Postoperative nausea and vomiting

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Abstract: Postoperative nausea and vomiting (PONV) remains a significant clinical issue that can detract from patients' quality of life in hospital/treatment facility, as well as in the days immediately postdischarge. In addition, PONV may increase perioperative costs, increase perioperative morbidity, increase postanesthesia care unit stay, prolong hospital stays, length of stay/delay discharge, delay the time that the patient can go back to work, and lead to readmissions. Despite the existence of multiple tools to stratify patients according to their risk of developing PONV and multiple PONV treatment guidelines, clinicians do not appear to systematically address the treatment and/or prophylaxis of PONV in a uniform fashion with both pharmacologic and nonpharmacologic strategies in attempts to minimize PONV occurrences.

Key Words: Postoperative; nausea; vomiting; dopamine receptor antagnosits; NK-1; 5-HT3

Introduction

Over 40 million patients undergo surgery per year in the United States and more than 100,000,000 patients worldwide with about 30% experiencing postoperative nausea and vomiting (PONV) (1). Postoperative nausea and vomiting (PONV) is one of the most commonly reported adverse effects of anesthesia. Even patients with zero known risk factors carry a 10% risk of PONV. This risk increases dramatically to 61% and 79%, respectively, when 3 or 4 risk factors exist (female gender, nonsmoker, history of motion sickness, postoperative opioid use, and a history of PONV) (2).

Untreated, PONV occurs in about 30% of the general surgical population and in up to 70-80% of high-risk surgical patients (3-5). The adverse effects of PONV range from patient-related distress to postoperative morbidity. PONV associated with ambulatory surgery increases health care costs due to hospital admission and accounts for 0.1-0.2% of these unanticipated admissions and PONV in nonambulatory surgery may contribute to increased costs, increased length of stay, increased perioperative morbidity and prolonged overall recovery.

Tools for assessing the risk of postoperative nausea/vomiting

Six popular predictive models for PONV have been developed (4,6-10). These models were compared with respect to validity (discriminating power and calibration characteristics) and practicability. Apfel and colleagues analyzed and compared these and found that the simplified risk scores provided better discrimination and calibration properties compared with the more complex risk scores (11).

The incidence of postoperative nausea and vomiting (PONV) still appears to be about 30% (2,12,13). The cost of prophylactic treatment may be contained by keeping the number of patients needed to be treated small through the use of a multimodal approach for identifying patients at high risk (14).

Pierre *et al.* examined the simplified Apfel score that considers four risk factors: female gender, previous history of PONV or motion sickness, non-smoking status and postoperative use of opioids (Apfel-score). A previously published score includes, in addition to these factors, duration, type of anesthesia and surgery (Sinclair-score). The simplified 4-item Apfel-score presented with favorable

Table 1 Assessment/Recommendations for prevention and management of PONV

Risk factors	Number of risk factors	PONV incidence	Prophylaxis strategy
	0	9%	None
Female gender	1	20%	4 mg dexamethasone ± 2nd antiemetic
Nonsmoker	2	39%	Avoid inhalation agents if possible +4 mg dexamethasone ± 2nd antiemetic
History of PONV or motion sickness	3	60%	Avoid inhalation agents if possible +4 mg dexamethasone + another prophylactic antiemetic (e.g., scopolamine patch)
Use of opioids >100 mcg fentanyl or equivalent	4	78%	Avoid inhalation agents if possible +4 mg dexamethasone + NK-1 Receptor Antagonist ± another prophylactic antiemetic (e.g., scopolamine patch)
Rescue strategy: antiemetic not used for prophylaxis, e.g., ondansetron 1 mg IV			
(Adapted from Apfel 2002) (11)			

discriminating and calibration properties for predicting the risk of PONV (*Table 1*) (15).

Sarin and colleagues attempted to develop a better model to predict the patient's risk for PONV by incorporating both non-modifiable patient characteristics and modifiable practitioner-specific anesthetic practices (16). Their experimental model (EM) was compared against the original Apfel model (OAM), refitted Apfel model (RAM), simplified Apfel risk score (SARS), and refitted Sinclair model (RSM) by examining the discriminating power calculated using area under the curve (AUC) and by examining calibration curves. The EM showed statistically significant improved discrimination over existing models and good calibration. However, the EM should be validated at another institution (16).

