



Postoperative Nausea and Vomiting in Paediatric Anaesthesia

Ivan Urits¹ , Vwaire Orhurhu¹ , Mark R. Jones¹ , Leena Adamian² , Matthew Borchart³ , Annemarie Galasso³ , Omar Viswanath⁴ 

¹Beth Israel Deaconess Medical Center, Department of Anesthesia, Critical Care, and Pain Medicine, Harvard Medical School, Boston, MA, USA

²Creighton University School of Medicine - Phoenix Regional Campus, Phoenix, AZ, USA

³Georgetown University School of Medicine, Washington, DC, USA

⁴Valley Anesthesiology and Pain Consultants, Phoenix, AZ; University of Arizona College of Medicine Phoenix, Department of Anesthesiology, Phoenix, AZ; Creighton University School of Medicine, Department of Anesthesiology, Omaha, NE, USA

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Abstract

Postoperative nausea and vomiting (PONV) is a common complication in paediatric anaesthesia and is a source of significant morbidity. Various independent risk factors have been implicated in the development of paediatric PONV, including higher pain scores postoperatively, the use of opioids for pain management and the use of volatile anaesthetics for the maintenance of anaesthesia. This review of the current literature regarding the prevention and treatment of paediatric PONV is based on a search of the PubMed database, which identified published clinical trials, systematic reviews and meta-analyses. While the occurrence of PONV in many cases is difficult to avoid entirely, the risk can be mitigated by the use of multimodal nonopioid analgesic regimens, total intravenous drugs in favour of volatile anaesthetics and an appropriate regimen of prophylactic pharmacotherapy. Frequently administered drug classes for the prevention of PONV include corticosteroids, 5HT₃ antagonists and anticholinergics. The clinical use of the findings in the literature may help to reduce the occurrence of PONV in children. In this review, we provide comprehensive and updated information on the risk factors contributing the occurrence of PONV in children, outline the current opinion on the drugs that are commonly used for management and provide an overview of the guidelines that are used to help establish the prophylaxis and treatment of paediatric PONV.

Keywords: Anaesthesia, guidelines for prophylaxis and treatment, postoperative nausea and vomiting, risk factors

Introduction

Postoperative nausea and vomiting (PONV) is a common complication in the paediatric population and is a source of significant morbidity. The incidence of PONV in children is alarmingly high, as it is estimated to be between 33.2% to 82% depending on patient risk factors (1). PONV typically describes nausea, vomiting, or retching that can occur starting in the post-anaesthesia care unit (PACU) and continuing through the 24 hours following surgery. Post-discharge nausea and vomiting includes symptoms that persist for up to 7 days after anaesthesia. PONV occurs twice as often in children than in adults and can lead to longer PACU stays, delays in hospital discharge and subsequent unplanned readmissions, which ultimately lead to significant financial burden on the patients (2). The syndrome of nausea, vomiting and dehydration is one of the leading causes of paediatric readmissions, accounting for 51.2% of such cases. Moreover, paediatric readmission, within one week of discharge, is estimated to contribute to \$1 billion in healthcare costs annually (3).

A variety of antiemetic regimens are recommended for the prevention and treatment of PONV in children, including pharmacotherapy with dexamethasone, 5HT₃ receptor antagonists, butyrophenones, prokinetics, anticholinergics and antihistamines. In this review, we provide an update of the current understanding in the management of paediatric PONV.

Risk factors

Various independent risk factors have been implicated in the development of paediatric PONV. In a multi-centre study of 1257 children, the following major risk factors were identified: a duration of surgery 30 minutes or longer, age 3 years or older, strabismus surgery and a history of PONV in the child or immediate relatives (parents or siblings) (4). Moreover, the risk of developing PONV was stratified and estimated to be 9%, 10%, 30%, 55% and 70% depending on the presence of 0, 1, 2, 3, or 4 risk factors respectively (Table 1). The duration of surgery is believed to contribute to the incidence of PONV because of longer exposure to emetogenic stimuli. Higher incidence of PONV is also associated with higher pain scores postoperatively, the use of opioids for pain management and the use of volatile anaesthetics for maintenance of anaesthesia (2). Age under 3 years seems to be protective against developing PONV, though the mechanism is poorly understood as the contrary holds true in adults whose age is less than 50 years (5). The female gender increases the risk for PONV, though this has not been shown to be clinically significant and is not considered to be a major contributory factor. It is further believed that there is a degree of genetic contribution to the development of PONV that resulted in the observed familial association, though the exact nature of this has not been described (4).

