



Intravenous acetaminophen: A study of effectiveness of practice of intraoperative administration in children undergoing adenotonsillectomy

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Abstract

Purpose: Adenotonsillectomy is one of the most common procedures performed in children. Perioperative pain management in this surgical population is challenging due to obstructive sleep apnea and other comorbidities. As a result, multimodal analgesia is increasingly advocated. Acetaminophen and non-steroidal anti-inflammatory drugs are the most popular drugs used as part of multimodal analgesia. The purpose of this study is to examine the impact of intraoperative administration of intravenous acetaminophen on opioid use pattern during the perioperative period in children undergoing adenotonsillectomy.

Methods: This is a retrospective study of prospectively collected data from electronic medical records. We reviewed the patient demographics, morphine use during the intraoperative and immediate postoperative period, pain scores, and need for rescue analgesics in the post-anesthesia care unit (PACU). The dose of Intravenous Acetaminophen used in the study was 15 mg/kg. Acetaminophen was administered by infusion over a period of 15 minutes. Case control matching between the morphine-only and intravenous acetaminophen groups was performed before analysis.

Results: After matching, we had 91 patients in both the morphine-only and intravenous acetaminophen groups. The intravenous acetaminophen group received significantly less morphine during the intraoperative period. However, this same group needed significantly more morphine in the PACU. Interestingly at the time of discharge, there was no difference in the total amount of morphine used between two groups. In addition, there was no significant difference in pain scores between the groups.

Conclusion: Intraoperative administration of Intravenous acetaminophen does not decrease the amount of morphine used during the immediate perioperative period in children undergoing adenotonsillectomy. Our results question the usefulness of timing of administration of intravenous acetaminophen as a part of multimodal analgesia in our surgical population.

Keywords: Intraoperative pain management, post operative pain management, intravenous acetaminophen, multimodal analgesia, adenotonsillectomy

Introduction

The most common indication for adenotonsillectomy in children is obstructive sleep apnea (OSA) or sleep disordered breathing [1]. Postoperative pain, nausea, and vomiting are the most common problems in the postoperative period. Frequently, children with OSA have other comorbidities, including obesity, which add to the management challenges in the perioperative period.

Traditionally, opioids have been the mainstay of pain man-

agement for adenotonsillectomy, intra- and postoperatively. Recently, awareness has increased about the harmful effects associated with opioid-based pain management [2-4]. It is well known that patients with OSA have altered sensitivity to opioid administration [3] leading to increased risk of apnea and respiratory depression and poor outcomes [5]. To prevent the side effects associated with opioids, multimodal analgesia is advocated [6]. The well-known regimen used to provide

multimodal analgesia in this patient population is infiltration of the tonsil bed with local anesthetics, nonsteroidal anti-inflammatory drugs, and acetaminophen.

Acetaminophen is administered by either the oral, rectal, or intravenous (IV) route. Since 2011, IV acetaminophen is Food and Drug Administration-approved for use in children older than 2 years of age. Since then, it has gained popularity for perioperative pain management here in the USA [7]. However, the evidence for superiority of IV acetaminophen over other routes of administration immediately after surgery is not well established, especially for pediatric adenotonsillectomies. Furthermore, use of IV acetaminophen is not without its drawbacks, which include potential accidental overdose and its high cost compared with other routes of administration.

The objective of this study was to examine the impact of intraoperative administration of IV acetaminophen on the opioid use pattern during the intraoperative and immediate postoperative period in children undergoing adenotonsillectomy in a tertiary care children's hospital.

Methods

After obtaining approval from our facility's Institutional Review Board, the anesthetic records of all children who had adenotonsillectomy during a six-month period between April and October 2016, in a tertiary care children's hospital in the Mid-Atlantic (USA), were examined. It is a retrospective study. All patients who had adenotonsillectomy during the above-mentioned period were identified from our hospital's electronic medical records (Epic, Verona WI USA), and data were extracted from our prospectively collected anesthesia module, Epic Anesthesia.

