Management of Postoperative Nausea and Vomiting: Tackling the Practical Issues

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Introduction

Postoperative nausea and vomiting (PONV) are two of the most common and unpleasant side effects after anesthesia and surgery. The overall incidence of PONV has decreased from 60% when ether and cyclopropane were used to approximately 30% nowadays (1). However, in certain high-risk patients the incidence is still as high as 70%. Furthermore, it is estimated that approximately 0.2% of all patients may experience intractable PONV, leading to a delay in recovery room discharge and/or unanticipated hospital admission after ambulatory surgery, thereby increasing medical costs. The estimated cost of PONV to a busy ambulatory surgical unit was estimated to range from $0.25 million to $1.5 million per year in lost surgical revenue (2).

The results of several studies suggest that patients not only rank the absence of PONV as being important (3) but also rank it more important than an earlier discharge from an ambulatory surgical unit (4). In one survey, patients were willing to pay up to $100 US, at their own expense, for a completely effective antiemetic (5).

Recent interest has focused on the use of a combination of antiemetics acting at different receptors and the adoption of a multimodal approach to tackle this problem. The search for the most cost-effective strategy has also been a major goal. This article will discuss the pathophysiology and risk factors of PONV, the use of a multimodal approach, novel therapy and the cost-effectiveness of PONV management. Finally, recommendations for the prophylaxis and treatment of PONV will be discussed.

Pathophysiology of PONV

The complex act of vomiting involves coordination of the respiratory, gastrointestinal, and abdominal musculature (6). It is controlled by the vomiting center, which is located in the lateral reticular formation of the medulla oblongata in close proximity to the nucleus of the solitary tract in the brainstem and has access to the motor pathways that are responsible for the visceral and somatic output involved in vomiting. The vomiting reflex has two main detectors of the need to vomit: the gastrointestinal tract (GIT) and the chemoreceptor trigger zone (CTZ) in the area postrema. The vagus is the major nerve involved in the detection of emetic stimuli from the GIT and has two types of afferent fibers involved in the emetic response: mechanoreceptors, located in the muscular wall of the gut that are activated by contraction and distension of the gut, and chemoreceptors, located in the mucosa of the upper gut, that are sensitive to noxious chemicals. Stimulation of the vagal afferents leads to activation of the CTZ in the area postrema. The latter is a U-shaped structure a few millimeters long located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle. It is one of the circumventricular organs of the brain and is outside the blood-brain barrier and the cerebrospinal fluid barrier, and thus can be activated by chemical stimuli received through the blood as well as the cerebrospinal fluid. Several other stimuli can affect the vomiting center, including afferents from the oropharynx, mediastinum, peritoneum, and genitalia as well as afferents from the central nervous system (CNS, cerebral cortex, labyrinthine, visual, vestibular apparatus) (6–8).

Different types of receptors are involved in the transmission of impulses to the vomiting center. Cholinergic receptors are found in the vomiting center and vestibular nuclei. The area postrema is rich in dopamine (D2), opioid, and serotonin ($5HT_3$) receptors. The nucleus tractus solitarius is rich in encephalins and in histaminic (H_1), muscarinic cholinergic, and NK-1 receptors; the latter are also found in the dorsal motor nucleus of the vagus nerve. Figure 1 represents the receptor mechanism involved in PONV.

Risk Factors for PONV

Identification of patients at high risk for PONV enables targeting prophylaxis to those who will benefit most from it. Universal PONV prophylaxis is not cost-effective, is unlikely to benefit patients at low risk for PONV, and would put them at risk from the potential side effects of antiemetic agents. Patient-, anesthesia-,

