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Does intravenous acetaminophen reduce perioperative opioid use in pediatric tonsillectomy?

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ABSTRACT

Objective: Postoperative pain control is of significant interest in pediatric otolaryngology given the safety concerns with opioid use. We sought to determine if addition of intraoperative intravenous acetaminophen decreases perioperative morphine use in pediatric tonsillectomy.

Methods: This study is a retrospective cohort study performed at a tertiary care academic children's hospital. 166 pediatric patients (aged 1–16 years) who underwent tonsillectomy with or without adenoidectomy were for review. Seventy-four patients received intraoperative intravenous acetaminophen (intervention cohort), while ninety-two patients served as our control and did not receive any intraoperative intravenous acetaminophen. Perioperative (intraoperative and postoperative) morphine use was our primary outcome measure. Rate of adverse events in the post anesthesia care unit and time for discharge readiness were secondary outcome measures. Wilcoxon two-sample *t*-test approximation and Fisher's exact test were used for data analyses.

Results: Patients in the intravenous acetaminophen cohort received less morphine (mg/kg) intraoperatively (0.058 versus 0.070, $p = 0.089$) and in the post anesthesia care unit (0.034 versus 0.051, $p = 0.034$) than the control cohort. The median time to discharge readiness for the intravenous acetaminophen and control groups was 108.5 versus 105 min ($p = 0.018$). There was no adverse respiratory event (oxygen desaturation < 92% lasting more than a minute, requiring bag mask ventilation or reintubation) in either group in the post anesthesia care unit. There were 5 (7%) episodes of postoperative vomiting in the IV APAP, while 2 (2%) were recorded in the control cohort ($p = 0.244$).

Conclusion: Our findings suggest intraoperative intravenous acetaminophen use in pediatric tonsillectomy can decrease the perioperative use of opioid for optimal pain management.

1. Introduction

Tonsillectomy is one of the most common surgical procedures in children in the United States [1], with roughly 80% being performed due to sleep-disordered breathing and obstructive sleep apnea (OSA) [2]. Intermittent hypoxia, as occurs in OSA, has been shown to upregulate the number of central μ-opioid receptors, thus increasing one's sensitivity to opioids and their side effects. Brown et al. has shown both a reduction in the dose of opioid needed for effective analgesia, as well as an increased sensitivity to opioids in children with OSA undergoing tonsillectomy [3,4].

In a recent review, opioid-related factors were cited as the third most common cause of post-tonsillectomy fatalities (16.3%) following surgical and anesthetic factors, while opioid-related fatality claims resulted in the largest median monetary award ($1,625,892) [5]. Severe adverse outcomes such as death and neurologic injury were related to respiratory events after tonsillectomy surgery in the post anesthesia care unit (PACU), hospital floor, and at home [6].

Intravenous acetaminophen (IV APAP) was approved by the United States Food and Drug Administration in 2010 for the treatment of pain and fever in children over two years of age [7]. With 100% bioavailability, IV APAP consistently achieves plasma concentration levels of 10–20 μg/mL, a level necessary to achieve adequate analgesia in the pediatric post-tonsillectomy population [8]. Furthermore, it achieves its maximum plasma concentration quickly, within 15 min, four and eight times faster than oral and rectal forms of acetaminophen, respectively

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We recently started using IV APAP at our institution as part of multimodal pain management in pediatric tonsillectomy. This study sought to determine if intraoperative IV APAP use decreases perioperative morphine use in ambulatory (same day) pediatric tonsillectomy surgery.

2. Methods

2.1. Study setting and design

This retrospective cohort analysis was performed at the University of Mississippi Medical Center (UMMC), a tertiary, academic hospital. The Institutional Review Board at UMMC approved this study and waived the need for written consent. Children who underwent ambulatory tonsillectomy with or without adenoidectomy at our hospital from January through August 2014 were included in the study. Methods of tonsillectomy included cold steel (snare) or monopolar electrocautery (Bovie). Primary indication for tonsillectomy was either sleep disturbed breathing (documented or suspected obstructed sleep apnea) or tonsillitis (recurrent or chronic tonsillitis). Patients with Down Syndrome, Muscular dystrophy or other genetic condition predisposing to hypotonia or airway compromise, as well as those undergoing concomitant procedures (aside from tympanostomy tube placement) were excluded from the study.

