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Research Article

Use of Aprepitant (80 mg) for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Sleeve Gastrectomy

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a complication after surgery, and more significantly after bariatric surgery (up to 79%) leading to increased treatment costs associated with prolonged hospital stays. In a community hospital setting, a standard prophylactic regimen was compared with the addition of aprepitant. **Methods:** A retrospective chart review of PONV among patients who underwent laparoscopic sleeve gastrectomy. Primary outcomes: efficacy of aprepitant 80 mg plus standard prophylaxis on PONV by measuring the number of antiemetics administered postoperatively to a standard prophylactic regimen. **Results:** A total of 354 patients showed that the aprepitant group required significantly fewer doses in four time periods: within 1 hour of post-anesthesia care unit (PACU) admission [74 vs 97 ($p = 0.049$)], 12 hours [192 vs 234 ($p = 0.049$)], 24 hours [293 vs 426 ($p < 0.001$)], and total doses during admission 365 vs 581 ($p < 0.001$). Average length of stay (LOS) was 1.19 days for the aprepitant group and 1.33 days for the control group ($p < 0.001$). **Conclusion:** Aprepitant significantly reduced antiemetic use postoperatively and should be considered in addition to a standard PONV prophylaxis regimen to prevent PONV in patients undergoing laparoscopic sleeve gastrectomy and to potentially reduce LOS.

Keywords: aprepitant, bariatric surgery, laparoscopic sleeve gastrectomy, postoperative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) are major causes of patient displeasure regarding surgery.[1,2] In bariatric surgery, incidence of PONV has been reported as high as 79% of patients.[3,4] PONV is defined as any nausea, gagging, retching, or actual vomiting occurring during the first 24–48 hours after inpatient surgery.[5,6] Risk factors for PONV include being female, young, a nonsmoker, and having a history of motion sickness or PONV. After bariatric surgery in particular, any increase in physical retching/vomiting is unfavorable, as it can lead to delayed or negligent oral intake resulting in dehydration and subsequent electrolyte imbalance and/or acute kidney injury. PONV can also result in pulmonary aspiration and provoke postoperative surgical pain. Altogether these barriers could contribute to an increased length of hospital stay, and reduced patient satisfaction.[5]

The physiology of PONV is complex and can be triggered by several perioperative stimuli, including anesthesia, opioids, anxiety, adverse drug reactions, and movement in general. Physiologically, multiple neurotransmitter pathways are associated with nausea and vomiting. The gastrointestinal tract releases serotonin (5-HT3), and downstream 5-HT3 receptors on the chemoreceptor trigger zone (CRTZ) stimulate the vagus nerve.[5,6] The vestibular system communicates with the nucleus tractus solitarius (NTS) via histamine-1 (H1) and acetylcholine (ACh) receptors, which in turn, connect with the CRTZ via dopamine-2 (D2) receptors.[5,6] In addition, anticipatory or anxiety-induced nausea and vomiting appears to originate in the cerebral cortex, which communicates directly with the NTS via these neuroreceptors.[5,6] This complex pathophysiology has led to the development of antiemetic drugs that target all these receptors, sometimes multiple simultaneously. However, no available antiemetic can reduce the

