

Aggressive Prophylactic Treatments for Postoperative Nausea and Vomiting Improve Outcomes in Pediatric Adenotonsillectomy Procedure

Tatyana Demidovich, MD; Orlando Perez-Franco, MD; Marco Silvestrini-Suarez, MD; and Pin Yue, PhD, AA

OBJECTIVE Postoperative nausea and vomiting (PONV) is an extremely common side effect of general anesthesia that is difficult to manage. We tested a hypothesis that an aggressive prophylactic intervention with additional antiemetic drugs will reduce the incidence of PONV in a high-risk pediatric population undergoing adenotonsillectomy.

METHODS In this retrospective study, pediatric patients undergoing adenotonsillectomy were screened for their risk factors for PONV. Patients who had 3 or more risk factors were identified as high risk and received either scopolamine patch preoperatively (for patients over 40 kg body weight) or diphenhydramine immediately postextubation in addition to ondansetron and dexamethasone, which are given routinely. Incidences of PONV within the first 60 minutes of a postanesthesia care unit (PACU) stay were collected and analyzed.

RESULTS Overall postoperative vomiting rates during the first hour of a PACU stay were 4.3% for the group that was treated with dexamethasone and ondansetron only and 3.9% for the group that was treated with additional antiemetic drugs. Aggressive prophylactic management of PONV did reduce the rate of nausea and vomiting in a group of high-risk patients ($p < 0.0001$). The postoperative antiemetic drug usage was also decreased during the first 60 minutes of a PACU stay. However, the approach did not reduce the overall rate of PONV for the entire study population ($p = 0.1612$ for nausea and $p = 0.0678$ for vomiting).

CONCLUSION Aggressive intraoperative management of PONV with additional antiemetic drugs are beneficial in high-risk pediatric population. Intraoperative diphenhydramine usage decreased the rate of PONV. However, preoperative scopolamine patch prevention did not improve PONV, which may be related to the drug's longer onset of action. Our result suggests that current clinical practice is undertreating PONV in pediatric patients receiving general anesthesia.

ABBREVIATIONS ASA, American Society of Anesthesiologists; BMI, body mass index; IV, intravenous; MAC, minimum anesthesia concentration; PONV, postoperative nausea and vomiting; PACU, postoperative anesthesia care unit; US Food and Drug Administration

KEYWORDS adenoidectomy; dexamethasone; diphenhydramine; ondansetron; pediatric; postoperative nausea and vomiting; scopolamine; tonsillectomy

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Introduction

Postoperative nausea and vomiting (PONV) is the most frequent undesirable side effect of general anesthesia. Despite improved methods of risk identification and prevention, the incidence of PONV could remain as high as 20% to 40% in a same-day surgery setting.¹ Although self-limiting, PONV can have a significantly negative effect on a patient's surgery recovery.² On the other hand, decreased incidence of PONV shortens a patient's recovery process, improves the patient's and family's satisfaction, reduces the patient's time to discharge and, eventually, decreases health care cost.^{3,4}

It is unclear whether the causes of PONV in the pedi-

atric population are the same as those in the adult population. Efune et al⁴ suggested that intraoperative and postdischarge opioids usage is the only independent risk factor in pediatric patients who have ambulatory surgery under general anesthesia. Other studies suggested that there are multiple independent risk factors that contribute to PONV in children.^{1,5} Risk factors for PONV in children that have been identified are age above 3 years old, history of motion sickness, history of PONV, family history of PONV, an exposure to volatile anesthetics, and certain types of surgeries.⁵ Otoplasty and adenotonsillectomy are among surgical procedures that are independent risk factors for PONV.^{5,6}

Great efforts have been made toward the prevention

and treatment of PONV. The multimodal approaches including combination of multiple antiemetic drugs, aggressive fluid replacement, reduction of opioids, and volatile anesthetics have some successes of dealing with this very common problem.^{2,7,8}

Despite these efforts, current interventions still lack universal efficacy. Chandrakantan et al⁹ recently reported that neither ondansetron nor dexamethasone is proved effective in preventing nausea, either alone or in combination. In our hospital, PONV still occurs frequently despite a standard institutional guideline that includes routinely rehydration with 10 mL/kg IV fluid, and administration of ondansetron and dexamethasone in children above 2 years of age. At the beginning of 2015, additional risk stratification and practice guidelines were established to prophylactically treat patients who were identified as high risk for PONV (patients had at least 3 risk factors). In this paper, we report a retrospective analysis of PONV incidence and prophylactic management in a pediatric population who underwent adenotonsillectomy procedures.