IV APAP (Ofirmev®, Cadence Pharmaceuticals, Inc. San Diego, California) was available at our institution starting May 2014. Therefore, our control cohort of 92 patients was identified in the immediate four months prior (January–April 2014), while our intervention cohort (IV APAP) of 74 patients was identified in the immediate four months after (May–August 2014). Demographic information, intraoperative and post-anesthesia care unit (PACU) morphine use, time until extubation (procedure finish to extubation), time until discharge readiness, and postoperative adverse events (adverse respiratory event, nausea and vomiting) were recorded. Adverse respiratory event was defined as oxygen desaturation < 92% lasting more than a minute requiring bag mask ventilation or reintubation.

In the control cohort, patients did not receive any form of acetaminophen. In the intervention cohort, patients received a standard weight based dose of 15 mg/kg of intravenous acetaminophen intraoperatively after induction of anesthesia. The anesthetic management in both groups included mask induction, tracheal intubation and general anesthesia with sevoflurane. This is the standard anesthetic technique practiced at this institution, used in both groups. IV dexamethasone 0.5 mg/kg and IV ondansetron 0.1 mg/kg were given as part of postoperative nausea and vomiting (PONV) prophylaxis. Intravenous morphine (up to a dose of 0.1 mg/kg) and/or Fentanyl (up to a dose of 1 μg/kg) were used in both groups at the discretion of the anesthesia team for intra-operative pain management.

In the PACU, the pain assessment was done by FLACC (facial expression, leg movement, activity, cry, consolability) scoring [8]. Additional morphine in titrated doses of (0.05 mg/kg) were given by PACU nursing every 10 min as needed to treat pain for FLACC score > 4.

Time to discharge readiness was calculated from time of arrival in PACU until the patient was discharged from the hospital. The patients were discharged from the hospital when their vitals were stable, pain was adequately controlled, and oral fluid intake was tolerated.

2.2. Statistical analysis

Patient characteristics are shown as median (25th quartile, 75th quartile) or number (%). In all analyses presented, continuous variables are compared using the Wilcoxon two-sample *t*-test approximation and categorical variables are compared using Fisher's exact test. *P*-values < 0.05 are considered statistically significant. Analyses were conducted using SAS software, Version 9.4 (SAS Institute, Inc., Cary, NC).

Table 1
Patient demographics.

Characteristic	Intravenous acetaminophen n = 74	Control n = 92	p-Value
Median age (months)	71.4 (51.5, 97.9)	64.9 (48.2, 89.6)	0.461
Male gender (number (%))	38 (51.4)	38 (41.3)	0.197
Median weight (kg)	23.5 (18.2, 32.2)	21.4 (16.8, 30.1)	0.449
Operation[a]			0.659
T	11 (14.9%)	8 (8.7%)	
TA	63 (85.1%)	84 (91.3%)	
Method of tonsillectomy			0.929
Cold steel (snare)	10 (13.5%)	12 (13.0%)	
Monopolar electrocautery	64 (86.5%)	80 (87.0%)	
Primary indication			0.478
Sleep disturbed breathing	51 (69.0%)	68 (74.0%)	
Tonsillitis	23 (31.0%)	24 (26.0%)	

[a] T = tonsillectomy; TA = adenotonsillectomy. Data is presented as median (25th, 75th percentiles), number of patients (%).

3. Results

A total of 166 pediatric patients aged 1–16 years of age were included in the study, 74 in the intervention cohort (IV APAP) and 92 in the control cohort.

3.1. Patient demographics (see Table 1)

There were no statistically significant differences between the intervention and control cohorts in terms of age, gender, weight, operation, method of operation or indication for operation.

3.2. Primary outcome measure (see Table 2)

The average intraoperative, postoperative and total amount of morphine (mg/kg) given in both groups is shown in Table 2. The patients in the IV APAP cohort received statistically significantly less morphine (mg/kg) in the post anesthesia recovery room (0.034 versus 0.051, p = 0.034) than the control cohort. The patients in the IV APAP cohort received less morphine (mg/kg) intraoperatively (0.058 versus 0.070, p = 0.089) and overall (total) morphine dose for the procedure (0.072 versus 0.100, p = 0.059) than the control cohort. Postoperative morphine use was given to 42 patients (56.8%) in the IV APAP group and 49 patients (53.2%) in the control group (p = 0.653).

3.3. Secondary outcome measures

The time to extubation was 4.0 min (3.0, 7.0) in IV APAP cohort and 5.0 min (3.0, 8.0) in control cohort (p = 0.215). The median time to discharge readiness for the IV APAP and control groups was 108.5 versus 105 min (p = 0.018). In the PACU, there was no adverse respiratory event in either group. There were 5 (7%) episodes of postoperative vomiting in the IV APAP, while 2 (2%) were recorded in the control cohort (p = 0.244) (Table 2).

