The effects of oral gabapentin premedication on postoperative nausea and vomiting and early postoperative recovery profile in pediatric patients undergoing adenotonsillectomy

An Essay Submitted for the Partial Fulfillment of the Master Degree in Anesthesiology

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Abstract

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In this study . believed that PONV is multifactorial in origin, with a reported incidence ranging from 23% to 73%. Multimodal approach for PONV constitutes both pharmacological and non-pharmacological therapies.This is randomized, controlled, double-blind study was designed to explore the possible effects of oral gabapentin as premedication on the incidence and severity of PONV and on the recovery profile of pediatric patients undergoing adenotonsillectomy. We studied 140 patients undergoing adenotonsillectomy randomized to oral gabapentin 16mg/kg (n=70) or placebo (n=70). Oral premedication was given 2 hours before induction ofsevoflurane anesthesia.The use of oral gabapentin as premedication in pediatric patients undergoing adenotonsillectomies under sevoflurane anesthesia reduced the incidence of PONV and emergence agitation in the early postoperative period

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List of abbreviation

PONV:	Postoperative nausea and vomiting
5-HT3:	5 hydroxytryptamine 3
CTZ:	Chemoreceptor trigger zone
NSAIDs:	Nonsteroidal anti-inflammatory drugs
PACU:	Post anesthesia care unit
PAED:	Pediatric Anesthesia Emergence Delirium
OIRD:	Opioid-induced respiratory depression
ASA:	American Society of Anesthesiologists
PAB:	Pediatric Anesthesia Behavior
OPS:	Objective pain scale
CBC:	Complete blood count
PTT:	Partial thromboplastin time
BT:	Bleeding time
CT:	Clotting time
ECG:	Electrocardiography
PSV:	Pressure support ventilation
SD:	Standard deviation
IQR:	Interquartile range

Introduction

Postoperative nausea and vomiting (PONV) continues to be one of the most common and unpleasant complications after surgery and it is believed that PONV is multifactorial, with a reported incidence ranging from 23% to 73. [(1)] Different anesthetic techniques are associated with different rates of occurrence. [(2)]

Multimodal approach for the prevention and management of PONV includes both pharmacological and non-pharmacological measures. [(3)] Many pharmacological agents were used to prevent and treat PONV following adenotonsillectomy in pediatrics e.g. ondansetron, metoclopramide, antihistamines, and dexamethasone. [(4,5)] However, each of these treatments is associated with limiting factors, namely cost with 5 hydroxytryptamine antagonists (5-HT3), extrapyramidal symptoms with dopamine antagonists, and excessive sedation and tachycardia with antihistamine drugs. [(6,7)]

The gabapentinoids (pregabalin and gabapentin) are both indicated for the treatment of post-herpetic neuralgia and as adjuvant therapy for seizure disorders in adults [(8)] and in children. [(9)] However, growing evidence suggests that the perioperative administration of gabapentin in adults is beneficial for preoperative anxiolysis [(10)], postoperative analgesia [(11)], attenuation of the hemodynamic response to laryngoscopy and intubation [(12)], reduction of postoperative nausea and vomiting [(13)], and delirium [(14)]. The anti-emetic potentials of preoperative gabapentinoids were not previously evaluated in children.

The present randomized double-blind controlled study was designed to evaluate the possible impact of oral gabapentin premedication on the inhalation induction characteristics and on the early postoperative recovery profile including the incidence of PONV in pre-school children undergoing adenotonsillectomy under sevoflurane anesthesia.

Premedication and Management of the Uncooperative Child

Uncooperative children, whether due to high anxiety, developmental or mental disorders, or repeated anesthesia, should be adequately treated to avoid postoperative behavior problems. [15-16] In the 1990s it was reported that up to 25% of children require physical restraint to facilitate anesthetic induction. [17] The first step in relieving anxiety should be getting a good contact with the child by receiving the child's attention, e.g. through cartoons, films, or computer games. Positive reinforcement, however, rarely works in the severely anxious child and a pharmacological approach is usually required. [18]

Premedication in childhood could be best performed via the oral route. Timing before separation from the parents should be appropriate to match the onset time of premedicant. One approach when a child rejects the drug may be sharing the drink without the drug with parents or anyone trusted by the child. [15] A rectal drug may be thrown out easily in young children and may be problematic in older children. [18]