Emetogenic procedures

Various surgeries are associated with a higher risk of developing PONV; some of the highest incidences occur in ocular and ENT surgeries including tonsillectomy, adenoidectomy, and strabismus correction (6). One study found that PONV rates were as high as 82% in paediatric patients undergoing tonsillectomy and another reported PONV rates of 54% in children undergoing strabismus surgery (7). Rates of PONV have also been reported to be greater than

50% in orchidopexy and hernia repair (6). Considering these high rates of PONV, antiemetic prophylaxis should especially be considered in patients undergoing these procedures.

Influence of the choice of the anaesthetic drug

Given the high prevalence of PONV in paediatric patients, it is important for clinicians to be cognisant of strategies to minimise the risk of PONV in their patients. One such strategy is to avoid using volatile anaesthetics in favour of total intravenous anaesthesia (TIVA) with propofol during the intraoperative period. This change alone reduces the rate of PONV by as much as 25% (8). When the use of inhaled anaesthetics cannot be avoided, one study recommends single-drug antiemetic prophylaxis, which was found to be equally effective as TIVA in preventing PONV after strabismus surgery in children (9). Regional anaesthesia is also preferred over general anaesthesia to reduce the risk of PONV. Studies have shown that using local anaesthesia instead of or in addition to general anaesthesia reduces the incidence of PONV in tonsillectomies (10).

Increased opioid use has been found to increase the risk of PONV in a dose-dependent manner (11). Non-opioid multimodal pain management is favoured for acute intraoperative and postoperative pain control in the operating room and on the medical floor after PACU discharge. It has been shown that using caudal blocks for regional anaesthesia in patients undergoing renal, bladder, or ureteral procedures reduced PONV and was associated with lower use of opioids and rescue anti-emetics (12). NSAIDs are additionally effective as part of a multimodal regimen that has been shown to be effective in managing postoperative pain. Moreover, their use can lead to fewer cases of PONV (13). Once thought that the use of NSAIDs may increase the risk of bleeding, in a study of patients undergoing tonsillectomy and adenoidectomy procedures, no increased incidence of bleeding was associated with the use of NSAIDs (13). Additionally, the use

Main Points:

- Postoperative nausea and vomiting typically describes nausea, vomiting, or retching that can occur starting in the post-anaesthesia care unit (PACU) and continuing through the 24 hours following surgery.
- Postoperative nausea and vomiting leads to significant morbidity and healthcare costs, indicating the need for appropriate management.
- A variety of antiemetic regimens are recommended for the prevention and treatment of PONV in children, including pharmacotherapy with dexamethasone, 5HT-3 receptor antagonists, butyrophenones, prokinetics, anticholinergics and antihistamines.
- The use of predictive risk scores to identify patients at increased risk of PONV is useful to determine the appropriate and cost-effective course of therapy while providing the greatest patient benefit, reducing the length of hospital stay and reducing the frequency of unplanned admissions.

Table 1. Risk factors for the occurrence of PONV

Surgical	Duration greater than 30 minutes Ocular surgery ENT surgery (adenoidectomy, tonsillectomy)
Anaesthetic	Use of volatile anaesthetic Use of opioids Increased postoperative pain
Patient	Age of >3 years History or immediate family history Prolonged preoperative fast State of dehydration
PONV: postoperative nausea and vomiting	

of nitrous oxide has also been associated with PONV and is recommended to be avoided in patients at an increased risk for developing PONV (8).

Preoperative optimisation

Another factor that may influence the incidence of PONV is preoperative fasting. The purpose of preoperative fasting is to reduce the volume of gastric contents during the procedure and thus lower risk of aspiration, which can lead to infection and acute respiratory distress syndrome. Prolonged preoperative fasting, however, has been associated with postoperative nausea (14). One study investigated the effects of a shorter preoperative fasting time and failed to find a significant difference in the reduction of PONV, but it did find that a shorter fasting period was associated with lesser postoperative pain following tonsillectomy procedures (14). It is important to note that if this reduction in pain results in less use of opioids to control pain, there may be a subsequent decrease in PONV.

