Effects of Perioperative Midazolam Administration on Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia: An Evidence-Based Practice Analysis

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Introduction

Patients undergoing general anesthesia are at risk of developing postoperative nausea and vomiting (PONV) with reported incidences ranging from 30% to as high as 80% in high-risk populations.[1] The fear of experiencing nausea or vomiting after surgery is often stated to be the number one concern of patients, even over postoperative pain.[2] PONV is a distressing experience for patients and can lead to longer stays in the post-anesthesia care unit (PACU), prolonged time to discharge, patient dissatisfaction, and increased costs.[3] The incidence of PONV depends on a variety of factors including age, sex, non-smoking status, use of opioids postoperatively, history of motion sickness or prior episodes of PONV.[4] Additional non-patient related factors include laparoscopic surgery, anesthetic gases, medications, and duration of surgery.[1]

Current literature shows that a multimodal approach is the best way to prevent PONV versus using a single drug alone.[1] Utilizing antiemetics that act on different receptors results in an additive effect and optimizes results. Management strategies should be based on the patient's risk for PONV as well as the patient's preexisting condition (e.g. avoiding QT prolongation in at risk patients[1]) while also considering cost-effectiveness and the patient's preference. The APFEL score is the most common method of assessing a patient's risk of developing PONV. The APFEL score includes four variables and assigns one point for each category and includes: female sex; history of motion sickness or postoperative nausea and vomiting; nonsmoker; and planned use of opioids postoperatively.[4] For each point scored, the risk of PONV increases with a score of 0 being 10% risk and a score of 4 being 80% risk.[4] Patients who score 0-1 are considered low risk, patients who score 2 are at moderate risk and those with 3 or more are considered high risk.[1] The most recent guidelines for management of PONV suggest that low risk patients should not receive preemptive treatment, moderate risk patients should receive 1 or 2 interventions, and high risk patients should receive more than 2 interventions.[1]

Midazolam is a short-acting sedative-hypnotic drug that binds to benzodiazepine receptors of the γ-aminobutryic acid (GABA) receptor, increasing the inhibitory effect of GABA in the central nervous system.[5] GABA neurons inhibit central dopaminergic pathways and benzodiazepines inhibit dopaminergic activity via binding to GABA receptors.[6] The precise mechanisms of midazolam's ability to prevent PONV is not

certain. Current theories center around the dopaminergic effect at the chemoreceptor trigger zone (CTZ). Midazolam decreases dopamine synthesis, release (mediated by decreased adenosine reuptake), and its action at the CTZ.[7,8,9,10] Other proposed mechanisms include a glycine mimetic inhibitory effect[7,8] and enhancement of the inhibitory effect of GABA.[7,8,9] Additionally, $5HT_3$ release is thought to be reduced by benzodiazepines via their binding to GABA receptors.[10]

The impact of postoperative nausea and vomiting is clear. There are many different multimodal approaches to preventing PONV in patients undergoing general anesthesia. Midazolam is a medication frequently used for its anti-anxiolytic properties in the perioperative period. The purpose of this evidence-based practice analysis is to examine the effects of perioperative administration of midazolam on postoperative nausea and vomiting in patients undergoing general anesthesia.

Methodology

A population, intervention, comparison, outcome (PICO) question was developed to guide the search of the current literature and provide the clinical framework. “Do patients undergoing general anesthesia (P) who receive midazolam perioperatively (I) experience a difference in postoperative nausea and vomiting (O) compared to patients who do not receive midazolam (C)?”

A review of current literature was conducted using the following databases: Cochrane Collection, PubMed, MEDLINE Complete, and CINAHL Complete for all available studies between 2009 and 2017. The following keywords were utilized individually or in combination: midazolam, nausea, vomiting, postoperative, PONV, general anesthesia. This search method yielded 110 studies and of those, seven studies met inclusion criteria with varying levels of evidence including one meta-analysis, one systematic review and meta-analysis, and five randomized-controlled trials (RCT).