Midazolam

Midazolam is the most commonly used benzodiazepine for premedication (more than 90% of cases), followed by fentanyl and ketamine in the US. [19] Easy separation from the parents and acceptance of mask placement when midazolam is used mainly depend on sedative and anxiolytic characteristics. The major problem in everyday practice with midazolam is its bitter taste when administered orally, even when added to syrup. The bioavailability of oral midazolam is around 36% (9–71%). [18] Midazolam is metabolized by CYP3A4 mediation which produces the primary metabolite 1-hydroxymidazolam. The parent drug and metabolite have similar effects on the central nervous system. [20]

Roche Laboratories introduced commercially prepared midazolam syrup (1998) that had a pleasant taste and a lower pH than intravenous form. This oral preparation might avoid problems related to the individual home-made formulations by providing a standard, consistent, and reliable formula with known purity, potency and stability. [20-21]

Midazolam sedative effects are seen within 5–10 min of oral administration. The minimum time interval for successfully separating premedicated children from their parents is 10 min and the peak effect is achieved in 20–30 min. [22] Sedative effects dissipate within 45 min in most cases. [22] Therefore, after oral administration, children should be kept in bed or in the arms of a parent and observed by medical staff, and they should not be left unattended later in the day. If induction of anesthesia is delayed, an additional dose should be considered (about 0.25 mg/kg). [18] Increasing the dosage of oral midazolam above 0.5 mg/kg does not enhance the sedative and anxiolytic effects and could result in more side effects in the recovery period. [18] Addition of an antacid (sodium citrate) is reported to shorten the onset of action of oral midazolam by around 4 min. [23] Cox and co-workers [24] reviewed 30 articles regarding the use of oral midazolam for premedication, and concluded that it is effective in reducing both separation and induction anxiety in children, with minimal effect on recovery times.

The administration of midazolam by the nasal route is associated with an unpleasant burning sensation due to its low pH and most children are quite upset by its use. [18] Contrary to several reports, Yildirim and colleagues [25] reported that intranasal midazolam is better accepted in infants than via the oral route. Plasma concentration of midazolam is higher after nasal administration as compared to the oral route. [18]

Benzodiazepines produce anterograde amnesia (amnesia of information learned after drug administration) which may be beneficial for children undergoing surgery. In 2005, Lonnqvist and Habre [26] questioned the role of the anterograde amnestic effect of midazolam on emergence agitation and postoperative misbehavior in children.

Ketamine

Oral ketamine is a popular alternative to oral benzodiazepines. Ketamine is not associated with respiratory depression, tachycardia or emergence agitation. [18] A large dose of oral ketamine (3–8 mg/kg) is well tolerated. [27] Oral administration is associated with high hepatic first-pass effect; only 16% of a given dose is bioavailable.[28] Horiuchi and colleagues [29] reported the use of trans-mucosal ketamine but could not show any

superiority over oral midazolam 0.5 mg/kg. Oral ketamine provides adequate sedation within 20–25 min. [28] Kararmaz and colleagues [30] reported that oral ketamine premedication reduces the incidence of emergence agitation without delaying recovery. The combination of midazolam and ketamine can be used in the extremely uncooperative child. [18] Intramuscular ketamine may be advised in the combative child. An intramuscular dose of ketamine 4–5 mg/kg provides effective sedation in 93–100% of children in 5 min. The duration of action is approximately 45 min. Ketamine 2–3 mg/kg (using a high concentration of 50 mg/ml to reduce the volume) plus 0.1 mg/kg midazolam can be administered in combination intramuscularly. [18] This combination may prolong recovery and delay discharge time. [31]

Clonidine

Clonidine is an α2-adrenergic agonist that has been used as an oral sedative premedication in children. In doses of 2–4 μg/kg, oral clonidine produces adequate sedation and anxiolysis. Sumiya and co-workers [32] demonstrated that plasma clonidine concentrations of 0.3–0.8 ng/ml produce satisfactory sedation without changes in hemodynamic parameters. Clonidine may blunt the heart rate response to atropine. [18] Unlike benzodiazepines, clonidine does not have any psychotropic effects. It causes a state of sedation similar to normal tiredness/sleepiness and the patient can easily be awoken. Another major difference from benzodiazepines is that clonidine does not have an amnestic effect. [33] It had also been shown that the need for sevoflurane and postoperative non-steroidal anti-inflammatory agents may be decreased, and that the incidence of sevoflurane agitation was reduced with clonidine premedication. [34]

Dexmedetomidine

Dexmedetomidine is a more selective α2-adrenergic receptor agonist than clonidine and is also being used as a premedicant in children. [34] Intravenous bolus of dexmedetomidine 0.5–1.0 μg/kg (given over 5–10 min) followed by an infusion of 0.5–1.0 μg/kg/h provides effective sedation in spontaneously breathing children. [34] The sedative effects of dexmedetomidine are similar to clonidine. [35] Bioavailability studies in adults reported good systemic absorption through the oral mucosa. [36] Zub and

colleagues [37] studied the use of oral dexmedetomidine in a group of 13 children aged 4–14 years. The results indicated that oral dexmedetomidine at a dose of 3–4 μg/kg produces effective sedation in 11 of 13 patients and intravenous cannula was placed without difficulty in seven of eight patients with neurobehavioral disorders.