Carbohydrate loading, i.e. the preoperative intake of a carbohydrate-rich fluid, has also been suggested as a method to reduce PONV. A randomised controlled trial found that carbohydrate loading resulted in fewer instances of postoperative nausea and suggested that there may also be a subsequent reduction of vomiting in these patients (15). It was suggested that preoperative carbohydrates may prevent the body from persisting in a prolonged catabolic state throughout surgery, possibly reducing inflammation, pain and resultant nausea/vomiting.

Hydration is yet another important factor in the development of PONV in paediatric patients. In a study of 150 children undergoing lower abdominal and penile surgery, liberal intraoperative fluid therapy resulted in significantly lower rates of PONV (16). They suggest that supplemental perioperative fluid helps to correct the existing fluid deficits that may have been caused by fasting, thereby helping to maintain adequate intravascular fluid volume, which prevents the activation of mechanisms that may otherwise trigger nausea and vomiting.

Pharmacologic Management (Table 2)

Dexamethasone

Dexamethasone is a synthetically derived corticosteroid that is commonly administered for the prevention of PONV. Its mechanism of action in preventing PONV is not fully understood, but it is thought that the agonism of glucocorticoid receptors found within the bilateral solitary tract nucleus and area postrema of the brainstem prevent activation of the chemoreceptor trigger zone, implicated as a central emetogenic mediator (8). Another theory centres around the anti-inflammatory properties of dexamethasone, which may help to reduce local inflammatory reactions caused by surgery and that

otherwise leads to parasympathetically driven stimulation of the chemoreceptor trigger zone (17). Dexamethasone is typically dosed at $150 \mu\text{g kg}^{-1}$ up to a total administered dose of 5 mg in children, though total doses as high as 8 mg have been demonstrated to be safe (17). Maximum anti-emetogenic efficacy is likely attained when administered at or prior to induction as dexamethasone achieves its peak effect approximately 2 hours after injection (17).

The success of dexamethasone in reducing PONV alone when compared with a placebo has resulted in its increased use in both paediatric and adult populations. There is a cumulative effect when it is given in combination with other therapies (18). The rate of PONV when dexamethasone was given in combination with a super-hydration therapy using lactated ringer solution was 5%, as compared to 35% when dexamethasone was administered as a monotherapy agent (19). Similarly, a combination of dexamethasone and ondansetron was shown to significantly reduce PONV rates in the first 3 hours postoperatively as compared to either group alone (20). Another study compared the rates of PONV in patients who received a dexamethasone-dimenhydrinate combination versus a dexamethasone-ondansetron combination and found that the dexamethasone-dimenhydrinate combination was more effective (21).

Despite its regular use and effectiveness in reducing PONV, there are several potential post-operative complications associated with the use of dexamethasone. These include increased risk of post-tonsillectomy bleeding, perioperative hyperglycaemia, increased postoperative infection risk and cancer recurrence (8). Though historically, dexamethasone use has been associated with increased post-tonsillectomy bleeding risk in children, the findings by Yiu et al. (22) and Mahant et al. (23) bring this association into question. Dexamethasone is a potent steroid and as such, a single dose can induce insulin resistance in the whole body and can alter cardiac glucose metabolism, which may potentially result in hyperglycaemia (24). Another commonly listed complication of dexamethasone for use with PONV is a risk of cancer recurrence due to perioperative immune impairment, however, studies by Colin and Gan (25) and Chanimov et al. (26) have failed to find any such correlation. Lastly, tumour lysis syndrome is listed as a possible complication and is associated with rapid onset of hyperphosphatemia, hyperkalaemia, lactic acidosis, acute renal failure and hyperuricaemia. The proposed mechanism associated with steroid induced tumour lysis syndrome is the induction of growth arrest and apoptosis in lymphocytes (26).