Literature Review

Honarmand et al.[8] conducted a randomized, double-blind, placebo-controlled study on prophylactic administration of IV midazolam and ondansetron together vs administration of either drug alone on reduction of PONV in 140 adult patients undergoing middle ear surgery. Patients were divided into 4 groups (n=35) where group M received midazolam 0.075 mg/kg, group O ondansetron 4 mg, group MO midazolam 0.075 mg/kg plus ondansetron 4 mg, and group S a normal saline (NS) placebo. PONV was evaluated at 0-2 hours and 2-24 hours. Postoperative nausea intensity was measured using visual analog scale (VAS) at 0-2 and 2-24 hours. Duration of PACU stay was evaluated using the Modified Aldrete Score. Sedation levels were measured utilizing the Observer’s Assessment of Alertness/Sedation scale. Patient satisfaction was rated on a 10-point scale.

The authors found a decrease in PONV at both 0-2h and 2-24h intervals in the group that received both midazolam and ondansetron compared to the groups that received ondansetron, midazolam, or the placebo ($P<0.05$). VAS of nausea in the midazolam/ondansetron group was significantly less than the other groups ($P<0.001$). The need for rescue antiemetics in the midazolam/ondansetron group was significantly less compared to the other groups ($P<0.05$). Rescue antiemetic use was highest in the placebo group (71.4%) and lowest in the midazolam/ondansetron combination group (11.4%) compared to the groups who received either drug alone (midazolam group 31.4% and ondansetron group 34.3%). There was no significant difference in time spent in PACU ($P=0.057$), time to extubation ($P=0.759$), or the occurrence of side effects such as dizziness and headache ($P=0.794$) among patients who received midazolam and those who did not. Patient satisfaction was rated on a 0-10 scale where 0 was no satisfaction at all and 10 was complete satisfaction. Patients' ratings showed satisfaction was greatest in the midazolam/ondansetron group (8.2) compared to the placebo (4.1), ondansetron only (5.7), and midazolam only (5.9) groups ($P<0.05$). The administration of midazolam with ondansetron was superior at reducing PONV compared to either drug alone in the first 24 hours after middle ear surgery and there was also reduced rescue antiemetic need. A limitation of this study was patients received a total IV anesthetic with propofol, which could have influenced the results as propofol has known antiemetic properties.[1,8]

The reduction of PONV with midazolam was not seen in all trials. Ozcan et al.[7] conducted a randomized, patient-parent, and investigator-blinded study of 66 children undergoing tonsillectomies or adenotonsillectomies, where one group received IM midazolam 0.1 mg/kg and the other did receive IM midazolam. Incidences of POV, PONV, and rescue antiemetic requirements were recorded at 0-4 hours and 4-24 hours post surgery. VAS was used to measure nausea. VAS nausea scores were not statistically significant at 0-4 or 4-24 hours ($P=0.597$ and $P=0.982$). Although the midazolam group had fewer incidences of nausea at both 0-4 and 4-24 hours, the results were not statistically significant compared to the group who did not receive midazolam ($P=0.621$ and $P>0.999$). Requirements for rescue antiemetics in 24 hours were significantly lower in the midazolam group ($P=0.027$) but the median antiemetic numbers did not differ significantly between the two groups ($P=0.070$). IM intraoperative midazolam administration does not prevent PONV in children undergoing tonsillectomy or adenotonsillectomy. A possible limitation and strength of this study is the use of IM midazolam versus the IV route. No other study had looked at the use of IM midazolam for prevention of PONV in the pediatric population, which adds to the literature but is difficult to compare outcomes. Another possible limitation is patients were not given any preventative antiemetic drugs other than the drug being studied due to cost restrictions at the facility.[7] Current recommendations encourage a multi-modal approach to preventing PONV.[1]

