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Special REPORT

Clinical and Economic Impact of Postoperative Nausea and Vomiting

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Introduction

Half of all surgical patients suffer from postoperative nausea, and nearly one-third of them will vomit within 24 hours after surgery.[1-4] In a subset of high-risk patients, the postoperative nausea and vomiting (PONV) rate can be as high as 80%.[2] Despite the consequences of PONV, clinicians may fail to appreciate the risks or provide appropriate management.

This monograph describes the epidemiology, pathophysiology, and burden of PONV, and discusses current strategies for its prevention and management, as well as the unmet needs and consequences that continue to hinder optimal patient outcomes.

Pathophysiology

PONV arises from the interplay between the central and peripheral nervous systems and gastrointestinal tract that manifests into nausea and/or vomiting/retching in the immediate 24 to 48 postoperative hours.[5] Several perioperative stimuli, such as volatile anesthetics, opioids, adverse drug reactions, anxiety, and motion, can trigger PONV.[5] These and other factors result in a combination of gastrointestinal stimulation and vagal and splanchnic nerve stimulation that subsequently activates the chemoreceptor trigger zone and high cortical centers in the medulla, resulting in nausea and vomiting.[5,6] The physiologic and cellular mechanisms underlying these pathways are mediated by at least 5 major neurotransmitters and their receptors: acetylcholine/cholinergic muscarinic M1 receptor, dopamine/D2 receptor, histamine/H1 receptor, serotonin/5-HT_3 receptor, and substance P/neurokinin-1 (NK-1) receptor.[4-7]

Consequences of PONV

PONV is one of the most unpleasant experiences during the postoperative period and has significant consequences for patient satisfaction, patient outcomes, and costs of care.[8,9] In a survey of patients (N=101) that examined the perioperative experience, vomiting was the most common reason for poor patient satisfaction during the perioperative period.[9]

Eberhart and colleagues analyzed data from 220 patients undergoing preoperative anesthetic examination before surgery under general anesthesia who were

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asked to rate their concerns regarding 9 scenarios during the immediate postoperative recovery based on 4 factors: alertness, pain, PONV, and extra costs.[10] Patients ranked the relative importance of the 4 factors as follows: PONV (49%), pain (27%), alertness (13%), and additional costs (11%).[10] In another study of 50 patients undergoing major abdominal surgery, patients prioritized their concern for vomiting over enhanced pain relief, suggesting that there is a need to balance opioid analgesia versus PONV to optimize the postoperative experience.[11]

Effect on Recovery and Rehabilitation

Interference with recovery (eg, eating, mobilizing, and meeting rehabilitation milestones) and postoperative rehabilitation is another consequence of PONV, potentially delaying recovery. In a multicenter, prospective, observational study of 376 patients at high risk for PONV, the proportion of those experiencing postoperative emesis ranged from 18% to 40% depending on the number of antiemetics administered.[12] The rate of functional interference with sleep, appetite, physical activity, and general interactions due to emetic symptoms was 44% over the 3-day study.[12]

PONV can lead to serious medical consequences.[12] Clinical reports have documented a variety of complications that can arise directly from PONV, including electrolyte abnormality and dehydration and aspiration pneumonitis associated with respiratory failure.[4,13,14] The increase in abdominal pressure associated with postoperative vomiting also can lead to a variety of pressure-related complications, including suture line tension or wound dehiscence, and venous hypertension that can result in hematoma formation at various sites (eg, under surgical flap or at vascular surgical sites).[4,13,14] Rare cases of pneumothorax, esophageal or tracheal rupture, severe subcutaneous emphysema, and loss of vision also have been reported.[15]

