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The Use of Ibuprofen in Posttonsillectomy Analgesia and Its Effect on Posttonsillectomy Hemorrhage Rate

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Abstract

Objective. To determine the effect of ibuprofen on posttonsillectomy bleeding when compared with codeine in posttonsillectomy analgesia.

Study Design. Case series with chart review.

Setting: Tertiary care children's hospital, Philadelphia, Pennsylvania.

Subjects and Methods. On July 1, 2012, our institution transitioned from acetaminophen with codeine to ibuprofen for posttonsillectomy analgesia. Pediatric patients (0-18 years old) who underwent surgery from July 1, 2010, to June 30, 2012, were placed in the codeine cohort, and those who underwent surgery from July 1, 2012, to June 30, 2014, were placed in the ibuprofen cohort.

Results. A total of 6014 patients underwent tonsillectomy between July 1, 2010, and June 30, 2014, and 211 patients presented for posttonsillectomy hemorrhage during the same period. The incidence of readmission for posttonsillectomy hemorrhage was 3.4% and 3.6% (P = .63; odds ratio [OR] = 1.07; 95% confidence interval [95% CI]: 0.811-1.410) for the codeine and ibuprofen groups, respectively, and the incidence of second operation for control of posttonsillectomy bleeding for the codeine and ibuprofen groups was 1.9% and 2.2% (P = .54; OR = 1.117; 95% CI: 0.781-1.600), respectively. Patients aged 11 to 18 years demonstrated a higher incidence of posttonsillectomy bleeding events overall. When age is controlled, multivariate logistic regression demonstrated no statistically significant increase in posttonsillectomy bleeding events among pediatric patients treated with ibuprofen versus patients treated with codeine (readmission: P = .617; OR = 0.932; 95% CI: 0.707-1.228; reoperation: P = .513; OR = 0.887; 95% CI: 0.618-1.272).

Conclusion. Age is an independent risk factor for posttonsillectomy bleeding. When age is controlled, there is no statistically significant increase in the incidence of posttonsillectomy bleeding events among patients treated with ibuprofen when compared to patients treated with codeine.

Keywords

tonsillectomy, posttonsillectomy hemorrhage, NSAID, ibuprofen

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Tonsillectomy is one of the most commonly performed surgical procedures in the pediatric population, with more than a half a million cases performed in the United States each year.[1,2] Tonsillectomy with or without adenoidectomy has been shown to have a clear clinical benefit in the treatment of children with chronic tonsillitis and sleep-disordered breathing.[1,3-6] Among the most feared complications of tonsillectomy is posttonsillectomy hemorrhage, occurring with an incidence of 0.1% to 3%.[1,7-9] The concern for increased postoperative bleeding remains the center of the debate regarding nonsteroidal anti-inflammatory (NSAI)–based pain control in patients undergoing tonsillectomy. While there have been conflicting conclusions within the existing literature regarding the association between ibuprofen and increased posttonsillectomy bleeding, many of the studies contain small population sizes and therefore lack statistical power.[10-15] The aim of our study is to produce, to the best of our knowledge, the largest institutional review to date that tests the null hypothesis that the use of ibuprofen for posttonsillectomy analgesia does not increase the rate of posttonsillectomy bleeding when compared with acetaminophen with codeine.

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Materials and Methods

After obtaining approval from Drexel University's Institutional Review Board, we conducted a chart review of pediatric patients 0 to 18 years old presenting for tonsillectomy with or without adenoidectomy and patients presenting for posttonsillectomy hemorrhage from July 1, 2010, through June 30, 2014. These dates were selected because our institution launched its transition from acetaminophen with codeine to ibuprofen for postoperative pain control in all patients undergoing tonsillectomy on July 1, 2012. The sample groups are consecutive according to the date of transition. Prior to July 1, 2012, patients were prescribed acetaminophen with codeine every 6 hours (120 mg of acetaminophen with 12 mg of codeine) for posttonsillectomy pain at an acetaminophen dosing of 12 mg/kg or a codeine dosing of 1 mg/kg with a maximum codeine dose of 75 mg/kg/d. After July 1, 2012, patients were prescribed ibuprofen every 6 hours at a dose of 10 mg/kg with a maximum dosage of 400 mg/dose.

