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REVIEW

Ambulatory anesthesia and postoperative nausea and vomiting: predicting the probability

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Abstract: Nausea and vomiting are distinctly unpleasant symptoms that may occur after surgery and anesthesia, and high priority is given to their prevention by patients. Research in this area is plentiful and has focused on event prediction and pharmacological prophylaxis but despite this, postoperative nausea and vomiting (PONV) typically occurs in 20%–30% of patients in contemporary practice. Prediction of postoperative and postdischarge nausea and vomiting is particularly important in the ambulatory surgical population as these symptoms may occur following discharge from hospital and continue for up to one week when access to antiemetic therapies is limited. Many of the existing predictive scoring systems are based on data from inpatient populations and limited to the first 24 hours after surgery. Scoring systems based on data from ambulatory surgical populations to predict PONV are only moderately good. The best-performing systems in ambulatory patients are those of Sinclair and Sarin with an area under the receiver operating characteristic curve of 0.78 and 0.74, respectively, but are limited by the short duration of follow-up and a greater emphasis on nausea than vomiting. Given that the ability to predict both PONV and postdischarge nausea and vomiting is clearly limited, emphasis has been placed on prophylactic strategies that incorporate antiemetic medication, intravenous hydration, and nonnarcotic analgesia. PONV has been reduced to <10% in institutions using multimodal approaches. Scoring systems may facilitate "risk tailoring" in which patient risk profile is used as a stratification method for pharmacointervention.

Keywords: postoperative nausea and vomiting, prediction, antiemetics, anesthesia

Introduction

Nausea and vomiting are distinctly unpleasant sensations that may occur after surgery and anesthesia. Prevention and treatment of these symptoms are of particular importance in ambulatory anesthesia. Although rarely the cause of major morbidity, they occur relatively frequently and may result in prolonged recovery room or hospital stays or unanticipated admission, adding cost and inconvenience to a patient's experience.[1,2] Patients who become nauseated or vomit stay on average an extra 20–25 minutes in the postanesthetic care unit (PACU).[3] In the ambulatory population, nausea and vomiting may occur or recur following discharge when patients have limited access to effective treatment. For patients, prevention of postoperative nausea and vomiting (PONV) ranks as high as pain control as a health care priority after surgery. Prevention of PONV is one of the extensively studied areas in perioperative medicine, and numerous interventions, pharmacological and nonpharmacological, are proven by double-blind placebo-controlled randomized trials to reduce but unfortunately not eliminate the

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incidence of these symptoms. Established clinical practice encourages clinicians to identify patients at risk of PONV and use a multimodal approach to prevent its occurrence. This review focuses on current approaches to risk prediction and reduction. Prediction of risk is important as not all patients will experience PONV even if not given antiemetic prophylaxis, and therefore, it is of clinical importance to identify patients who might benefit from interventions. In this way, patients who are not at risk of PONV would not receive medications that they have little likelihood of benefitting from, and they would also avoid the risk of possible side effects. The ability to accurately predict PONV coupled with an effective prophylactic or treatment strategy would result in avoidance of symptoms, faster recovery, and increased patient satisfaction, limit the occurrence of side effects, and improve resource utilization.

Postdischarge nausea and vomiting

Postdischarge nausea and vomiting (PDNV) is experienced by 35%–49% of patients and may continue for up to one week.[4–6] Pain may be an additional risk factor for late PDNV.[5] PDNV is particularly concerning, as patients may have limited access to effective therapies, and untreated symptoms have a significant impact on quality of life, functional status, and satisfaction.[5] The ability to accurately predict PDNV would be arguably more valuable than PONV as it would allow clinicians to provide easier access to interventions, eg, longer-acting agents and oral or transdermal preparations. In a multicenter study of 2,170 adults undergoing ambulatory anesthesia, Apfel identified a number of risk factors for PDNV, such as female sex, age <50 years, a history of nausea or vomiting, and opioid administration or nausea in the postanesthesia care unit. Depending on the number of risk factors, the patient's risk for PDNV was predicted as 7%, 20%, 28%, 53%, 60%, and 89%, broadly in keeping with PONV prediction (Figure 1).[6] The area under the receiver operating characteristic curve (AUC ROC) was 0.72.