Strain on Resources and Increasing Costs

Optimizing facility throughput and reducing costs of care are important considerations for both inpatient and ambulatory surgery centers. However, PONV is associated with a prolonged post-anesthesia care unit (PACU) stay, prolonged hospital stays, and the need for additional hospital care.[8,16-18] This can be significant, as delays in PACU discharge or the need for unanticipated hospital admission due to PONV can produce a cascade effect that can adversely affect patient throughput. Habib and colleagues reported that PONV was associated with a 20% increase in PACU stay duration and additional costs (Figures 1 and 2).[19] Pizzi and colleagues reported that postoperative emesis was associated with a 23% increase in the duration of hospitalization.[20] Also, PONV is a major factor limiting early discharge of ambulatory patients after surgery and a leading cause of unexpected hospital admission after planned ambulatory surgery.[8]

Parra-Sanchez and colleagues performed an analysis of costs and resource utilization associated with PONV in 100 patients undergoing ambulatory surgery.[21] Patients with PONV spent 1 hour longer in the PACU than patients without PONV.[21] The amount of nursing time required for patients with PONV was significantly greater than that required for patients without PONV (82 vs 68 minutes).[21] The total cost of postoperative recovery was significantly greater for patients with PONV/post-discharge nausea and vomiting than for those without ($730 vs $640).[21] This analysis did not explore the costs associated with an unanticipated hospital stay. Data show that the average cost of an in-patient day was $2,338 in 2016.[22]

Management of PONV

The data discussed in this monograph suggest that prevention and management of PONV have the potential to reduce hospital costs, improve patient outcomes, and increase patient satisfaction. The clinical significance of the complex interplay between multiple pathophysiologic mechanisms of PONV is that a multimodal approach may be required for appropriate prevention and management of this condition.

Implementing ERAS

Proponents of enhanced recovery after surgery (ERAS) advocate a multimodal approach to accelerate postoperative recovery.[23] This approach includes optimized anesthesia care to reduce surgical stress response, effective pain control, and reduction of PONV.[23,24] As a multidisciplinary, multimodal protocol toward the standardization of perioperative care, ERAS

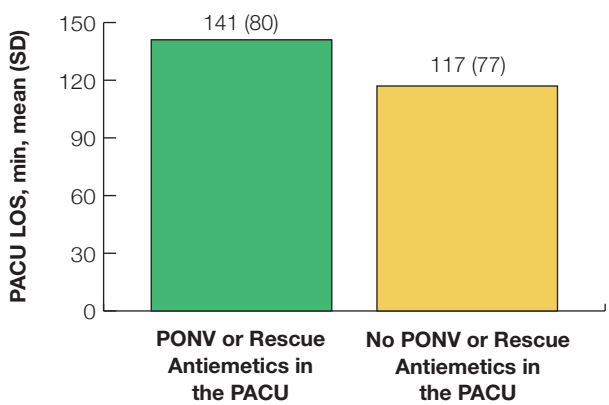

Figure 1. Additional time associated with PONV.

LOS, length of stay; **PACU,** post-anesthesia care unit; **PONV,** postoperative nausea and vomiting

Based on reference 19.

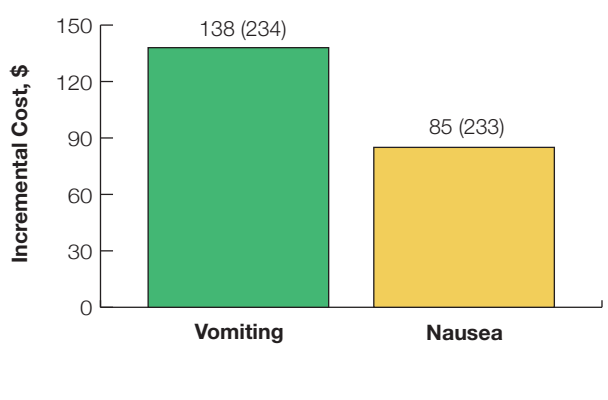

Figure 2. Additional cost associated with PONV.

