Double-Blind Randomized Placebo-Controlled Trial of Single-Dose Intravenous Acetaminophen for Pain Associated With Adenotonsillectomy in Pediatric Patients With Sleep-Disordered Breathing

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OBJECTIVES Adequate pain control is an important component in the postoperative outcome for pediatric adenotonsillectomy patients with sleep-disordered breathing (SDB). Intravenous acetaminophen appears to be a favorable analgesic adjunct owing to its predictable pharmacokinetics and opioid-sparing effects; however, its role in pediatric adenotonsillectomy pain management remains unclear.

METHODS In this prospective, randomized, double-blinded, controlled study, subjects with the diagnosis of SDB, aged 2 to 8 years, who required extended postoperative admission, received intravenous acetaminophen (15 mg/kg) or saline placebo intraoperatively in addition to morphine (0.1 mg/kg) for postoperative surgical analgesia. Pain scores in the postanesthesia care unit (PACU) using the FLACC (Faces, Leg, Activity, Cry, Consolability) score were used to determine the need for supplemental analgesic agents in the PACU. The PACU time and time to the first request for pain medication on the inpatient ward were also measured.

RESULTS A total of 239 patients were included in the final data analysis (118 in the intravenous acetaminophen group and 121 in the saline placebo group). The 2 groups did not differ in the proportion of patients reaching FLACC scores ≥ 4 in the PACU ($p = 0.223$); mean FLACC scores in the PACU ($p = 0.336$); mean PACU time ($p = 0.883$); or time to requesting pain medication on the inpatient ward ($p = 0.640$).

CONCLUSIONS A single intraoperative dose of intravenous acetaminophen did not alter the postoperative course of pediatric patients with SDB following adenotonsillectomy.

ABBREVIATIONS AHI, Apnea-Hypopnea Index; ASA, American Society of Anesthesiologists; BMI, body mass index; ETCO_2 , end-tidal carbon dioxide; FiO_2 , fraction of inspired oxygen; FLACC, Faces, Leg, Activity, Cry, Consolability; MAC, minimum alveolar concentration; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnea; PACU, postanesthesia care unit; PAED, pediatric agitation and emergence delirium; PONV, postoperative nausea vomiting; SDB, sleep-disordered breathing

KEYWORDS acetaminophen; pain; pediatric; sleep apnea syndromes; tonsillectomy

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Introduction

Tonsillectomy is one of the most common pediatric surgical procedures in the United States for patients with the diagnosis of sleep-disordered breathing (SDB) or obstructive sleep apnea (OSA). In 2006, an estimated 530,000 tonsillectomies were performed in children younger than 15 years.¹ For pediatric patients undergoing tonsillectomy, adequate pain control is an important component in their postoperative care. Poorly controlled oropharyngeal pain may lead to decreased oral intake, dysphagia, and dehydration and has been cited as one of the leading causes of the need for hospital readmission.^{2–4} For the medical team caring for the OSA or SDB patient presenting for tonsillectomy,

the control of postoperative pain can be challenging. A balance must be struck between the analgesic needs of the patient and the understanding that OSA patients exhibit an increased sensitivity to opioids and are at risk for postoperative respiratory complications, morbidity, and even mortality.^{5–8} These issues underscore the requirement for the careful titration of opioids in a monitored setting and the use of non-opioid analgesic agents in this patient population.

Acetaminophen is a first-line antipyretic and analgesic for mild and moderate pain. The availability of intravenous acetaminophen has emerged as another agent in the clinician's armamentarium for the treatment of acute pain in pediatric patients. Given its predictable pharmacokinetics, minimal adverse effect profile,

reported opioid-sparing effects, and cost-effectiveness in pediatric tonsillectomy patients, intravenous acetaminophen would appear to be a favorable analgesic adjunct for pediatric patients undergoing tonsillectomy who are at risk for increased opioid sensitivity and postoperative respiratory complications.^{9–13} The primary objective of this prospective, randomized, placebo-controlled trial was to determine if a single intraoperative dose of intravenous acetaminophen provided an analgesic benefit for pediatric patients following adenotonsillectomy for the diagnosis of SDB. The primary measure of efficacy was the proportion of patients with pain scores ≥ 4 in the postanesthesia care unit (PACU). Secondary outcomes included pain scores at each time point in the PACU and time to the first request for supplemental pain medication on the inpatient ward.

