Postoperative Nausea and Vomiting: Prevention and Treatment

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Introduction

Historically, postoperative nausea and vomiting (frequently abbreviated PONV) has been an all too common complication for both inpatients and outpatients undergoing virtually all types of surgical procedures, regardless of the anesthetic regimen used. PONV encompasses a triad of signs and symptoms, which include not only physical signs (i.e., retching and vomiting) but also the unpleasant subjective feeling (nausea) experienced by the patient. A given episode of PONV can manifest any or all of these signs and symptoms and can last from minutes to hours or even days.

Risk Factors

A variety of independent factors have been associated with the occurrence of PONV. These can be divided into non-anesthetic, anesthetic, and postoperative-related factors. Typically, younger age, female gender, large body habitus, history of motion sickness or prior history of PONV, anxiety, concomitant disease, and longer duration of surgery have all been said to be contributors to an increased incidence of PONV. Females have been noted to have an increased incidence of PONV, even when corrected for surgical procedure. In addition to the gender bias for development of PONV, the day of the female menstrual cycle has also been implicated as a risk factor for the development of PONV.

Site of operation or type of surgery has been felt to be a risk factor for the development of PONV. Procedures involving the oropharynx, auditory system, or eyes, and intra-abdominal surgery, particularly laparoscopy, have all been shown in the past to have increased incidence of PONV. In addition, anxiety, obesity, concomitant disease, and gastroparesis have all been reported to increase the incidence of PONV. However, these associations are not well established in recent literature, despite frequent reference to them as risk factors for PONV in review articles.

A variety of factors related to the administration of an anesthetic have also been implicated. These factors include the type of preanesthetic medication used, gastric distention occurring during the course of the anesthetic and/or surgery, gastric suctioning, and the specific anesthetic technique. Typically, the administration of opioids as part of a preanesthetic regimen, or during the course of an anesthetic, has been shown to increase the incidence of PONV. However, this association is not clear cut. Historically, general anesthesia has carried a higher risk of PONV than regional anesthesia, major conduction anesthesia (subarachnoid or epidural block), or monitored anesthesia care. Various factors associated with the administration of general anesthesia have been implicated as causative for PONV. Perhaps the most controversial of these is the independent risk associated with the administration of nitrous oxide. No major differences have been noted in the incidence of PONV between isoflurane or enflurane anesthesia. In most, though not all cases, an opioid-based technique has resulted in a higher incidence of PONV. This may or may not be a function of the specific opioid (i.e., fentanyl, sufentanil, or alfentanil) which is used. Data suggest that the incidence and severity of PONV following sevoflurane and desflurane anesthetics may be similar to PONV after isoflurane anesthesia. On the other hand, the risks of PONV associated with a propofol-based anesthetic appear to be substantially lower than that for anesthesia maintained with potent inhalation agents.

Various postoperative factors including pain, dizziness, ambulation, oral intake, and the use of opioid analgesics have also been implicated, though paradoxically, the administration of opioids in PACU with the subsequent relief of pain may actually result in a decreased incidence of nausea.

Pharmacologic Approaches to Management

The introduction of serotonin antagonists (specifically the 5-HT_3 subgroup) in the early 1990s offered considerable promise for the management of PONV. Five different serotonin antagonists have been identified as having therapeutic efficacy in managing PONV. Of these, 3 (ondansetron, dolasetron, and granisetron) are currently approved for this indication in the United States. Prophylactic administration has been shown to decrease the incidence of PONV in various patient populations. For ondansetron, the optimal dose for prophylaxis seems to be 4 mg administered intravenously at the end of surgery, prior to emergence with a number needed to be treated (NNT) of 5.5-6.5. When used for treatment, 1 mg of ondansetron administered intravenously is as effective as higher doses (NNT=3.8-4.8). The

optimal dose of dolasetron appears to be 12.5 mg for both prevention and treatment with numbers needed to treat similar to ondansetron. Timing of administration for prophylaxis appears to be less important than for ondansetron. There is no evidence to support giving additional doses of a 5-HT_3 antagonist if there is no effect from the initial dose. Comparisons of ondansetron and dolasetron for PONV prophylaxis suggest that there are no clinically or statistically significant differences between these medications (Zarate E, et al. *Anesth Analg* 2000;90:1352-8).

