

Should we be more rigorous with anti-emetic prophylaxis ?

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Postoperative nausea and vomiting – usually summarized as PONV – remains one of the most common and distressing complications after surgery (1, 2). About 30% of patients receiving a general anaesthetic are affected and the incidence is known to rise up to 80% or more in high-risk patient groups (3). Despite the introduction of new anti-emetic agents, short acting anaesthetics, and minimally invasive surgical techniques, the incidence of PONV has remained largely unchanged over the past two decades (4, 5). The high incidence of PONV has persisted in part because of the tremendous growth in ambulatory surgery and the increased emphasis on earlier mobilisation and discharge after both minor and major operation (6).

PONV is a major problem in ambulatory surgery since it prolongs the time to discharge and reduces patient satisfaction and is perceived by patients worse than pain (7-10). In this context, nursing labour costs are directly related to the duration of PACU stay. Serious complications are relatively rare and include aspiration of vomit, dehydration, alkalaemia, rupture of the oesophagus (Boerhaave's syndrome) and Mallory-Weiss syndrome (11). While the prophylaxis and management of PONV occurring in the post anaesthesia care unit (PACU) has significantly improved, nausea and vomiting occurring following discharge from PACU remains under treated. Nausea and vomiting occurring in PACU may not accurately predict the incidence after discharge. Approximately 36% of patients who experience post-discharge nausea and vomiting do not experience any PONV prior to discharge. In an analysis of all studies evaluating patient-reported symptoms after outpatient surgery, the overall incidence of nausea and vomiting occurring following discharge from hospital has been estimated to be 17% (range 0-55%) and 8% (range 0-16%) respectively (12). This can be distressing to the patients in the absence of available treatment (13).

RISK FACTORS OF POSTOPERATIVE NAUSEA AND VOMITING

Several studies have outlined the factors related to an increased incidence of PONV with the aim to target specific patients who might need effective anti-emetic prophylaxis (1, 3, 5, 14-24). It is assumed that PONV has a multifactorial origin, such as patient-related factors (e.g. female gender, history of motion sickness, or PONV), anaesthetic factors (e.g. mask ventilation, volatile anaesthetics, opioids), and surgical factors (5, 15). In most analyses, opioid use is considered one of the major predictors for PONV (14). DERSHWITZ *et al.* showed that when propofol-based total intravenous anaesthesia (TIVA) is used for arthroscopic surgery, short acting opioids, i.e. remifentanyl or alfentanil, do not significantly affect the risk of PONV (25). Other studies have yielded conflicting results. ELTZSCHIG *et al.* concluded in a randomized, double-blinded study that children undergoing strabismus surgery under balanced anaesthesia with remifentanyl, compared with fentanyl, showed less frequent postoperative vomiting (26). Alfentanil, compared with fentanyl and sufentanil was associated with a lower incidence of postoperative nausea and vomiting in outpatients (27). Intravenous anaesthesia with propofol and alfentanil seems superior to inhalational maintenance with nitrous oxide and enflurane in that it is associated with less PONV and unplanned admission to hospital after day-case gynaecological surgery (28). These studies suggest that the selection of an opioid can affect the incidence of PONV in outpatient surgery. Concerning

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volatile anaesthesia, NELSKYLÄ *et al.* have reported that titration of sevoflurane using the bispectral index monitor decreased PONV after outpatient gynaecological laparoscopic surgery (29).

There is also some confusion about the contribution of residual paralysis to the occurrence of PONV after ambulatory anaesthesia. Despite the widespread belief that anticholinesterase drugs may be emetic, there is no convincing evidence, based on clinical studies, that omitting pharmacological reversal at the end of anaesthesia decreases the risk of PONV (30).