Materials and Methods

Eligible patients were those 2 to 8 years of age with a diagnosis of OSA or SDB, undergoing adenotonsillectomy and requiring postoperative admission for extended observation with continuous pulse oximetry (minimum of 6–8 hours) based on the pediatric otolaryngologist's preoperative assessment, polysomnography results consistent with OSA, or in accordance with hospital admission guidelines for adenotonsillectomy patients (Table 1) if 1 more clinical and/or age criteria were met.¹⁴ Patients who did not have a sleep study performed preoperatively were designated for postoperative observation by the pediatric otolaryngologist if they had SDB symptoms that included snoring with restless sleep, daytime fatigue, gasping, and witnessed apneas in the home setting. Eligible patients were required to have parents/guardians who were compliant with medical care and who were able to provide written informed consent. Exclusion criteria included patients who had an American Society of Anesthesiologists (ASA) Physical Status ≥ 4 , a known hypersensitivity or allergy to acetaminophen, a known allergy or intolerance to morphine or fentanyl, patients who were receiving chronic opioid analgesic therapy prior to surgery, had renal disease, had hepatic disease, or were considered obese (body mass index [BMI] percentage $> 95\%$).

This was a prospective, single-dose, randomized, double-blinded, placebo-controlled study approved by the Institutional Review Board of Nationwide Children's Hospital. The study was registered at Clinicaltrials.gov. Parents or legal guardians of eligible patients were informed about the study during the preoperative visit and consent was obtained on the day of the surgery. Each patient was followed by a research nurse throughout the perioperative process, which began from the time of enrollment in the preoperative area until transport from the PACU to the hospital inpatient ward where a study hand-off was given to the nursing team.

Study patients received a standardized anesthetic

consisting of a premedication with oral midazolam (0.5 mg/kg) administered 15 to 20 minutes before the induction of anesthesia with sevoflurane in a mixture of nitrous and oxygen. Following intravenous catheter placement, propofol (1–1.5 mg/kg) and morphine (0.1 mg/kg) were administered prior to endotracheal intubation. Morphine dosing was consistent with previous studies examining pediatric tonsillectomy pain management.^{15,16} Patients were maintained with isoflurane titrated to a range from 0.8 to 1 MAC (minimum alveolar concentration) with a mixture of air and oxygen to maintain an FiO_2 (fraction of inspired oxygen) of less than 30% for the duration of the procedure and until the completion of the surgical procedure when the patient was ready for transport to the PACU. All patients received antiemetic therapy consisting of ondansetron (0.15 mg/kg) and dexamethasone (0.25 mg/kg). Intraoperative fluid therapy included a minimum of 10 mL/kg of lactated Ringer solution. Intravenous acetaminophen (15 mg/kg) or saline placebo was infused intraoperatively over 15 minutes following computer-generated randomization by pharmacy, who prepared and dispensed the study drug, but did not participate in data gathering. All study participants and their family members, the designated research nurse responsible for data collection, health care providers from anesthesiology, otolaryngology, and nursing care teams who interacted with the subjects at the preoperative, PACU, and inpatient ward were all blinded to the study intervention that the subject received intraoperatively.

Following completion of surgery, the patient was readied and transported to the PACU where tracheal extubation time was noted. Per our usual clinical practice, for rapid turnover operating rooms, tracheal extubation was performed in the PACU. Baseline vital signs were obtained and pain scores assessed with the FLACC (Faces, Legs, Activity, Cry, Consolability) scale. The presence of emergence delirium was measured with the PAED (Pediatric Agitation and Emergence Delirium) scale. Those subjects whose pain score was assessed as < 4 received standard postoperative care and no analgesic agents, whereas subjects whose assessed pain scores were ≥ 4 received fentanyl (0.5 mcg/kg) every 10 minutes as needed. Variables such as surgical time, anesthetic time, time to tracheal extubation, time to first analgesic delivery in the PACU, pain scores, number of doses and total dose of opioids administered in the PACU, presence of nausea/vomiting, presence of respiratory complications (oxygen saturation $< 90\%$ requiring intervention in the form of supplemental oxygen or pharmacologic management), and total PACU time were recorded during the duration of the patient's PACU stay. Subjects were then discharged to the inpatient ward from the PACU once standard discharge criteria were met. On the inpatient ward, time to first oral analgesic agent, type of analgesic agent, and time to hospital discharge were recorded.