5HT₃ Antagonists

Three commonly used 5-HT₃ antagonists are ondansetron, granisetron and dolasetron. They have a shared mechanism of action and function by acting on both the peripheral and cen-

Table 2. Summary of commonly used perioperative antiemetics in paediatric anaesthesia

Drug class	Mechanism of action	Adverse effects	Dose and time of administration
Corticosteroid - Dexamethasone	Poorly understood: thought to act on glucocorticoid receptors May centre around the ability of dexamethasone to reduce local inflammatory reactions after surgery.	Increased risk of post-tonsillectomy bleeding, tumour lysis syndrome, perioperative hyperglycaemia, increased postoperative infection risk and cancer recurrence.	150 µg kg ⁻¹ up to 8 mg. Administer drug immediately before or after induction of anaesthesia instead of after surgery.
5-HT ₃ Antagonist - Ondansetron - Granisetron - Dolasetron	Antagonising the action of serotonin in the 5HT ₃ receptor-rich areas of the brain	Headache, dizziness, elevated liver enzymes, constipation, diarrhoea, arrhythmias and QT prolongation	Ondansetron: - 100 µg kg ⁻¹ or max 4 mg IV - 8 mg oral - administer at end of surgery Granisetron: - 0.35 to 3 mg IV (5-20 µg kg ⁻¹) - administer at end of surgery Dolasetron: - 12.5 mg IV at end of surgery or at time of induction
Butyrophenone - Droperidol	Potent centrally acting D2 receptor antagonist	Drowsiness, sedation, headaches Rare: EPS	50 µg kg ⁻¹ ; 30 minutes before the end of surgery
Prokinetics - Metoclopramide	Peripheral and central (basal ganglia) DA receptor antagonist	EPS (akathisia, dystonia, Parkinsonism and dyskinesia), sedation, diarrhoea Rare: Apnoea, anaphylaxis, respiratory distress or arrest, NMS, TD. Galactorrhoea. Gynaecomastia, urinary retention, priapism (*all resolved with treatment/ discontinuation)	Single dose: 0.1 to 0.5 mg kg ⁻¹ intravenously Multiple dose: *No PONV-specific data, but CINV: 1.15 mg kg ⁻¹ day ⁻¹ intravenously or orally to 12 mg kg ⁻¹ day ⁻¹ intravenously
Anticholinergics - Scopolamine	Competitive smooth muscle muscarinic antagonist Percutaneous absorption, detected in plasma within 4 hrs of patch application	Sedation, dry mouth, vision changes, decreased gastric motility and delayed gastric emptying Caution with other anticholinergics (antihistamine, TCA, muscle relaxant)	0.25-0.75 mg via a transdermal patch
Antihistamines - Dimenhydrinate - Hydroxyzine	Reversible H1 receptor inhibition More commonly used for motion sickness	Sedation, CYP 450 inhibitor, dry mouth, constipation Less common: confusion, blurry vision, urine retention	0.5 mg kg ⁻¹ , up to 25 mg (rectal) 2 mg kg ⁻¹ day ⁻¹ PO 1.1 mg kg ⁻¹ IM

PONV: postoperative nausea and vomiting

tral nervous system. Enterochromaffin cells in the gut release 5-HT in response to gastric irritation or cellular damage and 5-HT binds to 5-HT₃ receptors on vagal afferents in the gastric mucosa, which project to the vomiting centre (28). 5-HT₃ antagonists act by inhibiting the action of serotonin in 5-HT₃ receptor-rich areas of the brain, thus alleviating emesis (28).

Dosing varies between these three drugs. Dosing for ondansetron is 100 µg kg⁻¹ or a maximum of 4 mg IV or 8 mg oral and works best when administered at the end of surgery (8). Gran-

isetron also functions best when given at the end of surgery and its dosing ranges from 0.35-3 mg IV (5-20 µg kg⁻¹) (8). Dolasetron is the only 5-HT₃ receptor that has been shown to be effective either at the end of surgery or at induction; its dosing is typically 12.5 mg IV (8).

Ondansetron, granisetron and dolasetron have all been found to be more effective than placebos in reducing PONV (29). Ondansetron and granisetron in combination with other drugs used for PONV have been found to be more

effective than either alone (8). Compared to 4 mg IV ondansetron and 1 mg PO granisetron, the incidence of PONV and the requirement for rescue anti-emetics were not statistically different (30). Despite this, the cost to achieve similar effects was approximately \$26 for ondansetron and \$47 for granisetron, indicating that ondansetron is more cost-effective (30). Interestingly, a Birmingham et al. (31) found no significant difference in PONV within the first 12 hours post-operatively, but in the subsequent 12 hours, 40 µg kg⁻¹ granisetron had shown significantly lower rates of PONV than 100 µg kg⁻¹ of ondansetron IV, suggesting that granisetron may be a better option for long-term PONV control. The difference in results may be attributed to a difference in the dose of medication administered. Comparisons of ondansetron and dolasetron have no significant difference in the rates of PONV between the two drugs, but dolasetron has been found to be more cost effective than ondansetron (29). When compared to traditional anti-emetics such as anticholinergics, antihistamines, butyrophenones and benzamides, 5-HT₃ antagonists are significantly more effective for PONV (32).

