The Effectiveness of Midazolam for Preventing Postoperative Nausea and Vomiting: A Systematic Review and Meta-Analysis

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BACKGROUND: Previous randomized controlled trials regarding the effectiveness of perioperative midazolam in preventing postoperative nausea and vomiting (PONV) have produced conflicting results. Consequently, the present systematic review was performed to assess the effect of perioperative administration of midazolam on PONV.

METHODS: The MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials databases were searched to identify all randomized controlled trials that investigated the effectiveness of midazolam under general anesthesia. The primary end points were defined as postoperative nausea (PON), postoperative vomiting (POV), and PONV.

RESULTS: From 16 studies, 1433 patients were included in the final analysis. Compared with the control group, patients who received midazolam showed a lower overall incidence of PON (risk ratio [RR], 0.51; 95% confidence interval [CI], 0.40–0.65; I² = 35%; number needed to treat [NNT] = 6; number of included studies [n] = 11), POV (RR, 0.46; 95% CI, 0.33–0.65; I² = 0%; NNT = 8; n = 10), and PONV (RR, 0.45; 95% CI, 0.36–0.57; I² = 31%; NNT = 3; n = 7).

CONCLUSIONS: Perioperative administration of midazolam was effective in preventing PON, POV, and PONV. (Anesth Analg 2015;XXX:00–00)

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The common and stressful adverse effects of postoperative nausea and vomiting (PONV) are a major concern in 30% to 70% of high-risk groups.1 Accordingly, numerous studies have assessed the efficacies of different drugs and treatment protocols in preventing PONV. Agents including anticholinergics, antidopaminergics, antihistamines, steroids, neuroleptics, and serotonin antagonists have shown variable effects.2–5 Hence, PONV remains a complication encountered frequently during the postoperative period.

Midazolam is a short-acting benzodiazepine that affects central benzodiazepine receptors, which contain a γ-aminobutyric acid receptor site and a chloride ion channel.6 Midazolam has a sedative effect and can be used for coinduction, because it reduces the requirements for propofol and thereby lowers the incidence of the cardiovascular effects of propofol.7 Midazolam is the most commonly used sedative agent in the ambulatory setting, most likely because it has fewer depressive cardiorespiratory effects than propofol.8

Numerous studies have reported that midazolam effectively prevents PONV.9–12 The use of midazolam not only may reduce the incidence of PONV but may also provide an anxiolytic effect. Moreover, midazolam may offer the benefits of lower cost and fewer side effects, such as headaches and extrapyramidal symptoms, that have been reported with other antiemetics.13 In several studies, such antiemetics did not provide superior benefits or outcomes compared with midazolam.14,15 However, the findings are variable, and the reported outcomes from several studies are conflicting, especially when midazolam has been used in combination with other antiemetics. Therefore, we aimed to determine the effectiveness of midazolam in preventing PONV by performing a systematic review and meta-analysis.

METHODS

Study Protocol Registration

This systematic review was registered in PROSPERO (CRD42014009425) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.16

Systematic Search

We conducted a systematic review and meta-analysis of randomized controlled trials that investigated the effectiveness of midazolam in preventing PONV in comparison with controls. Studies combining midazolam and other drugs were included, provided the only difference between the groups was the use of midazolam. The MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for all relevant articles written in English up to March 1, 2014 (inclusive). In addition, the reference lists of all full articles retrieved were searched manually. The search strategy, which included a combination of free text, Medical Subject Headings, and EMTREE terms, is described in the Appendix.

Study Selection

Inclusion and exclusion criteria were determined before the systematic search. Two authors independently scanned the
Meta-Analysis for Midazolam and PONV

titles and abstracts of the reports identified via the search strategies described earlier. If a report was determined eligible from the title or abstract, the full article was retrieved. Potentially relevant studies chosen by at least one author were retrieved, and full-text versions were evaluated. Articles that met the inclusion criteria were assessed separately by 2 authors, and any discrepancies were resolved through discussion. If no agreement could be reached, a third investigator was involved to provide a resolution.

**Inclusion and Exclusion Criteria**

We included randomized controlled trials that collected data on the effectiveness of midazolam as a prophylactic agent for PONV compared with a control. Control groups were compared with an experimental group, including subjects who did not receive a drug or who received another drug, with the only difference between the groups of midazolam administration (e.g., midazolam + ondansetron versus ondansetron). The studies also included adult patients undergoing general anesthesia involving IV administration of midazolam. Data from abstracts, posters, case reports, comments, or letters to the editor, reviews, and animal studies were excluded. Studies that were not published in English were likewise excluded (Fig. 1).

**Study Outcomes**

The primary end points were the incidence of postoperative nausea (PON), postoperative vomiting (POV), and PONV. The severity of PON was also assessed. The use of rescue antiemetics and the incidence of adverse effects, such as headache, dizziness, and sedation, were secondary outcomes in the systematic review.

Subgroup analysis was performed regardless of whether PON, POV, and PONV incidence data were collected as primary outcomes or secondary outcomes. Also, a subgroup analysis was performed to rule out the effects of propofol as an induction agent. In addition, administration times were divided into 2 phases representing the induction and conclusion of surgery. In studies with >1 midazolam group or control group, all midazolam groups or all control groups were combined to avoid a unit of analysis error.