Table 1. Nationwide Children's Hospital Pediatric Adenotonsillectomy Guidelines

Parameter	Guideline
Age	
<3 yr	Adenotonsillectomy
<2 yr	Adenoidectomy (exception is for patients with eustachian tube dysfunction, serous otitis, sinusitis as sole diagnosis)
Sleep study	
Apnea-Hypopnea Index	>10
Pulse oximetry reading	<80%
ETCO ₂	>50 mm Hg
Obesity	Body mass index > 95 percentile for age
Craniofacial syndromes	Yes (e.g., trisomy 21, Pierre Robin)
Comorbid conditions	Asthma (moderate/severe), cystic fibrosis, congenital heart disease, hematologic disorders, diabetes mellitus, and hypotonia and other significant medical conditions

ETCO₂, end-tidal carbon dioxide

The study was powered for a comparison of the primary outcome, FLACC pain score ≥ 4 in the PACU, between the experimental and control groups. A reduction from 50% to 30% in the proportion of patients scoring ≥ 4 on the FLACC scale was anticipated in the group receiving intravenous acetaminophen. Given this assumed effect size, a test of proportions was determined to have 90% power for rejecting the null hypothesis at a 95% confidence level when 124 patients were enrolled in each group. For the purposes of study recruitment, this was rounded to a total sample size of 250 patients divided evenly into experimental and control groups. In addition to a test of proportions comparing the primary outcome, continuous variables were compared across the experimental and control groups by using *t* tests, while categorical variables were compared across the 2 groups with chi-square tests or the Fisher exact tests, as appropriate. Kaplan-Meier survival curves and log-rank tests were used to analyze time from the administration of the study drug to first analgesic delivery on the inpatient ward.

Results

A total of 250 patients were enrolled in the study with 125 randomized to the intravenous acetaminophen group and 125 to the saline placebo arm. Eighteen patients had preoperative polysomnography results of whom 15 patients had an Apnea Hypopnea Index (AHI) < 5 and 3 had an AHI > 5 . Eleven patients (7 in the acetaminophen group and 4 in saline group, 4% overall) were withdrawn from the study owing to changes in the surgical procedure or surgery cancellation ($n = 5$) and patient ineligibility or deviation from the study protocol ($n = 6$), leaving 239 patients for data analysis (118 in the acetaminophen group and 121 in saline group). Comparisons of withdrawn patients versus those who completed the study revealed no statistically significant

differences in height, weight, BMI, age, sex, or ASA physical status. After excluding withdrawn patients, no significant differences in demographic or clinical variables were noted between the acetaminophen and saline groups (Table 2).

Five pain measurements were performed at 0, 5, 15, 30, and 60 minutes after PACU arrival. Fifty-eight (49%) patients in the acetaminophen group and 69 (57%) patients in the saline group reached a FLACC score ≥ 4 at 1 or more time points. The difference in proportions was not statistically significant (OR = 0.73; 95% CI: 0.44, 1.21; $p = 0.223$). Furthermore, no significant differences in PACU FLACC scores were observed between the acetaminophen and saline groups when comparing each time point (Figure 1), or comparing minimum, maximum, or average FLACC scores in the PACU (Table 2). Other aspects of the PACU stay, including PAED scores, did not vary between these 2 groups (Table 2). Opioid analgesia was required in 20 patients given acetaminophen and 29 patients receiving saline with total doses of 0.79 ± 0.34 and 0.79 ± 0.35 mcg/kg, respectively ($p = 0.949$). Among patients requiring opioid analgesia in the PACU, mean time to first drug administration was not significantly different between the acetaminophen (56.80 ± 14.15 minutes) and saline (60.46 ± 20.51 minutes) groups ($p = 0.770$).