Economics of PONV

The ability to accurately predict the risk of PONV would also have economic advantage by reducing the PACU stay and the amount of medication used unnecessarily.[7] Kumar et al[3] recently estimated the cost of PONV prophylaxis at STG £70 per case in a UK practice. The cost of the more commonly administered antiemetic agents has decreased substantially in recent years, and acquisition costs have become less of an issue.[8,9] Parra-Sanchez et al[4] in the United States calculated

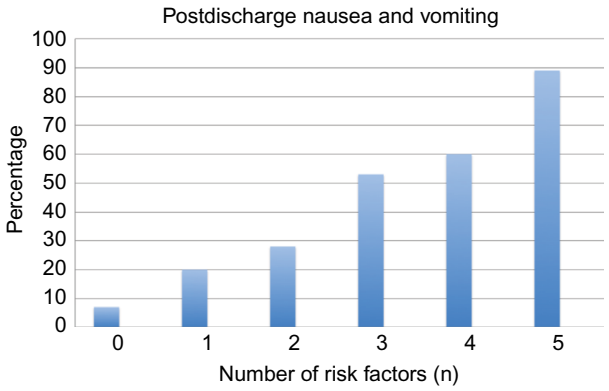

Figure 1 Projected incidence of postdischarge nausea and vomiting using the Apfel score.
Notes: The factors considered are female sex, age <50 years, nausea in the postanesthetic care unit, prior history of PONV, and postoperative opioid administration.
Abbreviation: PONV, postoperative nausea and vomiting.

that PONV added an incremental cost of $75 per patient, which given an institutional incidence of PONV of 37% projects to $2,775 per hundred patients. Habib et al[10] also estimated that the occurrence of nausea and vomiting added USD 85 and 138, respectively, mainly through increased time in PACU and associated nursing costs.

Pathophysiology of PONV

The physiology of PONV is complex and not fully understood. The centers for coordinating vomiting are located throughout the pons and medulla. The chemoreceptor trigger zone (CTZ) and the nucleus tractus solitarius (NTS) receive input, which can contribute to nausea and vomiting (Figure 2). The CTZ then projects to the NTS, which triggers vomiting by stimulating multiple other nuclei (rostral nucleus, nucleus ambiguous, ventral respiratory group, and the dorsal motor nucleus of the vagus). The CTZ receives input from vagal afferents in the gastrointestinal tract. As it is located in the area postrema of the fourth ventricle outside the blood–brain barrier, it can also be stimulated by emetogenic drugs, toxins, and metabolites in the blood and cerebrospinal fluid. The NTS receives input from vagal afferents and from the vestibular and limbic apparatus; therefore, it is sensitive to motion sickness. It also appears to receive input directly from the cerebral cortex in anxiety-induced nausea. There are multiple neurotransmitter pathways involved in transmitting these signals: $5HT_3$ is the principal neurotransmitter for vagal afferents to the CTZ, dopamine-2 transmits from the CTZ to the NTS, and the vestibular apparatus uses histamine-1 and acetylcholine as its neurotransmitters. PONV can be triggered by various stimuli acting on different neurotransmitter

