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ORIGINAL CONTRIBUTIONS

The Role of Aprepitant in Prevention of Postoperative Nausea and Vomiting After Bariatric Surgery

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Abstract

Background Postoperative nausea and vomiting (PONV) is common with bariatric surgery. We examined the PONV rate in bariatric surgical patients who received triple antiemetic prophylaxis (dexamethasone, droperidol, and ondansetron) with and without antiemetic aprepitant.

Methods Medical records of female patients undergoing laparoscopic bariatric surgery from January 1, 2014, to July 28, 2016, were reviewed for PONV episodes during 48 postoperative hours.

Results In total, 338 patients received triple antiemetic, of whom 172 (51%) also received aprepitant. Rates of PONV in the postanesthesia care unit (PACU) among patients with and without aprepitant therapy were 11 vs 17% (P = .09). Within 1 h after PACU discharge, fewer patients in the aprepitant group had PONV (19 vs 31%; odds ratio [OR] [95% CI], 0.5 [0.30–0.80]; P = .007). During the first 48 postoperative hours, PONV rates were similar between the groups (68 and 66%; P = .73), but fewer emesis episodes occurred in the aprepitant group (6 vs 13%; OR [95% CI], 0.45 [0.21–0.95]; P = .04). Analyses were also performed with a subset of patients matched on propensity for receiving aprepitant. In this subset, OR estimates quantifying aprepitant effect on PONV were similar to those obtained from multivariable regression analyses.

Conclusion Addition of aprepitant to a multimodal antiemetic prophylactic regimen may be associated with significant reduction of PONV during early recovery and potentially with reduced incidence of vomiting during the first 48 postoperative hours. The high PONV rate in the first 48 postoperative hours is suggestive that introduction of scheduled anti-PONV prophylactic treatment may be desirable.

Keywords Aprepitant · Bariatric surgery · Postoperative nausea and vomiting

Abbreviations

CI	Confidence interval
NK-1	Neurokinin-1
OR	Odds ratio
OSA	Obstructive sleep apnea
PACU	Postanesthesia care unit
PONV	Postoperative nausea and vomiting
SD	Standard deviation

Introduction

Postoperative nausea and vomiting (PONV) is common after laparoscopic bariatric surgery [1, 2]. Some characteristics of the surgical patients—female sex, nonsmoker status, and use of opioid medications—pose a cumulative risk of high PONV rates [3, 4]. PONV has adverse implications, such as intolerance to oral intake, dehydration, electrolyte imbalance, acute kidney injury [5, 6], pulmonary aspiration, and decreased patient satisfaction [7].

Because of multiple risk factors among patients with laparoscopic bariatric surgery, antiemetic prophylaxis is advocated with multimodal agents rather than a single medication [7, 8].

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Our standard bariatric PONV prophylaxis includes a triple antiemetic regimen: droperidol, dexamethasone, and ondansetron. Despite this prophylaxis, the PONV rate continues to be increased for these patients, and we have demonstrated that PONV was the primary cause for delayed postanesthesia discharge [1]. In our practice, these observations have led to the adoption of more aggressive PONV prophylaxis with preoperatively applied transdermal scopolamine patch, intraoperative use of propofol infusion, and more recently, use of the neurokinin-1 (NK-1) inhibitor aprepitant. An NK-1 receptor antagonist, aprepitant, blocks substance P activity in centers of the brain and in viscera associated with nausea and vomiting [9]. It is commonly used for prophylaxis against nausea from chemotherapy [10]. Aprepitant is a superior agent for PONV prophylaxis compared with ondansetron used as a single agent [11]. Since, opioid-induced nausea and vomiting is mediated through up-regulation of NK-1 receptors in cortical neurons, it seems reasonable to consider aprepitant as a useful agent for treatment of PONV due to opioids [12]. Aprepitant has been used successfully in multimodal PONV prophylaxis [13] and has been shown to be effective for patients receiving intravenous patient-controlled analgesia with fentanyl [14].

The aim of this study was to test the hypothesis that addition of a single preoperative dose of aprepitant to a multimodal prophylactic regimen is associated with additional reduction of PONV among female patients undergoing laparoscopic bariatric surgery.

Methods

This study was approved by the institutional review board on May 5, 2015. Consistent with state statute, the study included only patients who had provided authorization for research use of their health records.