The commonly listed side effects of 5-HT₃ antagonists include headache, dizziness, elevated liver enzymes, constipation, diarrhoea, arrhythmias and QT prolongation (8). Studies investigating the effects of granisetron and ondansetron on QT prolongation have found that granisetron significantly reduces the heart rate and prolongs the QT interval as compared to ondansetron (33, 34). However, a meta-analysis comparing rates of QT prolongation and other arrhythmias with the use of various 5-HT₃ antagonists alone and in combination with other anti-emetics found a minimal statistical difference between the groups. The only significant finding was that dolasetron plus dexamethasone when compared to ondansetron plus dexamethasone prolonged the QTc (35). The clinical consequences of these QT prolongations in practice are negligible (36).

Butyrophenones

Droperidol is a potent, centrally acting dopamine receptor antagonist with known antiemetic properties in adults (37). Although given as a low-dose prophylactic medication, its known adverse effects include sedation, drowsiness, headaches and extrapyramidal symptoms (EPS) (38). Bourdaud et al. (39) found that low-dose droperidol given near the end of surgery did not decrease the incidence of POV when added to a two-drug combination of ondansetron and dexamethasone, rather, it significantly increased the incidence of drowsiness and headache. An additional study found no significant decrease in POV when given in combination with dexamethasone at recommended paediatric doses (40). Due to its adverse effect profile and no increase in efficacy, droperidol remains largely unused in the paediatric population, limited to refrac-

tory emesis in an inpatient setting (39). Low-dose prophylactic haloperidol also has known anti-emetic properties in adults, although its use has not extended to children to date.

Prokinetics

The prokinetic metoclopramide is a peripheral and central-acting dopamine receptor antagonist with antiemetic properties. Although it is used in adults, it carries a 'black box' warning for tardive dyskinesia and has subsequently declined in popularity in younger paediatric patients and remains an alternative to the use of corticosteroids and serotonin receptor antagonists (41). Currently, Canadian and EU drug regulatory agencies contraindicate its use in children younger than 1 year of age and caution against its use in children younger than 5 years (38). The British National Formulary for Children (BNFC) also restricts metoclopramide use in patients younger than 20 years of age to cases of severe intractable vomiting of a known cause, vomiting associated with radiotherapy and cytotoxins, as an aid to gastro-intestinal intubation, a prokinetic in neonates and as a pre-medication for diagnostic procedures (39). A meta-analysis of metoclopramide use in 2699 children identified common adverse effects, in accordance with doses given (42). In studies administering multiple doses, the most common side effects were extrapyramidal symptoms, sedation and diarrhoea. When given as a single dose, the primary adverse effect was sedation. Adverse effects that were life threatening or slow to resolve were rare. Thus, it is recommended to limit its use to refractory or severe cases of emesis and care should be taken to teach parents to recognise its signs and symptoms to minimise alarm.

Anti-Cholinergics

Scopolamine is a competitive muscarinic antagonist with anti-nausea and antiemetic properties and is often used as adjunctive therapy (43). Its transdermal delivery produces a low-dose and steady plasma concentration, minimising adverse effects such as sedation, dry mouth, vision changes, dizziness, decreased gastric motility and delayed gastric emptying. Although widely used in adults for PONV, few studies have examined the use of scopolamine in children; however, the BNFC recommends the use of a quarter of a patch from the ages of 1 month to 3 years and a half of a patch from ages 3-10 years (44).

Anti-histamines

Dimenhydrinate is a reversible H₁ receptor inhibitor with antiemetic properties (45). Adverse effects in the paediatric population include increased sedation and longer observation time in the PACU, with no difference in time to arousal and hospital discharge (46). Although dose estimation remains unclear, it is worth considering as an inexpensive antiemetic. Further studies are needed to determine the safety and efficacy of dimenhydrinate in the paediatric population (45).

Treatment and prevention

PONV remains a significant adverse effect for patients receiving general anaesthesia, particularly for paediatric patients. Several risk score models exist for adults, although many of these scores are not applicable in children (37). The use of predictive risk scores to identify patients at increased risk of PONV is useful to determine the appropriate and cost-effective course of therapy while providing the greatest patient benefit, reducing the length of hospital stay and reducing the frequency of unplanned admissions (47).