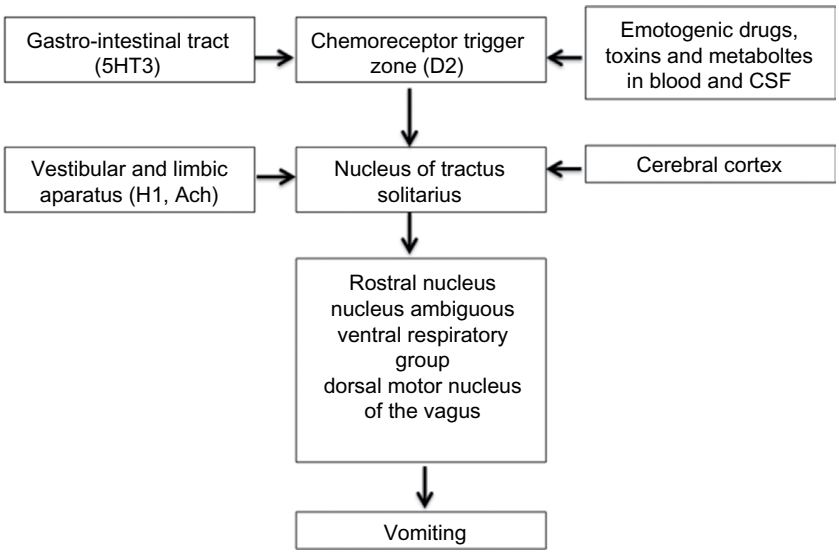

Figure 2 Pathophysiology of nausea and vomiting after anesthesia and surgery.

pathways, including anxiety, pain, drugs, and motion. There are several different classes of antiemetic medications available targeting these different pathways (vide infra).

Antiemetics: risks and benefits

A large number of drugs have been shown in well-designed trials to prophylactically reduce PONV with numbers needed to treat ranging from 2 to 9.[11–17] It is estimated that even the most effective agents reduce the symptoms in only 25%–30% of those who receive them. Since a patient is likely to experience simultaneous activation of multiple emetogenic pathways, the use of drugs that act on different pathways is logical. Used in combination, antiemetic agents from different classes have greater efficacy than used alone.[18] Although in theory, the use of multiple drugs at lower individual doses is more effective than single therapy, evidence for antagonism between some antiemetic agents is evolving.[19]

Available antiemetic agents include $5HT_3$ receptor antagonists, corticosteroids, neurokinin-1 receptor antagonists, butyrophenones, antihistamines, anticholinergics, benzodiazepines, alpha-2 agonists, and phenothiazines. More recently, investigated interventions include gabapentin and mirtazapine that act at $5HT_3$ and histamine receptors.[20] Other drugs can influence PONV through omission or substitution, eg, opioids, volatile anesthetic agents, nitrous oxide, and reversal agents. Given the range of options and dose variations, it is perhaps unsurprising that no optimal combination of agents has been determined. In a Cochrane review of 737 studies involving 103,237 patients, Carlisle and Stevenson[21] studied eight proven antiemetics and estimated that in a population experiencing a 30% incidence of PONV, administration of a proven antiemetic would benefit only 10%. The remainder would not benefit but would be exposed to side effects. A study aiming to investigate all possible combinations of single fixed doses of eight drugs would require 256 groups. Overall, side effects are usually mild and are estimated to be experienced by 4% of those who receive them.[21] The side effects of the drug classes are as follows: $5HT_3$ receptor antagonists: headache, elevated liver enzymes, constipation, and QTc prolongation in higher doses;[22] corticosteroids: hyperglycemia, shortened duration of rocuronium-induced neuromuscular blockade, perineal pruritus, and bradycardia,[23–26] the incidence of postoperative wound infections does not appear to increase following the use of dexamethasone;[27] NK-1 receptor antagonists: dizziness, headaches, and constipation;[28,29] butyrophenones: sedation, hypotension, and extrapyramidal symptoms,[22] pathological QTc prolongation does not occur with doses used for PONV prophylaxis;[30] antihistamines: sedation, dry mouth, and constipation;[29,31] anticholinergic agents: dry mouth, drowsiness, and visual disturbances;[32] benzodiazepines: sedation;[33] alpha-2 agonists: hypotension and sedation; phenothiazines: sedation;[34] gabapentin: somnolence and dizziness;[35] PC6 acupoint stimulation: skin irritation, blistering, redness, and pain.[36]

Risk factor prediction

Internationally agreed consensus guidelines advocate that a clinician assesses each individual patient's risk of PONV using a validated risk score based on independent predictors.[9] The characteristics of a useful risk score are clinical credibility, accuracy, generalizability, and clinical effectiveness.[39] The ability of different scoring systems to predict PONV can be compared using the AUC ROC.[38] A perfect predictive system