Park et al.[9] studied 126 females undergoing laparoscopic gynecological surgeries and compared those who received ramosetron to those who received both ramosetron and midazolam in a randomized, double-blind controlled trial. They also investigated the

timing of administration of midazolam by administering midazolam at induction and the conclusion of surgery to determine if timing of administration affected the incidence of PONV. These patients were considered high-risk as they all had at least three risk factors for PONV. Episodes of PONV were recorded at 0-2, 2-24, and 24-48 hours after surgery. Secondary outcomes included the incidence of severe nausea, number of emetic episodes, and the need for rescue antiemetics. Severity of nausea was measured using a verbal rating scale. Adverse events including headache, dizziness, drowsiness and weakness were also recorded. Patients were divided into three groups: group R received NS IV at induction and at the conclusion of surgery, group RM1 midazolam 0.050 mg/kg IV at induction and NS at conclusion, group RM2 NS at induction and midazolam 0.050 mg/kg at conclusion. All patients received 0.3 mg ramosetron at the conclusion of surgery.

Both the RM1 and RM2 groups had statistically significantly less nausea compared to the placebo group ($P<0.05$). The authors found the ramosetron/midazolam groups (RM1 73%; RM2 71%) had a significantly higher incidence of absence of PONV and no use of antiemetics (complete response) compared to the placebo group (44%; $P<0.05$) but no difference between the two groups. Regarding timing of administration of midazolam, the authors did not find a significant difference in reduction of PONV between the two groups whether it was given at induction or the conclusion of surgery. However, the study was not sufficiently powered to compare these differences. Sedation levels and the incidence of adverse effects did not differ significantly between the groups ($P>0.05$). There was no significant difference in the incidence of severe nausea, number of emetic episodes or the use of antiemetics among the groups. Midazolam in combination with ramosetron was more effective in preventing PONV than either drug alone in females at high risk of PONV undergoing laparoscopic gynecological surgery under general anesthesia. Limitations of this study were that concentrations of sevoflurane and the infusion levels of remifentanil were not measured, so the amount of anesthetic could not be compared among the groups. Additionally, a sedation scale was not utilized, which limits the comparison of this adverse effect to other studies. A strength of this study is it included patients who were high risk for experiencing PONV.[9]

In a randomized and double-blind controlled study, Riad et al.[10] compared midazolam administration alone or in combination with dexamethasone in 100 children undergoing strabismus repair. Patients were allocated into four groups, group 1 received a NS placebo, group 2 midazolam 0.050 mg/kg, group 3 dexamethasone 0.5 mg/kg, and group 4 a combination of midazolam 0.050 mg/kg and dexamethasone 0.5 mg/kg. All drugs were given IV after induction of anesthesia. Episodes of PON (postoperative nausea), POV (postoperative vomiting), and PONV were recorded for 24 hours after surgery. Secondary outcomes included time spent in PACU. The Aldrete scoring system was used to evaluate recovery time. The authors' results showed a statistically significant decrease in PON in the midazolam/dexamethasone (0%; $P<0.001$), midazolam (12%; $P<0.001$), and dexamethasone (32%; $P<0.01$) groups compared to the placebo group (48%). Results also showed a statistically significant difference in the incidence of POV in the midazolam/dexamethasone (0%; $P<0.001$) and midazolam only (0%; $P<0.001$) groups

compared to the placebo (52%) and the dexamethasone (32%) groups. POV in the midazolam and midazolam/dexamethasone group was also statistically significantly less than the dexamethasone group ($P<0.05$). Children who received a combination of midazolam and dexamethasone had zero incidences of nausea or vomiting while the midazolam only group had nausea in 12% with no vomiting. The authors reported recovery time (extubation until discharge from PACU) was prolonged in the midazolam/dexamethasone group (23 minutes) vs the placebo group (15 minutes), however, the recovery time in the dexamethasone group was 24 minutes and 17 minutes in the midazolam group. The prolongation of recovery time was found to be significant in both the dexamethasone and the midazolam/dexamethasone group, but not in the midazolam only group. Administration of midazolam in combination with dexamethasone in children undergoing strabismus repair leads to a reduction in PONV during the first 24 hours after surgery better than either drug alone. Limitations of this study include the lack of additional secondary outcomes such as sedation levels, headache or dizziness that are included in many other studies. Strengths of the study include studying IV midazolam use in children for prevention of PONV.[10]