The impact of nausea/vomiting

Chancellor and colleagues conducted a two-stage study in France, Germany, Italy, Spain, Sweden, and the United Kingdom of the stated preferences of chronic pain sufferers treated with classic strong opioids and of physicians treating such patients. Sufferers ranked nausea, pain impact, energy, alertness, and constipation; physicians ranked pain response, central nervous system (CNS) effects, nausea, dose form, and constipation in descending order of importance. Sufferers were unwilling to incur severe side effects to decrease pain and chose the opt-out in approximately one half of the choice tasks, whereas physicians were willing to trade between profiles (17).

Macario and colleagues performed surveys of one

hundred one patients in the preoperative clinic completed a written survey (18). Patients were asked to rank (order) 10 (nine and one-normal) possible postoperative outcomes from their most undesirable to their least undesirable perioperative outcome. Patients were also asked to distribute $100 among the 10 outcomes, proportionally more money being allocated to the more undesirable outcomes. The dollar allocations were used to determine the relative value of each outcome. Rankings and relative value scores correlated closely (r^2=0.69). Patients rated from most undesirable to least undesirable (in order): vomiting, gagging on the tracheal tube, incisional pain, nausea, recall without pain, residual weakness, shivering, sore throat, and somnolence (*F*-test <0.01) (*Table 2*) (18).

In 2001, Gan *et al.* reported that patients associated a value with the avoidance of PONV and were willing to pay between US $56 and US $100 for a hypothetical completely effective antiemetic (19).

Ponv prophylaxis

Prophylaxis is rarely warranted in low-risk patients, moderate-risk patients may benefit from a single intervention, and multiple interventions should be reserved for high-risk patients (*Table 2*) (5). High-risk patients may require multiple agents for effective PONV prophylaxis. Honarmand and colleagues conducted a randomized, double-blind, placebo-controlled study, in which patients were divided into 4 groups of 20 each and received haloperidol 2 mg i.v. (Group H); midazolam 2 mg i.v. (Group M); haloperidol 2 mg plus midazolam 2 mg i.v.

Table 2 Ranking and relative value of anesthesia outcomes

Outcome	Rank	Relative value[a]
Vomiting	2.56±0.13	18.05±1.09
Gagging on endotracheal tube	2.97±0.15	17.86±1.43
Pain	3.46±0.20	16.96±1.59
Nausea	4.02±0.17	11.82±0.87
Recall without pain	4.85±0.26	13.82±1.58
Residual weakness	5.34±0.17	7.99±0.8
Shivering	5.36±0.20	7.60±0.6
Sore throat	8.02±0.11	3.04±0.26
Somnolence	8.28±0.11	2.69±0.25
Normal	10.00	0

Values are mean ± sem. [a]This means that, for example, patients assigned $18.05 of $100 to avoid vomiting. (adapted from Macario 1999) (18)

(Group HM); saline i.v. (Group C) (20). Patients in group HM had significantly lower incidence of PONV compared with groups H, M, and C throughout 0-24 h (P<00.5). The HM group had the lowest incidence of PONV (0-2, 2-24, and 0-24 h) and the highest incidence of complete response. Postoperative anti-emetic requirement was significantly less in group HM compared with group M or H (P<0.05) (20).

Pharmacologic treatment strategies for PONV

Kooij and colleagues conducted a prospective study of 2,662 patients (1,681 in the intervention period and 981 in the control period) and found that automated reminders decrease postoperative nausea and vomiting incidence in a general surgical population and improve patient outcome by improving treatment guideline adherence (21).

In selected high-risk populations, the incidence may be as high as 80% (4,22). PONV is the second cause (after pain) for unplanned admission after day-care surgery and can also be a contributing factor to several complications, such as suture dehiscence and aspiration (23,24). A large body of research exists on the evaluation and management of PONV, which has led to the development of risk scores, guidelines, and treatment protocols (5,11,25,26). Kooij revealed that adherence to PONV prophylaxis guidelines to be as low as 37% (27).