**Validity Scoring**

The quality of eligible studies was assessed independently by 2 members of the review group using the “risk of bias” tool within the Review Manager software program (version 5.2, The Cochrane Collaboration, Oxford, UK). Quality was evaluated based on potential sources of bias, including random sequence generation, allocation concealment, blinding of the participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and overall risk bias. The data were then cross-checked. The methodology of each trial was graded as “high,” “low,” or “unclear,” to reflect a high risk or a low risk of bias, and uncertainty regarding the risk of bias, respectively.17

**Data Extraction**

All interrelated data from the included studies were independently extracted and entered into a spreadsheet by 2 authors, and then cross-checked. Any discrepancy was resolved through discussion. If an agreement could not be reached, the dispute was resolved with the aid of a third investigator. The spreadsheet included the following items:

![Figure 1. PRISMA flow diagram of the search, inclusion and exclusion of randomized controlled trials.](image-url)
RESULTS

Literature Search and Study Characteristics

A search of the MEDLINE, Embase, and CENTRAL databases returned 1296 studies that were initially evaluated. After excluding duplicates, 1197 studies remained. Another 1040 studies were excluded after the review of titles and abstracts. Studies that were not published in English were likewise excluded. Of the 151 studies that remained, 83 additional studies were excluded because 39 of the studies involved children and 44 studies involved administration of experimental drugs. Forty-two studies were excluded because they were performed under monitored or regional anesthesia care and not under general anesthesia. The full texts of the remaining 26 studies were reviewed in detail, and 11 additional studies were excluded because 8 did not include a control group, 10, 19–22 2 administered midazolam for therapeutic management, 14, 36 and 1 did not report findings for PON, POV, or PONV. 57 Manual review of the references of the included studies identified 13 additional studies for assessment. However, only one met the inclusion criteria for the present review. 28 Collectively, 16 studies met the inclusion criteria and were included in this systematic review and meta-analysis. 6, 8–10, 12, 14, 26, 28–38

The characteristics of the 16 studies that met the inclusion criteria are summarized in Tables 1, 2, and 3. Midazolam was administered at induction in 11 studies 8–10, 12, 29, 30, 32, 33, 35, 37, 38 and at the end of the surgery in 3 studies. 6, 28, 31 Two studies compared the timing of administration. 34, 36 2 studies included a nausea visual analog scale for assessing the severity of PON, 10, 32 and 3 studies did not involve administration of perioperative opioids. 12, 37, 38 Twelve of the 16 studies 8, 10, 12, 28, 29, 31–34, 36–38 were aimed at comparing the incidence of PONV, and 4 studies involved the collection of PONV incidence as a secondary end point. 6, 9, 30, 35

In the studies by Park et al. 34 and Safavi and Honarmand, 36 subjects were divided into groups based on drug administration at the induction or conclusion of surgery. The group receiving midazolam or placebo administration at induction was designated Park1 and Safavi1, respectively, and the groups receiving the drugs at the end of surgery were designated Park2 and Safavi2, respectively. To avoid duplicate counting, the groups were divided in both studies.

In the study by Honarmand et al. 32 4 separate cohorts received haloperidol, midazolam, haloperidol plus midazolam, or saline. Similarly, 4 separate cohorts in the study conducted by Makhdoom and Fardid 33 received dexamethasone, midazolam, dexamethasone plus midazolam, or saline. Therefore, comparison of midazolam with a placebo was designated Honarmand1 and Makhdoom1, respectively, and the comparison of midazolam plus another drug with the second drug was designated Honarmand2 and Makhdoom2, respectively.

The postoperative period was divided into the overall, early, and late phases. The early phase was defined as 0 to 6 hours postoperatively, and the late phase as 6 to 24 hours postoperatively. The overall phase was included to capture the maximal number of studies that contained PON, POV, and PONV data with a variable data collection period and was defined as the first period of data collection (Table 4). Because several studies defined the early and late phase differently, we combined the earliest period of data collection...
with early incidence of PON, PONV, and severity of PON. For the early phase, 3 studies included postanesthesia care unit data, \( \chi^2 = 31\% \); 2 studies compared data collected at 0 to 2 hours, \( \chi^2 = 32\% \); and 1 study collected data at 0 to 60 minutes, \( \chi^2 = 35\% \). In addition, the widest overlapping period of data collection for late incidence of PON, PONV, and late PON severity was combined. For the late phase, one study included data from 8 to 14 hours, \( \chi^2 = 32\% \); a second study contained 2- to 24-hour data, \( \chi^2 = 36\% \); 3 studies reported data 6- to 12-hour data, \( \chi^2 = 37\% \); and 1 additional study included 6- to 24-hour data, \( \chi^2 = 38\% \).

### Risk of Bias

Fifteen studies referenced the random sequence generation method, \( \chi^2 = 36\% \); and only 2 studies described allocation concealment, \( \chi^2 = 32\% \). In every study, outcome assessors were blinded, and no incomplete data were reported. The overall risks of bias are shown in Table 5.

### Postoperative Nausea

#### Overall, Early, and Late PON

Eleven studies compared the effectiveness of midazolam in preventing overall PON with those of a placebo or another drug. \( \chi^2 = 32\% \); 2 studies compared its effects on late PON, \( \chi^2 = 34\% \); and 2 studies compared its effects on early PON, \( \chi^2 = 35\% \). Analysis of the combined results revealed that midazolam was associated with a statistically significant reduction in the overall incidence of PON (risk ratio [RR], 0.51; 95% CI, 0.40–0.65; \( \chi^2 = 35\% \); \( P_{x} = 0.10 \); NNT = 6; number of included studies \( \chi^2 = 36\% \); \( n = 11 \)). compared with the control groups. However, the effect of midazolam on the incidence of early and late PON compared with the control groups is unknown (RR, 0.56; 95% CI, 0.17–1.82; \( \chi^2 = 31\% \); \( P_{x} = 0.069; F = 51\% \); NNT = 7; \( n = 5 \); and RR, 0.74; 95% CI, 0.42–1.31; \( \chi^2 = 32\% \); \( P_{x} = 0.14; F = 49.7\% \); NNT = 11; \( n = 2 \), respectively).

#### Effect of Administration Timing on Overall PON

Nine studies compared the effectiveness of midazolam administered at induction of surgery in preventing overall PON, whereas 2 studies assessed its effect after administration at the conclusion of surgery. The combined results of both analyses indicated that midazolam caused a statistically significant reduction in the incidence of overall PON, regardless of the timing of administration (RR, 0.53; 95% CI, 0.39–0.71; \( \chi^2 = 36\% \); \( P_{x} = 0.16 \); NNT = 7; \( n = 5 \); and RR, 0.30; 95% CI, 0.14–0.66; \( \chi^2 = 37\% \); \( P_{x} = 0.61 \); NNT = 4; \( n = 2 \), respectively; Fig. 2).