Oral trans-mucosal fentanyl

The oral trans-mucosal lollipop form of fentanyl has a pleasant taste. Fentanyl readily crosses the mucosal barrier of the oral cavity and peak blood levels are usually achieved 15–30 min after sucking. [18] Oral trans-mucosal fentanyl loses efficacy and bioavailability when chewed or swallowed. Adequate sedation is achieved by 10–20 μg/kg. [18] Oral trans-mucosal fentanyl is not as effective as midazolam in achieving anxiolysis, and may cause facial pruritus, respiratory depression and increased risk of nausea/vomiting. [18]

Postoperative Nausea and Vomiting (PONV) in Pediatrics

Nausea is the conscious recognition of excitation of an area in the medulla that is associated with the vomiting (emetic) center, which mediates the vomiting response. Vomiting is forceful expulsion of gastric contents through the mouth with contraction of external oblique and abdominal muscles as well as pyloric portion of stomach. [38] The medullary vomiting center is located in the lateral reticular formation of the medulla close to the fourth cerebral ventricle. [39] It receives afferents from the chemoreceptor trigger zone (CTZ), vestibular apparatus, cerebellum, higher cortical and brainstem centers, and solitary tract nucleus. These structures are rich in dopaminergic, muscarinic, serotoninergic, histaminic and opioid receptors. [40] Block of these receptors may be the mechanism of the antiemetic action of drugs. Efferents are transmitted via cranial nerves V, VII, IX, X and XII to the gastrointestinal tract and through the spinal nerves to the diaphragm and abdominal muscles to cause the mechanical act of vomiting. [41] The CTZ is not protected by the blood-brain barrier. Hence, it can be activated by chemical stimuli received through the systemic circulation as well as the cerebrospinal fluid. The cerebral cortex is stimulated by smell and physiologic stresses. Motion can stimulate the vestibular apparatus, which may also stimulate the CTZ. Blocking of impulses from the CTZ does not prevent vomiting due to stimuli arising from the gastrointestinal tract. [41]

Incidence and assessment of PONV

The average incidence of PONV in childhood is 30-80% and can be two folds the incidence in adults.[42-43] This high incidence warrants the use of antiemetic prophylaxis instead of therapy. [44-46] Eberhart et al. [47] identified four risk factors for PONV in pediatric anesthesia: previous PONV or a positive family history, duration of anesthesia (>30 min), age (>3 years), and strabismus surgery. The risk of PONV was predicted as 9, 10, 30, 55, and 70%, respectively, depending on the presence of 0, 1, 2, 3, and 4 risk factors.

The incidence of post-discharge nausea and vomiting (PDNV) in children highly depends on the type of surgery. After tonsillectomy, 20% of children experience PDNV on day 3

and 8% on day 7.[48] Davis et al. [49] were able to reduce this high risk from 32 to 14.5% using ondansetron disintegrating tablets (two times daily for 3 days).

Surgical procedures associated with increased risk of PONV in children

Postoperative nausea and vomiting has multifactorial causes.[50] One important risk factor is the surgical procedure. Strabismus and ear–nose–throat surgery like tonsillectomy or adenoidectomy are associated with PONV incidences as high as 54 and 82%, respectively.[51] Even after prophylaxis, this incidence is still as high as 30%. Interestingly, emerging data show that appendectomy might be associated with 42% nausea and 19.9% vomiting. Furthermore, combined minor pediatric surgery e.g. herniotomy and orchidopexy are also associated with a very high risk for PONV: 42.9% nausea and 28.6% PONV. [52]

General antiemetic strategies during anesthesia

Anesthetists are able to reduce the baseline risk factors and can decrease the incidence of PONV with simple strategies.[52]

(1) Avoidance of volatile anesthetics and preferential use of propofol total intravenous anesthesia.

(2) Preferential use of regional anesthesia or combined general and regional anesthesia to reduce postoperative opioids.

(3) Multimodal postoperative pain therapy to reduce postoperative opioids.

(4) Avoidance of nitrous oxide.