All study subjects required breakthrough pain medication on the inpatient ward except for 1 patient who left the hospital upon ward arrival owing to social reasons. Average time until first analgesic received after leaving the PACU did not differ between the 2 groups (Table 2) and a Kaplan-Meier plot and log-rank test confirmed no statistically significant difference in the hazard of receiving an analgesic after leaving the PACU (Figure 2; $p = 0.399$). Analgesics administered after arrival to the inpatient ward are noted in Table 3. There were no statistically significant differences between the acetaminophen and saline groups with regard to type

Table 2. Patient and Case Characteristics by Assignment to the Acetaminophen or Saline Groups

Variable	Acetaminophen (n = 118)		Saline (n = 121)		p value
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Demographics					
Age, yr	4.87 ± 1.53	(4.59, 5.15)	4.84 ± 1.42	(4.58, 5.10)	0.880
Height, cm	109.31 ± 10.82	(107.33, 111.28)	108.78 ± 10.37	(106.91, 110.64)	0.700
Weight, kg	18.85 ± 4.74	(17.99, 19.72)	18.27 ± 4.02	(17.55, 19.00)	0.307
BMI, kg/m²	15.56 ± 1.57	(15.28, 15.85)	15.29 ± 1.36	(15.04, 15.53)	0.147
Procedure time, min	15.85 ± 5.78	(14.79, 16.90)	16.65 ± 5.90	(15.59, 17.72)	0.288
Time to extubation, min*	16.65 ± 7.68	(15.24, 18.06)	15.38 ± 8.52	(13.83, 16.92)	0.230
PACU time, min	64.57 ± 23.41	(60.30, 68.84)	64.98 ± 19.25	(61.51, 68.44)	0.883
FLACC in PACU					
Average	1.13 ± 1.30	(0.89, 1.36)	1.29 ± 1.25	(1.06, 1.51)	0.336
Minimum	0.04 ± 0.46	(−0.04, 0.13)	0.00 ± 0.00	(0, 0)	0.312
Maximum	3.63 ± 3.43	(3.00, 4.25)	4.14 ± 3.38	(3.53, 4.75)	0.245
PAED in PACU					
Average	10.12 ± 1.49	(9.85, 10.39)	10.02 ± 1.33	(9.78, 10.26)	0.596
Minimum	4.66 ± 3.74	(3.98, 5.34)	4.23 ± 3.57	(3.59, 4.87)	0.365
Maximum	12.85 ± 1.75	(12.53, 13.17)	12.83 ± 1.50	(12.56, 13.10)	0.921
Time to first analgesic in inpatient unit, min†	289.41 ± 294.98	(272.04, 306.77)	295.34 ± 100.17	(277.23, 313.45)	0.640

BMI, body mass index; FLACC, Faces, Leg, Activity, Cry, Consolability; PACU, postanesthesia care unit; PAED, pediatric agitation and emergence delirium

* Missing data in 1 acetaminophen case and 2 saline cases.

† Missing data in 1 saline case.

of postoperative pain medication ($p = 0.318$).

Tracheal extubation was performed in 3 patients in the operating room and in the PACU in the remainder of the study cohort. Unanticipated postoperative complications were noted for study subjects (Table 4). The incidence of breakthrough postoperative nausea or vomiting (PONV) was low in the study cohort with an overall incidence of 2% (acetaminophen = 1, saline = 4; $p = 0.373$). Respiratory complications were noted overall in 22 patients (acetaminophen = 10, saline = 12; $p = 0.824$). Of these 22 patients, oxygen desaturation requiring supplemental oxygen in the PACU was seen in all of the 22 patients with 72% (16 patients) requiring supplemental oxygen at PACU discharge to the inpatient ward. Eight of the 22 patients who experienced a respiratory complication exhibited bronchospasm or laryngospasm necessitating active therapy ranging from jaw thrust maneuvers, albuterol, racemic epinephrine with 1 of the 8 patients requiring propofol and succinylcholine to manage the postoperative laryngospasm. None of the respiratory events were severe enough to warrant an admission to the intensive care unit and were managed in the PACU by an attending anesthesiologist. Most patients (92%) were discharged by the first postoperative day (Table 4; acetaminophen = 112, saline = 108, $p = 0.223$). Eighteen patients (acet-

aminophen = 6, saline = 12; $p = 0.157$) required extended hospitalization (2–3 days) owing to pain control issues

Figure 1. Average pain scores in the postanesthesia care unit by treatment assignment, with 95% confidence intervals.