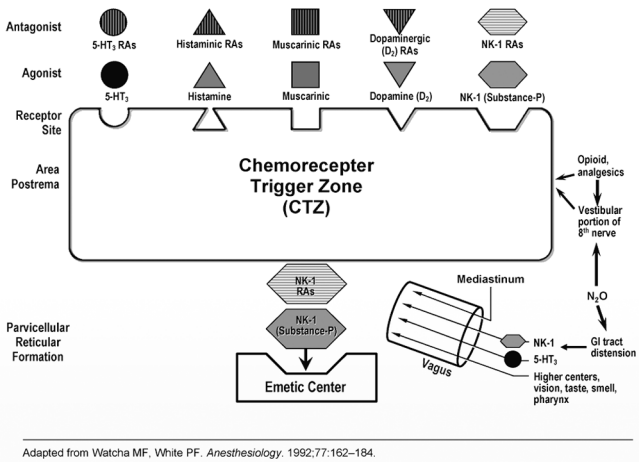

Figure 1. Receptor mechanism of PONV. 5HT, 5 hydroxytryptamine; NK-1, neurokinin 1.

and surgery-related risk factors have been identified (Table 1). Anesthesia-related risk factors include the use of volatile agents, which cause PONV especially during the early postoperative period (within 0–2 h) (9), nitrous oxide, which increases the risk for postoperative vomiting (10), opioids (9,11) and high doses of neostigmine (>2.5 mg) for the reversal of neuromuscular blockade (12). Patient-related factors include female gender (11,13), history of PONV or motion sickness (11,13,14), and nonsmoking status (11,13). High levels of anxiety and postoperative pain, especially of pelvic or visceral origin, may also be associated with a higher incidence of PONV (15–17).

Although some studies reported an increased susceptibility to PONV during the first 7 days of the menstrual cycle (18,19), this was not confirmed in other studies (20). Recently, a systematic review of the results of all available studies suggested that the phase of the menstrual cycle had no impact on the occurrence of PONV (21). Another recent systematic review also reported that an increased body mass index (BMI) is not a risk factor for PONV (22). Long surgical procedures (each 30-min increase in duration increases PONV risk by approximately 60) (13) and certain types of surgery also carry a greater risk of PONV (13,23,24). In adults, high incidences of PONV are found in intraabdominal surgery, major gynecological surgery, laparoscopic surgery, breast surgery, neurosurgery, and eye and ear-nose-throat surgery. Pediatric operations at high risk for PONV include strabismus, adenotonsillectomy, hernia repair, orchidopexy, penile surgery, and middle ear procedures (25–27). However, in a prospective validation study, an association between type of surgery and the risk of PONV was not apparent (11). It was suggested that the high incidence of PONV after certain operations might be caused by the involvement of high risk patients. The incidence of PONV increases after the age of 3 yr, with a peak incidence of approximately 40% in the 11- to 14-yr age group (11,28,29). Before puberty, gender differences for postoperative vomiting have not been identified (30).

A number of PONV risk scoring systems have been developed. Using logistic regression analysis, Palazzo and Evans (31) demonstrated that the probability of PONV in the first 24 h can be estimated using the following equation: logit postoperative sickness = $-5.03 + 2.24$ (postoperative opioids) + 3.97 (previous sickness history) + 2.4 (gender) + 0.78 (history of motion sickness) − 3.2 (gender × previous sickness history).

Subsequently, Koivuranta (14) used a logistic regression model to generate a score based on the strongest five predictors for PONV in inpatients: Score = 0.93 (if female) + 0.82 (if previous PONV) + 0.75 (if duration of surgery over 60 min) + 0.61 (if nonsmoker) + 0.59 (if history of motion sickness).

More recently, Apfel et al. (11) developed a simplified risk score consisting of four predictors: female gender, history of motion sickness or PONV, nonsmoking status and the use of opioids for postoperative analgesia. If none, one, two, three or four of these risk factors were present, the incidences of PONV were 10%, 21%, 39%, 61%, and 79%, respectively.

Combination Antiemetic Therapy

There are at least four major receptor systems involved in the etiology of postoperative nausea and vomiting (PONV). The concept of combination antiemetic therapy was first introduced in 1988 in chemotherapy-nduced vomiting (32). Its success prompted similar research in the field of PONV. More than 50 randomized controlled trials have been published comparing the relative efficacy of combination versus single-gent antiemetic prophylaxis. Most of these studies suggested that a better prophylaxis against PONV might be achieved by the use of two or more antiemetics acting at different receptors compared with monotherapy (33–35). In a recent meta-analysis, Habib et al. (36) found no statistically significant difference in the incidence of early or overall PONV when a 5-HT_3 receptor antagonist was combined with either droperidol or dexamethasone. Both combination regimens provided significantly better PONV prophylaxis compared with 5-HT_3 receptor antagonists alone.