Although risk factors for postoperative nausea are generally assumed as being the same as those for vomiting, STADLER *et al.* found that some risk factors were predictive of both nausea and vomiting (female gender, non-smoking status, general anaesthesia) but that history of migraine and type of surgery were solely related to nausea (24). These results could be explained by the difference in the physiology of nausea and vomiting (11, 31). Nausea is a subjective sensation requiring activation of neural pathways, which eventually project to areas of the cerebral hemispheres dealing with conscious sensations (32). Nausea is not always followed by retching or vomiting. Vomiting is a complex reflex under the control of two functionally distinct medullar centers: the vomiting center in the dorsal portion of the lateral reticular formation and the chemoreceptor trigger zone in the area postrema of the floor of the fourth ventricle. Furthermore, it is well proved that an anti-emetic drug may have more anti-nausea efficacy, i.e. droperidol, or more anti-emetic efficacy, i.e. the 5-HT₃ antagonists (33).

MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING

Anesthesiology literature is particularly abundant on the management of PONV. Effectiveness studies of anti-emetics used during the perioperative period have made it possible to adopt some well-justified therapeutic attitudes (34). MACARIO *et al.* performed a survey asking Californian anaesthesiologists to report their clinical practice patterns for PONV prophylaxis. In absence of well-accepted guidelines for the most appropriate therapy, these authors found a wide range of management patterns. This variation in clinical practice may reflect uncertainty about the efficacy of available interventions, or differences in practitioners' clinical judgement and beliefs about how to treat PONV (35).

Antiemetic treatment

1. Which drugs, what combination ?

Classic anti-emetics, like metoclopramide or dimenhydrinate, are not very effective, or no more so than the placebo (36, 37). HENZI *et al.* summarized in their review that "... metoclopramide, although used as an antiemetic for almost 40 years in the prevention of PONV, has no clinically relevant antiemetic effect ... it is very likely that the doses used in daily clinical practice are too low" (36).

The reference drugs for this indication are the serotonin type 3 (5-HT₃) receptor antagonists, and the two most important medications are droperidol and dexamethasone. (38-62). HELMY showed that pre-anaesthetic intravenous ondansetron was superior to droperidol, metoclopramide and placebo as a prophylactic anti-emetic in patients undergoing day-case laparoscopic cholecystectomy under TIVA, especially during the first 4 hours (63). HENZI *et al.* found in a meta-analysis that the anti-nausea effect of droperidol is not dose dependant, is more pronounced than the anti-vomiting effect, and is short-lived (64).

HABIB *et al.* compared the association of 5-HT₃ receptor antagonists with droperidol or dexamethasone and concluded that there was no significant difference in anti-emetic efficacy or side effects profile between both combination regimens (65). Both combinations provided better PONV prophylaxis compared with 5-HT₃ receptor antagonists alone. Ondansetron in combination with droperidol or dexamethasone seems more effective than dexamethasone in combination with droperidol in women undergoing general anaesthesia for gynaecological surgery (66). Same results have been obtained by SPLINTER *et RHINE* after strabismus surgery in children (67). In the prophylactic and the treatment setting, effective drugs increase the number of complete responders by about 20-30% over placebo, but not one of these drugs is sufficient on its own against PONV in any given population.

Recently, a panel of experts agreed that there is no evidence of any difference in the efficacy of the 5-HT₃ receptor antagonists in the prophylaxis of PONV (68). For example, the anti-emetic efficacy of prophylactic ondansetron and dolasetron was comparable in dexamethasone-pretreated children undergoing ambulatory tonsillectomy (69).