Methods

Study Design. Adenotonsillectomy is the most common surgical procedure in children.¹⁰ In our hospital, adenotonsillectomy accounts for 20% to 30% of overall operating room (OR) cases. We chose adenotonsillectomy to study the incidence and the treatment effectiveness of PONV because 1) it has been identified as an independent risk factor for PONV^{6,11}; 2) it is, usually, of a predictable length; 3) it warrants routine use of prophylactic agents for PONV; and 4) has had a previously standardized anesthesia protocol at our department. Therefore, longitudinal comparisons are feasible. In brief, children who underwent adenotonsillectomy were required to follow standard oral guidelines, received oral acetaminophen (10–15 mg/kg up to 650 mg) and, sometimes, oral midazolam (0.3–0.5 mg/kg up to 15 mg) if a patient was inconsolable at preoperative holding area) 15 to 30 minutes prior. General anesthesia plan included inhalational induction with N₂O and sevoflurane, peripheral IV access, intubation, extubation when end-tidal sevoflurane <0.3%, and IV fluids (up to 15 mL/kg) during the case. Intraoperatively, general anesthesia was maintained with 70% nitrous oxide and sevoflurane at 1 to 1.2 minimum anesthesia concentration (MAC). Intraoperative opioids included fentanyl and/or morphine depending on the anesthesiologist's preference. Patients older than 2 years of age would receive IV ondansetron (0.15 mg/kg up to 4 mg) and dexamethasone (0.15 mg/kg up to 10 mg).

After arriving, postanesthesia care unit (PACU) patients were continuously assessed for pain, nausea, and vomiting. Aldrete score¹² was reported every 15 minutes until patients met discharge criteria. Postoperative nausea was assessed with the Baxter Animated Retching Face scale every 15 minutes.¹³ An episode of

vomiting was documented at the time of occurrence. If a patient had a persistent nausea or vomiting (i.e., symptoms lasted more than 15 minutes), then the attending anesthesiologist was notified; antiemetic drugs (rescue medications), such as diphenhydramine (5–15 mg IV), droperidol (0.1 mg/kg up to 12.5 mg IV), or metoclopramide (0.5 mg/kg up to 10 mg IV), were given as necessary depending on the attending anesthesiologist's preferences. However, droperidol was used sparsely as the rescuer antiemetic drug because of the FDA boxed warning.²

Data collected between June 2012 and the end of 2014 were designated the “Before-2015” group. At the beginning of 2015, a number of interventions were implemented with the goal to decrease PONV rates (designated the “After-2015” group). Interventions started with identification of PONV risk factors in our patients (age >3 years, history of PONV, family history of PONV, history of motion sickness, type of surgery, and surgical length greater than 30 minutes).^{2,5,11} In addition to the tonsillectomy procedure as an independent risk factor, patients with 2 or fewer risk factors would continue to receive IV dexamethasone and ondansetron intraoperatively. Patients with 3 or more risk factors would also receive a preoperative transdermal scopolamine patch (1 mg for patients over 40 kg body weight) 30 to 60 minutes prior to surgery or a single dose of 0.5 mg/kg diphenhydramine (up to 15 mg) intravenously immediately after extubation.

Perioperative data from July 2012 through June 2017 was retrieved from anesthesia electronic information management system (EPIC, Madison, WI). We included patients between 1 and 13 years old who had adenotonsillectomies and were transferred to PACU units for recovery in our hospital during this period. Patients who had tonsillectomy but transferred to intensive care unit for recovery were excluded. Data from June 2012 through 2014 (Before-2015) were used as our baseline indicator for standard PONV management. Data from January 1, 2015, to June 30, 2017, were used as the comparison (After-2015).