#### Severity of PON

Two studies compared the effects of midazolam on the severity of PON using a visual analog scale score. The postoperative periods of the 2 studies were divided into the early phase (0–6 hours after surgery) and the late phase (6–24 hours after surgery). However, we were not able to clarify the effect on the severity of PON after administration of midazolam in the early or late postoperative phases when compared with a placebo (MD, −0.38; 95% CI, −3.39 to 2.64; \( \chi^2 = 32\% \); \( P_{x} = 0.063; F = 2 \); and MD, −0.04; 95% CI, −0.71 to 0.62; \( \chi^2 = 33\% \); \( P_{x} = 0.39; F = 0 \); \( n = 2 \), respectively).

### Table 1. Data Extracted from the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Risk factors for PONV</th>
<th>ASA PS</th>
<th>Age</th>
<th>Duration of anesthesia (min)</th>
<th>Type of surgery</th>
<th>Induction agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (2004)</td>
<td>≥0</td>
<td>I–III</td>
<td>18–65</td>
<td>79 (6.5)</td>
<td>Outpatient surgery</td>
<td>No limitation</td>
</tr>
<tr>
<td>Gilliland et al. (1996)</td>
<td>≥2 (female, IV-PCA)</td>
<td>I–II</td>
<td>&lt;75</td>
<td>Not mentioned</td>
<td>Total abdominal hystectomy</td>
<td>Propofol propofol plus midazolam</td>
</tr>
<tr>
<td>Goddard et al. (1995)</td>
<td>≥1 (postoperative opioid)</td>
<td>I–IV</td>
<td>Not mentioned</td>
<td>34.9 (19.7)</td>
<td>Orthopedic, urologic, or general surgery who can use LMA™</td>
<td>Propofol or propofol plus midazolam</td>
</tr>
<tr>
<td>Hasani et al. (2011)</td>
<td>≥0</td>
<td>I–II</td>
<td>35–65</td>
<td>41 (19)</td>
<td>Inguinal hernia surgery</td>
<td>Propofol, fentanyl</td>
</tr>
<tr>
<td>Heidari et al. (2004)</td>
<td>≥1 (nonsmoking)</td>
<td>I–II</td>
<td>Adult</td>
<td>Not mentioned</td>
<td>Cholecystectomy</td>
<td>Thiopental sodium, fentanyl</td>
</tr>
<tr>
<td>Honarmand et al. (2012)</td>
<td>≥1 (postoperative opioid)</td>
<td>I–II</td>
<td>18–60</td>
<td>221.9 (23.1)</td>
<td>Middle ear surgery</td>
<td>Propofol, fentanyl</td>
</tr>
<tr>
<td>Jung et al. (2007)</td>
<td>≥1 (female)</td>
<td>I–II</td>
<td>Not mentioned</td>
<td>184.9 (62.4)</td>
<td>Middle ear surgery</td>
<td>Propofol</td>
</tr>
<tr>
<td>Kim et al. (2013)</td>
<td>≥3 (female, nonsmoking, IV-PCA)</td>
<td>I–II</td>
<td>20–65</td>
<td>150 (126.3–173.8)</td>
<td>Thyroidectomy</td>
<td>Thiopental sodium, fentanyl</td>
</tr>
<tr>
<td>Makhdoom and Farid (2009)</td>
<td>≥1 (female)</td>
<td>I–II</td>
<td>Not mentioned</td>
<td>136.5 (25.4)</td>
<td>Middle ear surgery</td>
<td>Thiopental sodium</td>
</tr>
<tr>
<td>Park et al. (2013)</td>
<td>≥3 (female, nonsmoking, IV-PCA)</td>
<td>I–II</td>
<td>19–64</td>
<td>103.5 (25.4)</td>
<td>Laparoscopic ovarian cystectomy or hysterecomy</td>
<td>Thiopental</td>
</tr>
<tr>
<td>Richardson et al. (1997)</td>
<td>≥2 (female, postoperative opioid)</td>
<td>I–II</td>
<td>Not mentioned</td>
<td>46 (13)</td>
<td>Laparoscopic tubal ligation</td>
<td>Thiopental sodium, fentanyl</td>
</tr>
<tr>
<td>Safavi and Honarmand (2009)</td>
<td>≥1 (postoperative opioid)</td>
<td>I–II</td>
<td>18–60</td>
<td>107.5 (7.9)</td>
<td>Lower abdominal procedure</td>
<td>Propofol, fentanyl</td>
</tr>
<tr>
<td>Shirashtatradeh et al. (2011)</td>
<td>≥1 (female)</td>
<td>I–II</td>
<td>15–40</td>
<td>44 (3.8)</td>
<td>Appendectomy</td>
<td>Thiopental</td>
</tr>
<tr>
<td>Yeo et al. (2009)</td>
<td>≥2 (female, IV-PCA)</td>
<td>I–II</td>
<td>19–62</td>
<td>182.9 (42.4)</td>
<td>Middle ear surgery</td>
<td>Propofol</td>
</tr>
</tbody>
</table>

