Updates in Postopertive Nausea and Vomiting

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Abstract

Antiemetic drug selection depends on efficacy, cost, safety, and ease of dosing. Safety concerns have arisen regarding the side effects of antiemetics, specifically their effect on the ECG with prolongation of the QTc interval by the butyrophenones and the first-generation 5-HT_3 receptor antagonist class of antiemetics. The impact of pharmocogenetics on antiemetic drug metabolism and their resulting efficacy has been correlated with genetic makeup affecting drug response. New antiemetic medications have added to our understanding of the peripheral and central nervous system (CNS) receptors and receptor antagonists targeting nausea and vomiting. These have included the second-generation 5-hydroxytryptamine-3 (5-HT_3) antagonist [palonosetron] and the class of neurokinin-1 (NK-1) receptors and NK-1 receptor antagonist (aprepitant)The long half-life (40 h) of these medications offer an alternative method for the prophylaxis and/or treatment of PONV and post-discharge nausea and vomiting (PDNV). An analysis of ambulatory surgery patients has estimated that PDNV occurs with an incidence of approximately 30 %. In conclusion PONV is common after surgery, occurring in up to 70–80 % of high-risk patients who did not receive prophylactic antiemetics. PONV and PDNV are associated with morbidity and increased healthcare costs. Patient-specific, anesthesia- and surgery-related PONV and PDNV risk factors should be evaluated to determine the appropriate antiemetic therapy for proper prophylaxis or treatment.

Keywords: Antiemetic drug; Postoperative; Nausea; Vomiting; anesthesia

Introduction

Postoperative nausea and vomiting (PONV) is an important clinical problem that still affects patients undergoing surgery with general anesthesia. With no prior prophylaxis, the highest incidence can be found in the first 6 hours after surgery. little attention has been paid to nausea and vomiting occurring during or after regional anesthesia.. ***(1)***

Nausea vomiting and retching frequently complicate recovery from anesthesia. Postoperative nausea and vomiting (PONV) is a patient-important outcome; patients often rate PONV as worse than postoperative pain. Hospital admission and delay recovery room discharge. In addition, vomiting or retching can result in wound dehiscence, esophageal rupture, aspiration, dehydration, increased intracranial pressure, and pneumothorax.***(2)***

dexmedetomidine, regardless of administration modes (by loading dose or loading dose plus continuous infusion or just infusion) significantly reduced the incidence of PONV in adult or children, dexmedetomidine increased adverse events such as bradycardia and hypotension in loading dose or loading dose plus continuous infusion mode ,indicating that dexmedetomidine in continuous infusion mode is superiority to prevent PONV.***(3)***

One of the challenges in preventing nausea and vomiting in women undergoing anesthesia for caesarian section is to find the best prophylaxis and treatment for mother and the fetus or newborn with respect to efficacy and safety aspects., many substance classes have proven efficacy in their routine clinical use Frequently used drugs are antihistamines such as dimenhydrinate, serotonin antagonists (eg, ondansetron), dopamine antagonists (metoclopramide) and corticosteroids (dexamethasone). Drugs from different classes seem to complement each other concerning their antiemetic effects. ***(4)***

Established medications used for spinal anaethesia or epidural anaethesia (local anesthetics and opioids) have a regional effect; they do not pass the placenta to a large extent The injected local anesthetic does not only specifically block the pain fibers but also leads to a vasodilatation by affecting sympathetic afferents. Due to the induced temporary sympathicolysis, blood pressure fluctuation in terms of significant hypotension can occur. On top of that, the increased vagal tone entails bradycardia

which is often accompanied with nausea and vomiting**.**

The pre-emptive or early use of antihypotensive agents is an important way to avoid one of the main causes for nausea and emesis throughout caesarian section. But simple relying on preventive administration should be avoided because of the risk of excessive blood pressure reactions and thus a possible insufficient placental supply. Ephedrine or phenylephrine is recommended as an antihypotensive drug. Meanwhile, phenylephrine may be viewed internationally as the first-choice agent. However, the use of phenylephrine is associated with an increased risk for resulting bradycardia, which makes the drug unsuitable if the heart rate is already lowered. Compared to phenylephrine, a higher rate of fetal acidosis was shown using ephedrine. ***(5)***

Studies of the effect of perioperative administration of intravenous (IV) dextrose solutions on PONV have reported mixed results. Patients who received 1000 mL of dextrose containing IV fluid in the post anaesthetic care unit had less need for rescue antiemetics and lower incidence of PONV than patients who received 1000 mL of Ringer's lactate (RL). ***(6)***.