Dexamethasone is a glucocorticoid that produces a strong anti-emetic effect (70-73). Dexamethasone appears as a cost-effective alterna-

tive to ondansetron in preventing PONV after paediatric strabismus repair (74). LIU *et al.* demonstrated that dexamethasone alone at doses of 5 mg and 2.5 mg reduces incidence of PONV by about 40% compared to placebo (75, 76). In a study by HUANG *et al.* the incidence of PONV was reduced by about 35% after pretreatment with a low dose of dexamethasone (5 mg) in patients undergoing laparoscopy for tubal ligation (77). Similar results were obtained with dexamethasone 10 mg in the same indication (78). ELHAKIM *et al.* showed that dexamethasone 8 mg combined with ondansetron was more effective than ondansetron alone for control of PONV (74). FUJII *et al.* in repeated publications demonstrated the usefulness of combination of 5-HT₃ and corticoids (79-85). WANG *et al.* have shown that the prophylactic administration of dexamethasone immediately before the induction, rather than at the end of anaesthesia, was more effective in preventing PONV (86). Dexamethasone seems to have a longer duration of action than droperidol in outpatients undergoing gynaecologic laparoscopy (87). In this study, the most frequent reported side effect of dexamethasone is perineal itching during IV administration.

FRIGHETTO *et al.* demonstrated that dolasetron and droperidol given intraoperatively are potentially more cost-effective than no prophylaxis for PONV in patients undergoing gynaecologic day-case surgery (88). In a recent meta-analysis, the number-needed-to-treat (NNT) to prevent post-discharge nausea following ambulatory surgery was 12.9, 12.2, and 5.2 following the prophylactic administration of ondansetron 4 mg, dexamethasone, and a combination of two anti-emetics respectively. For post-discharge vomiting, the NNT was 13.8 for ondansetron and 5 for combination treatment. In this analysis, droperidol was not effective for prophylaxis against post-discharge nausea and vomiting. These results suggest that ondansetron alone should not be used routinely in low-risk ambulatory patients and that high-risk patients are best managed with a combination strategy (89). Similar results were obtained by THOMAS et JONES after day-case gynaecological surgery (90).

None of the available anti-emetics is entirely effective for preventing PONV, especially in high-risk patients. Since at least four major receptor systems are involved in the etiology of PONV, a better prophylaxis might be achieved by using a combination of agents acting at different receptors sites. The most commonly studied combinations have thus included a 5-HT₃ receptor antagonist with

either droperidol or dexamethasone. Both combination regimens appear to be equally efficacious (65). It is generally accepted that to effectively control PONV one needs to use several drugs acting on different receptors types involved in the pathogenesis of emesis. The complete response rate as well as patient satisfaction have been reported to be higher than 90% when a 5-HT₃ receptor antagonist is associated with another anti-emetic, e.g. dexamethasone or droperidol.

2. Which dose and when ?

There is more consensus on the appropriate dose of anti-emetics : e.g. ondansetron 4mg, dolasetron 12.5 mg, droperidol 0.625 mg, than on when it is best to administer them. Given the relative short elimination half-life of ondansetron (3-4 hours), TANG *et al.* demonstrated that administration of the drug immediately before the end of surgery was the most efficacious in preventing PONV, facilitating both early and late recovery, and improving patient satisfaction after outpatient laparoscopy (91). In outpatients undergoing otolaryngologic procedures, ondansetron should be given at the end of the operation rather than prior to induction of anaesthesia (92). Most of the available anti-emetics have short half-lives and may not be effective after discharge from the hospital in a day-case setting. Administration of prophylactic anti-emetics following discharge may therefore be warranted in high-risk patients. GAN *et al.* evaluated the administration of ondansetron in a new-dried oral formulation and found a decrease in the incidence of PONV after ambulatory surgery (93). SPLINTER *et al.* have previously studied this formulation in the prevention of vomiting after tonsillectomy in children (94). The use of a transdermal scopolamine patch has also been proposed (95).