Granisetron, tropisetron, ramosetron, and palonosetron have also been evaluated for the management (either prevention or treatment) of PONV. In all cases these medications have been shown to be effective (i.e., superior to placebo in randomized prospective clinical trials); however, only granisetron is currently approved in the United States. More aggressive pricing by the manufacturer coupled with lower doses may make granisetron an alternative in the future. None of the other 5-HT_3 antagonists mentioned are currently available in the United States.

Other classes of medications are also available for prevention and treatment of PONV. These include butyrophenones (e.g., droperidol), benzamides (e.g., metoclopramide), antihistamines (e.g., promethazine, dimenhydrinate), steroids (e.g., dexamethasone, betamethasone), phenothiazines (e.g., promethazine, prochlorperazine), and anticholinergics (e.g., scopolamine). All are available as generic formulations and are considerably less expensive than the 5-HT_3 antagonists; however, various side effects including sedation, dysphoria, and extrapyramidal reactions have been a concern for clinicians, particularly when treating outpatients. Nevertheless, many of these generic medications (e.g., droperidol, dexamethasone) are effective when administered prophylactically. For instance, low-dose droperidol compares favorable with ondansetron for preventing PONV. The NNT for early nausea is 5 while the NNT for early and late vomiting is 7. Dexamethasone can prevent PONV when administered prophylactically. A single dose of 4-5 mg may be effective for up to 24 hours following surgery; however, unlike ondansetron, dexamethasone must be given at the beginning of surgery since the time to onset of peak effect seems to be 1-2 hours after administration. The NNT for preventing early vomiting is 7.1 and is 3.8 for late vomiting, which compares favorably with ondansetron. In contrast, metoclopramide in the doses typically employed for PONV prophylaxis (i.e., 10 mg IV) appears to be inadequate for a clinically significant effect and cannot be recommended for this indication.

Numerous trials have been undertaken to compare the efficacy of 5-HT_3 antagonists with that of older generic medications. Most commonly studies have compared the efficacy of ondansetron with either droperidol or metoclopramide. Droperidol in doses of either 0.625 mg or 1.25 mg compares favorably with ondansetron 4 mg in outpatients. In fact, the higher dose of droperidol (i.e., 1.25 mg) is more effective than ondansetron in preventing nausea (Fortney JT, et al. *Anesth Analg* 1998;86:731-8). There are no difference in side effect profiles, including sedation, extrapyramidal reactions or cardiac arrhythmia between the ondansetron and droperidol-treated patients when these doses are used.

Recently, it has been shown that combinations of antiemetics administered prophylactically appear to be more effective than either antiemetic alone. For instance the combination of ondansetron and droperidol is more effective than either of the two medications alone. The same is true for the combination of ondansetron and dexamethasone.

As noted above, the use of propofol for maintenance of anesthesia appears to result in lower incidences of PONV than are observed when anesthesia is maintained with potent inhalation anesthetics. This has led to the speculation that propofol may in fact not only be an anesthetic with a low potential for nausea and vomiting, but that it may also possess specific antiemetic properties. Numerous studies have attempted to resolve this issue. While it appears that relatively low doses of propofol may be sufficient to control symptoms in PACU, it may be necessary to achieve higher plasma levels of propofol intraoperatively in order to prevent PONV from occurring during PACU stay and beyond.

Droperidol

On December 5, 2001, the FDA issued a "black box" warning on droperidol. This is the most serious warning for a FDA-approved drug. The warning on droperidol cautioned that it should only be used when other first-line therapy fails. Droperidol already carries a warning about cases of sudden cardiac death at high doses (>25 mg) in psychiatric patients at risk for cardiac arrhythmias. However, the present safety issue is related to death associated with QTc prolongation and torsades de pointes in patients treated with doses of droperidol well below the approved range.

