Postoperative Nausea and Vomiting after Inpatient and Outpatient Breast Surgery: Incidence and Effects of Midazolam

S. Wilson, H. Meyer, and K. Fecho

Abstract

Aims: Determine the incidence and identify risk factors for postoperative nausea and vomiting (PONV) after inpatient and outpatient breast surgery.

Methods: Retrospective cohort study of 196 females undergoing mastectomy in Chapel Hill, North Carolina, USA. Anesthesia and PACU records were data sources. Data were analyzed using Chi Square, Fisher Exact Test and ANOVA.

Results: Incidence of severe PONV was 31.1% and was similar for inpatients and outpatients, Rates of PONV were higher for those who did not receive prophylactic antiemetic treatment (62.5%) than for those who did (29.8%), although this difference was not significant due to the small number of subjects who did not receive prophylactic antiemetics. Outpatients who experienced PONV also used greater amounts of opioids in the PACU. Rates of PONV were higher in outpatients not premedicated with midazolam.

Conclusions: 31.1% incidence of PONV after breast surgery. The anxiolytic midazolam may have beneficial antiemetic properties in ambulatory breast surgery patients.

Keywords: mastectomy, breast surgery, postoperative nausea and vomiting, PONV, midazolam, antiemetic.

Authors' addresses: Department of Anesthesiology, University of North Carolina Hospitals, Chapel Hill, NC

Corresponding author: Karamarie Fecho PhD, Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7010, 919-966-1470 *Tel:* 919-966-4873 *Fax:* kfecho@aims.unc.edu

Introduction

Postoperative nausea and vomiting (PONV) occurs in 20–30% of surgical patients in the general population and in up to 70% of high risk patients within the first 24 hours after surgery [1–4].

This common anesthetic side-effect has been reported to increase patient dissatisfaction [5] and can be more distressing to patients than postoperative pain [6–7]. The strongest predictive factors for PONV are female sex, non-smoking status, a history of PONV or motion sickness and intraand postoperative use of opioids [4,8]. Of these factors, female gender is the greatest risk factor [6,9–11].

Notably, the breast surgery population, which is almost completely female, is at increased risk of PONV, with a reported incidence of up to 68% within the first 24 hours after surgery [9,12–15]. Because ambulatory breast surgery operations are becoming more common, severe PONV is potentially dangerous and costly, as PONV remains one of the few causes of unanticipated admission and patient dissatisfaction [5,7,16]. A few studies have suggested that the anxiolytic midazolam also is effective as a prophylactic treatment for PONV [17–21], but none of these studies focused on the high risk breast surgery population. The primary aim of this study was to determine the incidence of severe PONV in breast surgery patients, a high risk population, and to determine whether rates of PONV differ for inpatients versus outpatients, and for patients receiving different types of intraoperative prophylactic antiemetic therapy. A secondary aim was to examine potential risk or protective factors, particularly the use of midazolam premedication for anxiolysis. The PACU period was the focus of this study, in order to examine both inpatients and outpatients.

Methods

This study was approved by the University of North Carolina Institutional Review Board (05–2262). A retrospective observational cohort design was employed. Data were collected for 196 subjects receiving general anesthesia for breast surgery (57 partial mastectomy patients, 78 complete mastectomy patients and 61 complete mastectomy patients with immediate reconstruction) in a two year period. Subjects were drawn from an original simple random sample of 100 subjects from each surgical group who had breast surgery during the sampling period. Subjects who did not have complete medical records (N = 104) were excluded from the study, which reduced the total number of subjects to 196. Data on the same cohort's acute and persistent postoperative pain was reported previously [22]. The data sources were paper anesthesia records and Post Anesthesia Care Unit (PACU) records.

The primary variable was whether or not (yes or no) a subject experienced severe PONV in the PACU. The presence of PONV was determined by documentation of severe nausea or emesis by the PACU nurse and verified by the administration of rescue antiemetic treatment. A variety of risk or protective factors for PONV were examined, including demographic data (age, ASA status, history of smoking), surgical procedure (partial mastectomy, complete mastectomy, immediate reconstruction after complete mastectomy), inpatient/outpatient status, length of surgery (measured as total time under anesthesia care), intraoperative fluid intake (total ml), opioids (drug, dose and route) administered intra- and postoperatively, intraoperative prophylactic antiemetic treatment (drug(s), total dose) and premedication with the anxiolytic midazolam (yes or no, total dose).