Table 1 Risk factors used to predict development of PONV

Authors	Sex	Smoking status	History of PONV	Opioids	Duration of surgery	Motion sickness	Type of surgery	Age	Type of anesthesia
Apfel et al[44]	+	+	+	+	−	+	−	−	−
Koivuranta et al[42]	+	+	+	−	−	+	−	−	−
Palazzo and Evans[41]	+	−	+	+	−	+	−	−	−
Sinclair et al[45]	+	+	+	−	+	−	+	+	+
Sarin et al[48]	+	−	+	+	+	+	+	+	+
Junger et al[46]	+	+	−	+	+	−	−	−	+

Abbreviation: PONV, postoperative nausea and vomiting.

would have a score of 1.0 and a system no better than chance a score of 0.5. Currently used predictive scores identify risk factors in specific surgical populations using logistic regression techniques. These comprise patient, surgical, and anesthesia-related factors (Table 1). A recent meta-analysis of 95,154 patients analyzed symptom occurrence after anesthesia and confirmed the following risk factors: sex (female > male), previous history of PONV, motion sickness, nonsmoking status, postoperative opioid administration, type of anesthesia (general > regional, volatile > total intravenous anesthesia, and nitrous oxide use), younger age, and greater duration of anesthesia.[39] Lower incidences of PONV are seen in patients who had peripheral, and to a lesser extent, central neuraxial blockade.[40,41] The choice of airway device (supraglottic airway vs endotracheal tube) has not been shown to be clinically relevant.[42] Interestingly, intraoperative use of Bispectral Index (BIS) monitoring has recently been shown to be associated with a lower incidence of severe PONV than non-BIS monitored patients, a finding ascribed to lower total dose of maintenance anesthetic agents.[43] Surgical site has not been consistently shown to influence risk of PONV.

In the original studies of PONV risk, different importance (mathematical weighting) was assigned to each factor. Palazzo and Evans[44] studied patients undergoing minor orthopedic surgery and identified female sex, opioids, and previous history of nausea as independent risk factors. These were incorporated into a complex equation that generated a probability of symptom occurrence during the time window studied in the original data set, eg, 0–24 hours postoperatively.[44,45] Such equations are sufficiently unwieldy to be impractical for bedside use and have been simplified for clinical utility.[46] Simplified scores such as those of Apfel and Koivuranta have been shown to be as accurate as their more complex original equations (Figure 3). In the Apfel score, the factors considered are female sex, nonsmoking status, prior history of PONV or motion sickness, and, finally, likelihood of postoperative opioid administration. Patients with no risk factors will have ~10% incidence of PONV. Patients with 1, 2, 3, and 4 factors will have approximate incidences of 20%, 40%, 60%, and 80%,