Nitrous oxide (N2O) has been reported to increase the risk of postoperative nausea and vomiting (PONV) in a dose-dependent manner. We investigated the effect of adding N2O at the end of isoflurane inhalational anesthesia on the recovery and incidence of PONV. Our hypothesis was that N2O would reduce the time to early recovery without increasing the incidence of PONV. Adding N2O during the last 30 min of an isoflurane-based inhalational anesthetic reduced the time to extubation, eye opening, and orientation.

Materials and methods

This is a review article, The search was performed in MEDLINE, Embase, Pubmed and CINAHL Plus in the same date range with the following medical terms: “antithrombotic drugs; Anesthesia; coagulation including articles from 2000 to 2019, Excluded articles from review are those of language other than English. Key words: Antiemetic drug; Postoperative; Nausea; Vomiting; anesthesia

Results

Pathophysiology

Five principle neurotransmitter receptors mediate nausea and vomiting: muscarinic M1, dopamine D2, histamine H1 5-hydroxytryptamine (HT)-3 serotonin, and

neurokinin 1 (NK1) – substance P [4]. All of these receptors may be targets for prevention or treatment of PONV **(7).**

●Central mechanisms

Nausea and emesis can be triggered by higher cortical centers communicating with the central pattern generator (formerly called the vomiting center) in the medulla. In the perioperative period, fear, pain, anxiety, conditioned nausea related to environmental cues, and stimulation of the vestibular system are central stimuli that may cause nausea and vomiting. As an example, during tympanoplasty, surgical stimulation of the vestibular system, transmitted via the H_1 histamine and M_1 acetylcholine receptors, may result in profound **PONV (8).**

●Peripheral mechanisms

Direct gastric stimulation from gastric trauma, blood, or toxins induces release of substance P and serotonin from enterochromaffin cells, thereby activating the vagal and splanchnic nerve 5-HT_3 receptors. Vagal and splanchnic nerve afferents terminate in the nucleus tractus solitarius in the brain stem, near or within the area postrema (also called the chemoreceptor trigger zone). Bowel surgery and blood in the gastrointestinal tract from oral or ear, nose, and throat surgery may cause nausea and vomiting via this pathway, though the mechanisms by which serotonergic stimuli cause nausea and vomiting are incompletely understood(**9).**

●Drugs and toxins

The molecular and neural mechanisms by which drugs and toxins, including anesthetics and opioids, causes nausea and vomiting are complex and incompletely understood. Both opioids and inhalation anesthetics may cause nausea and vomiting by stimulation of the area postrema at the base of the fourth ventricle in the medulla. The area postrema then communicates with the central pattern generator via dopamine and serotonin to trigger the vomiting reflex **(10).**

Patient risk factors

Patient characteristics that increase the risk of PONV include the following, in decreasing order of risk (**11**):

●Preoperative nausea and vomiting

The most evident, but often overlooked, factor is nausea and vomiting prior to the anesthetic (e.g., patients with renal colic).

Anesthetic factors

A number of anesthetic factors have been associated with PONV, some of which may be modified to reduce risk **(12)**

●Anesthetic technique

General anesthesia is associated with a higher incidence of PONV compared with purely regional anesthesia. Regional anesthesia, in both adults and children, may reduce PONV by reducing opioid administration for postoperative pain.

●Intravenous (IV) anesthetics

Ketamine and etomidate do not independently increase PONV at doses commonly administered for induction of anesthesia. Low-dose ketamine may reduce PONV by decreasing postoperative opioid requirements.

A meta-analysis of 30 studies including approximately 4600 patients reported a modestly-higher incidence of PONV with N_2O compared with N_2O-free anesthesia (33 versus 27 percent). The maximal risk reduction with avoidance of N_2O was in women (OR 0.7), and the difference between groups was eliminated by administration of a propofol infusion.