In 2006, Carlisle and Stevenson performed a Cochrane Sysetmic Review and published that for 100 people, of whom 30 would vomit or feel sick after surgery if given placebo, 10 people would benefit from a drug and 90 would

not. Between one to five patients out of every 100 people may experience a mild side effect, such as sedation or headache, when given an antiemetic drug (25).

NSAIDs (and acetaminophen) reduced postoperative opioid consumption, however, only NSAIDs decreased the incidence of PONV (P<0.05) (28). The enhanced recovery after surgery (ERAS) group recommendations (29) integrated a range of perioperative interventions in order to improve postoperative recovery and enhance hospital discharge.

Postoperative nausea and vomiting (PONV) has been identified as an essential component in achieving patient satisfaction (30) and can be more distressing than pain (19,31). Untreated, one third of patients who undergo surgery will experience PONV, which is associated with prolonged inpatient length of stay (LOS) (32). esophageal rupture, delayed recovery, wound dehiscences and pulmonary complications (e.g., aspiration pneumonia) (5). PONV assessment allows appropriate antiemetic administration. A previous history of PONV, female gender, non-smoking and postoperative opioid administration are the most important predictors of developing PONV (4).

A prospective factorial trial of six placebo controlled interventions/trials (5) preventing PONV included all of the interventions recommended by the ERAS protocol. These included total intravenous anesthesia (TIVA) and the administration of intravenous dexamethasone and ondansetron. Two RCT's assessed the efficacy of TIVA in reducing the incidence of PONV (5,33). and demonstrated a statistically significant reduction in the immediate

incidence of PONV in the TIVA group compared to the traditional anesthesia group. No significant reduction in PONV was observed at 48 or 72 h postoperatively (33). Three RCTs (5,34,35) assessed the efficacy and timing of the administration of intravenous dexamethasone. All trials demonstrated a significant reduction in PONV with dexamethasone compared to placebo. There were no statistically significant differences between the timing of giving steroids at the beginning or end of surgery at 24 h.

Four RCTs (5,36-38) assessed the efficacy and timing of 5-HT3 antagonist administration in preventing PONV. Three trials (5,37,38) of four RCTs (5,36-38) assessing 5-HT$_3$ antagonists demonstrated a significant improvement in PONV in the treatment group compared to placebo. In one trial (5), the 5-HT3 antagonist was given at the end of surgery, while in the other two trials (37,38). it was given at induction and no signify cant differences were found.

Apfel *et al.* (5) demonstrated that PONV occurs in 59% of all patients undergoing GA with inhalational agents and nitrous oxide. The use of propofol reduces the risk of PONV by 19% and avoiding nitrous oxide by 12%. Combining propofol and air reduces the risk of PONV by 25% (26).

Current ERAS recommendations advise the use of 5-hydroxytryptamine (5-HT3) receptor antagonists (ondansetron) and steroids (dexamethasone). These antiemetics are currently recommended for patients at moderate to severe risk of PONV. Ondansetron and dexamethasone are equally effective and each independently reduce the risk of PONV by 25% (5).

Schaub and colleagues analyzed 25 trials (2,957 patients) (39). Doses varied from 0.25 to 1.0 mg. For prevention of early nausea (within 6 h postoperatively), relative risk (RR) was 0.45 (95% CI, 0.35 to 0.58); number needed to treat (NNT) was 7, 4, and 2 for low, medium and high baseline risk (i.e., control event rate 25%, 50%, 75%). For prevention of early vomiting, RR was 0.65 (95% CI, 0.57 to 0.74), NNT 11, 6, and 4. For prevention of late nausea (within 24 h), RR was 0.74 (95% CI, 0.62 to 0.87), NNT 15, 8, and 5. For prevention of late vomiting, RR was 0.61 (95% CI, 0.47 to 0.80), NNT 10, 5, and 3. Droperidol decreased the risk of headache but increased the risk of restlessness (39).

The glucocorticoid receptors exist in the part of the brain stem where the nucleus of solitary tract and area postrema reside (40). Recent animal experiments have proved that glucocorticoid receptors on both sides of the nucleus of the solitary tract, not area postrema, in the brain stem act to conduct the main antiemetic effect of dexamethasone (41-43). Other possible explanations for dexamethasone preventing PONV include central inhibition of prostaglandin synthesis, reduction of central serotonin activity, and change of permeability of blood-brain barrier to plasma proteins (44).

