Perioperative Intravenous Acetaminophen in Pediatric Tonsillectomies

Brandi Bowman¹, Leslie Sanchez¹, and Preeyaporn Sarangarm¹

Abstract

Purpose: This study investigated the effect of perioperative intravenous (IV) acetaminophen on opioid requirements in pediatric patients undergoing tonsillectomy at a single center. **Methods:** This retrospective chart review included patients who were less than 18 years old and underwent an outpatient tonsillectomy procedure. Patients who received non-Food and Drug Administration (FDA)-approved dosing of IV acetaminophen, without documented weights, and on chronic pain medications at the time of the procedure were excluded. The primary outcome was opioid requirements postoperatively prior to discharge measured as morphine equivalents per kilogram. Descriptive statistics were used to compare differences between groups. A multivariate analysis was performed, accounting for differences between groups in baseline and procedural characteristics. **Results:** In total, 157 patients were included in this study, of whom 55 had received IV acetaminophen and 102 had not. The average IV acetaminophen dose for was 14.5 mg/kg for patients weighing less than 50 kg ($n = 22$); the remaining patients received the maximum 1 g dose. Patients who received IV acetaminophen were less likely to be administered postoperative opiates as compared with those did not (45.5% vs 63.7%, odds ratio = 0.48, $P = .036$). There was a trend toward a decrease in total amount of opiates administered with IV acetaminophen (0 vs 0.033 $\mu\text{g/kg}$, $P = .61$). After adjusting for age and documented pain assessment, IV acetaminophen administration remained a significant factor for postoperative opiate administration. **Conclusions:** Perioperative administration of IV acetaminophen was associated with less frequent administration of symptom-directed opiates in pediatric tonsillectomies. This finding indicates that the agent may have an opioid-sparing effect in this patient population.

Keywords

pediatrics, analgesics, pain management, adenotonsillectomies

Introduction

Tonsillectomy is one of the most common outpatient day surgery procedures performed in children. These procedures are frequently complicated by pain, which can delay hospital discharge when not adequately controlled.¹ However, despite advances in surgical and anesthetic technique, and the prevalence of this procedure, determination of an optimal pain control regimen remains unclear.

Several modalities are available for perioperative pain control, each with its own set of limitations. Opioids are commonly used and are effective; however, in the outpatient surgery setting, the associated sedation and respiratory depression can be a significant drawback and can necessitate prolonged durations of stay. The US Food and Drug Administration (FDA) has cautioned against the use of tramadol in pediatrics and specifically against codeine to treat postsurgical pain in pediatric tonsillectomies and adenoidectomies due to the risk of serious respiratory difficulties in ultra-rapid metabolizers.² It remains standard to administer alternative short-acting opioids such as fentanyl

intraoperatively with clinicians frequently utilizing adjunctive agents to minimize postoperative opioid requirements. Nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated efficacy as analgesics, but many clinicians avoid them due to the risk of bleeding through their antiplatelet effect.³ Oral acetaminophen, also effective for pain, is limited perioperatively by its inability to quickly achieve effective plasma concentrations. As such, the IV formulation of acetaminophen has been proposed as an adjunctive analgesic in the perioperative setting. Intravenous (IV) acetaminophen has demonstrated similar analgesia to the rectal formulation, although its effects appear to be shorter lived.⁴ Conversely, a retrospective study comparing the use of IV and rectal acetaminophen in infants

¹University of New Mexico Hospital, Albuquerque, USA

Corresponding Author:

Preeyaporn Sarangarm, Department of Pharmacy, University of New Mexico Hospital, 2211 Lomas Blvd NE, Albuquerque, NM 87106, USA.
Email: psarangarm@salud.unm.edu

undergoing laparoscopic pyloromyotomy found no difference in postoperative pain scores or need for additional analgesics between groups.⁵ In other pediatric procedures, IV acetaminophen has been shown to have a fentanyl-sparing effect when used in combination with fentanyl in ureteroneocystostomy; however, it did not reduce oxycodone consumption after major spine surgery in children and adolescents.^{6,7}

Though commonly used, there is little data for IV acetaminophen efficacy in tonsillectomies. Two small studies that compared IV acetaminophen with IV tramadol and intramuscular (IM) meperidine perioperatively found that pain control was similar with IV acetaminophen, and compared with meperidine, time to discharge was decreased by 10 minutes.^{8,9} The objective of our study was to determine whether the addition of perioperative administration of IV acetaminophen, as an adjunct to perioperative opiates, decreased opiate consumption while maintaining pain control in pediatric tonsillectomies.

Methods

This is a retrospective cohort study of pediatric patients who underwent tonsillectomy procedure between January 2012 and September 2015. The University Health System Consortium Clinical Database was used to identify patients for study inclusion. Patients were included if they were less than 18 years of age and had undergone an outpatient tonsillectomy procedure during the allotted time period. Exclusion criteria included documented analgesics in the 48 hours prior to the procedure, IV acetaminophen doses greater than 15% outside of FDA-approved dosing (15 mg/kg every 6 hours for children 2-12 years of age or <50kg, and at 1000 mg every 6 hours for older children greater than 50 kg), no documented weight at the time of procedure or weights amended after the acetaminophen dose was given, and patients admitted to the hospital for the procedure.¹⁰ Patients who met inclusion criteria were stratified into 2 groups based on whether they had received perioperative IV acetaminophen. This study was approved by the local institutional review board.