Type of surgery

Studies of the effect of the type of surgery on the incidence of PONV have reported conflicting results. The best evidence suggests that cholecystectomy, gynecologic, and laparoscopic procedures are associated with modestly increased risk of PONV compared with other general surgical procedures .In children, strabismus surgery is an independent, and possibly the most significant, predictor for POV . In addition, POV occurs in as many as 70 percent of children without prophylaxis who undergo adenotonsillectomy and 40 percent of those who undergo inguinal scrotal or penile procedures **(13).**

Risk score for postoperative nausea and vomiting for adults

We use the simplified risk score for PONV that was created by Apfel, et al. to evaluate adults preoperatively, and base the preventive strategy on the resulting degree of predicted risk. The simplified risk score is easy to use and accurately predicts the risk for PONV in our adult patients. The components of the simplified risk score include the following four highly predictive risk factors (**14):**

The risk of POV for children with 0 to 1, 2, 3, or 4 of these risk factors is associated with an incidence of PONV of 10, 30, 50, and 70 percent, respectively. This scoring system has also been validated for children having surgery other than strabismus surgery; POV was observed in 3, 11, 30, and 40 percent for children who had 0, 1, 2 or 3 risk factors, respectively **(15).**

REVENTION

The management strategy for PONV should include risk assessment, multimodal preventive measures based on the individual patient's risk, and evidenced-based interventions when PONV occurs (**16).**

We employ a multimodal, opioid-sparing strategy for effective postoperative pain control; the reduction of pain has been correlated with a reduction in PONV. Additional preventive measures may include modification of anesthetic technique and medications used administration of antiemetics, and use of nonpharmacologic measures for prophylaxis (**17).**

High-risk adults

Patients at high risk for PONV (ie, those with four risk factors according to Apfel's simplified risk score) should receive three or more interventions (ie, antiemetics, modification of anesthesia, acupuncture) using a multimodal approach. Based practice of both ambulatory and inpatient surgeries where we have a limited hospital-based drug formulary, our strategy for PONV prophylaxis for high-risk adults is described here (**9).**

High-risk children

In hospital-based practice of both ambulatory and inpatient surgeries where we have a limited hospital-based drug formulary, our strategy for PONV prophylaxis for high-risk children (ie, those with history of prior postoperative vomiting (POV), or three to four risk factors according to the Eberhart scoring system) is described here **(7)** .

Moderate-risk adults

For adults who are at moderate risk of PONV (ie, with two or three risk factors according to Apfel's simplified risk score) we choose one or two interventions. We administer an antiemetic, and may also choose to either modify the anesthetic technique (ie, regional anesthesia or TIVA with propofol) or perform acupuncture **(18).**

Moderate-risk children

Children at moderate risk of POV include those who undergo ear nose and throat, ophthalmologic, or gastrointestinal diagnostic procedures, undergo anesthetics >2 hours long, or require large doses of opioids (ie, morphine ≥0.2 mg/kg IV or fentanyl ≥5 to 10 mcg/kg IV). We treat moderate-risk children as we would high-risk children, as described above, without using TIVA **(19).**

Low-risk adults and children

Prophylaxis for PONV for low-risk adults and children should be based on clinician and patient preferences, formulary choices, and cost **(20).**

Glucocorticoids

Data on the safety of prophylactic dexamethasone are inconclusive, and the use of dexamethasone should be individualized. Most studies have shown no increase in wound infection with one dose of dexamethasone . Dexamethasone may be relatively contraindicated in patients with impaired glucose tolerance. Serum glucose may rise for 6 to 12 hours after dexamethasone administration in patients with and without diabetes. In pediatric oncology patients who undergo anesthesia for bone marrow biopsy or lumbar puncture, glucocorticoids can interfere with cell counts and, ultimately, chemotherapeutic management or, rarely, can cause tumor lysis syndrome . The patient's oncologist should be consulted prior to administration of dexamethasone **(21).**