The resulting dataset was nearly complete (<0.01% missing data points). Data were graphed using SigmaPlot (SPSS Inc., Chicago, IL)

and statistical analysis was performed using SPSS (version 15.0; SPSS Inc.). Data were expressed as counts (with corresponding percentage) or means (with standard error of the mean (SEM)). The cumulative incidence of PONV was calculated for the whole cohort and for stratified subsets. Characteristics of subjects with and without PONV were compared using Chi Square or Fisher's Exact Test for categorical variables and Analysis of Variance (ANOVA) for continuous variables, with α=0.05. Relative risks (odds ratios) and 95% Confidence Intervals (CI) also were calculated.

Results

The overall incidence of severe PONV in our breast surgery cohort was 31.1%. Breast surgeries were conducted on an outpatient basis for 77.2% of partial mastectomies, but only 1.3% of complete mastectomies and 4.9% of complete mastectomies with immediate reconstruction ($p<0.0005$). Rates of PONV were similar for inpatients and outpatients (30.4% vs. 33.3%; N.S.). Nearly all subjects (95.9%) received intraoperative prophylactic antiemetics. Rates of PONV were higher for those who did not receive prophylactic antiemetic treatment (62.5%) than for those who did (29.8%), although this difference was not significant due to the small number of subjects who did not receive prophylactic antiemetics. Three main types of prophylactic antiemetic therapy were used: ondansetron as a monotherapy (29.6% of total subjects); ondansetron with dexamethasone (33.2%); and ondansetron with dexamethasone and droperidol (24.5%). The mean $\pm$ SEM dose of prophylactic antiemetic was 4.05 $\pm$ 0.04 mg for ondansetron, 8.94 $\pm$ 0.20 mg for dexamethasone and 0.65 $\pm$ 0.02 mg for droperidol. Rates of PONV did not vary by type of prophylactic antiemetic therapy.

Characteristics of subjects with and without PONV were compared as a first step to identify potential risk or protective factors for PONV (Tables 1&2). Inpatients and outpatients were evaluated separately since their intraoperative and postoperative care varied greatly. Age, race, ASA status, smoking history, the use of nitrous oxide, fluid intake, length of surgery (measured as total time under anesthesia care) and intraoperative opioid use were not significantly different amongst subjects who did and did not experience PONV, for both inpatients and outpatients. However, for outpatients, subjects who experienced PONV were less likely to have received premedication with the anxiolytic midazolam ($p<0.05$; Figure 1). The same result was not found for inpatients (Figure 1). Outpatients who experienced PONV also used greater amounts of opioids in the PACU ($p<0.01$). PACU opioid use was similar for outpatients who did or did not receive midazolam premedication (12.26+1.00 versus 9.85+1.60, N.S.). When relative risks were calculated, outpatient subjects who did not receive midazolam premedication were found to have a 6.82-fold (95% CI: 1.15-40.41) increased risk of PONV relative to outpatient subjects who did receive midazolam premedication. The average dose of midazolam was 2.16 $\pm$ 0.06 mg.

Discussion

The emetic center is located in the lateral reticular formation of the medulla oblongata of the mid-brainstem in the central nervous system. Located at the level of the dorsal motor nucleus of the vagus nerve, it is proximal to the nucleus tractus solitarius and area postrema. The area postrema contains the chemoreceptor trigger zone (CTZ), a well vascularized area where the blood brain barrier is not as effective. Together, the CTZ, nucleus tractus solitarius and area postrema serve as sensors relaying impulses to the vomiting center. These impulses are controlled by the stimulation of multiple neuroreceptors including acetylcholine (muscarinic receptor), dopamine (D2 receptor), histamine, opioids and serotonin. Consequently, blockade of these receptors is the primary target of direct antiemetic medications [1,3,23–24]. In our cohort, nearly all subjects received prophylactic antiemetic therapy using the direct acting antiemetics ondansetron, a serotonin antagonist, alone or in combination with droperidol, a dopaminergic antagonist, or dexamethasone, a steroid and indirect acting antiemetic.

The incidence of PONV was 31.1% in our cohort. Age, race, history of smoking, ASA PS score, type or length of surgical procedure, intraoperative morphine equivalents, intraoperative nitrous oxide use and intraoperative intravenous fluid intake were not different among inpatient or outpatient subjects who did or did not experience PONV. Although tobacco abuse has been shown to significantly decrease the rate of PONV [4, 8], a decrease in PONV rates was not observed in our cohort among subjects with a history of tobacco abuse. The failure to find a difference likely relates to the fact that we were unable to distinguish retrospectively subject's with active tobacco use at the time of surgery from those subjects who had a history, recent or distant, of using but no longer actively using tobacco. There were relatively few smokers in either group.

