Effects of Midazolam on Postoperative Nausea and Vomiting and Discharge Times in Outpatients Undergoing Cancer-Related Surgery

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Midazolam, a short-acting benzodiazepine used for preoperative anxiolysis, may also have pharmacologic properties that could further reduce the incidence of postoperative nausea and vomiting (PONV) in high-risk patients when included in a multimodal antiemetic protocol. However, concerns remain that the sedating properties of midazolam will delay discharge after short outpatient procedures. A retrospective data analysis (N = 4,057) investigated effects of midazolam on postoperative antiemetic administration and length of stay following cancer-related outpatient procedures over 15 months. Following initial univariate analysis, a multivariable model adjusting for Apfel score, surgical service, age, length of surgery, and type of anesthesia was created to test these associations. The multivariable analysis demonstrated that midazolam was associated with reduced need for postoperative antiemetic medications (3.2% lower than no-midazolam group; 95% confidence interval = 0.03%-6.0%, P = .032). Furthermore, the multivariable analysis demonstrated no clinically significant effect on postoperative length of stay (7.9 minutes shorter in midazolam group; 95% confidence interval = –20 to 4.4, P = .2). In patients for whom midazolam is not otherwise indicated, evidence is insufficient to warrant midazolam administration solely to prevent PONV. Randomized trials are needed to provide an accurate estimation of the effect size of midazolam for PONV in these patients.

Keywords: Benzodiazepine, cancer, midazolam, outpatient, postoperative nausea and vomiting.

Postoperative nausea and vomiting (PONV) continues to be a stressful consequence of outpatient surgery despite pharmacologic advances. Patients often find experiencing nausea and vomiting more distressing than postsurgical pain. Furthermore, PONV can delay recovery and discharge in patients undergoing outpatient procedures.[1-3] As a result of these complications, substantial research has been generated to establish appropriate pharmacologic and nonpharmacologic interventions to reduce the incidence of PONV.

Patients with a higher risk of PONV often require a combination or multimodal approach of 2 or more interventions for effective risk reduction.[1,3] Thus, researchers have explored additional nontraditional antiemetics, such as midazolam, that would aid in the multimodal prevention of PONV.[4,5]

Midazolam is often administered in the perioperative period to reduce anxiety in addition to causing sedation and amnesia. The pharmacologic qualities allow for a rapid onset, short duration, and short half-life. The clinical effects of midazolam result from an agonist action on the γ-aminobutyric acid A ($GABA_A$) receptor throughout the central nervous system. Benzodiazepines do not work directly on the GABA receptor, so there is a physiologic ceiling effect, which contributes to their safety and low toxicity.[6,7]

Although the exact antiemetic mechanisms remain unknown, researchers postulate that midazolam works on the chemoreceptor trigger zone by reducing the synthesis, release, and postsynaptic dopamine.[7] It remains debatable whether midazolam reduces dopamine directly or blocks the reuptake of adenosine leading to an adenosine-mediated reduction of dopamine release. Additionally, the binding of midazolam to the GABA benzodiazepine complex may cause dopaminergic neuronal activity and the release of 5-hydroxytryptamine. The reduction of PONV may also be a secondary effect of the anxiolytic properties of benzodiazepines.[8]

Despite literature demonstrating the PONV benefits of midazolam in the perioperative period,[4,5] published consensus guidelines have not yet included midazolam as a standard intervention for PONV prevention.[1] A small retrospective analysis concluded that midazolam had beneficial antiemetic properties in patients undergoing breast cancer-related surgery, but only 48 of the

patients studied underwent outpatient procedures.[9] The study was limited to partial and complete mastectomies and did not include postoperative length of stay, which is a critical value in outpatient surgeries and a clinical concern for anesthesia providers. Also, the researchers did not investigate plastic reconstructive procedures or other types of outpatient cancer surgeries. Therefore, the current literature exhibits a gap in the effect of midazolam on PONV and length of stay in patients undergoing outpatient cancer surgeries. Our study focused on a large outpatient surgical center where the use of midazolam is high because of the anxiety associated with cancer surgery, enabling us to measure these associations.

The primary aim of this study was to determine whether patients undergoing cancer-related outpatient surgeries who received midazolam intraoperatively had a decreased incidence of postoperative rescue antiemetic administration compared with those patients who did not receive midazolam. The secondary aim examined whether patients who received midazolam had a longer time to discharge compared with patients who did not receive midazolam.