Midazolam

The literature on the efficacy of midazolam for PONV prophylaxis is inconclusive. Meta-analyses of trials of perioperative midazolam have reported 38 to 55 percent reduction in overall PONV .However, there was high risk of bias in the included studies, and a clinically relevant increase in postoperative sedation could not be ruled out.We do not administer midazolam solely for PONV prophylaxis because of the potential for postoperative sedation and delirium in some patient populations (eg, older adults, mentally ill**) (22*).***

RESCUE THERAPY

When postoperative nausea and vomiting (PONV) occurs in the post-anesthesia care unit (PACU) or operating room, rescue treatment should include a drug from a different class than those that have already been administered unless the effect of the first drug has worn off or a potentially inadequate dose has been administered (**23).**

The serotonin receptor antagonists are particularly beneficial as rescue drugs in the PACU, especially for same-day surgery patients, because they are non-sedating. For opioid-induced PONV or postoperative vomiting (POV), low-dose naloxone infusion (0.25 mcg/kg/hour IV) can reduce opioid-induced side effects in children and adolescents, including nausea and vomiting, without affecting analgesia (**24).**

POSTDISCHARGE NAUSEA AND VOMITING

Post-discharge nausea and vomiting (PDNV) (ie, nausea and vomiting within 48

hours of discharge) occurs in 37 percent of adult patients who undergo general anesthesia for same-day surgery .Risk factors for PDNV include those that predict PONV and, in addition, administration of opioids in the PACU and nausea in the PACU. A simplified risk scoring system has been developed for PDNV, including the following risk factors **(25)**

Preventive strategies for PDNV include risk stratification followed by a multimodal prophylactic approach, similar to prophylaxis for PONV. Other options may be limited by availability of the newer antiemetics and formulary issues. The addition of either long-acting antiemetics (e.g., aprepitant, palonosetron, transdermal scopolamine) or repeat, scheduled dosing of shorter-acting medications in the postoperative period (eg, oral disintegrating ondansetron [ODO]) may reduce PDNV**(26).**

The incidence of PDNV in children may be lower than in adults. In a prospective observational study of 1041 children who underwent ambulatory surgery, the incidence of PDNV was 14 percent. Risk factors for PDNV included perioperative opioid administration, inhalational anesthetics, and the use of opioid medications at home; no patient who received total intravenous anesthesia (TIVA) had PDNV. There was no association between PDNV and age, gender, duration of anesthesia, use of nitrous oxide (N_2O) for maintenance of anesthetic, intraoperative antiemetic administration, airway management strategy, or the length of time from recovery room discharge to first oral intake **(27).**

Multimodal antiemetic prophylaxis for the prevention of PONV and PDNV

When a combination of antiemetics with different mechanisms of action is administered, the efficacy is optimized and the side effects are decreased .A meta-analysis suggested that combining dexamethasone with a 5-HT3 receptor antagonist provided greater antiemetic efficacy, and this combination therapy was recommended as the 'optimal' choice for prophylaxis against PONV. However, in a study involving an outpatient surgery population at varying risks of PONV, the addition of ondansetron failed to improve upon the antiemetic efficacy of a combination of low-dose droperidol and dexamethasone **(28**).

The impact of PDNV requires that the prophylactic treatment of this complication would ideally extend well beyond the time

of discharge from the hospital .New research centered on different antiemetics, administered at various time points, has been done to evaluate the effects on reducing PDNV. A study demonstrated that patients who received the combination of 4 mg IV ondansetron and ondansetron oral disintegrating tablet 8 mg immediately before discharge had less severe nausea and fewer vomiting episodes compared to 4 mg ondansetron IV alone (3 vs 23%) (**29).**

Multimodal strategies for treating established PONV

When PONV occurs in patients who did not receive prophylaxis or failed prophylaxis, prompt antiemetic treatment is indicated. If PONV occurs despite prophylaxis, particularly in the immediate postoperative phase (within 6 h postoperatively), an antiemetic from a pharmacologic class that is different from the prophylactic drug initially given should be administered. However, if the PONV occurs more than 6 h postoperatively, repeat dosing of the initial prophylactic drug may be considered. If no prophylaxis was given, the recommended treatment is a low-dose 5-HT3 antagonist (e.g., ondansetron 1–2 mg IV). Alternative treatments for active PONV include metoclopramide (10 mg), droperidol (0.625 mg), dexamethasone (2 mg), promethazine (6.25–12.5 mg), dolasetron (12.5 mg), granisetron (0.1 mg), or tropisetron (0.5 mg) **(18).**