PON = postoperative nausea and vomiting; PS = physical status; LMA™ = laryngeal mask airway; PCA = patient-controlled analgesia.
### Table 2. Further Data Extracted from the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Maintenance agent</th>
<th>Administration route</th>
<th>Administration timing</th>
<th>Intervention/control</th>
<th>Period of data collection</th>
<th>Timing of rescue antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (2004)</td>
<td>No limitation</td>
<td>IV</td>
<td>Before induction</td>
<td>M 0.04 mg/kg/placebo</td>
<td>0–24 h (PON, POV), PACU</td>
<td>PONV</td>
</tr>
<tr>
<td>Gilliland et al. (1996)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>At induction, followed by 48 h infusion</td>
<td>M 5 mg/70 kg bolus + 1 mg/70 kg/h for 48 h infusion</td>
<td>0–48 h (PON, rescue antiemetics)</td>
<td>PONV</td>
</tr>
<tr>
<td>Godsiff et al. (1995)</td>
<td>Enflurane, N₂O</td>
<td>IV</td>
<td>At induction</td>
<td>M 2.5–5 mg + propofol 30–100 mg/propofol 60–200 mg</td>
<td>PACU/0–24 h (PON)</td>
<td>PONV</td>
</tr>
<tr>
<td>Hasani et al. (2011)</td>
<td>Propofol, fentanyl, N₂O</td>
<td>IV</td>
<td>Before induction</td>
<td>M 0.05 mg/kg + 1.5 mg/kg diclofenac/diclofenac 1.5 mg/kg</td>
<td>PACU (PON, POV)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Heidari et al. (2004)</td>
<td>Halothane, N₂O</td>
<td>IV</td>
<td>Before induction</td>
<td>M 75 μg/kg/placebo</td>
<td>0–2/2–8–14–14–24 h (NVAS)/0–24 h (PON)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Honarmand et al. (2012)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>End of surgery</td>
<td>2 mg haloperidol + M 2 mg/M 2 mg/2 mg haloperidol/placebo</td>
<td>0–2/2–24/0–24 h (PONV)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Huh et al. (2010)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>In the PACU followed by PCA infusion</td>
<td>5 mg morphine + M 1 mg + M 0.4 mg/mL + 1 mg/mL morphine PCA/5 mg morphine + 1 mg/mL morphine PCA</td>
<td>0–24 h (PON, PO, PONV, rescue antiemetics)</td>
<td>Antiemetics required for vomiting</td>
</tr>
<tr>
<td>Jung et al. (2007)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>At induction</td>
<td>M 75 μg/kg/placebo</td>
<td>0–24 h (PON, PO, PONV, rescue antiemetics)</td>
<td>Antiemetics required for vomiting</td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td>Sevoflurane, N₂O</td>
<td>IV</td>
<td>End of surgery followed by PCA infusion</td>
<td>M 5 mg + 16 mg ondansetron in PCA 16 mg ondansetron in PCA</td>
<td>PACU/PACU-6/6–24 h (PONV), 0–24 h (rescue antiemetics)</td>
<td>PONV</td>
</tr>
<tr>
<td>Kim et al. (2013)</td>
<td>Sevoflurane, N₂O</td>
<td>IV</td>
<td>Before induction</td>
<td>M 75 μg/kg + 0.3 mg ramosetron /0.3 mg ramosetron</td>
<td>0–2/2–6/12–12–24 h (NVAS, PON, rescue antiemetics)</td>
<td>NVAS &gt; 5</td>
</tr>
<tr>
<td>Makhdoom and Farid (2009)</td>
<td>Isoflurane</td>
<td>IV</td>
<td>Before induction</td>
<td>M 75 μg/kg + 10 mg dexamethasone/10 mg dexamethasone/M 75 μg/kg/placebo</td>
<td>0–24 h (PON, PO, PONV, rescue antiemetics)</td>
<td>PONV &gt; 2</td>
</tr>
<tr>
<td>Park et al. (2013)</td>
<td>Sevoflurane, remifentanil</td>
<td>IV</td>
<td>RM1: at induction/RM2: end of surgery</td>
<td>M 50 μg/kg/placebo</td>
<td>0–2/2–24/24–48 h (PON, PO, rescue antiemetics)</td>
<td>Severe nausea, vomiting episode &gt;2</td>
</tr>
<tr>
<td>Richardson et al. (1997)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>Before induction</td>
<td>M 40 μg/kg/placebo</td>
<td>0–60 min (PON, rescue antiemetics)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Safavi and Honarmand (2009)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>MP: before induction/MI: end of surgery</td>
<td>M 35 μg/kg/placebo</td>
<td>0–2/2–6/12–12–18–24 h (PONV), 0–24 h (rescue antiemetics)</td>
<td>Nausea &gt; 15 min, vomiting</td>
</tr>
<tr>
<td>Shirdashtzadeh et al. (2011)</td>
<td>Halothane, N₂O</td>
<td>IV</td>
<td>Before induction</td>
<td>M 50 μg/kg/placebo</td>
<td>0–2/2–6/12–12–18–24 h (PONV), 0–24 h (PONV)</td>
<td>Antiemetics required for vomiting</td>
</tr>
<tr>
<td>Yeo et al. (2009)</td>
<td>Isoflurane, N₂O</td>
<td>IV</td>
<td>At induction</td>
<td>M 75 μg/kg + 10 mg dexamethasone/10 mg dexamethasone/placebo</td>
<td>0–24 h (PON, PO, PONV, rescue antiemetics)</td>
<td>Antiemetics required for vomiting</td>
</tr>
</tbody>
</table>

PCA = patient-controlled analgesia; N₂O = nitrous oxide; M = midazolam; PON = postoperative nausea; POV = postoperative vomiting; PONV = postoperative nausea and vomiting; PACU = postanesthesia care unit; NVAS = nausea visual analog scale; RM = Ramacetrone plus midazolam; MP = Midazolam premedication; MI = Midazolam intraoperative.
Table 3. Further Data Extracted from the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of patients</th>
<th>Sex (male/female)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Rescue analgesics</th>
<th>Airway device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (2004)</td>
<td>88</td>
<td>32/56</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Fentanyl, morphine</td>
<td>No limitation</td>
</tr>
<tr>
<td>Gilliland et al. (1996)</td>
<td>45</td>
<td>0/45</td>
<td>67 (9)</td>
<td>Not reported</td>
<td>Morphine</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Godsiff et al. (1995)</td>
<td>40</td>
<td>23/17</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Fentanyl, NSAIDs</td>
<td>LMA™</td>
</tr>
<tr>
<td>Hasani et al. (2011)</td>
<td>90</td>
<td>47/43</td>
<td>57 (11)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>LMA™</td>
</tr>
<tr>
<td>Heidari et al. (2004)</td>
<td>82</td>
<td>45/37</td>
<td>68 (14)</td>
<td>170 (8)</td>
<td>Not reported</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Honarmand et al. (2012)</td>
<td>80</td>
<td>53/27</td>
<td>68.8 (13.8)</td>
<td>Not reported</td>
<td>Meperidine</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Huh et al. (2010)</td>
<td>90</td>
<td>90/00</td>
<td>59.3 (6.3)</td>
<td>159.4 (7.6)</td>
<td>Ketorolac, morphine</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Jung et al. (2007)</td>
<td>90</td>
<td>90/00</td>
<td>58.7 (6.3)</td>
<td>159.1 (6.2)</td>
<td>Ketorolac</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td>90</td>
<td>90/00</td>
<td>57.1 (7.8)</td>
<td>159.0 (4.1)</td>
<td>Ketorolac</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Kim et al. (2013)</td>
<td>94</td>
<td>94/00</td>
<td>60.7 (8.5)</td>
<td>159.3 (8.4)</td>
<td>Ketorolac</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Makhdoom and Farid (2009)</td>
<td>80</td>
<td>0/80</td>
<td>52.3</td>
<td>Not reported</td>
<td>Paracetamol</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Park et al. (2013)</td>
<td>126</td>
<td>0/126</td>
<td>58.8 (9.4)</td>
<td>160.6 (5.2)</td>
<td>Ketorolac</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Richardson et al. (1997)</td>
<td>30</td>
<td>0/30</td>
<td>66 (13)</td>
<td>Not reported</td>
<td>Morphine sulfate</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Safavi and Honarmand (2009)</td>
<td>60</td>
<td>34/26</td>
<td>68.2 (8.7)</td>
<td>166.0 (4.7)</td>
<td>Meperidine</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Shirdashtzadeh et al. (2011)</td>
<td>75</td>
<td>0/75</td>
<td>55 (5.6)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Yeo et al. (2009)</td>
<td>120</td>
<td>0/120</td>
<td>57.6 (8.3)</td>
<td>161.1 (4.2)</td>
<td>Ketorolac</td>
<td>Endotracheal intubation</td>
</tr>
</tbody>
</table>