Yadav et al.[11] studied oral midazolam vs oral clonidine and its effect on PONV in 120 adult patients undergoing laparoscopic cholecystectomy in a randomized, double-blinded controlled trial. Primary outcomes were PONV incidences and rescue antiemetic use during the first 24 hours following surgery. Severity of PONV was graded on a numerical scale. Secondary outcomes included sedation utilizing the Ramsay sedation score (RSS), VAS for pain, mean pulse rate, and systolic blood pressure. Patients were randomized into three groups: group 1 received midazolam 15 mg orally, group 2 clonidine 150 mcg orally, and group 3 glucose 5 g orally. All drugs were given one hour prior to induction of anesthesia, and additionally all patients received granisetron 1 mg IV prior to induction. The authors' results showed PONV to be significantly reduced in the clonidine group (15%) vs the midazolam (22.2%) and placebo (59%) group ($P=0.002$). The need for rescue antiemetic was found to be significantly lower in both the midazolam (13.88%) and clonidine (5%) group when compared to the placebo (52.27%) group ($P<0.001$). RSS at 2 hours postoperatively was lower in the placebo group (less sedation) compared to the clonidine and midazolam groups ($P=0.007$). Oral clonidine was more effective at preventing PONV than oral midazolam in granisetron premedicated patients undergoing laparoscopic cholecystectomy. A possible limitation of this study is the utilization of oral midazolam, which many studies have not done, so it is difficult to compare results. Additionally, the pharmacokinetics of oral midazolam and clonidine differ, which could have affected the outcomes. A strength of this study is it compares clonidine to midazolam for the prevention of PONV, which had not been adequately studied.[11]

A systematic review and meta-analysis of 16 RCT studies which included 1,433 adults undergoing surgery with general anesthesia by Ahn et al.[5] aimed to determine the effectiveness of midazolam in preventing PONV. Studies included utilized IV midazolam as a prophylactic agent and were compared to a control group. The dose of IV midazolam ranged from 0.035-0.075 mg/kg or boluses of 2-5 mg. Primary outcomes included PON,

POV, and PONV. Two studies included a nausea VAS to assess PON. Secondary outcomes included use of rescue antiemetics and adverse effects such as headache, dizziness, and sedation. Eleven of the studies administered midazolam at induction, three at the conclusion, and two studies compared the timing of administration. The authors found a statistically significant reduction in overall PON (RR=0.51; 95% CI, 0.40-0.65), POV (RR=0.46; 95% CI, 0.33-0.65), and PONV (RR=0.45; 95% CI, 0.36-0.57), whether midazolam was given at induction or the conclusion of surgery, however the reduction was greatest when midazolam was given at induction of surgery. Ahn et al.[5] also found a statistically significant decrease in requirements for rescue antiemetics when patients received midazolam (RR=0.52; 95% CI, 0.37-0.74). The authors did not find a statistically significant effect of midazolam on the incidence of postoperative sedation (RR=0.90; 95% CI, 0.46-1.77).

Midazolam is effective for prevention of PON, POV, and PONV, with effects being greatest when administered at induction of surgery. Additionally, midazolam administration was not found to be associated with adverse effects such as headache, dizziness, or sedation. A limitation to this review is many studies did not include side effects or adverse events as outcomes. The strengths of this review are the high level of evidence, the large sample size, the rigorous methodology, and its contribution to the body of literature as the first systematic review assessing the prophylactic effect of midazolam on PONV.[5]