For existing PONV treatment, a multimodal strategy should also be considered, since, despite treatment, the recurrence rate of PONV over the subsequent 24 h is 35–50% , A combination of ondansetron plus dexamethasone, dolasetron or haloperidol have been found to be superior to monotherapy alone . Those interventions that have proven to be effective for prophylaxis of PONV have also been shown to be effective for PONV treatment (**30**).

Recommendations for reducing the risk for PONV and PDNV

The management strategy for each individual patient should be based on level of risk for PONV, patient's preexisting condition, patient preference, and cost-efficiency. In addition to using a combination of antiemetics with different mechanisms of action, the multifactorial etiology of PONV might be better addressed by the adoption of a multimodal approach to reduce the baseline risk for PONV in high-risk patients. Several effective strategies are recommended for reducing the baseline risk for PONV: (1) local and regional anesthesia (e.g., local infiltration and/or peripheral

nerve blocks); (2) propofol induction and maintenance; (3) minimization of perioperative opioids; (4) minimize use of volatile anesthetics; (5) avoidance of nitrous oxide and reversal drugs; and (6) insure adequate intraoperative hydration (**31).**

Non-pharmacological therapies for PONV and PDNV

A variety of non-pharmacologic techniques have been used to control emetic symptoms in the postoperative period, including acupressure, acupuncture, and transcutaneous electrical stimulation. In an earlier study, White et al. demonstrated that the combination of ondansetron and transcutaneous electro-acustimulation was more effective than ondansetron alone in preventing PONV. These preliminary findings were subsequently confirmed by Gan et al. who further suggested that acustimulation could produce analgesic effects (**32).**

Risks and mechanisms of PONV/intraoperative nausea and vomiting (IONV)

Current literature indicates a high incidence of IONV during CS under SPA up to 80%. Pregnant women are already likely to suffer from nausea and vomiting because of the pregnancy itself. This is applicable not only to the first 3 months of pregnancy but also to the third and last trimester due to the reduced tone of the esophagogastric junction and an increased intraabdominal pressure. Moreover, pregnant women can be assigned to a high-risk group regarding the likelihood of the occurrence of nausea and vomiting of any origin (motion sickness, chemotherapy-associated nausea and vomiting and PONV). Females undergoing CS might be affected by different mechanisms that trigger nausea and vomiting than patients who undergo general anesthesia **(33).**

Direct PONV prophylaxis

A systematic review on the use of antiemetic drugs was published by Griffiths et al. A total of 41 RCT s with 5,046 participants conducted between 1986 and 2012 were included and analyzed regarding the occurrence of IONV and PONV. The authors found a significant reduction for both IONV and PONV with dopamine receptor antagonists (metoclopramide and droperidol) and sedatives (mostly propofol) **(34).**

Referring to an RCT by Stein et al, the NICE guidelines set antiemetics equal to acupressure, as no significant difference in the efficiency of both methods was shown in this particular study. Indeed, the effects of P6 point stimulation (pericard 6, also Nei

Guan) have been investigated in many clinical trials **(35).**

NITROUS OXIDE AND PONV

NITROUS oxide is a well-recognized risk factor for postoperative nausea and vomiting (PONV), particularly in more extensive surgical procedures in which exposure to nitrous oxide is prolonged. Most episodes of PONV are transient and perhaps insignificant; in contrast, persistent or recurrent PONV has distinct clinical importance. However, most studies characterizing any PONV or the effectiveness of antiemetic regimens have focused on minor and ambulatory surgery. In this study, we focused on protracted and/or repeat episodes of PONV occurring up to 3 days after surgery **(36).**

Postoperative nausea and vomiting (PONV) is an important cause of morbidity after anesthesia. Recent surveys reported incidences of nausea and vomiting ranging from 18% to 38% and 11% to 26%, respectively. Although regarded as a minor and often inevitable complication of anesthesia and surgery, PONV may cause significant distress to patients; in outpatients, it may delay discharge and necessitate hospital admission. With an increasing number of operations being performed on an ambulatory basis, such an outcome is undesirable for patients, surgeons, and anesthesiologists **(36).**