Values of weight and height are mean (SD).

LMA™ = laryngeal mask airway; NSAIDs = nonsteroidal antiinflammatory drugs.

Table 4. Effect of Midazolam on PON, POV, and PONV Versus Phases and Administration Times

<table>
<thead>
<tr>
<th>Phase</th>
<th>PON</th>
<th>POV</th>
<th>PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery period</td>
<td>Early</td>
<td>RR, 0.56; n = 5 95% CI, 0.17–1.82</td>
<td>RR, 0.48; n = 4 95% CI, 0.32–0.79</td>
</tr>
<tr>
<td>Late</td>
<td>RR, 0.74; n = 2</td>
<td>RR, 0.40; n = 3</td>
<td>RR, 0.40; n = 2</td>
</tr>
<tr>
<td>Overall</td>
<td>RR, 0.51; n = 11</td>
<td>RR, 0.46; n = 10</td>
<td>RR, 0.45; n = 10</td>
</tr>
<tr>
<td>Administration</td>
<td>Induction</td>
<td>RR, 0.53; n = 9</td>
<td>RR, 0.45; n = 8</td>
</tr>
<tr>
<td>End</td>
<td>RR, 0.30; n = 2</td>
<td>RR, 0.49; n = 2</td>
<td>RR, 0.49; n = 2</td>
</tr>
</tbody>
</table>

PON = postoperative nausea; POV = postoperative vomiting; PONV = postoperative nausea and vomiting; RR = relative risk; CI = confidence interval; NNT = number needed to treat.

Effect of Midazolam in Conjunction with Propofol as an Induction Agent on Overall PON

Seven studies evaluated the effectiveness of midazolam in reducing overall PON with the use of propofol as an induction agent, whereas 3 studies assessed its effectiveness without propofol. The combined results of both analyses revealed that midazolam caused a statistically significant reduction in the incidence of overall PON, regardless of propofol administration (RR, 0.64; 95% CI, 0.47–0.87; I² = 45%; P₁ = 0.09; NNT = 9; n = 7; and RR, 0.39; 95% CI, 0.23–0.65; I² = 35%; P₁ = 0.19; NNT = 5; n = 3, respectively).

Data Collected as Primary or Secondary Outcomes

PON incidence was collected as a primary endpoint in 7 studies, whereas 4 studies collected PON incidence as a secondary endpoint. The combined results of both analyses regarding primary and secondary outcomes revealed that midazolam caused a statistically significant reduction in the overall incidence of PON, regardless of the aim of the study (RR, 0.46; 95% CI, 0.34–0.63; P = 5%; P₁ = 0.39; NNT = 5; n = 7; and RR, 0.64; 95% CI, 0.44–0.93; I² = 42%; P₁ = 0.16; NNT = 8; n = 4, respectively).

Postoperative Vomiting

Overall, Early, and Late POV

Ten studies assessed the effects of midazolam on the overall PON, whereas 4 studies compared the effects on the incidence of early PON and 3 studies evaluated its effects on the incidence of late PON. The combined results revealed that midazolam caused a statistically significant reduction in the incidence of overall PON (RR, 0.46; 95% CI, 0.33–0.65; P = 0%; P₁ = 0.87; NNT = 8; n = 10; Fig. 3). Also, the results suggest the beneficial effect of midazolam on the incidence of early or late PON when compared with a placebo, but these did not reach the statistical significance (RR, 0.48; 95% CI, 0.22–1.01; P = 0%; P₁ = 0.54; NNT = 16; n = 4; and RR, 0.40; 95% CI, 0.13–1.27; P = 0%; P₁ = 0.85; NNT = 23; n = 3, respectively).

Effect of Administration Timing on Overall PON

Eight studies assessed the effects of midazolam on the overall PON when administered at induction, and 2 studies assessed the effects of midazolam administered at the conclusion of surgery. The
combined results revealed that midazolam administered at induction caused a statistically significant reduction in the incidence of overall PONV (RR, 0.45; 95% CI, 0.31–0.65; $I^2 = 0%$; $P = 0%$; $P_1 = 0.61$; $I = 0%$; NNT = 7; $n = 8$). Also, the effect of midazolam administered at the end of surgery showed the tendency of reduction in the incidence of overall PONV (RR, 0.49; 95% CI, 0.20–1.19; $I = 0%$; $P_2 = 0.56$; NNT = 8; $n = 2$).