The FDA issued the black box warning based on 9 case reports. In 7 cases, 4 deaths occurred when 2.5 mg droperidol was administered. Cardiac arrests also occurred in 2 patients receiving droperidol 1 mg, with death in 1 patient and a non-fatal cardiac arrest in the other. Based on these reports, the FDA went on to warn that all patients should undergo a 12-lead electrocardiogram (ECG) prior to administration of droperidol to determine if a prolonged QTc interval is present, and to continue ECG monitoring for 3 hours after administration. Since low-dose droperidol is most commonly used in outpatients undergoing ambulatory surgery, these recommendations would be totally impractical and enormously costly to the patients and the healthcare system. Furthermore, there were no data presented to support this recommendation nor are there any published reports where droperidol, in doses used for the management of PONV, has been associated with QTc prolongation, arrhythmias, or acute cardiac arrest. A variety of drug classes have been identified that are associated with QT prolongation and/or arrhythmia induction including antihistamines, butyrophenones, phenothiazines, and selective (5-HT3) serotonin receptor antagonists. In fact, the package inserts for the serotonin antagonist group of drugs such as ondansetron, dolasetron, and granisetron include comments about potential dysrhythmias.

Adjuvants to Management

A variety of non-pharmacologic approaches to management of PONV have been investigated. These include stimulation of the Nei-Guan P6 acupoint, use of supplemental oxygen (i.e., FiO_2>0.30) perioperatively, and aggressive intravenous rehydration. Stimulation of the P6 acupoint has been carried out using a variety of techniques including acupuncture, electroacupuncture, transcutaneous acupoint electrical stimulation (TAES), and acupressure. These techniques have been shown to be effective in treating both motion sickness and pregnancy-induced vomiting. Recently a multicenter, randomized, double-blinded, placebo and sham-controlled study of TAES using the ReliefBand® device (now commercially available) demonstrated a significant decrease in the incidence of moderate-to-severe nausea as determined by the Functional Living Index-Emesis score for up to 9 hours following surgery. Use of the device, however, did not reduce the incidence of vomiting (Zarate E, et al. *Anesth Analg* 2001;92:629-35).

Administration of supplemental oxygen (i.e., FiO_2=0.8, balance nitrogen) intraoperatively and for the first 2 hours postoperatively decreased the incidence of PONV (i.e., vomiting and any complaint of nausea) from 30% to 17% ($p = 0.027$) in patients undergoing colon resection (Greif R, et al. *Anesthesiology* 1999;91:1246-52). The benefit of supplemental oxygen appears to remain intact if the higher concentration (i.e., FiO_2=0.8) is administered only during the intraoperative portion of patient care. In fact, 80% intraoperative oxygen reduced the incidence of PONV over the first 24 hours by half (44% vs. 22%) compared to 30% oxygen in patients undergoing gynecologic laparoscopy (Goll V, et al. *Anesth Analg* 2001;92:112-17). This reduction was greater than that observed in patients receiving ondansetron 8 mg IV as prophylaxis. These finding have, however, been questioned recently (Purhonen S, et al. *Anesth Analg* 2003;96:91-96).

Aggressive intravenous rehydration also appears to decrease the incidence of a number of postoperative symptoms (Yogendran S, et al. *Anesth Analg* 1995;80:682-6.). Patients receiving 20 mL/kg of IV fluid had a decreased incidence of thirst, drowsiness, and dizziness compared to those patients receiving 2 mL/kg. Vomiting was also decreased though statistical significance was not achieved until postoperative day 1.