Study Design

This study was a retrospective chart review of postoperative PONV rate among female patients who underwent laparoscopic bariatric surgery. PONV was defined as use of rescue antiemetics or notation of nausea, vomiting, or retching (*severe PONV*) during phase I postanesthesia recovery in the postanesthesia care unit (PACU) at 1 h after discharge from the recovery room (*PACU + 1 h*). This approach accounted for the emetogenic effect of patient transport to the ward also during the first 24 (*PACU + 24 h*) and 48 h (*PACU + 48 h*) following discharge from the PACU. When health records did not contain notation of PONV or when documentation of PONV treatment was missing, we considered the patient PONV-free.

Study Participants

The present study included consecutive adult female patients from January 1, 2014, to July 28, 2016, who underwent laparoscopic bariatric weight loss surgery, received triple antiemetic therapy, were transferred from the operating room to the PACU, and had provided research authorization for use of their health records. As previously described [1], these health records were reviewed for clinical, anesthetic, and postanesthesia variables. We excluded from review all patients who had revision surgery or had the same type of surgery but for reasons other than weight loss. Finally, we included patients with failed laparoscopic banding who were referred for a major bariatric surgery.

Preoperative Treatment

All patients enrolled in the bariatric surgical program are initially evaluated by an endocrinologist. All obesity-associated comorbidities, such as hypertension and diabetes mellitus, are treated as indicated. In addition, special attention is directed toward detection of obstructive sleep apnea (OSA), and depending on indications, a pulmonologist conducts evaluation and orders either overnight pulse oximetry or polysomnography. All patients who have no indication for formal OSA evaluation are screened for OSA the day of surgery using Flemons criteria [15]. If needed, patients have psychological or psychiatric evaluation, or both, and if smokers, receive a smoking cessation program.

Preoperative Medications

Standard preoperative order consists of 1000 mg acetaminophen orally. Recognition that the bariatric surgical population is at high risk for PONV prompted 1 surgeon to start prescribing a single oral 40-mg dose of aprepitant, a change in practice that motivated the present study. Of note, as standard practice, all female patients are counseled to use two forms of birth control, including a barrier or spermicidal method, for the first six postoperative months, which makes interaction between aprepitant and hormonal contraceptives moot.

Anesthetic Management

All bariatric operations are performed with general endotracheal anesthesia. Anesthetic maintenance most commonly includes use of desflurane; nitrous oxide is not used. Because bariatric surgical patients have a high risk of PONV (due to the typical characteristics of age < 50 years, female sex, nonsmoker, and postoperative opioid analgesics administration) [1, 4, 16], use of triple antiemetic prophylaxis (i.e. 0.625 mg droperidol, 4 mg dexamethasone, and 4 mg ondansetron) is strongly encouraged [3, 17]. At the discretion of the

supervising anesthesiologist, a scopolamine patch or propofol infusions, or both, are also used for high-risk patients. Rocuronium and vecuronium are the standard neuromuscular blocking drugs, and their effects are universally reversed with neostigmine and glycopyrrolate at the end of the operation. Standard intraoperative opioid management includes fentanyl and hydromorphone. At the end of the procedure, 15 mg ketorolac is administered and port sites are infiltrated with 0.25% bupivacaine.

PACU Management

Registered nurses who have received training in phase I recovery make up the PACU staff, together with a first- or second-year anesthesia resident. The attending anesthesiologist is accessible for any medical issue that requires advanced expertise. Discharge criteria for phase I anesthesia recovery have been described previously [1], but germane to this report is a goal PONV level of mild to none.

Nausea Management

An episode of PONV was identified when a patient required rescue antiemetic therapy or when documentation in the nursing records cited nausea or vomiting. Rescue therapy was administered for patients who had nausea or vomiting, with ondansetron as the first-line agent. For recalcitrant cases, dexamethasone, droperidol, promethazine, or metoclopramide was administered under the guidance of the attending anesthesiologist (during PACU stay) or the surgeon (remainder of hospitalization).

Data Abstraction

The electronic health records of study patients were reviewed for demographic information, American Society of Anesthesiologists physical status score, body mass index, smoking status (current smoker), surgical duration, type of bariatric procedure, and perioperative medications, including antiemetic use and opioid dose. Intraoperative opioid administration was converted to intravenous morphine equivalents. The postoperative records were reviewed for occurrence of PONV or emesis, or both.