The inclusion criteria for the study were children younger than 10 years of age who had adenotonsillectomy and morphine only as the opioid in the perioperative period. The exclusion criteria include children with weight over 50 kilograms, use of dexmedetomidine during the perioperative period, use of narcotics other than morphine during the perioperative period, American Society of Anesthesiologists (ASA) class III and IV, total tonsillectomy, and ear tube placement along with adenotonsillectomy.

All patients were premedicated with intranasal or oral midazolam with dose standardized as per weight (put in dosages). The standard dose of intranasal and oral midazolam in our practice were 0.2 mg/kg and 0.5 mg/kg respectively and it is administered 30 minutes before the start of procedure. Anesthetic induction was achieved with a combination of oxygen, nitrous oxide, and sevoflurane and was maintained with sevoflurane, oxygen, and air. All patients received dexamethasone at the dose of 0.5 mg/kg to the maximum of 10 mg and ondansetron 0.1 mg/kg as prophylaxis for nausea and vomiting at the time of induction. During the intraoperative period, administration of morphine was at the discretion of the anesthesiologist. Postoperatively, morphine, ketorolac, and oral acetaminophen were used for breakthrough pain. As

per hospital protocol, the criteria for overnight hospital stay after this surgery is age younger than 3 years, severe clinical or sleep study diagnosed sleep apnea, and/or any intra- or postoperative complication. Patients who planned to go home after the surgery were discharged after 120 minutes only if they met the discharge criteria prescribed by the post-anesthesia care unit (PACU).

Based on medical record review, the patients were divided into two groups depending on whether they received IV acetaminophen intraoperatively or not. The dose of Acetaminophen is standardized in our practice as 15 mg/kg. Acetaminophen was administered by infusion over a period of 15 minutes. Continuous variables such as age, weight, total intraoperative morphine received, total postoperative morphine received, number of rescue doses of morphine, maximum pain score recorded in the PACU, and time to discharge were recorded. Nominal data such as gender, the presence or absence of OSA, and the presence or absence of postoperative complications were collected. Ordinal data included ASA status. Derived data, such as the total morphine received during the encounter and morphine received per kilogram, were calculated and recorded.

Case control matching estimating common odds ratio utilizing the Mantel-Haenszel test was achieved using age, weight, gender, and presence of OSA as covariates. Student's t-test was used for continuous variables with significance at 95% confidence interval (CI). IBM SPSS Statistics 22.0 software was used to analyze the data.

Results

Figure 1 shows a consort diagram illustrating the selection of patients. Case control matching yielded 91 patients in each group. By design, there was no difference between the groups in terms of age, weight, gender, and incidence of OSA.

The IV acetaminophen group received significantly less intraoperative morphine (1.64 ± 0.73 mg; 95%CI, 1.48–1.79, P Value 0.01) compared with the control group (1.91 ± 0.69 mg; 95%CI, 1.77–2.06) (**Table 1**). The IV acetaminophen group also received less intraoperative morphine per kilogram (0.08 ± 0.02 mg/kg; 95%CI, 0.08–0.09) versus the control group (0.10 ± 0.02 mg/kg; 95%, 0.09–0.10 P Value 0.00) (**Table 1**). However, the IV acetaminophen group received more morphine per kilogram in the PACU (0.04 ± 0.03 mg/kg; 95% CI, 0.03–0.05) versus the morphine-only group (0.03 ± 0.03 mg/kg; 95% CI, 0.02–0.04, P Value 0.03) (**Table 1**). Neither the total morphine nor the total morphine per kilogram received in the operating room and the PACU combined was statistically different.

The percentage of patients receiving rescue doses of opioid in the PACU; the maximum faces, legs, activity, cry, consolability (FLACC) pain scores recorded; and the time to discharge was not statistically significant between the two groups (**Table 2**).