(5) Adequate hydration. Radke et al. [53] showed that prolonged postoperative fasting did not reduce the incidence of vomiting after general anesthesia in children when compared with a liberal regimen.

One part of a multimodal postoperative pain therapy to reduce opioid requirements is the use of nonsteroidal anti-inflammatory drugs (NSAIDs). However, there is still an ongoing debate about the potentially increased postoperative bleeding risk, especially after tonsillectomy. Cardwell et al. [54] reviewed 12 trials evaluating the effect of NSAIDs

on PONV. Apart from the expected decrease in emesis, Cardwell found no increase in bleeding events after the use of NSAIDs following tonsillectomy and adenoidectomy.

Anti-emetics

- Butyrophenones

Droperidol is the only commonly used butyrophenone for its antiemetic action. It is a heterocyclic neuroleptic which inhibits dopaminergic receptors in the chemoreceptor trigger zone of the medulla. Side effects include sedation, dose-dependent drowsiness, dysphoria, restlessness and extrapyramidal reactions. Children may be more vulnerable to droperidol-related extrapyramidal symptoms. The likelihood of droperidol-related sedation increases with increasing doses above 0.625 mg, from a risk of one in 24 with 1.25 mg, to one in 8 with 2.5 mg. Its anti-nausea effect is not dose dependent, is more pronounced than the anti-vomiting effect, and is short-lived. [(55)] Droperidol, in doses as low as 0.625 or 1.25 mg has been shown to be as effective as ondansetron 4 mg without increasing sedation, agitation, anxiety or delaying discharge. [(56)]

- Metoclopramide

The most effective antiemetic of this class and has been used for almost 40 years. It is a dopamine antagonist that is structurally similar to procainamide. Its antiemetic effect results from antagonism of dopamine's effects in the chemoreceptor trigger zone. At high doses, it also antagonizes 5-HT3 receptors.[(57)] There was no evidence of dose-responsiveness, with the best documented regimen in adults being intravenous (i.v.) 10 mg and in children i.v. 0.25 mg/kg. [(58)] Side effects include: abdominal cramping, sedation, dizziness, and rarely dystonic extrapyramidal reactions (oculogyric crises, opisthotonus, trismus, torticollis), and cardiac dysrhythmias. [(59)] Metoclopramide should not routinely be used as a prophylactic drug.

- Histamine receptor antagonists

Histamine-1 receptor antagonists are competitive antagonists of histamine by occupying H1 receptors on cell membranes, thus preventing histamine binding and activity. They have sedative effects, especially first generation drugs. Dimenhydrinate's efficacy in

motion sickness and inner ear diseases results from inhibition of the integrative functioning of the vestibular nuclei by decreasing vestibular and visual input. Intravenous dimenhydrinate 20 mg decreases vomiting after outpatient surgery in adults. In children, i.v. dimenhydrinate 0.5 mg/kg significantly decreases the incidence of vomiting after strabismus surgery and is not associated with prolonged sedation. [60] Placebo-controlled trials suggest that its antiemetic efficacy may be similar to the 5-HT3 receptor antagonists, dexamethasone, and droperidol. However, dimenhydrinate-treated patients tend to be more sedated and require significantly longer observation in the post anesthesia care unit (PACU). [60] Furthermore, optimal timing and dose–response relationships have not yet been studied.

- Muscarinic receptor antagonists

Morphine and synthetic opioids increase vestibular sensitivity. [61] The vestibular apparatus of the inner ear and the nucleus of the tractus solitarius are rich in muscarinic and histamine receptors. It is postulated that scopolamine blocks transmission to the medulla of impulses arising from overstimulation of the vestibular apparatus. [62] Application of a scopolamine patch before the induction of anesthesia protects against PONV after middle ear surgery. [62] Transdermal scopolamine patches can reduce PONV in patients receiving epidural morphine. Side effects include: sedation, dry mouth and visual disturbances. [62]

- 5-HT3 (5 hydroxy tryptamine 3) receptor antagonists

The introduction of this class of drugs in the 90s represents a major improvement in the pharmacotherapy of chemotherapy and radiation therapy-induced nausea and vomiting. Ondansetron as one agent of the 5-HT3 antagonist group is widely used for PONV prophylaxis and therapy. Schnabel et al. [63] concluded in a systematic review that 5-HT3 antagonists (ondansetron or granisetron) were more effective antiemetics than perphenazine in children.

Low dose of 0.04 mg/kg granisetron is effective in the prevention of PONV. [64] The elimination half-life of granisetron (nine hours) is 2.5 times longer than that of