Patients' information was deidentified prior to analysis. The information collected included patients' demographic data (age, sex, American Society of Anesthesiologists score, body mass index, and preoperative and postoperative pain scores); procedure length; preoperative, intraoperative, and postoperative medications; length of the PACU stay; incidence of nausea or vomiting every 15 minutes; and post-PACU destination. We have only assessed PONV data from the first 60 minutes of a PACU stay because some patients left the PACU after 60 minutes with proper postoperative assessment, and the data collected thereafter were deemed unreliable.

Statistical Analysis. All data analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, NC). Two-sample comparisons or analysis of variances

Table 1. Demographic Information of Adenotonsillectomy Population

Demographics	Ages			p value
	0 to 2 yr (n = 1059)	3 to 6 yr (n = 3314)	>6 yr (n = 2743)	
Male/female, n	653/406	1757/1557	1244/1499	
BMI, mean \pm SD	16.8 \pm 2.0	16.7 \pm 3.0	22.8 \pm 7.3	<0.001
ASA score, mean \pm SD	2.1 \pm 0.5	2.0 \pm 0.4	2.0 \pm 0.5	
Length of OR stay, mean \pm SD, min	49.6 \pm 20.6	47.4 \pm 17.6	51.4 \pm 19.6	0.0769
Length of PACU stay, mean \pm SD, min	96.6 \pm 81.3	86.9 \pm 91.2	98.7 \pm 79.8	0.1643
% of PON*	1.32	4.28	5.47	<0.001
% of POV†	4.91	3.50	4.12	0.1028

ASA, American Society of Anesthesiologists; BMI, body mass index; OR, operating room; PACU, postoperative anesthesia care unit; PON, postoperative nausea; POV, postoperative vomiting

* PON within 60 min of arrival in the PACU.

† POV within 60 min of PACU in the PACU.

for continuous variables and a χ^2 test for categorical variables were conducted. Significant p value was set at $p < 0.05$.

Results

This study analyzed data from patients who had adenotonsillectomies at Cardinal Glennon Children's Medical Center between July 2012 and June 2017. A total of 7116 patients met our inclusion criteria (Table 1). Three hundred one patients (4.2%) were under 2 years of age. The average stay in the OR was 49 minutes, and average PACU stay was approximately 92 minutes. Among age groups, there were no significant differences in an OR or a PACU stay (Table 1). Approximately 15% of the patients were discharged home or to a step-down unit within the first 60 minutes; and once they were discharged from the PACU, their electronic records were incomplete and deemed unreliable.

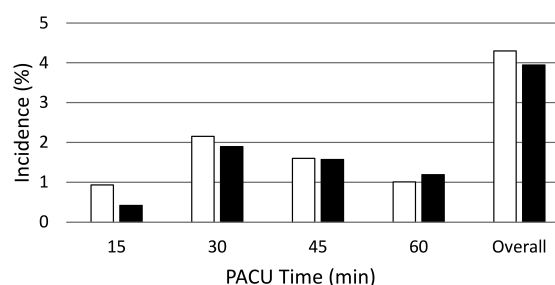
PONV Occurrence in the PACU. During the first hour of a PACU stay, 4.3% of all patients experienced nausea and 3.9% experienced vomiting. Children older than 3 years of age had a 2- to 3-fold higher incidence of nausea than the younger children ($p < 0.001$). Incidence of vomiting was not different among 3 age groups ($p = 0.1028$) (Table 1). Upon examination of the time sequence of PONV, the highest incidence of PONV occurred at approximately 30 minutes after arrival in the PACU (Figure 1). When data were split between Before-2015 and After-2015, the trends did not change (Figures 2 and 3). There was no significant difference in nausea and vomiting incidences at any given time between the 2 groups.

Prophylaxis Did Not Alter PONV Rates. As stated in the Methods section, aggressive prophylactic PONV prevention, including a preoperative scopolamine patch or intraoperative diphenhydramine administration, were given to patients with 3 or more additional risk factors (the tonsillectomy procedure was considered as an additional independent risk factor) for PONV.