Statistical Analysis

Data are summarized as mean and standard deviation (SD) for continuous variables and as frequency count and percentage for categorical variables. Baseline characteristics were compared between the patient group that received aprepitant and the patient group that did not have it. Two-sample *t* test analyzed continuous variables, and Fisher exact test analyzed categorical variables. The frequencies of PONV at PACU, PACU + 1 h, PACU + 24 h, and PACU + 48 h and of emesis at any time during the first 48 postoperative hours were analyzed with logistic regression. A propensity-matched analysis was also performed because many baseline patient characteristics differed significantly between the patient group that received aprepitant and the group that did not. To calculate propensity scores, a logistic regression model was fit with aprepitant use as the dependent variable. Patients who received aprepitant were matched 1 to 1 with patients who did not receive it, on the basis of logit of the propensity score (±0.2 SDs). Balance between propensity-matched groups was assessed by calculating standardized differences. For the propensity-matched sets, PONV and emesis outcomes were analyzed using generalized estimating equations with robust standard error estimates. For each outcome, findings are summarized by presenting the odds ratio (OR) and corresponding 95% confidence interval (CI) for aprepitant use. Two-sided tests were used, and $P \leq .05$ denoted statistical significance. Analyses were performed with statistical software (SAS version 9.4; SAS Institute Inc.).

Results

Study Cohort

During the study time frame, 338 women underwent laparoscopic bariatric surgery; most (n = 257, 76%) underwent malabsorptive procedures of the 247 laparoscopic gastric bypass and 10 biliopancreatic diversion and duodenal switch procedures. In total, 81 patients (24%) had restrictive procedures (19 gastric banding and 62 sleeve gastrectomy). All patients received intraoperative triple antiemetic regimen, and of these patients, 172 (51%) also received aprepitant. Table 1 compares the characteristics of patients who received aprepitant with patients who did not receive it. A consistent anesthetic management was provided: Desflurane was used in 334 patients (99%) (in aprepitant group, 3 patients had sevoflurane, and in patients who did not receive aprepitant, 1 had isoflurane). All patients received succinylcholine for tracheal intubation followed by vecuronium or rocuronium for muscle relaxation, and all therapies (100%) were reversed with neostigmine (median [interquartile range] dose, 5 mg [5–5]).

Comparison Between Aprepitant and No-Aprepitant Groups

Compared with the patients who did not receive aprepitant, patients who received the agent were younger (P = .049), had longer operations (P = .008), and were more likely to receive preoperative scopolamine patch (P = .047) and intraoperative propofol infusion

Table 1 Demographic and procedure characteristics of patients who underwent laparoscopic bariatric surgery with and without aprepitant

Characteristic	All patients[a] (*N* = 338)			Propensity-matched set[a] (*n* = 236)		
	Received aprepitant			Received aprepitant		
	Yes (*n* = 172)	No (*n* = 166)	*P* value	Yes (*n* = 118)	No (*n* = 118)	Standardized difference
Age, mean (SD), year	45.3 (12.5)	47.9 (12.1)	.049	47.1 (12.5)	47.4 (12.3)	0.02
ASA-PS			.77			0.00
III	167 (97)	160 (96)		114 (97)	114 (97)	
IV	5 (3)	6 (4)		4 (3)	4 (3)	
Current smoker	7 (4)	11 (7)	.34	6 (5)	8 (7)	0.07
BMI, mean (SD)	45.5 (9.3)	44.7 (10.8)	.51	44.5 (10.9)	45.1 (9.1)	0.06
Operation duration, mean (SD), min	170 (84)	149 (60)	.008	154 (67)	150 (52)	0.07
Surgical type			.53			0.04
Malabsorptive[b]	128 (74)	129 (78)		87 (74)	89 (75)	
Restrictive[c]	44 (26)	37 (22)		31 (26)	29 (25)	
Perioperative medications						
Opioid dose, $_{iv}$MEQ	31.7 (14.0)	33.5 (12.7)	.21	32.6 (12.1)	32.4 (13.3)	0.02
Propofol infusion	129 (75)	82 (49)	<.001	71 (60)	79 (67)	0.14
Scopolamine patch	62 (36)	43 (26)	.047	34 (29)	32 (27)	0.04

ASA-PS American Society of Anesthesiologists–Physical Status, *BMI* body mass index, *$_{iv}$MEQ* intravenous morphine equivalents in milligrams

[a] Continuous variables are presented as mean (SD) and compared between groups using two-sample *t* test; nominal variables are presented as number and percentage of patients and compared between groups using Fisher exact test

[b] In total, 247 patients (73%) had laparoscopic gastric bypass; 10 (3%), biliopancreatic diversion or duodenal switch

[c] In total, 19 patients (6%) had banding procedures; 62 (18%), sleeve gastrectomy