Materials and Methods

Following institutional review board approval, we conducted a retrospective chart review of a cohort of 4,417 patients who underwent a total of 4,954 outpatient surgical procedures at Memorial Sloan Kettering Cancer Center's Josie Robertson Surgery Center from January 2016 to March 2017.

Prespecified exclusion criteria excluded patients with preexisting benzodiazepine prescriptions (n = 294), 2 surgical procedures on the same day (n = 35), preoperatively placed paravertebral nerve blocks (n = 17), an ASA classification 4 exhibiting substantial comorbidities (n = 7), unexpected admissions to the hospital (n = 6), or receipt of only local anesthesia (n = 1). Also excluded from the analysis were any subsequent secondary procedures performed in the same patient at a later date (n = 537).

Patients undergoing general anesthesia received standard prophylactic antiemetics of dexamethasone and ondansetron, and all patients with an Apfel score for PONV of 4 also received aprepitant. Patients undergoing monitored anesthesia care (MAC) received prophylactic antiemetics based on clinician judgment. In the postanesthesia care unit (PACU), antiemetics were administered for treatment of nausea or vomiting based on the standard-of-care treatment protocol. Prophylactic antiemetics were not administered before opiate administration in the PACU. Data on intraoperative opioid use, in morphine milligram equivalents, were also collected.

The primary aim was to determine whether the intraoperative administration of midazolam was associated with a reduction in the use of PONV as indicated by use of antiemetic rescue medications in the PACU. To test this hypothesis, we created logistic regression models for the outcome of rescue medication use in the treatment of PONV. A univariate logistic regression model helped assess the association between midazolam and use of rescue medication for PONV. A multivariable logistic regression model analyzed whether midazolam reduced the use of PONV rescue medication after adjusting for factors that may influence PONV such as Apfel score, surgical service, age, length of surgery, and type of anesthesia (general anesthesia or MAC). Cubic splines were created for age and were included in the multivariable model if significant nonlinearity was identified. It was hypothesized that the effect of midazolam on the use of PONV rescue medication differs depending on the length of surgery, because the effects of midazolam may have dissipated before the postoperative period for patients who have longer surgeries. To test this hypothesis, we tested an interaction between the use of midazolam and operative time.

The secondary study aim was to determine whether the use of intraoperative midazolam increased postoperative length of stay. This was calculated as the time in hours from PACU admission to the time of discharge. Linear regression models were created to test this association. The association was tested using both a univariate model and a multivariable model, which was adjusted for Apfel score, surgical service, age, length of surgery, surgery start time, and type of anesthesia (general anesthesia or MAC). Cubic splines were also included in this multivariable model if significant nonlinearity was identified.

It was hypothesized that intraoperative midazolam use is lower in patients aged 65 years and older. An analysis was conducted on whether the effect of midazolam on the need for postoperative rescue medications for PONV or length of stay differed depending on patient age. An interaction term was added between intraoperative midazolam use and patient age in the multivariable models used for the outcomes of use of rescue medications for PONV and length of stay.

We did not include intraoperative opioid use or prophylactic antiemetic use in our primary analysis, because opioid and antiemetic use are standardized at our facility and are highly correlated with anesthesia type. However, we performed a sensitivity analysis to confirm that these factors did not influence our results by repeating the analyses, including intraoperative opioid use (in morphine milligram equivalents) and dexamethasone and ondansetron use (in milligrams) in the multivariable models. All analyses were performed using Stata 15 (StataCorp).

Results

A total of 4,057 patients were included in our analysis after removing those who met the prespecified exclusion criteria. Patient characteristics are presented in the Table. Most patients received midazolam (76%). The most common dose of midazolam was 2 mg (92%), with 6.0%

Characteristic	No midazolam (n = 993)[a]	Midazolam (n = 3,064)[a]	*P* Value[b]
Male sex	53 (5.3)	88 (2.9)	.0002
Age, y, median (IQR)	65 (51-74)	52 (44-60)	< .0001
ASA score			< .0001
1	32 (3.2)	137 (4.5)	
2	436 (44)	1,817 (59)	
3	525 (53)	1,110 (36)	
Surgical service			< .0001
Breast	692 (70)	1,545 (50)	
Gastric	1 (0.1)	8 (0.3)	
Gynecology	107 (11)	508 (17)	
Head/neck	57 (5.7)	84 (2.7)	
Plastic surgery	125 (13)	906 (30)	
Urology	11 (1.1)	13 (0.4)	
Type of anesthesia			< .0001
General	346 (35)	1,641 (54)	
MAC	647 (65)	1,423 (46)	
Operative time, min, median (IQR)	79 (62-105)	92 (67-126)	< .0001
Apfel score			.0002
0	1 (0.1)	1 (< 0.1)	
1	11 (1.1)	23 (0.8)	
2	107 (11)	277 (9.0)	
3	732 (74)	2,128 (69)	
4	142 (14)	635 (21)	
Intraoperative opioid use, MMEs, median (IQR; N = 4,054)	20 (10-25)	20 (15-40)	< .0001