Opioid use is a known risk factor for PONV [4, 8]. Inpatient and outpatient subjects with and without PONV received similar amounts of intraoperative opioids, expressed as morphine equivalents. However, postoperative opioid use was higher among outpatient (but not inpatient) subjects who experienced PONV. The fact that we did not observe an association between increased intraoperative opioid use and increased PONV likely relates to the fact that all subjects were similarly exposed to opioids intraoperatively, a high risk factor. The study population also was at high risk for PONV due to its composition as females undergoing a surgery associated with high rates of PONV [9,12–15]. Other studies have shown an increase in the incidence of PONV with an increase in the number of high risk factors [14], but this effect may be masked in a population as relatively homogenous as the one studied here.

The current study did not find a difference in rates of PONV among subjects receiving ondansetron monotherapy, ondansetron plus dexamethasone, or ondansetron plus dexamethasone plus droperidol. These results contrast with those of Apfel et al. [4], who conducted a multicenter, randomized, controlled, factorial trial to evaluate the effectiveness of ondansetron, dexamethasone and droperidol, alone and in combination. Their results demonstrated that ondansetron, droperidol and dexamethasone used as monotherapies reduced the incidence of PONV by 24-26% in high risk patients after general anesthesia. In addition, the incidence of PONV was further reduced by multimodal therapy from a 52% risk (no prophylaxis) to 37%, 28% and 22% with the use of one, two and three antiemetics, respectively, and it did not matter which combination of antiemetics were used. Our results are not in agreement with those of Apfel et al. [4]. This may be due to the retrospective design of our study and the limited postoperative time frame. A difference might have been observed if subjects were randomized subjects to treatment groups with standardized dosing and PONV also evaluated at later time points.

The present study showed that the incidence of PONV was higher when the anxiolytic midazolam was not used, but only among outpatients. Outpatient breast surgery patients who did not receive midazolam premedication were at a 7-fold increased risk of PONV compared to those who did receive midazolam. The effect of midazolam appears to be unrelated to the effect of postoperative opioids observed in outpatients, as subjects with and without midazolam premedication received similar amounts of opioids. Other studies have suggested that midazolam might be effective in PONV prevention without delayed emergence, prolonged PACU stays or

Table 1 Demographic, Clinical and Surgical Characteristics of Inpatient Breast Surgery Patients.

	Total (N=148)	No PONV (N=103)	PONV (N=45)	p value[2]
Type of Surgery				
Partial Mastectomy	13 (8.8%)	9 (8.7%)	4 (8.9%)	N.S.
Complete Mastectomy	77 (52.0%)	49 (47.6%)	28 (62.2%)	
Immediate Reconstruction after Complete Mastectomy	58 (39.2%)	45 (43.7%)	13 (28.9%)	
Demographic and Clinical Characteristics				
Age (mean + SEM years)	52.2±1.1	52.4±1.4	51.8±2.0	N.S.
Female	148 (100.0%)	103 (100.0%)	45 (100.0%)	N.S.
Non-Hispanic White Race	103 (69.6%)	70 (68.0%)	33 (75.0%)	N.S.
History of Smoking	33 (22.3%)	23 (22.3%)	10 (22.2%)	N.S.
ASA PS				
1	5 (3.4%)	3 (2.9%)	2 (4.4%)	N.S.
2	97 (65.5%)	71 (68.9%)	26 (57.8%)	
3	45 (30.4%)	28 (27.2%)	17 (37.8%)	
4	1 (0.7%)	1 (1.0%)	0 (0.0%)	
Prophylactic Antiemetics				
Ondansetron Monotherapy	36 (24.3%)	24 (26.7%)	12 (32.4%)	N.S.
Ondansetron + Dexamethasone	53 (35.8%)	40 (44.4%)	13 (35.1%)	
Ondansetron + Dexamethasone + Droperidol	38 (25.7%)	26 (28.9%)	12 (32.4%)	
Preoperative Data				
Midazolam Premedication	133 (90.0%)	94 (91.3%)	39 (86.7%)	N.S.
Intraoperative Data				
Nitrous Oxide	43 (29.1%)	32 (31.1%)	11 (24.4%)	N.S.
Fluid Intake (mean + SEM ml)	2919.6±143.7	3025.2±181.4	2677.8±224.7	N.S.
Total Time Under Anesthesia Care (mean + SEM min)	315.6±13.8	323.9±17.8	298.2±21.1	N.S.
Opioid Use				
Intraoperative Morphine Equivalents (mean±SEM mg)	39.1±2.2	39.9±2.7	37.4±3.8	N.S.
PACU Morphine Equivalents (mean±SEM mg)	13.8±1.1	14.3±1.5	12.6±1.3	N.S.