3. To whom ?

Prophylactic anti-emetic therapy seems cost-effective for situation with a high frequency of emesis, whereas treatment of PONV is more cost effective when the frequency is lower. Recent clinical guidelines suggest that the choice between prophylactic or rescue anti-emetic treatment should depend on the patient's risk for PONV. A previous recommendation suggested to classify patients into one of four risk groups for PONV : low risk (< 10%), mild to moderate risk (10-30%), high risk (30-60%), and very high risk (> 60%) of PONV (96). PIERRE *et al.* suggest that a risk score-dependent anti-emetic strategy through a quality

improvement initiative, effectively reduces the incidence of PONV (97). APFEL *et al.* confirms preceding results and stated that prophylaxis is rarely warranted in low-risk patients, that moderate risk patients may benefit from a single intervention, and that multiple interventions should be reserved for high-risk patients (98). The resulting data of this meta-analysis suggest that anti-emetics with different mechanisms of action have additive (rather than synergistic) effects on the incidence of PONV. This observation has been made previously by WU *et al.* (99).

Prophylaxis versus treatment

WATCHA *et al.* SMITH found that the incidence of PONV at which prophylaxis is more effective than treatment of established symptoms is 30% for ondansetron and 13% for droperidol, considering the difference in acquisition cost of these drugs in the United States (100). WATCHA suggested guidelines for prophylaxis and treatment according to the presence of risk factors, from one (no prophylaxis and rescue treatment with 5-HT₃ receptor antagonists) to four (triple prophylaxis with droperidol, steroids and a 5-HT₃). These choices are based on drug effectiveness, side-effect profile, and associated reduction in total costs (96).

Quantitative systematic reviews show that, for prophylactic anti-emetics, the relative reduction rate of PONV is in the range of 30 to 40% (33). Routine anti-emetic prophylaxis in unselected patients is questionable. Therefore it appears more reasonable to manage PONV according to the individual risk of each patient. As proposed by BIEDLER *et al.*, prophylaxis should be limited to patients with a high risk of PONV (101). Nevertheless, there is an ongoing debate regarding the most cost effective strategy for the management of PONV (103). No major benefit for routine anti-emetic prophylaxis has been shown when drugs are administered non-selectively. For example, routine prophylaxis with 5-HT₃ antagonists improves the satisfaction of patients at high risk of PONV but not the satisfaction of low-risk patients (102). Therefore a cost-effective approach to the management of PONV would be to provide prophylactic anti-emetic therapy in situations with a high-risk of emesis and to give treatment for established PONV in situations where the risk is lower. In order to make such decisions, it is mandatory to know the incidence of PONV in the local setting. But numerous studies have demonstrated that prophylaxis with 5-HT₃ antagonists as the single anti-emetic in high-

risk patients appears to be of limited efficacy in the reduction of PONV (101). It can be assumed that for a better efficacy of prophylaxis in higher-risk patients the combination of two or more anti-emetics may increase the efficacy of prophylaxis and reduce the number of patients with PONV (96).

PONV AND AMBULATORY SURGERY

The current approach to the problem of PONV goes far beyond the simple strategy of prescribing anti-emetic drugs. At each step of the anaesthesia process and the perioperative period, all available knowledge is applied to avoiding PONV. The choice of induction and maintenance anaesthetics appears to be important in a day-case surgery setting. Propofol is the preferred induction agent for outpatient surgery over sevoflurane as shown in a meta-analysis by JOO *et al.* PERKS (103). When compared with inhalation agents, maintenance of anaesthesia with propofol is associated with a lower incidence of PONV (mean NNT = 7.1) (104).

Recently, HABIB *et al.* GAN provided evidence-based guidelines for the prophylaxis and treatment of PONV (105). In addition of using a combination of anti-emetics acting at different receptors sites, these authors proposed a multimodal approach, considering the multifactorial etiology of PONV. The different strategies for keeping the baseline risk of PONV low are: preference to regional anaesthesia, TIVA with propofol, avoidance of nitrous oxide and volatile agents, and minimizing intraoperative and postoperative opiates. Other strategies that might reduce the incidence of PONV include the use of supplemental oxygen, adequate hydration specially using colloids, anxiolysis with benzodiazepines, and the use of alpha-2 agonists.