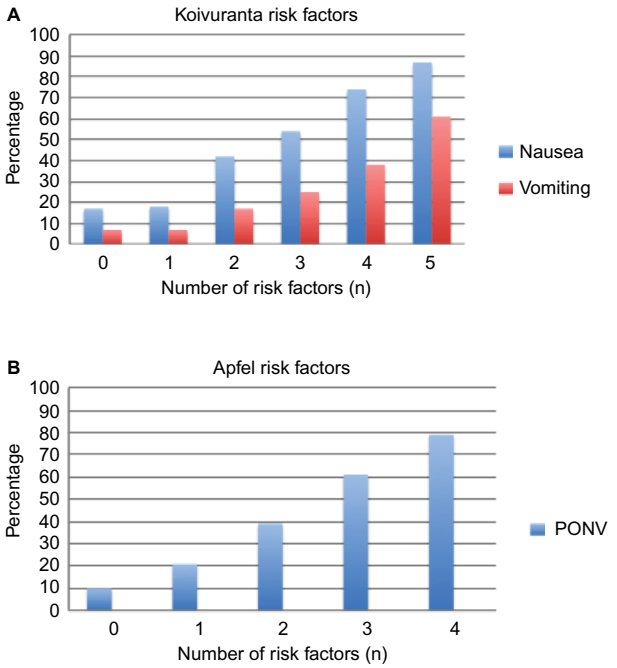

Figure 3 Koivuranta and Apfel Scores
Notes: (**A**) Projected incidence of PONV using the Koivuranta score. The factors considered are female sex, nonsmoking status, prior history of PONV, postoperative opioid administration, and duration of surgery >60 minutes. (**B**) Projected incidence of PONV using the Apfel score. The factors considered are: female sex, nonsmoking status, prior history of PONV or motion sickness, and postoperative opioid administration.
Abbreviation: PONV, postoperative nausea and vomiting.

respectively (Figure 3A).[47] Koivuranta's system that was also simplified uses duration of surgery (>60 minutes) in addition to the aforementioned Apfel factors (Figure 3 A and B).[45] Overlap between these systems is not surprising as they were based in part on the same data set. In Koivuranta's system, the presence of 0, 1, 2, 3, 4, and 5 factors resulted in a predicted incidence of nausea of 17%, 18%, 42%, 54%, 74%, and 87%, respectively. Sinclair et al[48] additionally determined that surgery type (plastic and orthopedic in particular), general anesthesia, and younger age increased the risk of PONV. Using an anesthesia information management system, Junger et al[49] created an algorithm to predict PONV in PACU using female sex, smoking status, age, duration of surgery, intraoperative use of opioids, use of N_2O, and intravenous anesthesia with propofol.

Table 2 AUC ROC for emetic symptoms

Authors	Duration of follow-up (hours)	Patient population	AUC ROC	
			PONV	Vomiting
Apfel et al[44]	0–24	Inpatient	0.7	0.73
Koivuranta et al[42]	0–24	Inpatient	0.71	0.73
Palazzo and Evans[41]	0–24	Inpatient	0.68	0.66
Sinclair et al[45]	0–24	Ambulatory	0.78	–
Sarin et al[48]	Unspecified	Ambulatory	0.74	–
Junger et al[46]	Unspecified*	Mixed	0.76	–
Peng et al[49]	0–24	Inpatient	0.82	–

Note: *Data were collected during PACU stay, the '–' indicates no data.
Abbreviations: AUC ROC, area under the receiver operating characteristic curve; PACU, postanesthetic care unit; PONV, postoperative nausea and vomiting.

The AUC ROC for the most widely used scoring systems is broadly similar with a range of 0.68–0.78 (Table 2).[44–50] Prediction based on surgical site alone is particularly poor with an AUC ROC of 0.53.[51] None has exceeded 0.8 even using highly sophisticated methodology and thus cannot be considered any better than moderately good. Advanced computer technology based on local data sets in the form of an artificial neural network has been shown to be somewhat superior to any of the aforementioned eponymous scoring systems but still falls well short of perfection and remains in the range of "moderately good".[52,53]

Using scoring systems

A practical issue encountered by clinicians using current risk scores is that certain risks cannot be evaluated when assessing risk factors. Although certain risk factors are binary, eg, male versus female, others are not. A patient who has never had an anesthetic before clearly does not have a history of PONV but may well be in a high-risk group. Alternatively, a patient who had a previous anesthetic but did not have PONV may not have experienced symptoms because they received antiemetics. Patients may also confuse delayed opioid-induced nausea with PONV. Additionally, neither the likelihood of postoperative opioid administration nor the duration of surgery can be known with absolute certainty. It is also unclear whether infrequent smokers should be categorized identical to heavy smokers. Similar issues relate to quantification of motion sickness. Thus, arguably, in a proportion of patients, many elements of a scoring system cannot be used with confidence.