Grant et al.[6] conducted a meta-analysis of 12 RCTs which included 841 adult patients undergoing general anesthesia. The aim of the review was to evaluate the ability of IV midazolam administration to prevent PONV when given either preoperatively or during the intraoperative period. Primary outcomes included PON, POV, PONV, and rescue antiemetic use in the first 24 hours. Secondary outcomes included side effects such as dizziness, headache, prolonged PACU stay, and sedation levels. The control was no midazolam administration and the intervention was IV midazolam administration. Results indicated administration of IV midazolam resulted in a significant reduction in PON (RR=0.62; 95% CI, 0.40-0.94), POV (RR=0.61; CI 95%, 0.45-0.82), and PONV (RR=0.55; 95% CI, 0.43-0.70) compared to control patients as well as a significant decrease in rescue antiemetic need (RR=0.49; CI 95%, 0.37-0.65). The authors found the timing of midazolam administration was insignificant in relation to reduction in PONV. Patients who received it preoperatively, at induction, or at the end of surgery all had significantly lower incidences of PONV. They did not find a significant difference in PACU stay time in minutes (mean difference = 0.74; 95% CI, -1.38-2.86, P=0.49) in patients who received midazolam, nor was there a difference between groups in the occurrence of significant sedation (RR=1.91; 95% CI, 0.58-6.25, P=0.29). Results from this review support the use of IV midazolam as part of a multimodal approach in preventing PON, POV, and PONV in adults undergoing general anesthesia and that its use reduces rescue antiemetic use.

Doses of IV midazolam in the included studies ranged from 0.035-0.075 mg/kg or a 2 mg bolus. Grant et al.[6] states that PONV can likely be prevented at subhypnotic doses (<0.05 mg/kg), which eliminates unwanted side effects. The authors also state that it is likely the antiemetic effect of midazolam outlasts the sedation profile because of the 24-hour antiemetic effect shown in their meta-analysis. Strengths of this review include the large sample size, the high level of evidence, and the contribution to the body of literature.[6]

Table 1

Author(s), Design	Sample	Anesthetic Agents	Independent Variable Groups, Route, Timing	Primary Outcomes (PONV, rescue antiemetic use)
Honarmand et al. (2016)[8] RCT	n=140 18-62 y/o M/F Middle ear surgeries	Induction: thiopental sodium, fentanyl Maintenance: propofol infusion	• Ond 4 mg (n=35) • NS placebo (n=35) • M 0.075mg/kg (n=35) • M 0.07mg/kg + Ond 4 mg (n=35) IV with induction	Midazolam + ondansetron more effective than midazolam alone in reducing PONV • PONV less at 0-2h and 2-24h in M+Ond group compared to other groups (P<0.05) • Decreased requirement for rescue antiemetic in M+Ond group compared to other groups (P<0.05)
Ozcan et al. (2017)[7] RCT	n=66 5-12 y/o M/F Tonsillectomies	Induction: sevoflurane, fentanyl Maintenance: sevoflurane, N_2O	• No M (n=33) • M 0.1 mg/kg (n=33) IM after induction	Midazolam has no statistically significant effect on PON, POV • POV not different between groups at 0-4h (P>0.999) or 4-24h (P=0.708) • antiemetic requirements less in M group compared to non-M group (P=0.027)
Park et al. (2013)[9] RCT	n=126 19-64 y/o F Laparoscopic GYN surgeries	Induction: thiopental sodium, remifentanil Maintenance: sevoflurane, remifentanil -all patients received	• NS at induction & conclusion (n=43) • M 0.05 mg/kg at induction + NS at conclusion (n=41)	Midazolam + ramosetron more effective than ramosetron alone in reducing PONV • Complete response (no PONV and no antiemetic use) during 48h in both M groups compared to NS group (P<0.05)