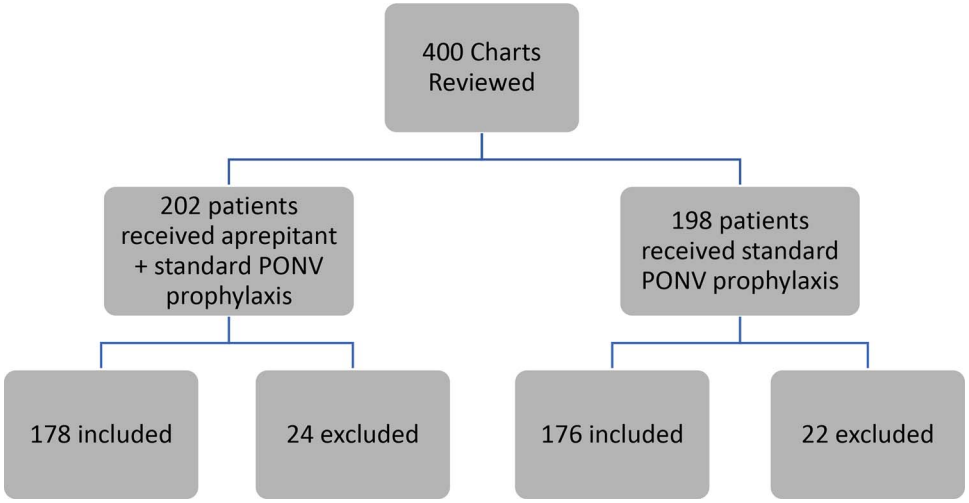

Figure 1. Data abstraction. PONV: postoperative nausea and vomiting.

incidence of PONV to zero. In fact, only 20–30% of patients will respond to any single antiemetic agent.[5,6] Agents including 5-HT3 and D2 receptor antagonists, corticosteroids, phenothiazine, prochlorperazine, antihistamines, and anticholinergics are all used to treat or prevent PONV with varying degrees of success.[7] Effective prophylaxis and treatment of PONV has evolved into a multimodal approach using multiple agents with different mechanisms.[8,9]

Aprepitant is a neurokinin-1 (NK-1) inhibitor that blocks substance P activity in centers of the brain and in viscera associated with nausea and vomiting.[10] According to the United States Food and Drug Administration, aprepitant is indicated for the prevention of nausea and vomiting in adults at 40 mg/day (orally) or 150 mg intravenously (IV) if associated with chemotherapy[10] However, it has not been approved for the treatment of established nausea and vomiting or for PONV using the 80-mg dosage form.

A number of studies have examined the role of aprepitant on PONV reduction, specifically for bariatric, plastic, gynecologic, and neurosurgical procedures.[3,4,11–15] These studies consistently report that aprepitant is more effective in preventing postoperative vomiting than reducing nausea scores.[3,4,11–15] Subsequently, additional studies have specifically studied the efficacy of aprepitant 80 mg on PONV following bariatric surgery. In a study done by Sinha et al.,[12] the time to first vomiting was significantly prolonged in the aprepitant group with no incidence of vomiting during the first 4 hours after emergence from anesthesia. This is significant because the incidence of nausea and vomiting postoperatively usually peaks during the first 4 hours after emergence from anesthesia. In another study by Habib et al.,[13] similar findings were reported. Both authors concluded that aprepitant has a considerably significant potential as a preventive agent for vomiting prophylaxis in morbidly obese patients.[12,13]

Standard antiemetic prophylaxis at our hospital consists of a scopolamine patch placed behind the ear 30 minutes before induction and IV dexamethasone 4 mg and IV ondansetron 4 mg on induction of anesthesia. Despite this regimen, patients undergoing laparoscopic sleeve gastrectomy still experience PONV, prompting the addition of a more aggressive PONV prophylactic agent to the existing regimen: aprepitant. Would the addition of aprepitant 80 mg PO compared with the standard prophylactic regimen be associated with additional reduction of PONV among patients undergoing laparoscopic sleeve gastrectomy? Is there a component of pain control associated with well-controlled PONV? To investigate this, we compared outcomes retrospectively after aprepitant was added to the regimen in January 2016.

METHODS

This retrospective chart review was approved by the institutional review board, and the requirement for informed consent was waived. The standard antiemetic regimen at this hospital consists of a scopolamine patch placed behind the ear at least 30 minutes before induction, dexamethasone 4 mg IV and ondansetron 4 mg IV on induction of anesthesia. Patients received either an 80-mg aprepitant capsule, opened and given in 30 mL of water 30 minutes before anesthesia induction in addition to the standard regimen or just the standard antiemetic regimen alone.