Table. Patient Characteristics by Use of Midazolam (N = 4,057)
Abbreviations: IQR, interquartile range; MAC, monitored anesthesia care; MMEs, morphine milligram equivalents.
[a]Data are presented as number (%) unless indicated otherwise.
[b]*P* values were determined by χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.

of patients receiving less than 2 mg and 1.7% receiving more than 2 mg. Patients under 65 years of age, receiving general anesthesia, and those with ASA scores less than 3, longer operative times, or higher Apfel scores were more likely to receive midazolam. We first investigated whether midazolam administration affected the use of rescue medications for PONV. Most patients did not require any rescue PONV medications (88%). Among the 491 patients who received rescue medications for PONV, the majority (73%) required only 1 dose, while 23% required 2 doses and 4.3% required 3 or more doses.

On univariate analysis, the use of midazolam was associated with an increased use of PONV rescue medications (13% in midazolam group vs 8.3% in the no-midazolam group, 95% CI = 3.0%-7.2%, *P* < .0001). However, when controlling for Apfel score, surgical service, age, length of surgery, and type of anesthesia, midazolam was associated with a reduced need for rescue PONV medications (adjusted rate in midazolam group of 11.6% [95% CI = 10.7%-12.6%] vs no-midazolam group of 14.8% [95% CI = 12.1%-17.4%]), a rate of PONV medication use that was 3.2% lower in the midazolam group (95% CI = 0.03%-6.0%, *P* = .032). In the sensitivity analysis, including opioid use and preventive antiemetic use, results were similar, with a 3.2% lower risk in the midazolam group (95% CI = 0.04%-6.1%, *P* = .020).

Longer length of surgery was associated with increased use of rescue PONV medications on multivariable analysis (OR =1.13, 95% CI = 1.11-1.16, *P* < .0001). There was some evidence that the use of rescue PONV medications also differed by service (*P* = .066), with higher rates of rescue medication use in plastic surgeries than in breast surgeries (OR =1.43, 95% CI = 0.98-2.08). Thus, the increased use of PONV medications seen on univariate analysis was likely due to differences between services, increased midazolam use, and increased PONV medication use among patients with longer operative times. We then investigated whether midazolam affected

use of rescue PONV medications differently depending on the length of surgery and found no evidence that this association differed based on operative time ($P = .6$).

We investigated whether the use of midazolam was associated with an increased length of stay. For our cohort, the median length of stay was 2.6 hours (interquartile range = 2.0-3.6). On univariate analysis, there was a significant association between midazolam and an increase in postoperative length of stay (3.5 hours in midazolam group vs 3.1 hours in no-midazolam group, 22 minutes longer in midazolam group; 95% CI = 8.6-34, $P = .001$). However, when controlling for Apfel score, surgical service, surgery start time, operative time and type of anesthesia, the association was not significant: length of stay 3.4 hours in the midazolam group (95% CI = 3.3-3.5) and 3.5 hours in the no-midazolam group (95% CI = 3.3-3.7), 7.9 minutes shorter in the midazolam group (95% CI = –20 to 4.4, $P = .2$). The confidence interval was narrow, with an upper bound of a 4.4-minute increase in length of stay, suggesting that we can exclude any clinically relevant increase in discharge time. Operative time was longer for patients receiving midazolam ($P < .0001$), and use of midazolam differed between services ($P < .0001$). In the multivariable model, operative time was also associated with an increase in length of stay (15-minute increase in length of stay per 10 minutes' operative time, 95% CI = 14-17, $P < .0001$) and there was a significant difference in length of stay between services ($P < .0001$). The differences between services, and the increased use of midazolam and longer length of stay among patients with longer surgeries is likely the reason for seeing an association between midazolam use and increased length of stay on univariate analysis. When including intraoperative opioid use and prophylactic antiemetic use in our model as a sensitivity analysis, results were similar, with an 8.1 minute shorter length of stay in the midazolam group (95% CI = –20 - 4.2, $P = .2$).