Following elective surgery, PONV is believed to result from gut ischemia, secondary to hypovolemia due to overnight fasting. A number of risk factors have been identified for PONV. Perioperative administration of a sufficient volume of intravenous fluids to correct the fasting hours' deficit may effectively prevent PONV, without the expense or the potential for side effects seen with pharmacological approaches. Therefore, the potential efficacy of intravenous fluid therapy in reducing PONV remains to be convincingly demonstrated (**37).**

ROLE OF DEXMEDETOMIDINE IN PONV

General anesthesia is widely used in several surgeries. It can cause some complications such as postoperative nausea and vomiting (PONV) and cognitive dysfunction. PONV is more common in general anesthesia than spinal anesthesia. Also, it can cause electrolyte imbalance and aggravate bleeding that delay hospital discharge. It is reported that PONV is even higher especially after gynecologic surgery, ranging from 24% to 75%, even up to 90%.Some clear risks including female

gender, postoperative opioid treatment, the history of motion sickness and/or PONV and nonsmoker have been shown to independently predict PONV **(38).**

Dexmedetomidine is a potent and highly selective α2-adrenoceptor agonist, which binds to transmembrane G protein-binding receptor located in the brain and spinal cord. It affects the functions of central nervous, circulatory systems and exhibits sedative, analgesic, sympatholytic properties. It has been widely used in different clinical settings like department of anesthesiology and intensive care unit (ICU). Recently, the effect of dexmedetomidine on PONV has been the focus of clinical researchers (**39).**

The incidence of PONV in pediatric patients was reported as high as 34%. However, the incidence in adult appears to decrease with age. In our meta-analysis, the results are consistent with previous study showing that the incidence of PONV in pediatric patients is much higher than that in adult. Operations such as strabismus, adenotonsillectomy may partially explain the higher incidence of PONV in children, although the potential mechanism is complex **(40).**

Discussion

New antiemetic drug developments, formulations, guidelines, risk evaluation, and controversies have occurred in the area of postoperative nausea and vomiting (PONV). These developments have helped improve our understanding of the prevention and treatment of PONV in the post-anesthesia care unit and after discharge home or to the hospital ward.

Antiemetic drug research has resulted in the introduction of the second-generation 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonist palonosetron and the neurokinin-1 (NK-1) receptor antagonist aprepitant, as well as new data on existing antiemetics. The next frontier and need for further nausea and vomiting research and therapy is the area of postdischarge nausea and vomiting after the patient is discharged home from phase II of the ambulatory stepdown unit or to the hospital ward.

Antiemetic drug selection depends on efficacy, cost, safety, and ease of dosing. Safety concerns have arisen regarding the side effects of antiemetics, specifically their effect on the ECG with prolongation of the QTc interval by the butyrophenones and the first-generation $5\text{-}HT_3$ receptor antagonist class of antiemetics. The impact of pharmocogenetics on antiemetic drug metabolism and their resulting efficacy has been correlated with genetic makeup affecting drug response.

New antiemetic medications have added to our understanding of the peripheral and central nervous system (CNS) receptors and receptor antagonists targeting nausea and vomiting. These have included the second-generation 5-hydroxytryptamine-3 (5-HT_3) antagonist [palonosetron] and the class of neurokinin-1 (NK-1) receptors and NK-1 receptor antagonist (aprepitant)The long half-life (40 h) of these medications offer an alternative method for the prophylaxis and/or treatment of PONV and post-discharge nausea and vomiting (PDNV). An analysis of ambulatory surgery patients has estimated that PDNV occurs with an incidence of approximately 30 %.

Conclusion

PONV is common after surgery, occurring in up to 70–80 % of high-risk patients who did not receive prophylactic antiemetics. PONV and PDNV are associated with morbidity and increased healthcare costs. Patient-specific, anesthesia- and surgery-related PONV and PDNV risk factors should be evaluated to determine the appropriate antiemetic therapy for proper prophylaxis or treatment.

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