Discussion

The goal of administration of IV acetaminophen as a part of

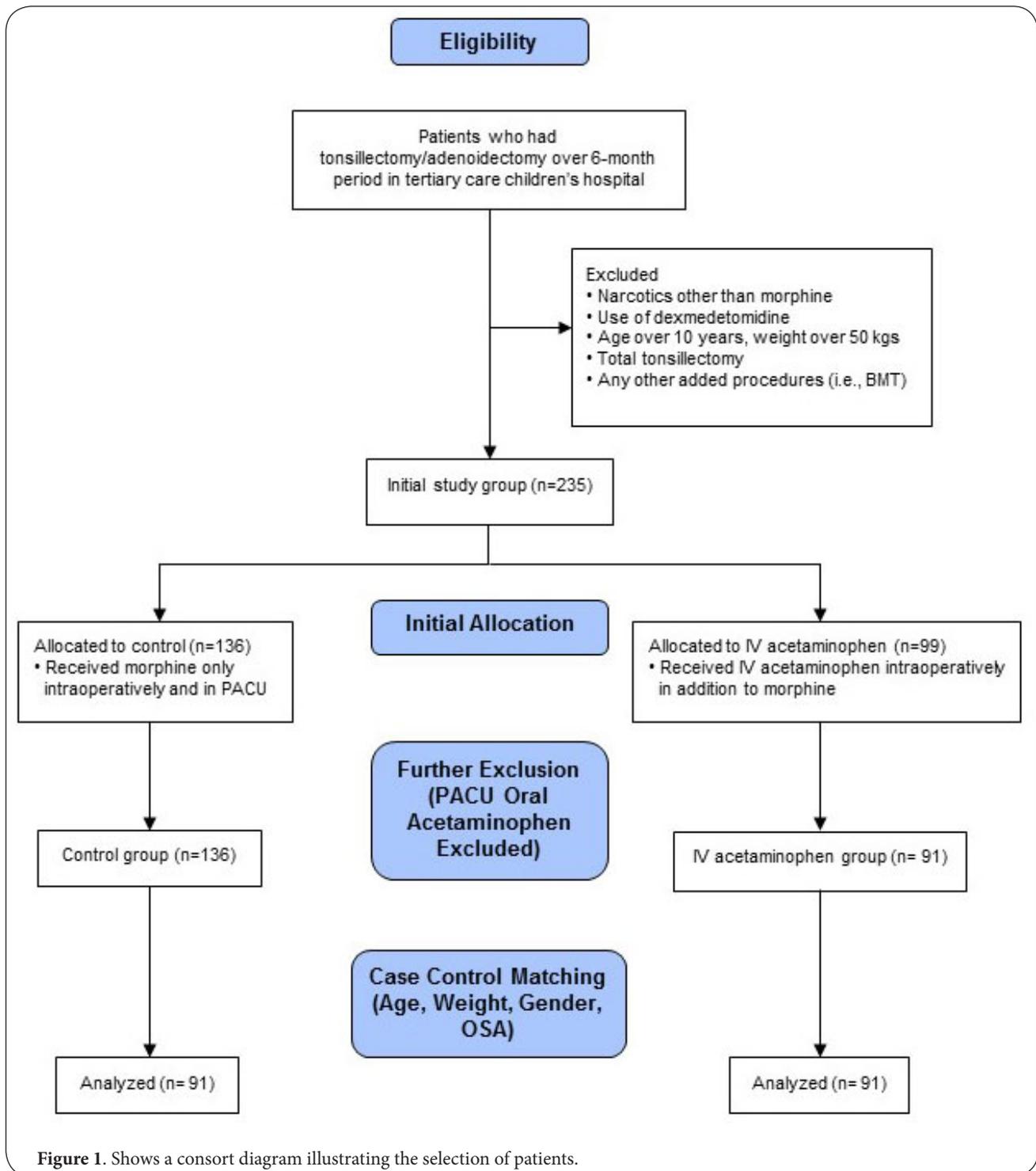


Figure 1. Shows a consort diagram illustrating the selection of patients.

multimodal analgesia is to decrease the amount of opioid administered during the immediate perioperative period in a patient population with the significant problem of OSA. In this environmental retrospective case control analysis, there was no decrease in morphine administration overall. While there appeared to be a conscious effort to reduce morphine administration intraoperatively, the morphine given in the

PACU made up for this lack resulting in no difference in total morphine administration. Additionally, administration of intraoperative IV acetaminophen decreased neither the pain scores nor the length of stay in the recovery room. As a result, we speculate that administration of IV acetaminophen in the post-operative period for breakthrough pain may be a better practice than intraoperative administration.