In December 2001, the U.S. Food and Drug Administration issued a black box warning, stating that the use of droperidol (butyrophenone class of drugs) may be related to fatal arrhythmia (torsade de pointes) (45). However, a combination of dexamethasone and serotonin antagonist appears to address both early and late nausea/emesis and thus, may be the most effective treatment of preventing PONV (46).

Chen and colleagues performed a meta-analysis of randomized controlled trials of a single dose of dexamethasone (8 mg) for prevention of postoperative nausea and vomiting in patients undergoing thyroidectomy (47). Five RCTs were included with a total of 497 patients. A statistically and clinically significant difference in the incidence of PONV was found in favor of dexamethasone [relative risk (RR) 0.38; 95% confidence interval (CI), 0.30-0.49]. No steroid-related complications were noted (47).

Wu and colleagues performed a systemic review and meta-analysis of efficacy of ondansetron *vs.* metoclopramide in prophylaxis of postoperative nausea and vomiting after laparoscopic cholecystectomy. The total incidence of postoperative nausea and vomiting within 24 hours after laparoscopic cholecystectomy was 31% (74 of 235) in the ondansetron group and 56% (127 of 225) in the metoclopramide group (OR=0.33, 95% CI, 0.22-0.49, P<0.00001, I^2=49%) (48). Thus, it appears that ondansetron has a better effect than metoclopramide for preventing postoperative nausea and vomiting after laparoscopic cholecystectomy (48).

In this systematic review and meta-analysis, transdermal scopolamine (TDS) was associated with significant reductions in PONV with both early and late patch application during the first 24 hours after the start of anesthesia. TDS was associated with a higher prevalence of visual disturbances at 24 to 48 hours after surgery, but no other AEs, compared with placebo (49).

Gan *et al.* conducted a randomized, double-blinded study of transdermal scopolamine used as prophylaxis for PONV compared combination therapy (4 mg IV ondansetron plus transdermal scopolamine patch) to ondansetron alone (4 mg IV) in 620 adult females considered at risk for PONV (50) in patients undergoing either outpatient laparoscopy or breast augmentation

surgery. The study was placebo controlled, in that some patients received a sham patch. Patients were assessed at 24 and 48 hours for PONV. The combination therapy of transdermal scopolamine and ondansetron significantly reduced nausea and vomiting/retching compared to ondansetron alone at 24 hours postsurgery. More patients in the combination group than the ondansetron-only group did not experience vomiting or retching and did not use rescue medication (48% versus 39%, P<0.02). The number of patients who had no nausea, no vomiting/retching, and no rescue medication was also significantly greater in the combination therapy group compared to the ondansetron-only group (35% versus 25%, P<0.01). The combination group had a significantly longer time to first episode of nausea, vomiting/retching, or rescue medication compared to the ondansetron-only group (P<0.05). In addition, the cumulative incidence of adverse events was significantly lower in the transdermal scopolamine plus ondansetron group compared to the ondansetron-only group (36.7% versus 49%, P<0.01) (51).

Singhal and colleagues performed a meta-analysis in efforts to compare the efficacy of 5HT3 antagonists against all non-5HT3 antagonism-based pharmacological approaches as a preemptive strategy for PONV in women undergoing breast surgery (52). Nineteen trials were included. All trials were of good methodological quality (Jadad score >3). 5HT3 antagonists are superior to other pharmacological interventions for the prevention of PONV in patients undergoing breast surgery under general anesthesia (52).

Patients with three copies of the CYP2D6 gene, a genotype consistent with ultrarapid metabolism, or both have an increased incidence of ondansetron failure for the prevention of postoperative vomiting but not nausea (53). Unlike patients with chemotherapy-induced nausea and vomiting, perioperative patients who failed ondansetron prophylaxis did not have a significant response to cross-over dosing with granisetron (54).