SCUDERI *et al.* tested a multimodal approach to the management of PONV, which resulted in a 0% incidence of vomiting before discharge in females undergoing outpatient laparoscopy. The main points of this management include premedication with midazolam, preoxygenation, anaesthesia with propofol and remifentanyl; prophylaxis with droperidol 0.625 mg and dexamethasone 10 mg after induction and with ondansetron 1 mg at the end of the procedure; 25 mg/kg total hydration; preemptive pain control with ketorolac and fentanyl (106). HABIB *et al.* demonstrated that a multimodal PONV prophylaxis regimen incorporating TIVA with propofol and a combination of ondansetron and droperidol was more effective

than a combination of these anti-emetics in the presence of an inhaled anaesthetic (107). KOKI *et al.* showed that ketoprofen administered i.v. during the operation produced analgesia and reduced opioid consumption and the incidence of vomiting in children after strabismus surgery (108).

Another multimodal perioperative management strategy that aimed at preventing PONV consisted of induction of anaesthesia with propofol, BIS control of inhalation maintenance, prophylactic droperidol 0.625 mg plus ondansetron 5 mg and dexamethasone 10 mg, and preemptive treatment of postoperative pain with ketorolac 30 mg plus intraperitoneal bupivacaine. This strategy proved to significantly shorten the postoperative length of recovery (109). EBERHART *et al.* assessed the efficacy of a multimodal approach to prevent PONV, and patient satisfaction using the willingness-to-paid method. High-risk patients received multimodal anti-emetic prophylaxis: total intravenous anaesthesia with propofol, high fractional inspired oxygen, omission of nitrous oxide, dexamethasone, haloperidol and 5-HT₃ receptor antagonists. The remainder low-risk patients did not receive anti-emetics. The multimodal anti-emetic approach reduced significantly the incidence of PONV in the high-risk group and was associated with a high patient satisfaction as measured by the willingness-to-paid method (110).

Optimal therapy ?

Nevertheless, despite the extensive literature describing strategies for the prevention of PONV, the optimal prophylactic anti-emetic regimen has not been established. TANG *et al.* found no advantage of adding an expensive 5-HT₃ antagonists to a combination of droperidol and dexamethasone in the prevention of PONV following office-based surgery (111). These authors proposed the combination of 0.625 mg intravenous droperidol and 4 mg intravenous dexamethasone. The outpatient surgery population studied by TANG *et al.* involved a variety of superficial, non-gynaecologic, and non-otolaryngologic procedures. It is entirely possible that these authors would have obtained a different result if they had studied an outpatient population at higher risk of developing PONV, e.g. those undergoing laparoscopic or otolaryngologic procedures.

After day-case gynaecologic laparoscopic surgery, the reported incidence of PONV exceeds 50% (113-115). PONV is often the most distressing aspect of patients' surgical experience, can

increase pain and cause unplanned hospital admission (5, 116). As more patients undergo surgery as a day case, the humanitarian and economic implications of PONV are becoming increasingly important (117). AHMED *et al.* evaluated the efficacy of a combination of ondansetron and cyclizine, an antagonist at muscarinic cholinergic and histamine-1 receptors, for the prophylaxis of PONV in patients undergoing day-case gynaecologic laparoscopic surgery. Compared with ondansetron alone, the combination group had a significantly lower incidence and severity of nausea after discharge and more patients with no PONV at any time during the study ($P < 0.001$). No patient receiving combination prophylaxis was admitted overnight for PONV management (118).

Many studies of anti-emetics show significant reductions on the incidence of PONV, often of the order of 50%, but the outcomes associated with single anti-emetic prophylaxis remain disappointing. (119-121).

Concerning Consensus guidelines, there are some expectations about how it arose, how the test cohort of experts was selected, and how consensus was determined. There have been many published consensus guidelines that had significant clinical impact that were not commissioned by a professional organization. Furthermore, a pharmaceutical company frequently supports publication of consensus guidelines. Questions naturally arise regarding a possible conflict of interest (122). As stated by TRAMÈR, attentive readers may discover discrepancies between the conclusions of different expert review articles, and these may throw doubt on the validity of these reports (123).