In Before-2015, only 3 patients received prophylactic transdermal scopolamine patches (1 mg), and 20 patients were given intraoperative diphenhydramine (at 0.5 mg/kg up to 15 mg; Table 2) because of their high-risk PONV history. With an aggressive regimen, a total of 200 patients were identified as high-risk PONV candidates in After-2015. These patients were given a scopolamine patch (1 mg) in the preoperative holding area, or 0.5 mg/kg of diphenhydramine immediately after extubation. Three patients experienced PONV (8.1%) in the scopolamine patch group (out of 37 patients). Two patients reported PONV (1.23%) in the diphenhydramine group (out of 163 patients). Overall, approximately 2% of high-risk patients still experienced nausea or vomiting even after prophylactic medications. However, the rate was significantly lower than the overall PONV rate ($p < 0.0001$), suggesting that additional pretreatment of high-risk patients decreased incidences of PONV.

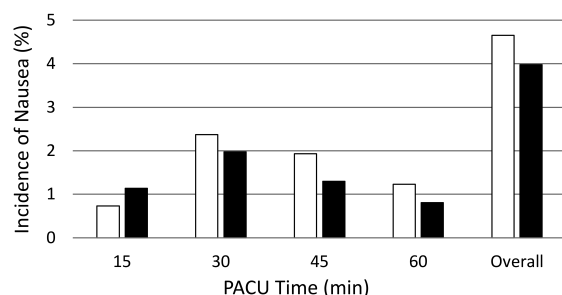
Prophylactic PONV treatment also significantly reduced postoperative use of rescue medications ($p < 0.0001$ and $p = 0.0053$) (Table 2). However, when the overall rates of nausea and vomiting were compared

Figure 1. Incidence of nausea and vomiting over a period of 60 minutes of a PACU stay.



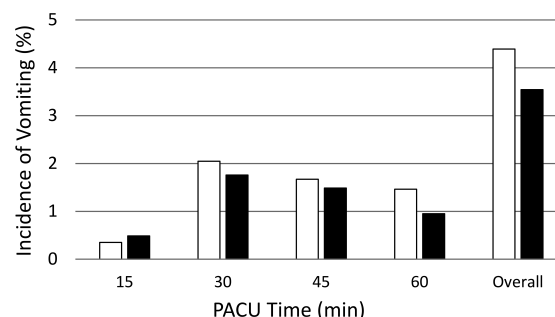
PACU, postoperative anesthesia care unit

□ % of Nausea; ■ % of Vomiting

Figure 2. Incidence of nausea over a period of 60 minutes of a PACU stay for Before-2015 and After-2015.

PACU, postoperative anesthesia care unit

□ Before 2015; ■ After 2015

Figure 3. Incidence of vomiting over a period of 60 minutes of a PACU stay for Before-2015 and After-2015.

PACU, postoperative anesthesia care unit

□ Before 2015; ■ After 2015

between the before and after aggressive approach (Before-2015 versus After-2015), our analysis indicated that the practice did not significantly change the incidence of postoperative nausea ($p = 0.1612$) or vomiting ($p = 0.0678$) (Table 2).

Nausea and Vomiting Are Not Always Linked. Our data showed that PONV events were highly correlated ($p < 0.0001$), yet 2 events were not always linked. Out of 306 patients who had nausea, 48% did not have vomiting. Out of 281 patients with episodes of vomiting, 43% did not have nausea. Young patients (under 3 years) tended to have a high incidence of vomiting without nausea ($p = 0.0017$; Table 1), whereas rates of nausea and vomiting were comparable in the other 2 age groups.

Discussion

Causes of PONV are complicated and involve multiple mechanisms.¹⁴ At the molecular level, several types of neurotransmitters, including serotonin, dopamine, muscarine, acetylcholine, neurokinin-1, and histamine are associated with PONV.^{2,3} Stimulation of the vestibular-cochlear, glossopharyngeal, or vagus nerves may also be the causative factor responsible for PONV.¹⁴ However, there are some pathophysiological differences between nausea and vomiting. Nausea is a subjective feeling, a desire to vomit not associated with expulsive muscular movement.¹⁵ Vomiting, on the other hand, is an autonomic reflex and, as such, directed by the brainstem.³ So, even if these symptoms were not necessarily related,^{16,17} our data demonstrated that they were highly associated. Out of all affected children, 57% had both nausea and vomiting, suggesting that there was some common mechanism that triggered both events.