Data Collection

All data were collected from the patient's electronic health records. Demographic and baseline characteristics gathered included patient sex, age, weight, and ethnicity. Procedure factors of interest included procedure type, procedure duration, and the name, cumulative dose, and route of any analgesics administered intraoperatively. Outcome-related variables included the dose and timing of IV acetaminophen if applicable, as well as the dose and timing of any postoperative analgesics. Pain scores (on a 0-10 scale, with 0 indicating no pain and 10 indicating severe pain) that were assessed in the postanesthesia care unit (PACU) were also collected as well as the time of discharge from the PACU to

determine length of stay. Any opiates administered were transformed into morphine equivalents per kilogram using validated dose equivalencies to facilitate comparisons between patients who received different drugs.¹¹

Outcomes and Statistical Analysis

The primary outcome assessed was opioid administration in the PACU, defined as whether a patient was administered any opiate postoperatively. Secondary outcomes included opiate requirement in the PACU (defined as morphine equivalents per kilogram), postoperative pain assessment documentation in the PACU, the time to first dose of rescue analgesia, pain scores in the PACU for patients with documented pain assessments, and time to discharge from the PACU.

Baseline traits, procedure information, and pain assessment were characterized using descriptive statistics, and assessed for between-group differences (using chi-square and Mann Whitney *U* for categorical and continuous variables, respectively). Opiate administrations between patients who received IV acetaminophen compared with those who did not were assessed via chi-square. All other secondary outcomes were verified via Mann Whitney *U*. A multivariate analysis was performed by backward conditional logistic regression, accounting for differences between groups in baseline and procedural characteristics. Only factors predictive of postoperative opioid administration were included in final model. All statistics were performed in SPSS (IBM SPSS Statistics for Windows, Version 19.0, Released 2010; IBM Corp, Armonk, New York).

Results

In all, 160 patients were screened for inclusion in the study. Three patients were excluded; 2 because they were on analgesics prior to the procedure and 1 who had received dosing outside of the study's required range. The final analysis consisted of 157 patients, of whom 55 had received IV acetaminophen and 102 had not.

Patient Characteristics

Table 1 describes baseline characteristics. The two groups were similar in terms of sex and ethnic make-up. Patients that received IV acetaminophen tended to be older (median age of 12 vs 11 years) and weigh more (64.9 vs 52.1 kg). Procedural characteristics are presented in Table 2. Close to 60% of patients in the overall study population had more than one procedure performed and significantly more patients who did not receive IV acetaminophen underwent multiple procedures. The majority of additional procedures performed were adenoidectomies, but also included turbinectomies, myringotomies, tympanic tube placement, and cerumen removal.

Table 1. Demographic and Baseline Characteristics.

	IV acetaminophen (n = 55)	No IV acetaminophen (n = 102)	P value
Female (n, %)	31 (56.4)	55 (53.9)	.769
Race/ethnicity (n, %)			.705
Hispanic	21 (38.2)	49 (48.0)	
White	14 (25.5)	19 (18.6)	
Native American	9 (16.4)	14 (13.7)	
Other/not reported	11 (20)	20 (19.6)	
Weight (kg; median, range)	64.9 (11.4-121.9)	52.1 (10.4-121.5)	.027

Table 2. Procedural Information.

	IV acetaminophen (n = 55)	No IV acetaminophen (n = 102)	P value
Duration (minutes; median, range)	25.0 (7-123)	20.5 (7-83)	.179
Intraoperative morphine equivalents (μg/kg; median, range)	0.129 (0-0.48)	0.167 (0.01-0.48)	.002
Intraoperative medications (n, %)			.113
Dexmedetomidine	11 (20)	11 (10.8)	
Other ^a	7 (12)	3 (3)	

^aKetamine (n = 5), ketorolac (n = 4), and celecoxib (n = 1).

Table 3. Postoperative Pain Management.

	IV acetaminophen (n = 55)	No IV acetaminophen (n = 102)	P value
Postoperative opiates administered (n, %)	25 (45.5)	65 (63.7)	.036
Postoperative morphine equivalents (μg/kg; median, range)	0 0 – 0.289	0.033 0 – 0.238	.061
Pain recorded postoperatively (n, %)	48 (87.3)	79 (77.5)	.005
Time to rescue analgesia (minutes; median, range)	32 (1-56)	33.5 (2-59)	.561
Pain scores (median, range)			
First pain score	3 (0-9)	5 (0-10)	.808
Peak pain score	5 (0-9)	5 (0-10)	.631
Last pain score	2 (0-9)	1 (0-9)	.113
PACU length of stay (minutes; median, range)	140 (81-508)	128 (39-514)	.086

Note. PACU = postanesthesia care unit.