1 The table provides demographical information, clinical characteristics and surgical data for patients that underwent breast surgery between 1/1/2003 and 12/31/2005. For categorical variables, the table lists frequencies and percents. For continuous variables, the table lists means ± SEM.

2 Significance levels are derived from Chi Square or Fisher Exact Test for categorical variables or ANOVA for continuous variables. "N.S." means not significant.

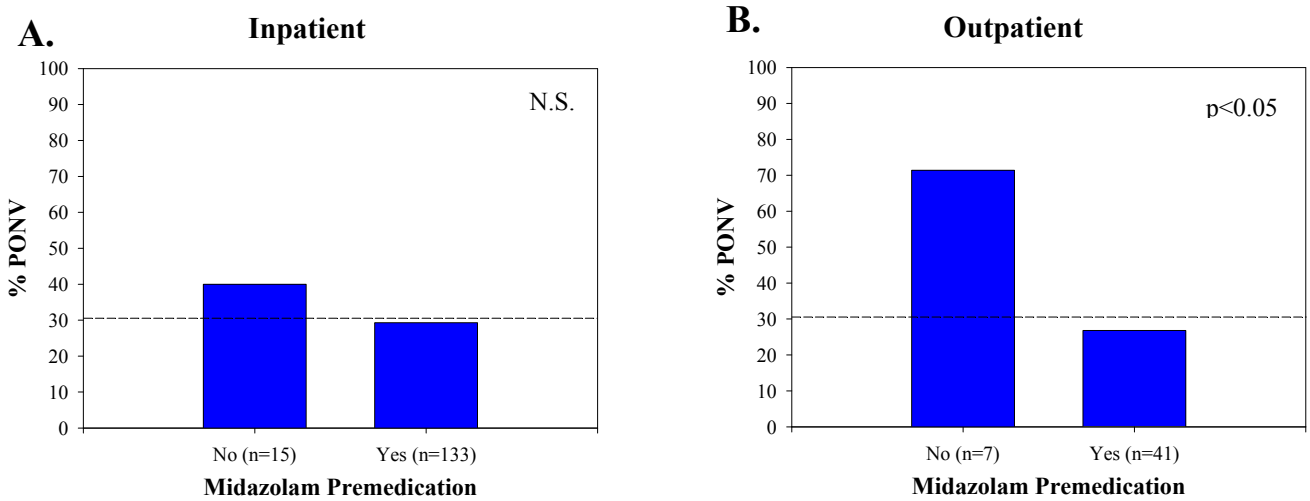

Figure 1 Rates of PONV with and without midazolam premedication for inpatients and outpatients.

The incidence of PONV is higher in subjects who did not receive midazolam premedication. The incidence of PONV for the cohort of breast surgery patients in the PACU (% ± 95% CI) is indicated on the yaxis. Whether subjects did or did not receive midazolam premedication is indicated on the x-axis. Data are shown for both inpatients (panel A) and outpatients (panel B). The dashed line marks the overall incidence of PONV in the entire cohort.

Table 2 Demographic, Clinical and Surgical Characteristics of Outpatient Breast Surgery Patients.

	Total (N=48)	No PONV (N=32)	PONV (N=16)	p value[2]
Type of Surgery				
Partial Mastectomy	44 (91.7%)	29 (90.6%)	15 (93.8%)	N.S.
Complete Mastectomy	1 (2.1%)	0 (0.0%)	1 (6.2%)	
Immediate Reconstruction after Complete Mastectomy	3 (6.3%)	3 (9.4%)	0 (0.0%)	
Demographic and Clinical Characteristics				
Age (mean + SEM years)	58.1±2.2	56.8±2.8	60.6±3.4	N.S.
Female	48 (100.0%)	32 (100.0%)	16 (100.0%)	N.S.
Non-Hispanic White Race	36 (75.0%)	27 (84.4%)	9 (56.2%)	N.S.
History of Smoking	7 (14.6%)	7 (21.9%)	0 (0.0%)	N.S.
ASA PS				
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	N.S.
2	32 (66.7%)	24 (75.0%)	8 (50.0%)	
3	16 (33.3%)	8 (25.0%)	8 (50.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Prophylactic Antiemetics				
Ondansetron Monotherapy	22 (45.8%)	15 (50.0%)	7 (50.0%)	N.S.
Ondansetron + Dexamethasone	12 (25.0%)	7 (23.3%)	5 (35.7%)	
Ondansetron + Dexamethasone + Droperidol	10 (20.8%)	8 (26.7%)	2 (14.3%)	
Preoperative Data				
Midazolam Premedication	41 (85.4%)	30 (93.8%)	11 (68.8%)	p<0.05
Intraoperative Data				
Nitrous Oxide	14 (29.2%)	9 (28.1%)	5 (31.2%)	N.S.
Fluid Intake (mean + SEM ml)	1449.0±154.3	1492.2±218.8	1362.5±158.0	N.S.
Total Time Under Anesthesia Care (mean + SEM min)	161.4±13.1	159.6±19.0	164.6±14.3	N.S.
Opioid Use				
Intraoperative Morphine Equivalents (mean±SEM mg)	20.1±1.5	19.7±1.8	21.0±3.0	N.S.
PACU Morphine Equivalents (mean±SEM mg)	6.6±0.91	4.9±0.9	9.9±1.9	p<0.01