Table 1. (Primary Outcome Measures - Morphine consumption during the surgery, in the PACU and total morphine administered at the time of discharge between two groups).

	Control Group	IV Acetaminophen Group	P value
Intraop morphine	1.91±0.69 (1.77–2.06)	1.64±0.73 (1.48–1.79)	0.0100
PACU morphine	0.63±0.74 (0.48–0.79)	0.77±0.69 (0.62–0.91)	0.2070
Total morphine	2.45±1.02 (2.22–2.67)	2.41±1.02 (2.22–2.67)	0.8350
Intraop morphine per kg	0.098±0.028 (0.092–0.104)	0.081±0.026 (0.076–0.087)	0.0000
PACU morphine per kg	0.031±0.032 (0.024–0.037)	0.041±0.037 (0.024–0.037)	0.0390
Total morphine per kg	0.125±0.042 (0.116–0.133)	0.123±0.045 (0.113–0.132)	0.7680
% Receiving rescue doses	62%	75%	0.0800

Data presented as mean ± standard deviation (95% confidence limits)

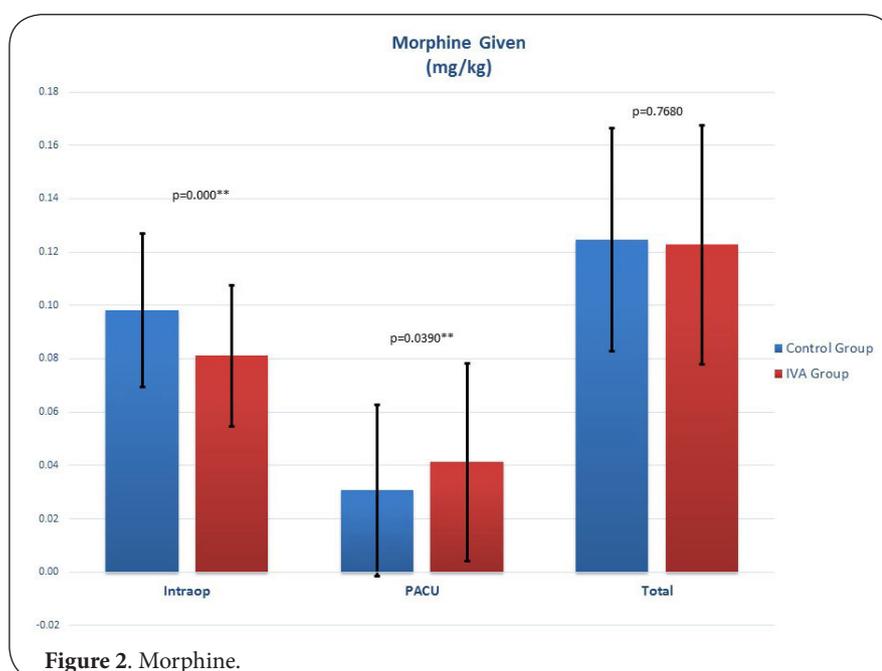
IV intravenous, PACU post-anesthesia care unit, Dose of Intravenous Acetaminophen used is 15 mg/kg.

Table 2. (Secondary outcome measures – Comparison of pain scores, time to discharge from PACU and percentage of patients received rescue doses of Morphine between two groups).

	Control Group (n=91)	IV Acetaminophen Group (n=91)	P value
% Receiving rescue opioid doses	62%	75%	0.0800
Max PACU FLACC pain score	4.51±3.14 (3.85–5.15)	4.93±3.15 (4.27–5.59)	0.3610
Time to discharge (min)	109±40 (101–118)	117±43 (108–126)	0.2150

Data presented as mean ± standard deviation (95% confidence limits).

IV intravenous, PACU post-anesthesia care unit, FLACC faces, legs, activity, cry, consolability scale.