Ability of risk factors scoring systems to predict PONV in different populations

A general principle of effective scoring systems is that they also predict events in different patient populations than those used to develop the original model.[37] Toner et al[54] found Palazzo's model to correctly predict the proportion of patients with PONV but only predicted 71% correctly for an individual patient. The score worked best for patients at highest risk. Thomas et al[55] compared four predictive scoring systems in a gynecological surgery population, all of whom received prophylactic antiemetics. Wide variations in prediction were evident. At the Academic Medical Centre of the University of Amsterdam, the Netherlands, van den Bosch et al[56] found that the Apfel score predicted very few patients with PONV in those with few risk factors and overestimated PONV in those with multiple risk factors. Engel et al[57] compared four scoring systems in a population with a low incidence of PONV and found that the AUC ROC of the Koivuranta model (0.62) and that of the Apfel model (0.63) were poorer than those achieved by the authors. The Sinclair (0.7) and Junger models (0.7) performed somewhat better.[57] The applicability of scoring systems across ethnic groups is the subject of ongoing research. Rodseth et al,[58] in a multiethnic South African population, found that the incidence of PONV varied between ethnic groups and was lowest in black South Africans. Adult risk scores have not been found to reliably predict risk in pediatric populations.[59] Factors predicting PONV in pediatrics include age (>3 years), duration of surgery (>30 minutes), strabismus surgery, and a family history of PONV.[59] Predictive systems based on "traditional" volatile anesthesia have been found to overestimate risk in xenon-based anesthesia.[60]

Incidence of PONV in contemporary practice

The average PONV rate in contemporary practice is thought to be ~20%–30%.[61] Examination of control groups in recent randomized controlled trials representing "usual care" in academic institutions shows even higher incidences. In a recent study of 1,483 patients, the incidence of PONV in the patient group who were subject to risk assessment and therapeutic recommendation was 42%. The "care as usual" group had an overall incidence of PONV of 50%. This ranged from 23% to 82% depending on risk profile.[62] A prior study from the same investigators yielded a 42% incidence of PONV in the "care as usual" group.[63] Ziemann-Gimmel et al[64] recently reported an incidence of 37.3% of PONV in bariatric patients who had volatile-based general anesthesia all of whom who received triple prophylaxis. White et al[65] reported a 45% requirement for rescue antiemetics in patients who had a minimum of two Apfel risk factors.

In the ENIGMA (Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia) trial, which was primarily intended

to investigate the effect of nitrous oxide administration on mortality, antiemetic administration was left to the discretion of the attending anesthetists. Severe PONV occurred in 16.6% of patients and was associated with female sex (odds ratio [OR] 2.06), age <55 years (OR 1.38), abdominal surgery (OR 1.74), N_2O administration (OR 2.5), duration of surgery >3.5 hours (OR 1.23–1.53), and the absence of BIS monitoring (OR 0.66).[43] In Spanish and Portuguese University Teaching Hospitals, the reported incidence of PONV was identical at 34%.[66,67]

Reducing baseline risk – importance of nonpharmacological interventions – hydration and acustimulation

Hydration

A number of well-conducted studies have investigated the effect of intravenous fluids in PONV.[68] McCaul et al[69] failed to find any benefit of balanced crystalloid in quantities targeted to replace fasting volume-deficit patients undergoing gynecological laparoscopy. In a similar patient population, larger quantities of fluid (30 mL/kg) did, however, reduce PONV substantially.[70] Pulmonary function was not adversely affected at these volumes, but it should be recognized that the patients in these studies did not have cardiorespiratory disease, and equivalent volumes of fluid may not be appropriate to all patient populations and surgeries.[71] Intravenous fluid administration has also been shown to reduce pain after laparoscopic surgery.[71,72] The results of the studies investigating colloids are conflicting.[73] Preoperative oral carbohydrate drinks taken 2 hours preoperatively have been shown to reduce PONV.[74]

Acustimulation

A recent Cochrane review assessed the literature regarding stimulation of the wrist acupuncture point PC6 for preventing PONV and found the technique to be noninferior to pharmacological antiemetics.[36]