PONV, postoperative nausea and vomiting

Based on reference 19.

uses evidence-based medicine to effectively move patients through the recovery process optimizing pain control, fluid and hemodynamic management, the ability to eat, and early mobilization.[24,25] Core components of ERAS include the use of short-acting anesthetic agents, goal-directed fluid therapy, multimodal analgesia with the routine use of nonopioid analgesics, and prevention of PONV.[25,26]

Current Guidelines for the Management of PONV

Several guidelines have been published on the management of PONV, including consensus guidelines from the Society for Ambulatory Anesthesia (SAMBA).[17,27,28] Published in 2014 and accounting for the most recently available information (eg, new antiemetics, risk scoring) and data, the SAMBA guidelines provide several comprehensive recommendations for the prevention and management of PONV.[17]

Risk Assessment

PONV management begins with an assessment of risk factors.[17] Several studies have identified risk factors for PONV.[5,29] For example, female sex is the most reliable patient-specific predictor for PONV. A meta-analysis of 22 prospective studies including over 95,000 adults found that female sex was the strongest overall predictor for PONV (odds ratio [OR], 2.57).[30] Other factors included a history of PONV and/or motion sickness (OR, 2.09), nonsmoker status (OR, 1.82), and age less than 50 years (OR, 1.79). Specific surgical procedures also are associated with a higher risk for PONV; these include ophthalmologic, gynecologic, otologic, thyroid, and various gastrointestinal procedures (eg, cholecystectomy).[5,29,31]

Although there is strong evidence for several independent risk factors for PONV, taken alone as single predictors, these factors are not clinically sufficient for a risk assessment or to make clinical decisions about the need for specific management strategies.[17] Therefore, investigators suggest that a patient's baseline risk for PONV should be assessed objectively using a validated risk score that is based on these independent predictors.[2,17] One such validated risk assessment metric—the Apfel simplified risk score—is based on 4 predictors: female sex, history of PONV and/or motion sickness, nonsmoker status, and use of postoperative opioids.[2] The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is ~10%, 20%, 40%, 60%, and 80%, respectively.[2] Therefore, patients with 0 to 1, 2 or 3, and more risk factors are considered as low-, medium-, and high-risk categories, respectively.[17]

Pierre and colleagues studied the utility of the Apfel risk assessment in 428 adults undergoing thyroid, throat, breast, or gynecologic surgery under general anesthesia.[32] Investigators prospectively assigned patients to intervention groups according to their risk for PONV: Low-risk patients did not receive any antiemetic prophylaxis; medium-risk patients received volatile anesthesia with 0.625 mg of droperidol or IV propofol anesthesia without droperidol; and high-risk patients received IV anesthesia supplemented with 4 mg of dexamethasone and 0.625 mg of droperidol.[32] This approach resulted in a decrease in the overall incidence of PONV from 49.5% to 14.3%.[32]

Another study assessing the need/efficacy of preventive strategies against PONV (N=4,086) also concluded that risk assessment was particularly valuable, as prophylaxis against PONV was less necessary for low-risk patients.[33] Whereas patients at moderate risk may benefit from a single intervention, high-risk patients benefit from a multimodal approach.[33]

Reducing Baseline Risk

Studies show that reducing the baseline risks can decrease PONV. SAMBA identifies several strategies to reduce the baseline risk factors, such as avoiding/minimizing the use of agents associated with PONV (eg, nitrous oxide, volatile anesthetics, and postoperative opioids).[17,33-35] Instead, anesthesiologists should consider the use of propofol induction and maintenance, regional anesthesia, and nonopioid analgesic adjuncts (eg, IV acetaminophen, ketorolac, and local anesthetics).[17]

PONV Prophylaxis

The most recent version of the SAMBA guidelines describes drug therapy currently available for the management of PONV.[17] In line with the multimodal pathophysiology underlying PONV, 6 main classes of drugs are described: anticholinergics, antihistamines, dopamine antagonists, serotonergic antagonists (specifically, 5-HT_3 antagonists), NK-1 antagonists, and corticosteroids.[17] Risk assessment and stratification can be used to help guide management decisions. For example, for patients at moderate or high risk for PONV, a 5-HT_3 antagonist (eg, ondansetron) is most commonly used for this purpose.[17] This prophylactic approach may be particularly helpful, as it is often easier to prevent nausea and vomiting than to stop vomiting once it has started.