Candiotti and colleagues conducted a randomized, double-blind study we assessed the efficacy and safety of three different doses of the 5-HT3 receptor antagonist palonosetron, compared with placebo, on the incidence and severity of postoperative nausea and vomiting (PONV) for 72 h postsurgery (55). Patients with > or =2 PONV risk factors were eligible and randomized to receive one of three doses of IV palonosetron (0.025, 0.050, or 0.075 mg) or placebo immediately prior to induction of anesthesia. A single 0.075-mg IV dose of palonosetron significantly increased the CR rate (no emetic episodes and no rescue medication) from 0 to 24 h, decreased nausea severity and patients experienced significantly less interference in their postoperative function due to PONV (55).

NK1 receptor antagonists in PONV

In a randomized, multicentre, double-blind phase III trial, 922 patients undergoing open abdominal surgery were allocated randomly to receive one of the three antiemetic treatments 3 hours or less before the operation: oral aprepitant 40 mg, oral prepitant 125 mg, or i.v. ondansetron 4 mg, or matching placebos for the prevention of PONV (56).

Aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 h (percentage of patients with no vomiting 84%, 86%, and 71%, respectively, in the aprepitant 40 mg, aprepitant 125 mg, and ondansetron groups); and at 48 h post-surgery (percentage of patients with no vomiting 82%, 85%, and 66%, respectively, in the aprepitant 40 mg, aprepitant 125 mg, and ondansetron groups); and in reducing nausea severity in the first 48 postoperative hours (56). The most commonly reported adverse events were pyrexia, constipation, headache, and bradycardia with no differences between the groups.

In another study based on a similar design, aprepitant was superior to ondansetron for prevention of vomiting in the first 24 and 48 h, but no significant differences were observed between aprepitant and ondansetron for nausea control, use of rescue antiemetic, or complete response (57).

A post hoc analysis of the pooled data from these two randomized active-controlled trials was performed on 541 patients in the aprepitant 40 mg group, 532 patients in the aprepitant 125 mg group, and 526 patients in the ondansetron group, in a modified intention-to-treat analysis This analysis showed that in the 24 h after surgery, aprepitant 40 mg was more effective than ondansetron (58).

Although not indicated for PONV, an i.v. form (fosaprepitant) [a prodrug of aprepitant], may be conceivably used for treatment of established PONV. Other NK-1 receptor antagonists at various stages of veleopment include: GR205171 (vofopitant, GlaxoSmithKline), CP-122721 (Pfizer), CJ-11974 (Pfizer), casopitant (GlaxoSmithKline), maropitant (Pfizer), netupitant (Helsinn Healthcare), rolapitant or SCH 619734 (Schering-Plough), T 2328 (Mitsubishi Tanabe Pharma), and vestipitant (GlaxoSmithKline) (59).

The dose of aprepitant for PONV prophylaxis is 40 mg administered 3 hours or less prior to surgery. Aprepitant,

effectively diminishes post-operative nausea and vomiting while increasing analgesic tolerance in laparoscopic gynecological procedures (60).

It appears conceivable that at least in certain circumstances NK-1 receptor antagonists and 5-HTRAs may be somewhat synergistic (61,62).

Nonpharmacologic treatment strategies for PONV

Apfel and colleagues performed a literature search and included prospective randomized controlled trials that reported PONV event rates in patients receiving supplemental i.v. crystalloids or a conservative fluid regimen after elective surgery under general anesthesia (63). Supplemental i.v. crystalloids were associated with a lower incidence of overall PONV and several PONV outcomes such as reduced need for antiemetic rescue treatment (63).

Holmér Pettersson and Wengström performed a systematic review of acupuncture prior to surgery to minimize postoperative nausea and vomiting and concluded that all kinds of acupuncture point stimulation, both non-invasive and invasive, seem to prevent PONV with minimal side effects (64).

Summary

Postoperative nausea and vomiting is a distressing symptom that may increase medical costs and delay discharge and recovery. Multiple tools exist to stratify patients according to their risk of developing PONV. Additionally, multiple PONV treatment guidelines exist to help health care providers a general PONV management "road-map". Although these tools exist, it appears that they are not commonly used in routine clinical practice and also it appears that no uniform to standardized approaches are utilized to evaluate and manage PONV in routine clinical practice.

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