		ramosetron 0.3mg	• NS at induction + M 0.05mg/kg at conclusion (n=42) IV	• PON in M groups compared to NS group at 2-24 and 24-48h (P<0.05)
Riad et al. (2007)[10] RCT	n=100 4-12 y/o M/F Strabismus repair surgeries	Induction: sevoflurane, N_2O, fentanyl Maintenance: sevoflurane, N_2O	• NS (n=25) • dex 0.5 mg/kg (n=25) • M 0.05 mg/kg (n=25) • M 0.05 mg/kg + dex 0.5mg/kg (n=25) IV after induction	Midazolam with or without dexamethasone reduces PONV, but combination is more effective than either drug alone • PON and POV in M and M+dex groups compared to NS group (P<0.001) • POV in M and M+dex group compared to dex group (P<0.05)
Yadav et al. (2013)[11] RCT	n=120 18-60 y/o F Laparoscopic cholecystectomy surgeries	Induction: propofol, fentanyl Maintenance: isoflurane, N_2O	• glucose placebo 5 g (n=44) • clonidine 150mcg (n=40) • M 15 mg (n=36) Oral 1 hour prior to anesthesia	Clonidine more effective than midazolam in reducing PONV • PONV less in clonidine group compared to other groups (P=0.002) • Rescue antiemetic requirement lower in M and clonidine groups compared to placebo group (P<0.001)

Abbreviations: n=number patients in study; GYN=gynecological; M=male; F=female; Ond=ondansetron; NS=normal saline; M=midazolam; dex=dexamethasone

Conclusions

Due to the adverse effects of experiencing nausea and or vomiting after surgery, the use of a multimodal regimen to prevent PONV by anesthesia providers is key in improving patient outcomes. The use of IV midazolam as part of a multimodal approach is an effective tool to prevent PONV in patients undergoing general anesthesia. Two large meta-analyses and three RCTs found midazolam administration reduced PONV.[5,6,8,9,10] Six of the seven studies found that midazolam administration reduces the need for rescue antiemetic administration.[5,6,7,8,11] Two studies did not find a statistically significant effect of midazolam on PONV.[7,11] Of note these two studies utilized alternative routes of midazolam administration, one IM[7] and the other PO.[11]

One concern anesthesia providers may have in giving midazolam is patients experiencing sedation resulting in prolonged wakeups or prolonged PACU stays. The dosages of midazolam (2-5 mg dose or 0.035-0.075 mg/kg) used in the studies included in this evidence-based practice analysis are not in excess of a normal anti-anxiolysis dose which may explain the low incidence of adverse outcomes such as excessive sedation or prolonged recovery times.[6]

Anesthesia providers should utilize IV midazolam as part of a multimodal approach in patients who are at risk of developing PONV, providing the patients are appropriate to receive the drug. Timing of administration did not appear to affect the reduction in PONV[5,6,9], but as this drug can be given as both an anti-anxiolytic and antiemetic, giving it prior to induction can maximize both effects. Although some variability exists in the dosing regimens of IV midazolam, the most common dose administered amongst the studies was 0.035-0.075 mg/kg, which in a 70-kg adult would be between 2.45-5.25 mg, a relatively standard dose of IV midazolam for anxiolysis.

Midazolam is another drug to add to the toolbox of anesthesia providers to prevent PON, POV, and PONV in patients who are at risk.[5,6,8,9,10] It is a drug that is both inexpensive and widely available for use. It should not be given as the sole antiemetic but in combination with another antiemetic drug to achieve a synergistic effect.[1] It is an effective tool when given at either induction or the conclusion of surgery[5,6,9] and when given in doses of 2-5 mg or 0.035-0.075 mg/kg boluses does not cause unwanted effects of excessive sedation[5,6,9], prolonged wakeups[8], or extended PACU stays.[6,8] The administration of midazolam also decreases the need for rescue antiemetic drugs.[5,6,8,9,11]

This evidence-based practice analysis has several limitations. One limitation is not all studies utilized the same administration route for midazolam. There are differences in pharmacokinetics with oral, IM, and IV routes of administration, and this could have affected the outcomes. Another limitation worth noting are the vast differences in induction, maintenance agents, and control drugs utilized in the different studies, which might also have effects on the outcomes. Despite its limitations, the present evidence-based practice analysis demonstrated strength through the use of a large sample size, the inclusion of both a systematic review and meta-analysis, and by utilizing only studies containing RCTs. Another strength is the comparison between the timing of the administration of midazolam and the occurrence of PONV. More research is needed to determine if oral or IM administration has similar benefits to IV administration. Additional research is also needed in the pediatric population regarding the use of midazolam for preventing PONV.

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