Studies have demonstrated that the administration of an antiemetic acting on 1 receptor typically reduces the incidence of PONV from 52% to 37%, and the use of a multimodal approach adding a second or third antiemetic reduces the incidence from 37% to 28% and 22%, respectively.[33] Therefore, the SAMBA guidelines suggest the use of 1, 2, and more than 2 drugs for those deemed at low, medium, and high risk for developing PONV, respectively, according to the Apfel risk stratification system.[2,17]

Patients receiving rescue therapy should be given any one or combination of drugs from the described classes.[17] However, the guidelines note that if prophylaxis fails, an antiemetic from a different class than the previously administered prophylactic drug should be used.[17] A study by Kovac and colleagues explored this issue in an assessment of 2,199 patients from 10 US centers who were given a prophylactic open-label IV dose of ondansetron (4 mg) immediately before the induction of anesthesia.[36] A total of 428 patients failed prophylaxis with ondansetron.[36] These patients received a repeat dose in the PACU (within 6 hours of the original dose); however, a repeat dose of ondansetron did not appear to offer additional control of PONV.[36]

Recognizing the Unmet Need in Managing PONV

Despite these advances in the management of PONV, there are several limitations to these strategies that define an unmet need in this field. A prospective, multicenter, observational study (N=376) evaluating the incidence and time course of PONV, and assessing prophylactic and rescue antiemetic use in high-risk patients, reported that while adherence to management guidelines resulted in a decrease in PONV at all time points, postoperative emetic symptoms and interference with patient functioning still occurred in ~30% of these high-risk patients.[12]

Many treatments for PONV have defined limitations in terms of suboptimal onset of action or safety considerations/adverse effects. Although approved for either prophylaxis and/or treatment, some PONV treatments include serious side effects.[5,17,36-40] In particular, the boxed warning regarding QT interval prolongation associated with the dopamine antagonist droperidol has limited the real-world utility of this otherwise

effective agent; the agent is now relatively difficult to obtain in the United States.[40,41] Furthermore, the Institute for Safe Medication Practices (ISMP) has alerted the medical community about the risk for patient injury resulting from inadvertent arterial injection or extravasation of injectable promethazine.[42] The 2018-2019 ISMP Best Practice recommendations include the removal of injectable promethazine from all areas of the hospital, the hospital formulary, and all electronic medication order sets or protocols.[42] The ISMP also supports implementing automatic therapeutic substitution to other antiemetic medications.[42] Thus, for patients failing typical prophylaxis with 5-HT_3 antagonists, rescue treatment choices are limited.

These observations underscore the unmet need in patients who develop PONV despite appropriate prophylaxis. Development of other agents with mechanisms of action distinct from those of 5-HT_3 antagonists, with favorable safety profiles, would benefit patients.

Conclusion

PONV is a common phenomenon that is associated with worse patient outcomes, a longer hospital length of stay, and higher costs of care. While appropriate prophylaxis and rescue management using risk assessment strategies and ERAS protocols can mitigate the incidence and consequences of PONV, treatment options are limited for patients failing typical prophylaxis with 5-HT_3 antagonists. This observation underscores the need for the development of new rescue treatments that act via mechanisms other than 5-HT_3 antagonism.

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Disclosures: Dr Bruno reported that he has nothing to disclose. Dr Gan reported that he is a consultant to Acacia Pharma, Edwards Lifesciences, Mallinckrodt, Medtronic, and Merck. He is also on the speakers bureau of Merck. Dr Rosenfeld reported that he is a shareholder of Acacia Pharma, on the speakers bureau of Merck, and has received honoraria from Acacia Pharma and Merck.