4. Discussion

Pain management after pediatric tonsillectomy can be a challenge. Many of these children needing tonsillectomy have some degree of obstructive sleep apnea (OSA) and are extremely sensitive to opioids respiratory depression [3,4]. Our study shows that IV APAP can decrease the perioperative use of morphine in pediatric tonsillectomy surgeries.

Table 2
Comparison of intravenous acetaminophen and control groups.

Study measure	Intravenous acetaminophen n = 74	Control n = 92	p-Value
Amount of intra-op morphine given (mg/kg)	0.058 (0.0, 0.1)	0.070 (0.03, 0.1)	0.089
Amount of PACU morphine given (mg/kg)	0.034 (0.03, 0.06)	0.051 (0.03, 0.08)	**0.034**
Total amount of morphine given (mg/kg)	0.072 (0.04, 0.1)	0.100 (0.06, 0.1)	0.059
Usage PACU morphine	42 (56%)	49 (53%)	0.653
Post-op nausea and vomiting	5 (7%)	2 (2%)	0.244
Time to extubation (minutes)	4.0 (3.0, 7.0)	5.0 (3.0, 8.0)	0.215
Total time to discharge (minutes)	108.5 (88, 134)	105.0 (88, 144)	0.918

p-value < 0.05

Previous studies have shown that IV APAP treated pain effectively and reduced pethidine consumption after tonsillectomy in adults [10], and reduced morphine use by almost 66% in neonates and infants undergoing major non-cardiac surgery within the first 48 h post-operatively [11]. Our study has shown that IV APAP is effective in children undergoing same day tonsillectomy surgeries.

Rectal APAP has been commonly used, especially for the placement of tympanostomy tubes in children, for postoperative pain management. However, the rectal form has the most varied absorption rates in children, with one study showing over half of the children receiving the rectal dose (40 mg/kg) failed to ever reach the effective concentration for pain relief [8]. Furthermore, rectal APAP takes up to 3–4 h to reach its maximum therapeutic concentration. Tonsillectomy procedures are short, often under 15 min of operative time. Therefore, IV APAP with faster onset of action would be more effective in surgeries of shorter duration to treat postoperative pain [8,12].

Increased length of stay in the PACU not only increases costs, but is an indicator for increased patient complications. In their study evaluating unplanned return visits within 3 weeks of adenotonsillectomy in children, Duval et al. found a 1% increase in odds of hospital admission with each additional minute spent in the PACU [13]. In our study, nursing assessments were done at fixed time intervals and not on a continuous basis, as it is the usual practice in most PACUs. This may have influenced our finding of similar discharge times between the groups.

Nausea and vomiting after adenotonsillectomy surgery have a high incidence, cited up to 40–65% [14]. Each episode of PONV increases the length of PACU stay by 30 min [15]. In this study, patients in both groups received IV dexamethasone and ondansetron as part of multimodal drug therapy to prevent PONV. This explains the low incidence of PONV in both the groups.

The downside of IV APAP (range of $13–$45 per 1 gram vial) is that it is relatively expensive as compared to commonly used opioids such as morphine and fentanyl. However, in a study to evaluate the cost-effectiveness of IV APAP for pediatric tonsillectomy, Subramanyam et al. found that use of IV APAP as an adjuvant to IV opioids reduces the overall costs by decreasing the adverse effects of rescue analgesics and shortened stay in PACU [16]. Other studies looking specifically at ofirmev use in tonsillectomy have shown mixed results in effects on postoperative opioid requirements [17–19].

Our study has several limitations. Since it is a retrospective study, anesthetic management including the use of intraoperative opioids was not standardized. Furthermore, in the PACU, morphine was given as needed based on FLACC assessment. The pain assessment in children waking up from anesthesia can be challenging and sometimes difficult to differentiate from emergence delirium [20]. This may be a confounding factor in accurately assessing use of morphine in PACU especially in a retrospective study.

It is important to consider that a reduction of perioperative morphine use may have the greatest clinical benefit in children with Down syndrome, Muscular Dystrophy, Cerebral Palsy or other special needs who are at a higher risk of postoperative adverse respiratory event from opioid use. This population was excluded in our study to attempt to eliminate confounding variables. Future studies should investigate the use of IV APAP in these high risk children.

5. Conclusion

Our findings suggest intraoperative intravenous acetaminophen use in the pediatric tonsillectomy population may decrease the amount of perioperative opioid use. However we did not find that the use of intraoperative IV APAP is advantageous in reducing adverse events associated with opioid use or decreasing recovery time. Future prospective studies should investigate its use in reducing opioid use in high risk airway patients.

Disclosures

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Declaration of competing interest

None.

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