IV acetaminophen was administered intraoperatively in 29 patients and postoperatively in 26 patients. For those patients in whom it was administered postoperatively, IV acetaminophen was the first postoperative analgesic administered. The average IV acetaminophen dose was 14.5 mg/kg for patients weighing less than 50 kg (n = 22). The remaining 33 patients received the maximum 1 g dose.

Outcomes

In the univariate analysis, patients who received IV acetaminophen were significantly less likely to be administered postoperative opiates as compared with those did not (45.5% vs 63.7%, odds ratio = 0.48, $P = .036$). There was a trend toward a decrease in total amount of opiates administered

with IV acetaminophen; however, this did not reach significance (0 vs 0.033 μg/kg, $P = .61$). Postoperative pain assessment was recorded at least once in 87.3% of patients who received IV acetaminophen and in 77.5% of patients who did not ($P = .005$). There was no difference between groups for the time to first dose of rescue analgesia, pain scores in the PACU, or time to discharge from the PACU (Table 3). After adjusting for age and documented pain assessment, IV acetaminophen administration remained a significant factor for postoperative opiate administration (Table 4).

Discussion

In this study, perioperative administration of IV acetaminophen was associated with less frequent administration of

Table 4. Multivariate Analysis of Postoperative Opioid Administration.

	Odds ratio	P value ^a
Age	1.117	.012
Pain recorded	3.535	.035
IV acetaminophen	0.328	.004

^aVia backward conditional logistic regression adjusting for age, documented pain assessment, and IV acetaminophen administration.

symptom-directed opiates in pediatric tonsillectomies. This finding indicates that the agent may have an opioid sparing effect in this patient population. When measured in terms in total amount of opiate administered, there was a trend toward a decrease in morphine equivalents given in those patients who received IV acetaminophen, but this did reach statistical significance. In this study, no difference was seen between groups in time to rescue analgesia, postoperative pain scores, or length of stay in the PACU.

There is a paucity of data regarding the use of IV acetaminophen in pediatric tonsillectomies, and differences in trial design do not facilitate comparisons between trials.¹² Two prospective trials done by Alhashemi and Daghistani⁸ and Uysal et al,⁹ comparing IV acetaminophen to IM meperidine and IV tramadol respectively, primarily evaluated pain and sedation scores in the recovery period, but also assessed the percentage of patients requiring opiate rescue analgesia. Of note, the percentage of patients requiring postoperative opiate analgesics was notably less in both of these studies than what was seen in our study. Alhashemi and Daghistani reported that 17.5% of patients given IV acetaminophen required rescue morphine while no patients given IM meperidine required morphine. In the Uysal et al study, 31.2% of patients given IV acetaminophen, compared with 28.1% of patients given IV tramadol, required rescue analgesia. These differences in the amount of patients requiring postoperative opiates may largely be explained by variations in how the recovery period was defined between studies. Both the studies by Alhashemi and Daghistani and Uysal et al used the Aldrete scoring system, an assessment of sedation and hemodynamic stability, to determine readiness for discharge.¹³ As such, both studies demonstrated much shorter recovery periods than what was seen in this study; PACU length of stay for patients receiving IV acetaminophen was 15 and 10 minutes for patients in the studies by Alhashemi and Daghistani and Uysal et al, respectively. Due to the retrospective nature of our study and the fact that Aldrete scores were not documented, we were required to use length of stay as a proxy for readiness for discharge. Also, discharge of patients from the PACU was not dependent on a clear protocol, making it likely that this variable was affected by many factors. Furthermore, because patients were assessed over a longer period of time after tonsillectomy in this study, it is not unexpected that more patients required rescue analgesia.

There were several potential limitations in this study. First, the retrospective nature made it impossible to control for variance in pain assessment and management between clinicians. Indeed, not only did a significantly larger percentage of patients that received IV acetaminophen have their pain assessment documented, it was also noted that having pain documented was a predictor of whether patients received postoperative opiates. Another potential limitation of our study was the before-and-after study design; there may have been variations in practice that occurred over time. Tonsillectomies that occurred over a 48-month period of time were included in the study, but IV acetaminophen was not used until the last 18 months. However, there was no statistically evident effect of time on pain assessment or postoperative opiate administration. Finally, decisions regarding postoperative pain assessment and management were made by nursing staff, who did not follow a standardized protocol that dictated frequency of assessment or treatment choices. As such, it is possible that administration of IV acetaminophen affected pain treatment decisions, particularly in those patients that received IV acetaminophen postoperatively. However, in our statistical analysis, the effect of IV acetaminophen administration on postoperative opioid administration was not dependent on whether the IV acetaminophen was given intra- or postoperatively.

The results of this study suggest that perioperative IV acetaminophen, used as an adjunct to perioperative opiates, does reduce the need for postoperative opiates. However, there is limited clinical data supporting its use over other measures, such as tramadol, meperidine, or NSAIDs. Furthermore, it remains unclear that IV administration of acetaminophen is superior to oral or rectal strategies that maximize the serum levels. There remains a need for large, prospective comparative trials to truly assess the cost-efficacy of routine IV acetaminophen use in this population.

Declaration of Conflicting Interests

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