1 The table provides demographical information, clinical characteristics and surgical data for patients that underwent breast surgery between 1/1/2003 and 12/31/2005. For categorical variables, the table lists frequencies and percents. For continuous variables, the table lists means ± SEM.

2 Significance levels are derived from Chi Square or Fisher's Exact Test for categorical variables or ANOVA for continuous variables. "N.S." means not significant.

adverse effects. In a study on 88 patients, preoperative midazolam (0.04 mg/kg) administration was shown to significantly decrease postoperative nausea compared with placebo in patients followed for 24 hours after intra-abdominal or peripheral outpatient surgery [18]. The prophylactic administration of midazolam has also been reported to reduce vomiting in children after tonsillectomy and strabismus surgery [17]. In another study on 88 adults undergoing cholecystectomy, both nausea and vomiting were significantly reduced and significantly fewer post-operative antiemetics were administered in the preoperative midazolam versus placebo group [19]. Jung et al. [20] administered midazolam after induction of anesthesia in 90 female patients undergoing general anesthesia for middle ear surgery and reported an incidence of PONV of 33.3% compared to an incidence of 60% with placebo. Lee et al. [21] found that midazolam was equally effective as ondansetron when administered 30 minutes prior to the end of urologic or gynecologic surgery. In our study, nearly all subjects received some prophylactic antiemetic treatment and the effect of midazolam was only observed when ondansetron alone was used prophylactically. In that case, the addition of midazolam premedication reduced rates of PONV to those observed with the combination therapies.

While the sedative-hypnotic effects of midazolam, a short-acting benzodiazepine, are well understood, the antiemetic properties continue to be investigated. It is hypothesized that dopamine input at the CTZ and adenosine re-uptake are inhibited by midazolam, resulting in an adenosine-mediated decrease in dopamine release, production and postsynaptic action in the CTZ [25]. Midazolam may also inhibit serotonin release and dopaminergic neuronal activity by binding to the gamma-aminobutyric acid (GABA) receptor [26]. Furthermore, the anxiolytic properties of midazolam have been suggested to contribute to its effects on PONV, apart from any direct antiemetic actions. However, anxiety has not been shown to reduce gastric pH, increase gastric volume or slow the rate of gastric emptying [27–8]. In addition, when other causes of PONV are taken into account, anxiety has only a weak association with PONV [29]. Although the mechanism of midazolam's antiemetic effects is unclear, our findings and those of others support midazolam's use as an effective part of prophylactic antiemetic therapy in some circumstances. Therefore, it is surprising that midazolam is not mentioned in the Society for Ambulatory Anesthesia's guidelines for the management of PONV [30].

Our study was limited by its retrospective nature and therefore our data are subject to both bias and confounding. Although the data were nearly complete, we cannot verify the accuracy of the data since all data were abstracted from medical records. PONV was assessed only in the PACU period and therefore the current findings may not generalize to later time periods. In addition, data were analyzed from a relatively small sample of subjects who did not receive midazolam, and a larger sample size and prospective design is required to validate our findings.

Conclusions

Approximately 60% of all operations in the United States annually occur in the ambulatory setting [31]. Surgery remains the primary treatment for over 213,000 women diagnosed annually with breast cancer, and most of these surgeries are conducted on an outpatient basis [32]. These women are at high risk for PONV as a result of their gender and surgical procedure, and PONV remains one of the few causes of unanticipated admission and patient dissatisfaction [5,7,16]. Our study examined the incidence of PONV in breast cancer patients receiving general anesthesia for mastectomy. Rates of PONV were similar among inpatient and outpatient subjects. Rates of PONV were higher among outpatient subjects who used greater amounts of opioids in the PACU and interestingly, who were not premedicated with midazolam. The anxiolytic midazolam may have beneficial antiemetic properties in ambulatory breast surgery patients.

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