Study Design

This study was a retrospective chart review of PONV rates among patients who underwent laparoscopic sleeve gastrectomy surgery (Fig. 1). PONV was defined as any nausea, vomiting, or retching postoperatively. Emesis was defined as the number of doses of antiemetics used during the postoperative windows on an as-needed basis. These included the following: post-anesthesia care unit (PACU)

Table 1. Demographic information

	Aprepitant (n = 178)	Control (n = 176)
Mean Age (y)	43.8	44.8
Women (%)	74.7	81.4
Mean BMI (kg/m^2)	46.2	44.7
History of Smoking (%)	43.3	40.9
White, n (%)	137 (76.9)	139 (78.9)
Black or African American, n (%)	35 (19.7)	33 (18.8)
Hispanic, n (%)	3 (1.7)	3 (1.7)
Asian, n (%)	2 (1.1)	1 (0.6)
Other, n (%)	1 (0.6)	0 (0.0)
Mean Surgical Duration (h)	2.2	2.2

plus 1 hour (defined as time upon entry to PACU + 1 hour), PACU +12 hours, PACU +24 hours, and any emesis while admitted thereafter. Interventional antiemetics included ondansetron, haloperidol, droperidol, promethazine, prochlorperazine, scopolamine, hyoscyamine, and/or metoclopramide as needed (last line alternative). Patients who underwent laparoscopic sleeve gastrectomy between January 1, 2014 and December 31, 2017, were reviewed. Retrospectively, we compared patients receiving a standard prophylactic regimen before January 2016 with patients receiving the same prophylactic regimen plus aprepitant starting in January 2016. A total of 400 charts were reviewed: 202 in the aprepitant group and 198 in the standard prophylaxis control group. Exclusion criteria included patients with an allergy or intolerance to scopolamine, ondansetron, dexamethasone, and/or aprepitant; women who were pregnant or breast-feeding; patients with a history of substance abuse or significant psychiatric disease; history of chronic nausea/vomiting or motion sickness; or home medications that had a significant interaction with aprepitant, scopolamine, ondansetron, and/or dexamethasone. See Tables 1 and 2. Length of stay (LOS) and pain control were followed as secondary outcomes to see if well-controlled PONV could affect these metrics. Pain control was defined as the total IV morphine equivalent dose (MED) each patient received throughout their admission. Combinations of IV hydromorphone and fentanyl and then PO hydrocodone or oxycodone were converted to MED for comparison. All patients received scheduled acetaminophen and ketorolac postoperatively.

Data Abstraction

The electronic health records of study patients were reviewed for demographic data. Age, gender, body mass index, smoking status, surgical duration, procedure performed, LOS, and opioid medications given were all recorded. Medications used for PONV, and postoperative number of doses of antiemetics used at PACU +1 hour, PACU +12 hours, PACU +24 hours, and of emesis at any time postoperative were recorded. LOS, defined as a whole number in accordance with the postoperative day, was recorded as post-op day 1 = 1, post-op day 2 = 2, and so on.

Table 2. Number of patients excluded.

	Aprepitant (n = 24)	Control (n = 22)
Age < 18 y, > 65 y	1	1
Allergy or intolerance	11	11
Breast feeding or pregnant	0	0
History of substance abuse	1	0
History of chronic nausea and vomiting	10	9
Significant drug interactions	1	1

Table 3. Primary outcome*

	Aprepitant (n = 178)	Control (n = 176)	p value
PACU + 1 h	74	97	0.049
PACU + 12 h	192	234	0.049
PACU + 24 h	293	426	< 0.001
TOTAL	365	581	< 0.001

*Number of doses of antiemetics required within 1 hour of admittance to post-anesthesia care unit (PACU) within 12 hours, 24 hours, and in total.

Statistical Analysis

Student's unpaired t test was used to determine demographic interval data among the groups compared. Pearson's chi-square test was used to compare frequency data, and ordinal data were compared using the Wilcoxon rank sum test. Comparison of nausea scores between the control and placebo groups at various time intervals was calculated using the multivariate analysis of variance test. The 95% confidence interval for the difference in proportions was computed using the normal approximation method.