Figure 2. Kaplan-Meier plot for time to first analgesic on the inpatient ward.

(n = 13), persistent oxygen desaturation (n = 4), or post-tonsillectomy bleeding (n = 1).

Discussion

Adequate pain management is an essential component in the postoperative management of pediatric patients undergoing adenotonsillectomy. Although opioid administration is the analgesic mainstay in this patient population, sequelae from its use has been cited as a primary cause of adverse outcomes. Concern over metabolism of pain medication and reported deaths in pediatric patients with OSA has prompted scrutiny of pain management in this population and increased attention to examine the analgesic role of non-opioid alternatives in pediatric adenotonsillectomy patients.^{8,17}

This prospective, randomized, controlled, double-blinded study demonstrates that the administration of a single intraoperative, intravenous dose of acetaminophen when administered in combination with intravenous morphine to pediatric patients undergoing adenotonsillectomy for the diagnosis of SDB does not improve the postoperative outcome. The quality of

postoperative outcome was judged by using various clinical outcomes including pain scores, PACU opioid consumption, length of PACU stay, and time to first analgesic on the inpatient ward. No improvement in analgesia was noted, as we saw no statistical significance in any measured analgesic variable between the study groups, including PACU pain scores, need for breakthrough PACU pain medications, amount of PACU pain medication administered, and the time to first analgesic on the inpatient ward. In addition, no differences were seen in PACU or hospital stay duration.

Although multiple studies^{18–20} have shown an opioid-sparing effect or enhanced analgesic efficacy of intravenous acetaminophen in the adult and pediatric population for various surgical procedures, a similar effect was not seen in our study cohort. One explanation is that our usual analgesic regimen for such patients included an intraoperative dose of morphine (0.1 mg/kg), which was adequate for many of the patients, thereby mitigating the ability to see any additional effect from a single intraoperative dose of a non-opioid analgesic. Support for this is provided by our finding that analgesia as judged by postoperative pain scores was adequate in most patients with only approximately 20% of the patients receiving fentanyl in the PACU. The finding was also supported by the fact that the average time to the administration of the first analgesic on the inpatient ward in both groups was between 4 and 5 hours and consistent with the duration of action for morphine. In addition to morphine, all of the patients also received an intraoperative dose of dexamethasone, which has also been shown to provide analgesic benefit following adenotonsillectomy.²¹

The other issue that may have impacted the outcome was the administration of acetaminophen, which was not continued into the postoperative period. Postoperative analgesia was provided by our institution's usual regimen of as-needed oral acetaminophen, non-steroidal anti-inflammatory drugs, oxycodone, or hydrocodone/acetaminophen for breakthrough pain on the inpatient ward. With this regimen, most patients were discharged to home on the first postoperative day.

There remains considerable debate among health care providers regarding what is the optimal pain regimen for pediatric tonsillectomy patients, especially

Table 3. First Analgesic Given in Inpatient Ward

	Acetaminophen (n = 118)	Saline (n = 120)
Hydrocodone/acetaminophen*	68 (58)	57 (48)
Oxycodone*	31 (26)	39 (33)
NSAID*	15 (13)	22 (18)
Acetaminophen*	3 (3)	2 (2)
Morphine*	1 (1)	0

NSAID, non-steroidal anti-inflammatory drug

* Data presented as No. (%).

Table 4. Postoperative Recovery Variables

	Acetaminophen (n = 118)	Saline (n = 120)	p value*
PACU desaturation < 90% [†]	10 (8)	12 (10)	0.824
Supplemental oxygen at PACU discharge [†]	8 (7)	8 (7)	>0.999
Bronchospasm/laryngospasm requiring active [†] intervention	2 (2)	6 (5)	0.281
PONV [†]	1 (1)	4 (3)	0.373
Hospital days [†]			0.223
0	3 (3)	2 (2)	
1	109 (92)	106 (88)	
2	5 (4)	12 (10)	
3	1 (1)	0	

PACU, postanesthesia care unit; PONV, postoperative nausea vomiting

* Fisher exact tests.