To guide paediatric PONV prophylaxis, Bourdaud et al. (7) created a risk-predictive scoring model for vomiting in the

postoperative period (VPOP). The calculated score identifies five independent risk factors for vomiting in children and stratifies these to indicate risk severity (Table 3). These factors include age, duration of anaesthesia, surgery at risk, a predisposition to POV and multiple opioid doses. The scores range from 0-6, with 6 representing children at the highest risk. An additional guideline published by the Society for Ambulatory Anaesthesia (SAMBA) described a scoring system ranging from 0-4, with a point given for family history of POV, surgery duration greater than 30 minutes, age greater than 3 years and strabismus surgery (48).

In the face of low compliance, Gan et al. (8) cites multiple studies supporting the efficacy of multimodal prophylactic pharmacologic therapy to reduce the baseline risk for PONV (Table 4). These findings highlight the additive nature of different drug classes in preventing and treating PONV. A combination of most 5-HT₃ antagonists with dexamethasone offers effective emesis risk reduction and is supported for use in children (49). Although the combination of dexamethasone and sub hypnotic propofol, or the combination of a 5-HT₃ antagonist with droperidol had equal efficacy, neither were recommended as first-line treatment options in children due to the adverse effects of droperidol and the painful delivery of propofol (8). One article proposed the use of monotherapy for small surgeries or minimal PONV predictive risk and multimodal prophylaxis in patients with moderate to high risk (50). Use of dimenhydrinate, droperidol and metoclopramide should be reserved for rescue therapy.

In addition to optimising perioperative pharmacologic treatment, it is beneficial to minimise risk factors for nausea and vomiting preoperatively. To this end, the use of regional anaesthesia as an adjunct to general anaesthesia can limit the amount of post-operative opioid use, thereby reducing opioid-associated PONV. To further reduce the risk, volatile anaesthetics and nitrous oxide can be used in favour of intravenous propofol (9).

Conclusions and Summary

The incidence of postoperative nausea and vomiting (PONV) in paediatric patients remains high, particularly after emetogenic procedures and in individuals with an increased level of risk factors. It is a frequent source of discomfort during postoperative recovery both after PACU discharge on the medical floors and also at home after undergoing a surgical procedure. PONV leads to significant morbidity and healthcare costs, indicating the need for appropriate management. While certain anaesthetic techniques can minimise emetogenic effects, it is imperative that paediatric clinicians be cognisant of specific risk factors that their patients may have that increase the likelihood of PONV manifestation. The

Age	0 points=class 1: ≤3 years 1 point=class 2: >3 years and <6 years or >13 years 2 points=class 3: ≥6 years and ≤13 years	
Duration of anaesthesia	0 points=≤45 min 1 point=>45 min	
Surgery at risk	1 point=tonsillectomy, tympanoplasty, strabismus surgery 0 points=others	
Predisposition to POV	0 points = no 1 point = yes	
Multiple opioid doses	0 points=no 1 point=yes	
Scoring and percent incidence	0=5% 1=6% 0-1=low risk 2=13% 3=21% 2-3=moderate risk 4=36% 5=48% >4=high risk 6=52%	
POV: postoperative vomiting		

Multimodal PONV prophylaxis therapy provides optimal outcomes	Dexamethasone plus sub hypnotic Propofol dose (1 mg kg ⁻¹ bolus followed by infusion at 20 mcg kg ⁻¹ min ⁻¹) 5-HT ₃ antagonist (0.05 mg kg ⁻¹) plus dexamethasone (0.015 mg kg ⁻¹) [most effective] 5-HT ₃ antagonist (0.1 mg kg ⁻¹) plus Droperidol (0.015 mg kg ⁻¹)
PONV: postoperative nausea and vomiting	

use of multimodal prophylactic antiemetic medication provides an effective alternative and adjunct for patients who are at a risk of PONV. A systematic review of the current literature supports the efficacy of several prophylactic pharmacological agents, many of which have shown minimal incidence of severe adverse effects when they are selected appropriately. Further, guidelines based on risk factor assessment can provide a predictive score to guide adequate prevention strategies, PONV treatment and a reduction in the baseline risk of PONV occurrence.

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