RESULTS

Primary outcome results are seen in Table 3 and Figure 2. Secondary outcomes are in Table 4. PACU doses of antiemetics were statistically lower (defined as a p value <0.05) in the aprepitant group vs standard prophylaxis control group in all four categories. Within 1 hour of PACU 74 vs 97 ($p = 0.049$), 12 hours 192 vs 234 ($p = 0.049$), 24 hours 293 vs 426 ($p < 0.001$), and total doses during admission 365 vs 581 ($p < 0.001$). Secondary outcome results are seen in Table 4. Average LOS in days for the aprepitant group was 1.19 days and average LOS in the control group was 1.34 days ($p = 0.014$). Most patients were hospitalized for 1 day postoperative but several patients in each group ended up being hospitalized for > 4 days because of uncontrolled nausea. The average MED was higher in the aprepitant

Table 4. Secondary outcomes

	Aprepitant (n = 178)	Control (n = 176)	p value
Mean LOS (days)	1.19	1.34	0.014
Mean (SD) MED	28.73 (18.01)	23.21 (18.18)	0.004

LOS: length of stay; MED: morphine equivalent dose.

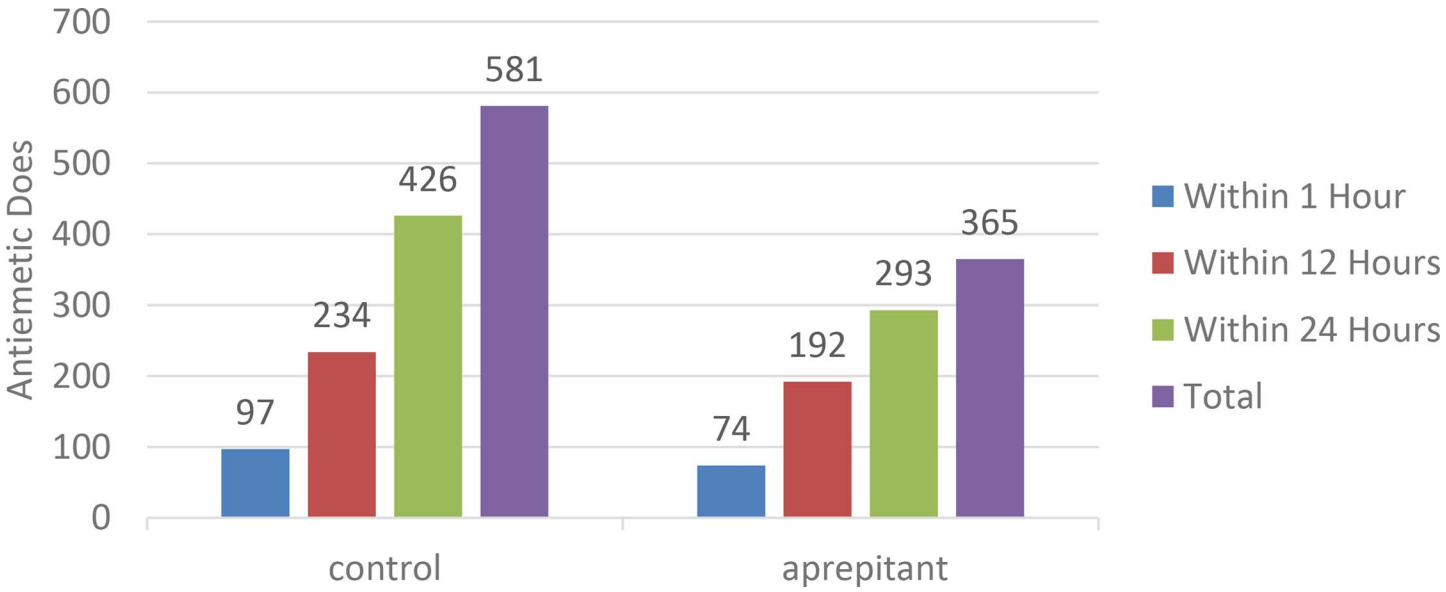

Figure 2. Doses of antiemetics administered after admission to the post-anesthesia care unit.

group (28.73 ± 18.01) than the control group (23.21 ± 18.18) (p value = 0.004).