Traditionally during the perioperative period, acetaminophen is administered either by the rectal or oral route. The advantages of enteral acetaminophen are easy availability, safety, and cost effectiveness. However, the clinical effectiveness of this therapy as a part of multimodal analgesia during the perioperative period is inconclusive [8,9]. Enteral acetaminophen has questionable potency, inconsistent absorption from the gastrointestinal tract, and a lack of evidence for optimal dose of administration [10]. Preoperative administration of oral acetaminophen raises a concern about exceeding safe gastric volume and of provoking anxiety in parents and children before the surgery [11]. Rectal acetaminophen has long been known to have poor and unpredictable absorption. In addition, rectal acetaminophen is inconvenient to administer in the operating room during fast-paced surgery such as ear tube placement and is not well accepted in older children and adults.

The introduction of IV acetaminophen has addressed some of the previously mentioned problems associated with the oral or rectal route. Compared with other routes, administration by the IV route allows effective peak plasma levels to be achieved consistently and rapidly during the surgery [12]. In addition, the dose of IV acetaminophen in children over the age of 2 years is uniform, and the current dosing regimen provides effective plasma concentration [12]. However, the evidence is inconclusive regarding the opioid sparing effectiveness of preoperative or intraoperative administration of IV acetaminophen compared with other routes in children who undergo adenotonsillectomy [13]. Moreover, the cost of IV acetaminophen is significantly higher than rectal or oral acetaminophen, and the potential for serious adverse events due to medication dosing errors raises concern among hospital management about its cost effectiveness and patient safety [14,15].

In our study, we compared the effectiveness of multimodal analgesia with the use of intraoperative IV acetaminophen and opioid-based management for perioperative pain control during adenotonsillectomy. We found no significant difference in the total opioid use between the morphine-only control and IV acetaminophen group at the time of discharge from the PACU. The patients in the acetaminophen group received significantly less morphine in the intraoperative period. We speculate that anesthesiologists may have administered less morphine in the IV acetaminophen group reasoning that IV acetaminophen will decrease opioid requirement in the recovery room. However, our finding that the IV acetaminophen group needed significantly more morphine in the PACU compared with the control group does not support this speculation. At the time of discharge, our data show that both the control and the IV acetaminophen groups received the same amount of morphine. We also recorded maximum pain scores in the PACU. Our PACU used the FLACC scale or numeric pain score depending on the age of the patient. Pain score was measured by the PACU nurses immediately after

the recovery of consciousness and at various times at the discretion of the nurses. There were no statistically significant differences in maximum pain scores between the two groups.

Obstructive sleep apnea is a frequent indication of adenotonsillectomy in children, and multimodal analgesia increasingly is recommended to reduce opioid-related side effects such as respiratory depression and hypoxia in the immediate postoperative period. Since intraoperative administration of IV acetaminophen did not reduce opioid consumption, we speculate that it may be used in the PACU for breakthrough pain instead of Morphine. In addition, more research exploring other drugs to consider as part of multimodal analgesia in children who undergo adenotonsillectomy is necessary. Drugs such as ketamine and dexmedetomidine recently have been used for adenotonsillectomy in children; however, for use in routine practice, more research about dosing and effectiveness is needed.

Our study has some limitations. While controlled studies have shown the opioid sparing nature of nonsteroidal anti-inflammatory drugs and IV acetaminophen, we failed to see this effect in an uncontrolled natural situation. We used a case control analysis to standardize the groups to the best of our ability. Still, our model is a retrospective review of prospectively collected data; therefore, one cannot assume causality, but only association. This method also runs the risk of incomplete data, which was a secondary reason to perform the case control analysis. In addition, the use of opioids in the operating room and the PACU was not controlled and was therefore at the discretion of the anesthesiologists and recovery room nurses.

Conclusion

Our six-month review showed there was no significant difference in the overall amount of opioid administered or pain scores between the morphine-only control and intraoperative IV acetaminophen groups. We speculate that intravenous acetaminophen may be more effective when used in the post anesthesia recovery room for breakthrough pain instead of Morphine to reduce the amount of opioid administered in this patient population.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	KS	BRB
Research concept and design	✓	✓
Collection and/or assembly of data	✓	✓
Data analysis and interpretation	✓	✓
Writing the article	✓	✓
Critical revision of the article	✓	✓
Final approval of article	✓	✓
Statistical analysis	✓	✓

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