In a large prospective study using a multifactorial design, Apfel and colleagues (33) recently evaluated 3 antiemetic interventions (ondansetron 4 mg, droperidol 1.25 mg, dexamethasone 4 mg) and 3 anesthetic interventions (total IV anesthesia with propofol, omitting nitrous oxide, and substituting remifentanil for fentanyl) for the prophylaxis of PONV. The design

Table 1. Risk Factors for PONV

Patient factors	Anesthetic factors	Surgical factors
Female	Volatile agents	Long duration of surgery
History of PONV or motion sickness	Opioids	Emetogenic procedures, e.g., intraabdominal, major gynecological, laparoscopic, breast, ENT, neuro, strabismus
Non-smoking status	Nitrous oxide	
	High doses of neostigmine (>2.5 mg)	

ENT = ear, nose and throat.

enables the investigators to evaluate the efficacy of each of the interventions as well as all possible combinations of 2 or 3 interventions. The resulting data suggest that antiemetics with different mechanisms of action have additive rather than synergistic effects on the incidence of PONV. Each antiemetic reduced the risk of PONV by approximately 26%. When combinations of interventions were used, the benefit of each subsequent intervention was always less than that of the first intervention. They also reported that the efficacy of the interventions depend on the patient's baseline risk; the greatest absolute risk reduction from the antiemetic interventions was achieved in patients with high risk for PONV.

Multimodal Approach

In addition to using a combination of antiemetics acting at different receptor sites, the multifactorial etiology of PONV might be better addressed by the adoption of a multimodal approach. This is especially important in patients at high risk for PONV. Table 2 summarizes different strategies for keeping the baseline risk of PONV low.

Scuderi et al. (37) reported a multimodal approach to the management of PONV in females undergoing outpatient laparoscopy. Their multimodal algorithm consisted of total IV anesthesia with propofol and remifentanil, avoiding nitrous oxide and neuromuscular blockade, aggressive IV hydration (25 mL/kg), triple prophylactic antiemetics (ondansetron 1 mg, droperidol 0.625 mg, and dexamethasone 10 mg), and ketorolac 30 mg. Control groups included standard balanced outpatient anesthetic with or without 4 mg ondansetron prophylaxis. Multimodal management resulted in a 98% complete response rate (no PONV and no antiemetic rescue) in PACU. No patient in this group vomited before discharge, compared with 7% of patients in ondansetron group and 22% of patients in the placebo group.

More recently, a multimodal approach incorporating total IV anesthesia with propofol, a combination of ondansetron and droperidol, and omitting nitrous oxide, was associated with a higher complete response rate and greater patient satisfaction in the PACU compared with similar antiemetic prophylaxis with isoflurane/nitrous oxide based anesthetic (38).

Recommended Strategy for PONV Prophylaxis

Figure 2 illustrates a suggested algorithm for PONV prophylaxis. The risk of PONV should be estimated for each patient. No prophylaxis is recommended for patients at low risk for PONV unless they are at risk for medical consequences from vomiting, e.g., patients with wired jaws. For patients at moderate to high risk for PONV, regional anesthesia may be considered. If this is not possible or contraindicated and a general anesthetic is used, strategies to minimize the baseline risk of PONV should be adopted (Table 2). The use of combination antiemetic therapy and more appropriately a multimodal approach in high-risk patients is recommended. However, the best available combination and the optimum doses of antiemetic agents when used in combination are yet to be established.