DISCUSSION

The addition of a single dose of aprepitant 80 mg orally to the standard antiemetic regimen used for laparoscopic sleeve gastrectomy significantly reduced PONV at PACU + 1 hour, PACU + 12 hours, PACU + 24 hours, and of emesis at any time during first admission. Uncontrolled emesis likely directly contributed to the increased LOS seen in the standard prophylaxis control group.

Aprepitant has been studied in bariatric, gynecologic, neurosurgical, and plastic surgery procedures uniformly reporting that aprepitant is more effective in preventing postoperative vomiting than reducing nausea scores.[3,4,11–15] Numerous studies have specifically studied the efficacy of aprepitant 80 mg on PONV following bariatric surgery finding that the time to first vomiting was significantly prolonged in the aprepitant group.[11–14,16] Patients were shown to have reduced PONV within the first 4 hours after emergence, which is significant because the incidence of nausea and vomiting postoperatively usually peaks during the first 4 hours after emergence.[12] This retrospective review showed a statistically significant reduction across all four time periods. Given the difference in the number of antiemetics administered overall between the control group and aprepitant, it is safe to conclude that LOS has been at least partially influenced by how well the patient's PONV is controlled.

Only a few of the previous studies showed correlation with LOS, and only one of them tracked pain scores[11–14,16]; the theory being that well-controlled PONV leads to earlier discharge. Pain scores are a general point of curiosity; would controlling PONV correlate to more comfortable patients and better control of postoperative pain? Our review showed a statistically significant improvement in LOS; however, significant higher pain scores were noted in the aprepitant group. The pain scores were fascinating, and we have developed some theories, none of which were associated with aprepitant. Our institution did make IV acetaminophen nonformulary in 2017, which would only affect the aprepitant group. This would indirectly affect the MED recorded for each patient. No major change in technique was noted, but liposomal bupivacaine was used intermittently throughout the study period as well. Thoughts on pain management and a correlation between controlled PONV is difficult to prove with so many confounding variables.

The results of this retrospective analysis were delayed in being reviewed and submitted for publication by the COVID-19 pandemic, as several of the providers were pressed into front-line working conditions of the pandemic. However, the authors still feel the results provide valuable insight and data even if more aprepitant studies have been published in the meantime.

Limitations

This study was a retrospective chart review, which presents several limitations, such as the definitions of the primary and secondary end points, and the possibility for bias exists. The intent was to capture real-world data using a standard antiemetic regimen and then compare results once we added another singular agent. No significant changes in surgical technique or general anesthesia practice were noted. PONV was defined as any nausea, vomiting, or retching postoperatively and measured by the number of antiemetics administered. The number of doses administered does not necessarily equate to excellent control, but it is the most natural data point. Data were collected and

uploaded manually presenting a possibility of user error. This approach also raises the possibility that patients may have had untreated PONV that they did not express or may have thought they were about to have nausea and therefore requested treatment that was not necessarily needed. More studies have been published on this topic while this study was being published.[16–18] Future studies could focus on distinguishing between nausea severity to help determine the relationship between aprepitant use and severity of PONV. This review is specific to one institution and may lack the generalizability to other practices as well. Further studies need to be completed to determine aprepitant's potential dosing strategies. Is 40 mg comparable to 80 mg when used in bariatric patients? Cost may be a prohibitive factor and further dosing analyses may be beneficial. Is there the potential to use aprepitant IV rather than giving PO, especially considering the practical considerations of patients undergoing bariatric surgery? Will fosaprepitant become more financially available in the future, and can it be administered for prophylaxis?

CONCLUSIONS

In this retrospective comparison, we found that the addition of aprepitant to the standard antiemetic regimen used at a community hospital was associated with a statistically significant decrease in antiemetic medication used postoperatively and should be used to prevent PONV in patients undergoing laparoscopic sleeve gastrectomy and to reduce LOS.

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