Implementation gaps

There is ample evidence that antiemetic prophylaxis is underutilized by providers.[29,75] In Scotland, Brampton et al[76] reported only a 67% adherence to local PONV guidelines and a 58% incidence of PONV. In the US, 61% and 52% compliances were reported for prophylaxis and rescue medication, respectively, in accordance with the American Society of Anesthesiologists and American Society of Peri-Anesthesia Nurses clinical practice guidelines.[65] In that study, conducted in an academic teaching center, 8% of patients did not receive any prophylactic antiemetic agents despite each having a high-risk profile. Compliance with institutional protocols is improved somewhat by educational strategies and decision prompting.[77,78] Kappen et al[79] recently reported their investigation into the failure of risk-prompting strategy for PONV to influence patient outcome. The reluctance of the clinicians to change practice was based in part on risk management, ie, the lack of risk–benefit consideration for drugs. Additional factors were the low priority given to PONV as an important health care outcome and the reliance on intuition to make decisions regarding prophylaxis.[79]

Variations in clinical practice

Leading experts argue for more liberal use of multimodal pharmacoprophylaxis irrespective of risk profile on the basis of proven efficacy and the modest cost and relatively benign side effect profile of antiemetics.[61] This included triple antiemetic prophylaxis, total intravenous anesthesia, intravenous hydration, nonsteroidal anti-inflammatory agents, and the avoidance of muscle relaxation.[80] Eberhart et al[81] achieved similarly low incidence of PONV (7%) using a multimodal approach that included prophylactic antiemetics. An alternative approach is "risk tailoring", in which patient risk profile is used as a stratification method for pharmacointervention.[82] Using this approach, Pierre et al[82] reported a 15.5% incidence of PONV using multidrug prophylaxis in the highest risk group and 14.3% in the lowest risk group, achieved without antiemetic prophylaxis. The third approach is to treat symptoms of patient as they arise.[83] The obvious drawback of this approach is the knowledge that PONV will occur commonly and might require an anesthetist to regularly leave the operating room to administer medication. The symptoms of PONV are not reliably detected in busy PACUs and might go untreated and worsen subsequently in ward areas where administration of intravenous agents is more difficult.[84]

Future directions

Given that PONV is influenced by local practice, it is intuitive that local data sets would be usefully incorporated into predictive models to generate site-relevant predictive scores. Such an approach has been generated by Junger et al,[49] who used routinely collected information from an anesthesia information management system at Justus Liebig University Giessen. Based on the analysis of 15 anesthesia-related, ten patient-related, and four postoperative factors, the computerized system automatically calculated PONV risk. In this way, risk factor prediction can be incorporated into decision-making aids, such as computer pop-up windows. This has been shown

to substantially increase the use of antiemetics administered as prophylaxis.[77] Smartphone-based applications may have similar utility in the future.

Pharmacogenomics has future implications for PONV prevention and treatment. Attempts to identify genetic loci that contribute to PONV are ongoing.[85] Investigations have shown that homozygous patients with the A118 variant of OPRM1 are at higher risk of PONV.[85] Rueffert et al[86] investigated variants of the serotonin receptor subunits A and B for genetic variants in 95 patients who had suffered from PONV and found patterns that were associated with an increased risk of postoperative vomiting. In a study of $5HT_3$ antagonists in chemotherapy-induced nausea, slow metabolizers of CYP2D6 substrates had high tropisetron levels, and ultrarapid metabolizers had higher frequency of vomiting than all the other patients.[87]

Summary

PONV remains a common clinical problem despite the availability of predictive scoring systems and efficacious interventions. The ability of scoring systems to predict the incidence of PONV in untreated patients is relatively consistent. The thresholds at which clinicians should initiate prophylactic medication regimens are less clear. This may explain in part why antiemetic prophylaxis based on risk stratification has been shown to reduce but not eliminate the incidence of PONV.[82,88,89] Clinicians should bear in mind that even if a perfect predictive system for PONV or PDNV were developed, these symptoms will persist until the perfect antiemetic strategy is established.

Disclosure

The authors report no conflicts of interest in this work.

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