Study end points were defined as (1) readmission for posttonsillectomy bleeding and (2) reoperation for hemostasis. Data were gathered per our billing department's *CPT* (*Current Procedural Terminology*) codes for tonsillectomy and adenotonsillectomy during the period of interest. Patients presenting with a diagnosis of posttonsillectomy bleeding were identified on the basis of their *ICD* (*International Classification of Diseases*) diagnosis code and admitting surgeon. The procedure code for control of posttonsillectomy hemorrhage was then applied to identify patients who required reoperation. Patients who did not have a CPT code for control of posttonsillectomy hemorrhage were patients who were managed medically with intravenous fluids and observation. Patients were eliminated from the data set if they presented to our hospital with a diagnosis code for posttonsillectomy bleeding but did not have an associated *CPT* code for tonsillectomy or adenotonsillectomy, indicating that they had undergone their initial tonsillectomy surgery at an outside hospital.

The sample groups were sorted according to age and sex, and their distribution was similar across both cohorts (**Table 1**). Indication for tonsillectomy or adenotonsillectomy was not specified, as the cohorts were based on *CPT* coding and no specific information was obtained from the medical record. The Coblator wand (Smith & Nephew, London, UK) is the instrument of choice at our institution for adenotonsillectomy, and all procedures included in the review were performed with this technique. The group of surgeons performing the procedures remained the same for the duration of the study, and resident physicians were permitted to assist in the surgical cases under the supervision of the senior author and his colleagues. None of the patients received preoperative or intraoperative NSAI medications. No perioperative antibiotics were administered for adenotonsillectomy or control of posttonsillectomy hemorrhage, and all patients received intraoperative dexamethasone at a dose of 0.3 to 0.5 mg/kg (maximum dosage, 10 mg) in accordance with our institutional standard.

Table 1. Age and Sex Distribution of Population Cohorts.[a]

Subgroup	Acetaminophen with Codeine	Ibuprofen
Overall	3317	2697
Males	1739 (52)	1363 (51)
Females	1578 (48)	1334 (49)
Age, 0-10 y	2766 (83)	2257 (84)
Age, 11-18 y	551 (17)	440 (16)

[a]Values presented in n (%).

Data analysis was conducted via SPSS software (IBM Inc, Armonk, New York). Patients requiring readmission and reoperation were compared according to age, sex, and analgesic per univariate chi-square analyses. Cox-Snell R^2 and Nagelkerke R^2 multivariate linear regression analyses were then performed to examine the effect of each variable independently (age, sex, and analgesic) and eliminate potential confounding. Multivariate logistic regression was used for each outcome (readmission and reoperation). The standard Wald test was done to assess significance. Statistical significance was set at $P < .05$, and univariate logistic regressions were used to obtain single-variable odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results

Over the 4-year study period, 3317 patients were treated with acetaminophen/codeine postoperatively, and 2697 patients were treated with ibuprofen (**Table 1**). The incidence of readmission for posttonsillectomy hemorrhage was 3.4% among the acetaminophen/codeine group and 3.6% among the ibuprofen group ($P = .63$; **Table 2**). The incidence of reoperation for control of posttonsillectomy bleeding among the acetaminophen/codeine and ibuprofen groups was 1.9% and 2.2% ($P = .54$), respectively (**Table 3**). Overall, there was no statistically significant increase in readmission ($P = .41$) or reoperation ($P = .7$) between males and females. With respect to age, there was a statistically significant increase in the rate of readmission and reoperation ($P < .001$) for the 11- to 18-year age group when compared with the 0- to 10-year age group. The results show no statistically significant increase in readmission among patients treated with ibuprofen as compared with patients treated with acetaminophen/codeine when age and sex are controlled ($P = .62$; OR, 0.932; 95% CI: 0.707-1.228) suggesting that age is an independent risk factor ($P < .001$; OR, 2.625; 95% CI: 1.949-3.536; **Tables 4** and **5**). Reoperation also demonstrated a statistically significant association with age ($P < .001$; OR, 3.136; 95% CI: 2.148-4.578) but when age and sex are controlled there is no statistically significant increase in reoperation among patients treated with ibuprofen versus patients treated with acetaminophen/codeine ($P = .513$; OR, 0.887; 95% CI: 0.618-1.272; **Table 6**).