(*P* < .001) (Table 1). The PONV rates in the PACU of the aprepitant group and the no-aprepitant group were 11 and 17% (*P* = .09) (Table 2). Within 1 h after PACU discharge, fewer patients in the aprepitant group had PONV (19 vs 31%; OR [95% CI], 0.5 [0.30–0.80]; *P* = .007). However, the first 48 h after PACU discharge showed that the percentage of patients with PONV was similar between the two groups (68 and 66% in aprepitant group and no-aprepitant group; *P* = .73) (Fig. 1). The cumulative episodes of emesis and vomiting through 48 postoperative hours were fewer in the aprepitant group than the no-aprepitant group (6 vs 13%; OR [95% CI], 0.45 [0.21–0.95]; *P* = .04). The Appendix summarizes the number of patients and

Table 2 Postoperative nausea and vomiting in female patients undergoing weight-reduction surgical therapy

Outcome	All patients[a] (*N* = 338)				Propensity-matched set[a] (*n* = 236)			
	Aprepitant, no. (%)				Aprepitant, no. (%)			
	Yes	No	OR (95% CI)	*P* value	Yes	No	OR (95% CI)	*P* value
Nausea								
PACU	19 (11)	29 (17)	0.59 (0.32–1.09)	.09	12 (10)	18 (15)	0.63 (0.29–1.37)	.24
PACU + 1 h	32 (19)	52 (31)	0.50 (0.30–0.83)	.007	20 (17)	37 (31)	0.45 (0.24–0.83)	.01
PACU + 24 h	104 (60)	100 (60)	1.01 (0.65–1.56)	.97	75 (64)	73 (62)	1.08 (0.63–1.82)	.79
PACU + 48 h	117 (68)	110 (66)	1.08 (0.69–1.71)	.73	80 (68)	78 (66)	1.08 (0.63–1.86)	.78
Emesis/vomiting (during 48 h)	11 (6)	22 (13)	0.45 (0.21–0.95)	.04	7 (6)	15 (13)	0.43 (0.17–1.10)	.08

OR odds ratio, *PACU* postoperative care unit

[a] For analysis of all patients, data were analyzed using logistic regression. For analysis using propensity-matched sets, data were analyzed using generalized estimating equations with robust standard error estimates. In all cases, findings are summarized by presenting the OR (95% CI) for aprepitant use. OR less than 1.0 indicates a protective effect of aprepitant for the given outcome

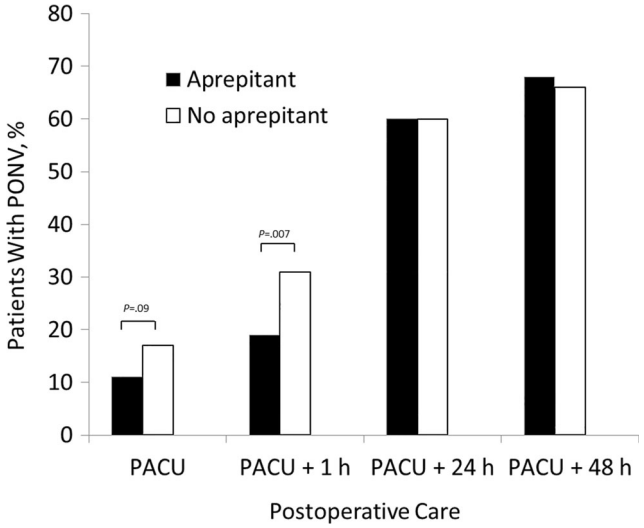

Fig. 1 Postoperative nausea and vomiting of patients who did and did not receive aprepitant in PACU, PACU +1 h, and PACU +24 and +48 h. *PACU* postoperative recovery care unit, *PONV* postoperative nausea and vomiting

types of antiemetics administered at various postoperative times.

Because of imbalance in baseline variables (Appendix Table 3) between patients who did and did not receive aprepitant, an analysis was performed for a subset of patients matched on the propensity for receiving aprepitant. All characteristics listed in Table 1 are included as explanatory variables for propensity matching. From this propensity-matched analysis, OR estimates quantifying the effect of aprepitant on PONV were similar to those obtained from unadjusted analyses.

Discussion

In the present study, we found that addition of a single 40-mg dose of aprepitant to a multimodal antiemetic regimen was associated with reduction of PONV during early recovery (PACU + 1 h) and potentially with reduced incidence of vomiting during the first 48 postoperative hours. The effect of aprepitant in combination with triple antiemetic therapy in attenuating PONV compared with triple antiemetic therapy alone did not persist beyond the initial recovery period, with high cumulative rates of PONV observed at 48 h after PACU discharge.