**Effect of Midazolam in Conjunction with Propofol as an Induction Agent on Overall PONV**

Four studies12,29,31,38 assessed the effectiveness of midazolam administered with propofol as an induction agent in preventing overall PON, whereas 5 studies14,32–34,37 assessed its effectiveness without propofol. The combined results of both analyses revealed that midazolam caused a statistically significant reduction in the incidence of overall PON, regardless of propofol administration (RR, 0.37; 95% CI, 0.20–0.68; $P = 0%$; $P_1 = 0.42$; NNT = 8; $n = 4$; and RR, 0.54; 95% CI, 0.35–0.84; $P = 0%$; $P_2 = 0.87$; NNT = 8; $n = 5$, respectively).

**Data Collected as Primary or Secondary Outcomes**

Nine studies10,12,29,31–34,37,38 collected the incidence of PONV as a primary end point, whereas only 1 study30 collected PONV incidence as a secondary end point. The results of the combined analysis revealed that midazolam caused a statistically significant reduction in the overall incidence of PONV as a primary outcome (RR, 0.48; 95% CI, 0.34–0.68; $P = 0%$; $P_1 = 0.90$; NNT = 8; $n = 9$). However, the analysis of PONV incidence as a secondary end point could not be performed because of the small number of studies included.

**Postoperative Nausea and Vomiting**

**Overall, Early, and Late PONV**

Seven studies assessed the effects of midazolam on overall PONV10,12,29,31–34,37,38. 4 investigations compared the effects on the incidence of early PONV10,32,34,36, and 2 studies evaluated the effects on the incidence of late PONV30,36. The combined results revealed that midazolam caused a statistically significant reduction in the incidence of overall, early, and late PONV (RR, 0.45; 95% CI, 0.36–0.57; $P = 0%$; $P_1 = 0.16$; NNT = 3; $n = 7$; RR, 0.50; 95% CI, 0.32–0.79; $P = 0%$; $P_2 = 0.22$; NNT = 6; $n = 4$;
and RR, 0.26; 95% CI, 0.12–0.59; \( P = 43\% ; P_x = 0.17; \) NNT = 5; \( n = 2, \) respectively; Fig. 4).

**Effect of Administration Timing on Overall PONV**

Five studies\(^{12,33,36–38}\) assessed the effects of midazolam on overall PONV after administration at surgical induction, and 3 investigations\(^{6,28,36}\) assessed its effectiveness at the end of surgery. The combined results indicated that midazolam administration at both the induction and the conclusion of surgery caused statistically significant reductions in the incidence of overall PONV (RR, 0.44; 95% CI, 0.33–0.59; \( F = 24\% ; P_x = 0.25; \) NNT = 3; \( n = 5 \); and RR, 0.50; 95% CI, 0.31–0.78; \( F = 48\% ; P_x = 0.12; \) NNT = 4; \( n = 3, \) respectively; Fig. 4).

**Effects on Overall PONV With or Without Perioperative Opioids**

Five studies\(^{6,28,31,33,36}\) compared the effectiveness of midazolam in reducing the overall PONV in combination with perioperative opioids, and 3 studies\(^{12,37,38}\) compared its effectiveness without perioperative opioids. The combined results revealed that midazolam administered with perioperative opioids caused a statistically significant reduction in the incidence of overall PONV (RR, 0.43; 95% CI, 0.32–0.59; \( F = 1\% ; P_x = 0.42; \) NNT = 3; \( n = 5 \)). Also, midazolam administered without perioperative opioids showed beneficial effect on the incidence of overall PONV, but this did not reach the statistical significance (RR, 0.46; 95% CI, 0.10–2.12; \( F = 66.4\% ; P_x = 0.05; \) NNT = 3; \( n = 3, \) respectively).

**Effect of Midazolam in Conjunction with Propofol as an Induction Agent on Overall PONV**

Four studies\(^{12,31,36,38}\) analyzed the effectiveness of midazolam in reducing the overall PONV when used in conjunction with propofol as an induction agent, whereas 4 separate studies\(^{6,28,33,38}\) assessed its effectiveness without the administration of propofol as an induction agent. The combined results of both analyses revealed that midazolam caused a statistically significant reduction in the incidence of overall PON independent of propofol administration (RR, 0.48; 95% CI, 0.36–0.65; \( F = 9\% ; P_x = 0.35; \) NNT = 3; \( n = 4 \); and RR, 0.41; 95% CI, 0.29–0.57; \( F = 42\% ; P_x = 0.12; \) NNT = 3; \( n = 4, \) respectively).

**Rescue Antiemetics**

Eleven studies\(^{9,12,28,29,31–36,38}\) compared the requirement for rescue antiemetics among midazolam recipients and controls. The combined results revealed statistically significant differences in the requirement for rescue antiemetics, but with substantial heterogeneity (RR, 0.52; 95% CI, 0.37–0.74; \( F = 53\% ; P_x = 0.009; \) NNT = 5; \( n = 11 \)). Exclusion of the study by Gilliland et al.\(^{9}\) before a sensitivity analysis revealed a decrease in heterogeneity and a statistically significant difference in the requirement for rescue antiemetics (RR, 0.56; 95% CI, 0.37–0.73; \( F = 28\% ; P_x = 0.03; \) NNT = 3; \( n = 10 \)).
significant reduction in the requirement for rescue antiemetics (RR, 0.44; 95% CI, 0.34–0.56; \( P = 0% \); \( P_2 = 0.67 \); NNT = 4; \( n = 10 \)). In addition, the same outcome was observed when the study by Yeo et al.\(^3\) was excluded (RR, 0.57; 95% CI, 0.45–0.71; \( P = 47% \); \( P_5 = 0.03 \); NNT = 5; \( n = 10 \)).

**Effect of Midazolam in Conjunction with Propofol as an Induction Agent in the Requirement for Rescue Antiemetics**

The effectiveness of midazolam with propofol as an induction agent in cases requiring rescue antiemetics was analyzed in 6 studies.\(^9,12,31,35,36,38\) Four studies\(^28,32–34\) assessed the effectiveness of midazolam without the use of propofol as an induction agent. The combined results of combined analyses indicated that midazolam with propofol as an induction agent showed no evidence of difference in the use of rescue antiemetics (RR, 0.54; 95% CI, 0.024–1.09; \( P = 0.002 \); \( P_2 = 0.022 \); \( P = 72\% \); NNT = 7; \( n = 6 \)). Conversely, the effects of midazolam on the requirement for rescue antiemetics without propofol revealed statistically significant reductions without heterogeneity (RR, 0.50; 95% CI, 0.31–0.79; \( P = 0% \); \( P_2 = 0.84 \); NNT = 7; \( n = 4 \)).