We then investigated whether the effect of midazolam differed by patient age. We found no evidence that the effect of midazolam on either use of postoperative PONV rescue medications ($P = .6$) or length of stay ($P = .2$) differed by age.

Discussion

Our multivariable analysis controlling for Apfel score, surgical service, age, length of surgery, and type of anesthesia demonstrated that midazolam was associated with a significantly reduced need for rescue antiemetic medications in the PACU. The administration of midazolam produced no clinically significant effect on the length of PACU stay in this large cohort of outpatients. Because both PONV and length of stay are top clinical concerns in outpatient surgeries, our results are important in reducing anesthesia providers' perceptions that midazolam results in longer PACU stays in outpatients.

This retrospective analysis of ambulatory cancer-related surgical patients suggests the important role that intraoperative administration of midazolam may play toward decreasing PONV rates. Most patients included in this retrospective analysis underwent breast and plastic reconstructive surgeries, which are surgeries that disproportionately represent women, who are at higher risk of PONV.[3]

These findings are consistent with the conclusions of a meta-analysis regarding the effects of midazolam on PONV rates.[4,5] The meta-analysis of 12 randomized controlled trials (N = 841) concluded the administration of preoperative or intraoperative intravenous midazolam is associated with a decrease in overall nausea, vomiting, and rescue antiemetic use.[4] Another meta-analysis reported a reduction in the incidence of PONV in the early, late, and overall recovery period.[5] The results indicated that midazolam treatment can prevent nausea and vomiting in approximately 1 in 3 patients who would otherwise experience PONV if given a placebo.[5] However, both studies pooled their results from a profoundly heterogeneous surgical population.

Our results are consistent with those of small studies included in the meta-analysis that examined the impact of midazolam on PONV in ambulatory surgeries.[4,5] One study (N = 70) reported a significantly lower incidence of antiemetic rescue medication administration in the midazolam group vs placebo in endoscopic outpatient procedures using general anesthesia.[10] Our study expanded on these results because our cohort was composed of 51% MAC cases. Furthermore, an additional study (N = 88) reported a decreased frequency of postoperative nausea and increased patient satisfaction compared with a placebo in a prospective study of patients undergoing a variety of ambulatory surgeries.[11] This study also included only a small number of patients undergoing a variety of procedures, which makes drawing conclusions about the broader population difficult. Our study results are consistent with a retrospective analysis of women undergoing breast surgery that reported significantly higher PONV rates in outpatients with breast cancer who did not receive midazolam.[9] In this small study, only 48 of the 196 patients underwent outpatient procedures. A crucial consideration in all outpatient procedures is the length of postoperative stay, and none of these studies addressed the impact of midazolam on this important variable.

The major limitation of the current study is using rescue antiemetic administration as a surrogate for PONV. Although this measure is consistent with the current literature in capturing the rates of PONV, the actual incidence may be higher. Furthermore, although the study examined the most common type of outpatient cancer surgeries, it did not include all types of outpatient cancer surgeries. The study also included a higher number of female than male patients, making it difficult to generalize

the results to male patients. Receipt of chemotherapy was not available for inclusion as a covariate. However, receipt of chemotherapy at the time of surgery was rare, because chemotherapy in this cohort is typically given before or after surgery, and likely did not affect our results.

The retrospective study collected data over the period of 15 months, which should address most of the issues of natural fluctuations related to seasonal or diurnal variation but may not have addressed all possible variables. Because of the selection bias possible in a retrospective design, we cannot exclude the possibility of important differences in confounders influencing the relationship between midazolam and outcomes even after multivariable adjustment. However, these findings can be used to motivate a randomized clinical trial to study the effect of midazolam without the influence of selection bias.

Conclusion

Our study focused on a large outpatient cancer surgical center where the use of midazolam is high because of the anxiety associated with these procedures. In addition to midazolam treating preoperative anxiety in a highly anxious patient population, we have observed potential secondary benefits in reducing the need for postoperative rescue antiemetics when controlling for Apfel score, surgical service, age, length of surgery, and type of anesthesia. Additionally, we demonstrated no significant increase in time to discharge after adjusting for these factors. In patients for whom midazolam is not otherwise indicated to treat anxiety, evidence is insufficient to warrant midazolam administration solely to prevent PONV. Randomized trials are needed to provide a more accurate estimation of the effect size of midazolam. Our findings have important clinical implications because both postoperative nausea and vomiting and length of stay are top concerns in outpatient surgeries.

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