receiving placebo needed a rescue medication, whereas none receiving midazolam 50 and 75 µg/kg needed it (both P = .026; Table 2). No clinically important adverse events, such as extrapyramidal signs, were found in any of the groups. None experienced drowsiness or excessive sedation (Table 2).

## Discussion

Thyroidectomy performed under general anesthesia is associated with a high incidence of PONV.1,3 The cause of PONV after thyroidectomy is not known but probably is related to several factors, including the age range and sex of patients (mostly middle-aged women) and intense preoperative vagal stimulation (surgical handling of neck structure).1,2 Other factors, including a history of motion sickness and/or previous PONV, menstruation,
smoking, operative procedure, anesthetic technique, and postoperative pain, are also considered to affect the incidence of PONV. In this study, however, the treatment groups were comparable with regard to patient demographics, types of operation, anesthetic administered, and analgesics used postoperatively. Patients with a history of motion sickness and/or previous PONV and those in a period of menstruation were excluded from the study because they had a remarkably high risk for PONV. Therefore, the difference in the incidence of PONV among the groups can be attributed to the study drug.

Midazolam is effective for reducing the incidence of PONV after middle ear surgery or strabismus surgery. The mechanism by which midazolam acts as an antiemetic is unknown. There is a possibility that midazolam decreases dopamine input at the chemoreceptor trigger zone (CTZ) and adenosine reuptake. This leads to an adenosine-mediated reduction in synthesis, release, and postsynaptic action of dopamine at the CTZ. It also decreases dopaminergic neuronal activity and serotonin release by binding to the γ-aminobutyric acid receptor. In this study, we found that midazolam 50 and 75 µg/kg were effective in the prevention of PONV after thyroidectomy and that patients receiving midazolam needed no rescue medication to treat 2 or more episodes of vomiting.

We did not find any report to determine the effective dose of midazolam for preventing PONV in patients undergoing thyroidectomy. Our results demonstrated that midazolam 50 µg/kg was as effective as midazolam 75 µg/kg and that both were more effective than placebo for preventing PONV (P = .004, midazolam 50 µg/kg vs placebo; P = .002, midazolam 75 µg/kg vs placebo). No difference in the antiemetic efficacy was found between the midazolam 50- and 75-µg/kg groups (P = .5). These data suggest that midazolam 50 µg/kg is the optimal effective dose in the prevention of PONV after thyroidectomy.

The use of propofol for maintenance of anesthesia has a positive effect on reducing PONV. Recently, Vari et al demonstrated that propofol, compared with sevoflurane, for maintenance of anesthesia reduced the incidence of PONV in patients undergoing thyroidectomy. However, the cost of propofol-based anesthesia is more expensive than that of sevoflurane-based anesthesia. In this study, therefore, general anesthesia was maintained with sevoflurane and air in oxygen.

Drowsiness is the most common adverse effect in patients treated with midazolam. However, in this study, no patients experienced drowsiness or excessive sedation. Clinically important adverse events, such as extrapyramidal signs, were not observed in any of the groups. Thus, prophylactic antiemetic therapy with low-dose midazolam administered IV immediately after induction of anesthesia is considered to be relatively free of side effects.

Droperidol, metoclopramide, dimenhydrinate, dexamethasone, subhypnotic doses of propofol, and serotonin receptor antagonists (ondansetron, granisetron) are effective in the prevention of PONV after thyroidectomy. In this study, we investigated the antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. Further studies are needed to compare the efficacy of low-dose midazolam with that of other antiemetics for prevention PONV after thyroidectomy.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 30)</th>
<th>Midazolam 50 µg/kg (n = 30)</th>
<th>Midazolam 75 µg/kg (n = 30)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV total</td>
<td>22 (73)</td>
<td>11 (37)</td>
<td>10 (33)</td>
<td>.004</td>
<td>.002</td>
<td>.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (33)</td>
<td>6 (20)</td>
<td>6 (20)</td>
<td>.191</td>
<td>.191</td>
<td>1.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (40)</td>
<td>5 (17)</td>
<td>4 (13)</td>
<td>.042</td>
<td>.019</td>
<td>1.0</td>
</tr>
<tr>
<td>Rescue</td>
<td>5 (17)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>.026</td>
<td>.026</td>
<td>1.0</td>
</tr>
<tr>
<td>Level of sedation</td>
<td>0/0/20</td>
<td>0/0/20</td>
<td>0/0/20</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Values are number (%). Level of sedation: 0 = awake, 1 = drowsy, 2 = asleep/excessive sedation. P1, midazolam 50 µg/kg versus placebo; P2, midazolam 75 µg/kg versus placebo; P3, midazolam 50 µg/kg versus midazolam 75 µg/kg.

**References**