**Data Collected as Primary or Secondary Outcomes**

Seven studies\(^6,12,31,33,36–38\) collected the incidence of PONV as a primary end point, but there were no studies that collected PONV incidence as a secondary end point. The results of the combined analysis revealed that midazolam caused a statistically significant reduction in the overall incidence of PONV as a primary outcome (RR, 0.45; 95% CI, 0.36–0.57; \( P = 0.65–2.71 \); \( P = 58\% \); \( P_2 = 0.04 \); NNT = 15; \( n = 4 \)).

**Safety Analysis**

**Headache**

The incidence of headaches among midazolam recipients was compared with controls in 4 studies.\(^6,12,34,38\) The analysis of the combined findings showed a neutral result (RR, 1.18; 95% CI, 0.56–2.49; \( P = 0% \); \( P_2 = 0.86 \); NNT = 1045; \( n = 4 \)).

**Dizziness**

The overall effect of midazolam on the incidence of dizziness was assessed in 4 studies\(^12,31,34,38\) but there was no statistically significant effect of midazolam relative to the placebo (RR, 0.90; 95% CI, 0.46–1.77; \( P = 0 \); \( P_2 = 0.79 \); NNT = 53; \( n = 4 \)).

**Sedation**

The overall effect of midazolam on the incidence of postoperative sedation was assessed in 4 studies,\(^9,12,31,34\) but there were no statistically significant effect (RR, 1.33; 95% CI, 0.65–2.71; \( P = 0.79 \); \( P_2 = 0.04 \); NNT = 53; \( n = 4 \)).

**Publication Bias**

Evidence of a publication bias was detected by the Egger linear regression test (\( P < 0.05 \); Table 4). Similarly, the funnel plot analyses for these values demonstrated asymmetry (Fig. 5). However, the funnel plots became symmetrical after adjustment using the trim-and-fill method (Fig. 5). The results before and after elimination of the effect of publication bias are shown in Table 6. The significance of the RR with 95% CIs did not change after the elimination of the publication bias.

**DISCUSSION**

The results of the current study suggested that midazolam reduced the overall incidence of PON, POV, and PONV, with an NNT of 3 for overall PONV. Furthermore, the results indicated that midazolam treatment can prevent nausea and vomiting in approximately 1 in 3 patients who would otherwise continue to suffer from PONV if administered a placebo.\(^18\) In addition, the need for rescue antiemetics was reduced among patients in the midazolam groups.

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**Figure 5.** Funnel for overall postoperative nausea. White circles, comparisons included; black circles, inputted comparisons using the trim-and-fill method; white diamond, pooled observed log risk ratio; black diamond, pooled inputted log risk ratio.
Meta-Analysis for Midazolam and PONV

Midazolam was shown to have a preventive effect on PONV in the early, late, and overall recovery period and was also effective in preventing overall PON and POV. However, we were not able to clarify the effects of midazolam on the early and late recovery period of PON or POV. The combined results of early and late PON were considerably heterogeneous, otherwise there was no substantial heterogeneity in PONV. It seems that subjective judgments of feeling nausea lead to a large variation among collected data, unlike vomiting.

The combined results of 2 studies indicated that midazolam appeared to be effective in preventing late PONV. However, 1 of the 2 studies administered midazolam as a continuous patient-controlled analgesia infusion, which might have adversely affected the results. Therefore, further studies are needed to evaluate the duration of the antiemetic effect. In addition, many patients currently receive antiemetics as opposed to no treatment. Therefore, further studies or a systematic review comparing midazolam with other antiemetics would be needed to confirm the potency of the antiemetic effects of midazolam.

Preoperative anxiety may increase gastric acid secretion, lower gastric pH, and delay gastric emptying, which leads to an increase in PONV. However, several studies reported that anxiety was not related to the incidence of PONV. In addition, the consensus guidelines for the management of PONV state that in adults, anxiety is not a proven risk factor and may be of limited clinical relevance. In the study conducted by Safavi and Honarmand, the incidence of PON was significantly lower among subjects who received midazolam at induction compared with those who received the agent at the end of surgery. However, Park et al. reported that no significant differences were observed between administration of midazolam at induction or at the end of surgery. In this meta-analysis, a statistically significant reduction in the incidence of PON, POV, and PONV relative to controls was observed after midazolam administration at induction. However, only the incidence of PON was significantly reduced after administration of midazolam at the end of surgery when compared with the control group. This would imply that the anxiolytic effect of midazolam may be important in its PONV efficacy, which is not in accord with the consensus guidelines.

In the study by Splinter et al., a 50 to 75 μg/kg midazolam dose was recommended for prophylactic antiemetic use. In the current meta-analysis, the doses of midazolam in the reviewed studies ranged from 35 to 75 μg/kg. However, the 35 to 75 μg/kg dosing range might be an excess of quantity for preventing PONV with the risk of sedation. Therefore, when using midazolam, which is a hypnotic agent, the sedative effects, respiratory depression, and prolonged recovery time might be a major safety concern. However, no significant differences were apparent between midazolam and control groups after a safety analysis, but the different sedation scoring scales in the studies limited the combination of data. Fifteen of the 16 relevant studies reported that there were no significant differences between midazolam and control groups. Among 3 studies in which midazolam was administered continuously, only 1 study reported that the incidence of mild sedation in the midazolam group was higher than levels in the control group. However, the incidence of moderate to severe sedation or respiratory depression was not observed in any group.

A subgroup analysis was performed to evaluate the effects of midazolam administration on PONV when used in conjunction with propofol as an induction agent. The results of the analysis indicated that midazolam had a statistically significant effect on overall PON, POV, and PONV whether propofol was administered or not. However, the requirement for rescue antiemetics showed no evidence when propofol was used in conjunction with midazolam as an induction agent. Conversely, the requirement for rescue antiemetics revealed a significant reduction compared with the control group when only midazolam was used as an induction agent without propofol. We suggest that the use of propofol, which has been reported to decrease the incidence of early PONV, might have affected the requirement for rescue antiemetics.