[†] Data presented as No. (%).

those with SDB or OSA. This includes not only which agent, but also the dose. Although controversy exists regarding the use of morphine in children with SDB or OSA, our clinical practice, at an institution that performs more than 8000 otolaryngology cases on a yearly basis, relies heavily on the intraoperative use of morphine to ensure appropriate postoperative analgesia. In our study cohort, most were pediatric patients who did not undergo preoperative polysomnography to definitively diagnose OSA, but had severe enough clinical symptoms of SDB and were within an age group of 2 to 8 years to warrant extended postoperative observation and monitoring, as recommended by our institutional guidelines as well as national guidelines. Therefore, all patients were admitted to the inpatient ward and received at least 6 to 8 hours of ongoing monitoring with continuous pulse oximetry. Such monitoring allows the safe and effective use of intravenous opioids in this patient population. Although previous studies have reported adequate analgesia with lower intraoperative doses of morphine, with the use of shorter-acting analgesics such as fentanyl in combination with non-opioid analgesics, the longer-acting agent morphine, when administered in appropriate doses with appropriate postoperative monitoring, offers the benefit of providing analgesia beyond the immediate recovery time in the PACU.^{20,22,23} In these subjects, the average time to the first request for an additional analgesic agent was 4 to 5 hours after admission to the inpatient ward. Although decreasing the morphine dose could highlight an opioid-sparing effect of the intravenous acetaminophen in the immediate PACU period, it may also lead to rebound postoperative pain.

The challenge of balancing analgesic needs with potential of postoperative respiratory complications in adenotonsillectomy patients with SDB was highlighted by our study. Unanticipated PACU respiratory events defined by oxygen saturation < 90% requiring

intervention in the form of supplemental oxygen or pharmacologic management occurred in 9.2% of our study cohort. This finding was consistent with previous published data showing a respiratory complication frequency of 9.4% in pediatric adenotonsillectomy patients.²⁴ Of the 9.2% of our study cohort who had unanticipated respiratory events, 40% also required breakthrough pain medications at some point during their PACU stay. None of these respiratory events were life-threatening and were easily managed by an attending anesthesiologist. No events led to admission to the intensive care unit. Despite the positive postoperative outcome for our study subjects, continued focus and research is needed toward optimizing and even differentiating postoperative pain management and education in pediatric patients with SDB versus OSA following adenotonsillectomy given the significant rates of readmission for pain-related issues and the alarming cases of posttonsillectomy mortality outside the hospital setting due to possible opiate overuse, especially in children with OSA.^{25,26}

Limitations of our study include the fact that it involves data from a single and not a multicenter enrollment process. In addition, patients were not enrolled if their BMI was > 95% or if there was a diagnosis of severe OSA necessitating planned intensive care unit admission. Given that most study patients did not have a preoperative polysomnography, but were admitted for extended observation on the basis of age (2–8 years) and symptoms of SDB as noted by the otolaryngologist, such a study enrollment pattern may have created selection bias toward this patient subset versus those with severe OSA and obesity in whom the analgesic efficacy and opioid-sparing effect of intraoperative acetaminophen may be different.

In the current era of medical cost-effectiveness and containment, we found no financial benefit for the administration of a single dose of intravenous acet-

aminophen in adenotonsillectomy patients. We found no significant differences with regard to PACU stay or hospitalization duration to justify the drug cost, which has been previously reported.¹⁹ In conclusion, a single dose of intraoperative intravenous acetaminophen when combined with morphine in a dose of 0.1 mg/kg and dexamethasone provided no added analgesic or recovery benefit in pediatric patients aged 2 to 8 years with SDB undergoing adenotonsillectomy.