Multimodal Management

Despite the apparent multifactorial nature of PONV, most attempts at limiting postoperative symptomatology have typically focused on a single contributing factor (e.g., elimination of nitrous oxide from the anesthetic regimen), a

single modification in the anesthetic regimen (e.g., propofol vs. potent inhalation anesthesia), or the addition of a prophylactic antiemetic to a standardized management plan (e.g., ondansetron vs. placebo for the prevention of PONV). While this approach conforms nicely to the typical model of the scientific method, it fails to take into account the complex nature of the physiology involved in the phenomena of PONV. While a series of studies performed by the same investigator (or the same sites in a multicenter trial) could gradually define, in a step-wise fashion, the "optimal" management technique, this approach has not yet been taken, perhaps because of the difficulty involved. Thousands of patients would need to be studied over many years in order to define the "best" strategy for limiting or eliminating PONV. As an alternative, we have recently defined a multimodal approach for the management of PONV (Scuderi PE, et al. *Anesth Analg* 2000;91:1408-14), which was compared to conventional monotherapy prophylaxis (ondansetron 4 mg) and placebo. The incidence of vomiting in PACU prior to discharge was 0% compared to 7% of those receiving ondansetron and 22% of those receiving placebo. The multimodal management group also had a complete response rate of 98% compared to 76% in the ondansetron ($p<0.001$) and 59% in the placebo ($p<0.001$) groups. This study does not define which elements of the algorithm are essential; rather, it does seem to indicate that a zero incidence of PONV is a potentially achievable goal with currently available therapies even in a high-risk patient population.

Post-Discharge Nausea and Vomiting

PONV is not confined to the time patients spend in PACU. Symptoms may persist after inpatients are discharged to hospital rooms and after outpatients are discharged to home. Previously, little emphasis has been placed on control of post-discharge PONV. Although recent studies have more commonly quantified post-discharge symptoms, none have specifically examined strategies to reduce PONV after patients have returned home. Despite the routine prescription of analgesics for post-discharge pain relief, little attention has been given to controlling post-discharge PONV. Measures taken to prevent or treat PONV pre-discharge may have little carryover effect. For instance, while both ondansetron and droperidol have been shown to be effective in preventing pre-discharge vomiting in children undergoing strabismus surgery, the incidence of post-discharge vomiting has been shown to be unchanged when compared to those patients receiving placebo prophylaxis. Although multimodal management can virtually eliminate pre-discharge vomiting, 12% of patients still experienced vomiting after discharge to home. Two recent studies have suggested that measures can be undertaken to limit the severity of post-discharge PONV. Post-discharge administration of ondansetron may be useful in controlling symptoms in females undergoing outpatient laparoscopy (Gan TJ, et al. *Anesth Analg* 2002;94:199-1200). In addition to 4 mg of ondansetron administered at induction, patients were randomized to receive an additional dose of ondansetron in the form of an 8 mg orally disintegrating tablet (ODT) or placebo 12 hours after surgery. The patients receiving the ODT experienced a marked reduction in post-discharge vomiting compared to those receiving placebo (3% vs. 23%, $p=0.02$). Similarly, in children undergoing outpatient strabismus surgery, administration of an additional dose of ondansetron immediately prior to discharge significantly delayed the time to first emetic episode (13.8±3.0 vs. 5.9±1.7 hrs; mean±SEM) (Scuderi PE, et al. *Anesthesiology* 2000;93:A37). These studies suggest that measures can be undertake to limit PONV once patients have returned home following outpatient surgery. Further studies will be necessary to define optimal management strategies.

Efficacy versus Outcome

Despite the undeniable efficacy of currently available approaches to management of PONV, little evidence yet exists to show that "objective" measures of outcome are affected by current methods of management of PONV. It has been proposed that end-points such as duration of PACU stay, incidence of unplanned admissions, and patient satisfaction should be evaluated in addition to simple measures of efficacy such as frequency of vomiting or severity of nausea. An even more basic approach would be to attempt to define the effects of management of PONV on the basic measures of outcome which would include mortality, morbidity, cost, and patient satisfaction.