Nonetheless, an apparent publication bias was evident in several comparisons of midazolam and controls in the current study and may have influenced the results. Nevertheless, the significance of the study findings was not altered after consideration of the apparent publication bias. Consequently, we had confidence in our findings, despite the omission of data from unpublished studies.

To include maximum data regarding the antiemetic effects of midazolam, several studies contained PONV data as an inevitable secondary end point, which might have increased the likelihood that confounding variables influenced the results. Therefore, we performed a subgroup analysis based on whether PON, POV, and PONV incidence data were collected as primary or secondary outcomes. The combined results of the analyses revealed that midazolam caused a statistically significant reduction in the incidence of overall PON, regardless of the aim of the studies.

The current study has several limitations. First, only published studies were included in our meta-analysis. Second, only 2 studies included the late effectiveness of midazolam on PONV, one of which included the continuous infusion of midazolam using a patient-controlled analgesia device.

### Table 6. Publication Bias

<table>
<thead>
<tr>
<th></th>
<th>Egger test (P value)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall PON</td>
<td>0.0200</td>
<td>0.53 (95% CI, 0.42–0.68)</td>
<td>0.73 (95% CI, 0.59–0.91)</td>
</tr>
<tr>
<td>Early PON</td>
<td>0.0195</td>
<td>0.26 (95% CI, 0.17–1.82)</td>
<td>0.95 (95% CI, 0.38–2.34)</td>
</tr>
<tr>
<td>Overall POV</td>
<td>0.0107</td>
<td>0.46 (95% CI, 0.33–0.65)</td>
<td>0.45 (95% CI, 0.30–0.68)</td>
</tr>
<tr>
<td>Early POV</td>
<td>0.0012</td>
<td>0.48 (95% CI, 0.22–1.01)</td>
<td>0.84 (95% CI, 0.42–1.67)</td>
</tr>
<tr>
<td>Rescue antiemetics</td>
<td>0.0151</td>
<td>0.52 (95% CI, 0.37–0.74)</td>
<td>0.76 (95% CI, 0.63–0.93)</td>
</tr>
</tbody>
</table>

RR = relative risk; PON = postoperative nausea; POV = postoperative vomiting; CI = confidence interval.
Third, many studies either did not assess side effects or adverse events or approached them in different ways. Hence, the late effectiveness of midazolam on PONV and the results of safety analyses should be interpreted cautiously. Despite its limitations, the present meta-analysis demonstrated strength through the application of rigorous methodology and provided the first systematic review assessing the prophylactic effect of midazolam on the incidence of PONV. Moreover, added strengths of our study included the large sample size, the thorough identification of articles, the data extraction, and the resolution of all discrepancies by 3 independent investigators. Furthermore, our subgroup and sensitivity analyses yielded stable and robust findings.

In summary, the prophylactic administration of midazolam reduced the incidence of overall PON, POV, and PONV. Furthermore, the effects were more evident during the early postoperative phase than during the late phase, and the reductions in the incidence of PON, POV, and PONV were greater when midazolam was administered at the induction of surgery.

**APPENDIX**

**Medline**
1. randomized controlled trial.pt
2. randomized controlled trial$.mp
3. controlled clinical trial.pt
4. controlled clinical trial$.mp
5. random allocation.mp
6. exp double-blind method/
7. double-blind.mp
8. 8.exp single-blind method/
9. single-blind.mp
10. or/1-9
11. clinical trial.pt
12. clinical trial$.mp
13. exp clinical trial/
14. (clin$ adj25 trial$).mp
15. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).mp
16. random$.mp
17. exp research design/
18. research design.mp
19. or/11-18
20. 10 or 19
23. Historical article.pt.
25. or/21-24
26. 20 not 25
27. exp postoperative nausea and vomiting/
28. vomit* OR nausea* OR PONV.mp
29. (postoperative adj6 nausea adj6 vomiting).mp
30. or/27-29
31. 26 and 30
32. exp midazolam/
33. midazolam.mp
34. or/32-33
35. 31 and 34

**EMBASE**
1. randomi?ed controlled trial$.mp.
2. ‘controlled clinical trial’/exp
3. controlled AND clinical AND trials
4. controlled clinical trial$.mp.
5. ‘randomization’/exp
6. ‘random allocation’/exp
7. random allocation.mp.
8. double-blind.mp.
9. single-blind.mp.
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. ‘clinical trial (topic)’/exp
12. clinical AND trial$.mp.
13. random$.mp.
14. rct
15. #11 OR #12 OR #13 OR #14
16. #10 OR #15
17. ‘case study’/exp
18. ‘case report’/exp
19. ‘abstract report’/exp
20. ‘letter’/exp
21. #17 OR #18 OR #19 OR #20
22. #16 NOT #21
23. ‘postoperative nausea and vomiting’/exp
24. ‘postoperative nausea’/exp
25. ‘postoperative vomiting’/exp
26. Nausea or vomiting or PONV.mp.
27. #23 OR #24 OR #25 OR #26
28. #22 AND #27
29. ‘midazolam’/exp
30. midazolam.mp.
31. #29 OR #30
32. #28 AND #31

**DISCLOSURES**
Name: Eun Jin Ahn, MD.
Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
Attestation: Eun Jin Ahn has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Hyun Kang, MD, PhD, MPH.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Hyun Kang has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Geun Joo Choi, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Geun Joo Choi has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Chong Wha Baek, MD, PhD.
Contribution: This author helped conduct the study and analyze the data.
Attestation: Chong Wha Baek has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yong Hun Jung, MD, PhD.
Contribution: This author helped design the study and write the manuscript.

Attestation: Yong Hun Jung has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Young Choel Woo, MD, PhD.

Contribution: This author helped conduct the study and analyze the data.

Attestation: Young Choel Woo has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

This manuscript was handled by: Tong J. Gan, MD, MHS, FRCA.

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37. Shirdashtizadeh N, Eshraghi N, Eshraghi A. Comparison of par enteral promethazine versus midazolam effect as a preoperative