Non-pharmacological approach to PONV

Non-pharmacological methods like acupuncture, acupressure and laser stimulation have shown comparable anti-emetic efficacy (124). AGARWAL *et al.* compared the efficacy of acupressure and ondansetron for the prevention of PONV following laparoscopic cholecystectomy. These authors showed that the incidence of PONV and the requirement for rescue anti-emetics were significantly lower in the acupressure and ondansetron groups in the first six hours after surgery, but not in PONV and anti-emetics required at 24 hours (125). Perioperative P6 electroacupuncture in pediatric patients reduced the occurrence of nausea but did not significantly reduce the incidence or number of episodes of emesis or the use of rescue anti-emetics (126).

SIDE EFFECTS OF PONV TREATMENT

The extra pyramidal side effects of droperidol are of some concern, particularly in day-case patients, and many clinicians may be reluctant to give steroids primarily for managing PONV (127, 128). EBERHART *et al.* SEELING showed that high dose droperidol (5 – 7.5 mg) induced depressed patient mood and well-being ratings 6 hours after surgery and recommend smaller dose (< 5 mg) (129). STEAD *et al.* demonstrated that prophylactic administration of 80 µg/kg of droperidol was more effective than lower doses of the same drug in reducing postoperative emetic symptoms without increasing time to discharge after paediatric strabismus surgery. In those patients who vomited and who also received prophylactic ondansetron, time to discharge was significantly delayed (130). Finally, the widely criticized, unfortunate Food and Drug Administration black box warning to droperidol has made it difficult to establish evidence-based recommendations for the control of PONV in countries in which droperidol has been withdrawn from the market (131).

Even though the clinical safety of 5-HT₃ receptor antagonists, adverse events have been reported. These include neuro-psychiatric events (dystonic reactions and acute depression), and cardiovascular events (acute myocardial infarction, arrhythmias) (132).

NEW PHARMACOLOGICAL APPROACH TO PONV

In a systematic review, ERNST *et al.* PITTER concluded that ginger (*Zingiber officinale*) is a promising anti-emetic herbal remedy, but, at this time, the clinical data are insufficient to draw firm conclusions (133).

Neurokinin 1 receptor antagonists are the latest generation of drugs undergoing investigation. They appear to act by preventing the vomiting process rather than by blocking the afferent input. In animal studies, these drugs appear able to prevent vomiting from any cause but whether they are effective in preventing nausea remains unclear. Early studies in human showed promise that this effectiveness in animal will be translated into humans; however, so far, such promise has not been realised (134).

CONCLUSION

Combination prophylaxis represents a major step forward in improving the outcome of day-case

surgical patients (101). It is important especially in this group of patients, to have effective control of symptoms. Combination prophylaxis may also have important economic implications. These include reduced costs associated with nursing time spent managing PONV as well as costs of delayed discharge or unplanned admission. Recently, TRAMER proposes the 'rule of three' for a rational control of PONV: first try to identify patients at risk; second, try to keep the baseline risk low; third, when you decide to give anti-emetic drugs, give them rationally: concentrate on drugs that are effective, and combine them (120).

In summary, the identification of patients at increased risk for PONV allows targeting anti-emetic prophylaxis to those who will benefit most from it. No prophylaxis is warranted for patients at low risk for PONV. For patients at moderate to high risk, anti-emetics should be used either as monotherapy or in combination for PONV prophylaxis. There is increasing evidence that a combination of drugs acting at different receptors achieves a better prophylaxis. The multimodal approach should be considered in patients at high risk for PONV.

In consideration of these scientific data, clinical evidence and the fact that health care professionals should consider patient's preferences and provide an excellent service to their clients, the question must definitively be answered with **yes**.

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