Recommendations for the Treatment of Established PONV

There is a paucity of data on the use of antiemetics for the treatment of PONV in patients who failed prophylaxis or did not receive prophylaxis. This is a result of the difficulty in performing such studies; a large number of patients would need to be recruited to obtain

Table 2. Strategies to Keep the Baseline Risk of PONV Low

Use of regional anesthesia
Avoid emetogenic stimuli
Nitrous oxide
Inhalation agents
Etomidate and ketamine
Minimize the following
Intraoperative and postoperative opioids. Adequate analgesia should be achieved by incorporating local anesthetics, NSAIDS, and opioids as needed
Consider limiting the dose of neostigmine to less than 2.5 mg in adults
Consider the following
Total IV anesthesia (TIVA) with propofol
Adequate hydration
Anxiolytics, e.g., benzodiazepines
Nonpharmacological techniques, e.g., acupuncture

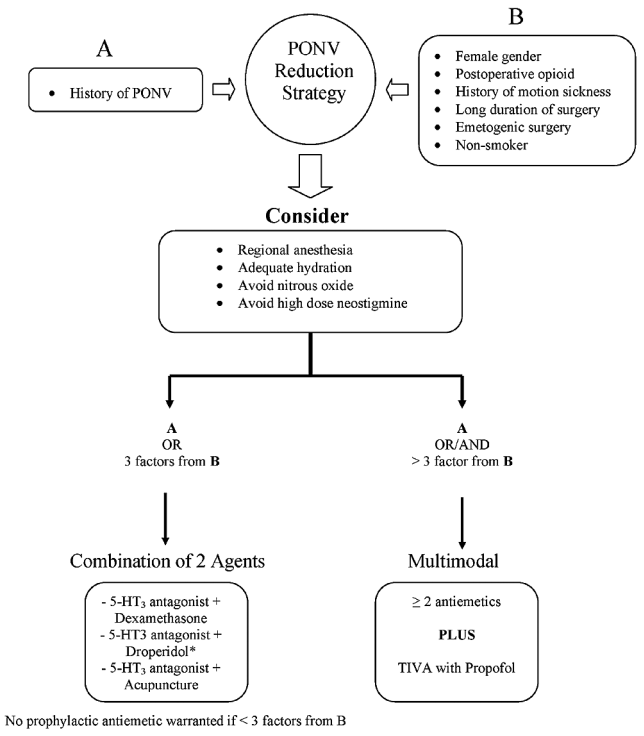

Figure 2. PONV management algorithm. Recommendations for the Treatment of Established PONV

the required target number of patients who eventually experience PONV.

The 5-HT_3 receptor antagonists were the most commonly tested drugs in rescue clinical trials. Similar to their use in PONV prophylaxis, the anti-vomiting efficacy of the 5-HT_3 receptor antagonists is more pronounced than their anti-nausea efficacy. There is no evidence of dose-responsiveness for these agents when used for rescue. Therefore, small doses of these agents have been recommended for treatment: ondansetron 1 mg, dolasetron 12.5 mg, granisetron 0.1 mg, and tropisetron 0.5 mg.

In patients who fail ondansetron prophylaxis, there is evidence to suggest that the use of ondansetron for rescue is no more effective than placebo. A drug acting at a different receptor might be more effective in this case (30). There is a lack of evidence on the therapeutic efficacy of older generation antiemetics in the treatment of established PONV. Droperidol was not different from ondansetron when used for the treatment of established PONV (39). On the other hand, ondansetron 4 mg was more effective than metoclopramide 10 mg in this setting (40,41).

When evaluating PONV after surgery, the role of medication and mechanical factors should be considered first. Such contributing factors might include opiates, blood draining down the throat, or bowel obstruction. Rescue therapy can then be initiated. If PONV occurs within 6 h postoperatively, patients should not receive a repeat dose of the prophylactic antiemetic; a drug from a different class should be used for rescue. Beyond 6 h, PONV can be treated with any of the agents used for prophylaxis except dexamethasone and scopolamine, which are longer acting.

In summary, PONV are still common after surgery. The thorough understanding of the mechanism of nausea and vomiting and a careful assessment of risk factors provide a rationale for appropriate management of PONV. Strategy to reduce baseline risk and the adoption of a multimodal approach will most likely ensure success in the management of PONV.

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