Several studies have examined the role of aprepitant on PONV reduction—specifically on bariatric, plastic, gynecologic, and neurosurgical procedures [2, 13, 14, 18]. The studies uniformly report that aprepitant was more effective in preventing postoperative vomiting than reducing nausea scores. These observations from single-center studies agree with the results of large, multicenter double-blind trials reporting that selective NK-1 receptor antagonists (aprepitant and rolapitant) were superior to ondansetron for prevention of vomiting in the first 24 and 48 postoperative hours, but no significant differences were observed between aprepitant and ondansetron for nausea control [11, 19]. In the present study, we found immediate postoperative reduction of PONV in patients who received aprepitant and evidence of association with a reduced rate of vomiting during the first 48 postoperative hours.

In our study population, 67% of patients had PONV within 48 postoperative hours. This high incidence of PONV may reflect that the cohort was limited to female and mostly nonsmoking patients (>95%)—two characteristics highly associated with increased PONV risk [20]. A reduction in PONV may be expected with aggressive antiemetic prophylaxis, and indeed, the PONV rate in PACU was 11 and 19% in aprepitant versus no-aprepitant groups, which reflect the protective effect of our intense perioperative antiemetic prophylactic regimen. It further may suggest the presence of a cumulative antinausea effect with increasing number of antiemetic agents used. This rate is lower than our previous bariatric study, where the PONV rate in the PACU was 25% and was the primary reason for delayed PACU discharge [1]. By comparison, however, in the present study where all patients received triple antiemetic prophylaxis, only 42.3% of patients received triple antiemetics [1].

In the present study, the rate of PONV within 1 h after PACU discharge increased to 19% for aprepitant recipients and to even more for patients who did not receive aprepitant (31%). These findings are suggestive of a fading effect of single prophylactic doses of antiemetics that resulted in an increase in PONV during transition from an undisturbed state in the PACU to a more active period associated with patient motion during transport. Subsequently, the effect of the single dose of perioperative antiemetics faded, culminating in 67% of patients reporting PONV by 48 h. This high rate may be explained by the fact that in our practice, antiemetics are administered on an as-needed basis. This high rate suggests the need for practice improvement. For example, these patients may benefit from more intense and structured postoperative antiemetic management.

Limitations

This report has all the limitations inherent in a retrospective study design. Specifically, the definition of the primary end point PONV was determined by the use of rescue medications or notation of its presence in the health records. This approach raises the possibility that a subset of patients may have had untreated PONV, in which case we would underestimate the already high

rate of PONV. The possibility also exists that in anticipation of nausea, some patients may have requested treatment, which would overestimate the true rate. Regardless, our rate indicates the clinical reality in our institution but may lack generalizability to other practices. The severity of nausea was not quantified using the formal nausea verbal rating scale, and therefore, association between aprepitant treatment and severity of PONV cannot be studied. Furthermore, no recommendations are available currently for the adjustment of perioperative aprepitant dose based on body weight in adults, and our institution follows the manufacturer recommended low dose (40 mg) for prevention of PONV [21]. Therefore, whether higher doses may be warranted for morbidly obese patients is unknown. Yet, several studies that used larger aprepitant doses of 80 and 125 mg suggested that higher doses may not necessarily provide better outcomes because of a possible ceiling effect [22]. Finally, our study cannot conclude about the size of the effect of aprepitant as a sole agent, but rather, it suggests that four antiemetics may have a stronger effect on prevention of PONV than three antiemetics.

Conclusions

In this study, we found that the addition of aprepitant to a multimodal antiemetic regimen was associated with a significant reduction of PONV during early recovery and potentially with a reduced incidence of vomiting during the first 48 postoperative hours. Regardless of antiemetic treatment used, a high cumulative rate of PONV was observed in bariatric patients at 48 h after PACU discharge, suggesting that scheduled anti-PONV treatment, rather than rescue therapy, may be a more desirable approach in this patient population.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study. This study was approved by the institutional review board on May 5, 2015. Consistent with state statute, the study included only patients who had provided authorization for research use of their health records.

Appendix

Table 3 Number of patients who received postoperative rescue antiemetics in various time periods after surgery

Timing of administration and type of antiemetic	Patients (N = 338)	
	Aprepitant (n = 172)	No aprepitant (n = 166)
In PACU	19 (11)	29 (17)
Droperidol	19	26
Promethazine	0	2
Granisetron	0	1
First hour after PACU	7 (4)	11 (7)
Droperidol	3	5
Ondansetron	5	6
1–24 h after PACU	78 (45)	61 (37)
Droperidol	20	23
Ondansetron	73	54
Metoclopramide	1	0
Proclorperazine	8	6
Promethazine	4	8
25–48 h after PACU	56 (33)	40 (24)
Droperidol	8	9
Ondansetron	57	39
Proclorperazine	7	3
Promethazine	4	3

PACU postoperative care unit

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