Multiple studies have explored the risk factors of PONV and possible treatment options.² However, many studies used heterogeneous patient populations, specifically different age groups with various procedures, which confounded many risk factors. The

consequences of these heterogeneous populations are that smaller contributors, such as drug combinations and dosages, of PONV were overshadowed by well-established, stronger predictors such as sex, length of surgery, and anesthetic agents, especially with smaller sample size, thus were overlooked. It is essential to have a homogeneous population to study relatively less significant, but persistent risk factors of PONV, especially when prophylactic management fails.

In our study, we used a homogeneous population of pediatric patients undergoing adenotonsillectomies to investigate the effect of aggressive preventative approach on PONV. Adenotonsillectomy is the most common pediatric surgery for children under 15 years of age.¹⁸ PONV has been common with this type of procedure and can be found in up to 50% of untreated tonsillectomy patients.¹⁹ Therefore, the procedure itself was previously reported as an independent risk factor for PONV.^{4,20}

We are reporting the PONV rate within an hour of the PACU stay to be approximately 4% to 5% with a combined intraoperative ondansetron and dexamethasone prophylaxis. The results suggest that the combination of both medications is very effective in PONV prevention. However, compared with the published results, our numbers may underestimate the overall rate of PONV because we collected data only for 1 hour in the PACU.

When we used a more aggressive preventive approach such as preoperative scopolamine patch or intraoperative diphenhydramine in high-risk (>3 risk factors) patients, the incidence of PONV was reduced even further.

Apparently intraoperative diphenhydramine is better than a preoperative scopolamine patch. Only 1.2% of diphenhydramine-treated patients reported PONV versus 8.1% of scopolamine-treated patients, possibly because a scopolamine patch requires a longer onset time.

However, when compared with the control population, the overall improvements were not significant. One

Table 2. Incidence of Postoperative Nausea and Vomiting Before and After Prophylactic Treatment Approach

	Before-2015	After-2015	p value
N	3419	3697	
% of PON	4.65	3.98	0.1612
% of POV	4.39	3.54	0.0678
Scopolamine*	3 (1)	37 (3)	<0.0001
Prophylactic diphenhydramine†	20 (5)	163 (2)	<0.0001
Rescue diphenhydramine‡	213 (6.2)	106 (2.9)	<0.0001
Other rescue medications‡	69 (2.0)	44 (1.2)	0.0053

PON, postoperative nausea; POV, postoperative vomiting

* Number of transdermal scopolamine patches applied (number of patients who still had incidences of nausea or vomiting with the treatment).

† Number of intraoperative diphenhydramine IVs given (number of patients who had incidences of nausea or vomiting with the treatment).

‡ Number of patients who received rescue medications because of postoperative nausea and vomiting (percentage of these patients over the populations).

possibility of this result is that we treated only a small portion of our patients (200 out of 3697; 5.4%). On the other hand, the results for the aggressive treatment group were significant for the decrease in PONV. It is very likely that the majority of our patients who are coming for adenotonsillectomy are very high risk for PONV and, therefore, require more aggressive pretreatment.

Despite our findings, there are several limitations of this study. We retrospectively examined our clinical practice; the result might be biased without randomized design. We reviewed only the first hour of the PACU stay, which might underestimate the rate of PONV in the population. It is unclear whether the aggressive pretreatment of PONV could extend the benefit after discharge. Due to age, children under 3 years may not verbally express nausea well; therefore, our conclusion about this age group may be inaccurate. Additional experiments with randomized design may shed more light on the benefit of aggressive treatment of PONV in pediatric surgical populations.

ARTICLE INFORMATION

Affiliations Division of Pediatric Anesthesiology, Department of Anesthesiology and Critical Care, Saint Louis University School of Medicine, Saint Louis, MO

Correspondence Pin Yue, PhD; pin.yue@health.slu.edu

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