Modern anesthesia has reached unparalleled levels of safety. It has been estimated that the incidence of death attributable solely to anesthesia is as low as 1:250,000 anesthetics. Given this extremely low mortality, it seems very unlikely that further reductions by alterations in management of PONV can occur, even if PONV could be eliminated

entirely. Changes in morbidity seem a more likely area for improvement. Lists of complications which have been attributed to PONV include dehydration, electrolyte imbalance, tension on sutures and potential evisceration, venous hypertension and bleeding, aspiration, and delay in discharge (particularly for outpatient surgery). It is, however, difficult to quantify the frequency of these complications occurring directly as a result of PONV. It is easier to estimate the incidence of unanticipated admission following outpatient surgery and the factors that contributed to that admission. It has been estimated that the risk of admission related solely to intractable vomiting is less than 0.2% (Gold BS, et al. *JAMA* 1989;262:3008-10). While the incidence of PONV in certain patient subgroups undergoing outpatient surgery can be as high as 50-90%, the number of patients who actually have to be admitted secondary to this complication is extraordinarily low.

In the current era of expanding managed health care, establishing the true cost associated with PONV is more important than ever. While a number of studies have attempted to quantify the economic impact of PONV, the ability to demonstrate significant cost savings is still lacking. Unwarranted economic assumptions are often used as justification for particular therapeutic modalities or approaches to management. It is apparent, however, that attempts to lower cost of care by decreasing PACU stay are unlikely to be successful. Even the complete elimination of PONV will not change PACU staffing needs. If staffing levels cannot be decreased, real savings in direct costs are not likely to be realized. Studies have attempted to provide economic justification by including the "cost" associated with unanticipated admissions due to PONV, which some have equated with the fully allocated cost of a day of hospitalization. The actual cost to the institution is not the "fully allocated" cost; rather, the true cost to the institution is additional incremental (or "marginal") cost associated with that admission. While complications and associated costs related to PONV are an important consideration, the true incidence of these complications and the associated costs are, at best, poorly demonstrated.

Regardless of the true economic consequences, PONV does play an important role in patient satisfaction. A strong preference for limiting emetic symptoms has been demonstrated in several prospective studies. Typically when patients are asked to rate possible postoperative outcomes from their most undesirable to their least undesirable outcome, vomiting is considered to be among the least desirable outcomes.

Prevention versus Treatment

The intuitive assumption that patients would prefer to avoid PONV seems to be confirmed by the currently available studies. What is not apparent is whether prophylactic administration of antiemetics confers benefit beyond that which can be achieved by early aggressive treatment of symptoms, should they occur in PACU. When patients receive routine prophylaxis, compared to rapid symptomatic treatment, there are higher satisfactions scores; however, the NNT is extremely high (i.e., NNT=25). There was, however, no difference in 5-day satisfaction with the entire outpatient surgical experience between patients receiving prophylaxis vs. placebo. There was also no difference between active prophylaxis and placebo in the times required to return to normal activity.

Although PONV may be viewed as highly unpleasant, these data indicate that there is little difference in outcomes when routine prophylactic medications are administered vs. simply treating PONV should symptoms occur. Any clinically significant differences that might occur are likely to be present in only those patients at highest risk for PONV.

Conclusions

A variety of anesthetic, non-anesthetic, and postoperative factors have been identified that can contribute to PONV. Some of these factors can be controlled, many cannot. In circumstances in which the risk factors for PONV cannot be independently controlled, a variety of prophylactic and therapeutic interventions exist. New drugs as well as new approaches to management have resulted in marked improvements in efficacy for both prevention and treatment. While a variety of potential complications have been attributed to PONV, the exact incidence of most of these complications is unknown. The incidence of unanticipated admission following day surgery solely because of PONV remains very low. The actual costs associated with the purported complications of PONV or the additional costs

incurred because of admission to hospital secondary to PONV remain difficult to quantify. Nevertheless, PONV remains an extremely important concern for patients undergoing surgery if for no other reason than it is highly unpleasant. This may be particularly true for patients undergoing ambulatory surgery. Multimodal management has made the goal of zero PONV a reality at least for the immediate postoperative period. There can now be a realistic expectation on the part of even high-risk patients that they can expect to be symptom free following anesthesia and surgery. Still, it is not apparent that prophylactic administration of antiemetics confers any benefit on outcome compared to rapid symptomatic treatment of symptoms should they occur in PACU.

Suggested Reading

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