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REFERENCES

- Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report*. 2009;28(11):1–25.
- Williams G, Bell G, Buys J, et al. The prevalence of pain at home and its consequences in children following two types of short stay surgery: a multicenter observational cohort study. *Paediatr Anaesth*. 2015;25(12):1254–1263.
- Mahant S, Hall M, Ishman SL, et al. Association of national guidelines with tonsillectomy perioperative care and outcomes. *Pediatrics*. 2015;136(1):53–60.
- Shay S, Shapiro NL, Bhattacharyya N. Revisit rates and diagnoses following pediatric tonsillectomy in a large multistate population. *Laryngoscope*. 2015;125(2):457–461.
- Brown KA, Laferriere A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. *Anesthesiology*. 2004;100(4):806–810.
- Sanders JC, King MA, Mitchell RB, et al. Perioperative complications of adenotonsillectomy in children with obstructive sleep apnea syndrome. *Anesth Analg*. 2006;103(5):1115–1121.
- Brown KA. Outcome, risk, and error and the child with obstructive sleep apnea. *Paediatr Anaesth*. 2011;21(7):771–780.
- Cote CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: Houston, we have a problem! *Anesth Analg*. 2014;118(6):1276–1283.
- Zuppa AF, Hammer GB, Barrett JS, et al. Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. *J Pediatr Pharmacol Ther*. 2011;16(4):246–261.
- Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology*. 1999;91(2):442–447.
- Hong JY, Kim WO, Koo BN, et al. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. *Anesthesiology*. 2010;113(3):672–677.
- Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. *Paediatr Anaesth*. 2013;23(6):475–495.
- Subramanyam R, Varughese A, Kurth CD, et al. Cost-effectiveness of intravenous acetaminophen for pediatric tonsillectomy. *Paediatr Anaesth*. 2014;24(5):467–475.
- Raman VT, Jatana KR, Elmaraghy CA, et al. Guidelines to decrease unanticipated hospital admission following adenotonsillectomy in the pediatric population. *Int J Pediatr Otorhinolaryngol*. 2014;78(1):19–22.
- Olutoye OA, Glover CD, Diefenderfer JW, et al. The effect of intraoperative dexmedetomidine on postoperative analgesia and sedation in pediatric patients undergoing tonsillectomy and adenoidectomy. *Anesth Analg*. 2010;111(2):490–495.
- Chidambaran V, Venkatasubramanian R, Zhang X, et al. ABCC3 genetic variants are associated with postoperative morphine-induced respiratory depression and morphine pharmacokinetics in children. *Pharmacogenomics J*. 2016;26(1):1–8.
- Racoosin JA, Roberson DW, Pacanowski MA, et al. New evidence about an old drug—risk with codeine after adenotonsillectomy. *N Engl J Med*. 2013;368(23):2155–2157.
- McNicol ED, Ferguson MC, Haroutounian S, et al. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. *Cochrane Database Syst Rev*. 2016;23(5):CD007126.
- Ceelle I, de Wildt SN, van Dijk M, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA*. 2013;309(2):149–154.
- Alhashemi JA, Daghistani MF. Effects of intraoperative i.v. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. *Brit J Anaesth*. 2006;96(6):790–795.

21. Hermans V, De Pooter F, De Groote F, et al. Effect of dexamethasone on nausea, vomiting, and pain in paediatric tonsillectomy. *Br J Anaesth*. 2012;109(3):427–431.
22. Moss JR, Watcha MF, Bendel LP, et al. A multicenter, randomized, double blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. *Paediatr Anaesth*. 2014;24(5):483–489.
23. Li X, Zhou M, Xia Q, Li J. Parecoxib sodium reduces the need for opioids after tonsillectomy in children: a double-blind placebo-controlled randomized clinical trial. *Can J Anesth*. 2016;63(3):268–274.
24. De Luca Canto G, Pachêco-Pereira C, Aydinov S, et al. Adenotonsillectomy complications: a meta-analysis. *Pediatrics*. 2015;136(4):702–718.
25. Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. *Laryngoscope*. 2013;123(10):2544–2553.
26. Cote CJ. Anesthesiological considerations for children with obstructive sleep apnea. *Curr Opin Anaesthesiol*. 2015;28(3):327–332.