Discussion

Postoperative pain is a significant morbidity among patients undergoing tonsillectomy. The majority of tonsillectomy

Table 2. Readmission Rates for Posttonsillectomy Hemorrhage according to Analgesic, Sex, and Age.[a]

		Readmission				
Subgroup	Total, n	n	%	*P* Value	OR	95% CI
Overall	6014	211	3.5			
Tylenol with codeine	3317	113	3.4	.63	1.07	0.811-1.410
Ibuprofen	2697	98	3.6			
Females	2912	108	3.7	.41	0.892	0.678-1.172
Males	3102	103	3.3			
Age 0-10 y	5023	141	2.8	<.001	2.632	1.958-3.539
Age 11-18 y	991	70	7.1			

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.
[a]Reference groups for calculation of ORs and 95% CIs are Tylenol with codeine, females, and age 0-10 years.

Table 3. Reoperation Rates for Control of Posttonsillectomy Hemorrhage according to Analgesic, Sex, and Age.[a]

		Reoperation				
Subgroup	Total, n	n	%	*P* Value	OR	95% CI
Overall	6014	122	2.0			
Tylenol with codeine	3317	64	1.9	.54	1.117	0.781-1.600
Ibuprofen	2697	58	2.2			
Females	2912	57	2.0	.7	1.072	0.749-1.536
Males	3102	65	2.1			
Age 0-10 y	5023	77	1.5	<.001	3.056	2.101-4.443
Age 11-18 y	991	45	4.5			

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.
[a]Reference groups for calculation of ORs and 95% CIs are Tylenol with codeine, females, and age 0-10 years.

surgery is now performed in an outpatient setting, making postoperative pain control one of the most common concerns among patients and providers. Opioid-based pain control has traditionally been the standard postoperative care in many institutions for the management of posttonsillectomy pain. With reports of opioid-related fatalities after tonsillectomy in children, the use of opioids has been more heavily scrutinized. These reports highlight a genetically altered cytochrome P4502D6 pathway that predisposes individuals to rapidly metabolize codeine into its parent drug, morphine.[16-19] The reported fatalities demonstrated lethal blood levels of morphine as a result of genetically altered metabolism. This is especially relevant when considering that (1) the majority of tonsillectomies performed in children are for sleep-disordered breathing and (2) elevated levels of opioids and their metabolites can lead to severe sedation, central nervous system compromise, and respiratory depression.[12,18,20] The recently issued Food and Drug Administration black box warning and American Academy of Otolaryngology—Head and Neck Surgery Foundation guidelines have resulted in a shift toward the use of ibuprofen in pediatric tonsillectomy patients.[1] NSAI medications such as ibuprofen have been shown to be equianalgesic when compared with other regimens in a variety of pediatric surgical procedures, including tonsillectomy,[21] because they have the ability to reduce both pain and inflammation.[1,14,22] NSAI drugs have the additional benefit of significantly reducing the incidence of postoperative nausea and vomiting that can be exacerbated by other pain medications.[14,16,22-24] Yet, their use in posttonsillectomy analgesia remains somewhat limited by concerns regarding their potential effects on the risk of posttonsillectomy bleeding.

NSAI medications such as ibuprofen are cyclooxygenase enzyme inhibitors that result in decreased prostaglandin synthesis, decreased platelet aggregation, and potentially increased bleeding time. Their mechanism of action raises concern for their use in tonsillectomy patients.[12] Several studies have shown that bleeding time remains normal in patients taking NSAI medications with normal coagulation pathways,[15,22,23] and the assertion that ibuprofen increases posttonsillectomy bleeding has not been supported by the existing literature.[10-12,15,23]

For the past 3 years, our institutional standard for posttonsillectomy analgesia has been ibuprofen every 6 hours at a dosing of 10 mg/kg, with a maximum dose of 400 mg. Our results are therefore somewhat unique in comparison with previous studies, including the Cochrane review, that have examined the effects of ibuprofen at a dosing of 5 mg/kg.[10,13,21] This study raises consideration for higher dosing

Table 4. Multivariate Linear Regression Comparing Age, Sex, and Analgesic: Readmission.

Variables	B	SE	*df*	*P*	OR	95% CI
Analgesic	–0.071	0.141	1	.617	0.932	0.707-1.228
Sex	0.021	0.142	1	.880	1.022	0.773-1.349
Age	0.965	0.152	1	.000	2.625	1.949-3.536
Constant	–4.432	0.359	1	.000	0.012	

Abbreviations: 95% CI, 95% confidence interval; B, log of odds ratio; OR, odds ratio.

Table 5. Rates of Readmission and Reoperation according to Analgesic and Age Group.

		Readmission			Reoperation		
Subgroup	Total, n	n	%	*P* Value	n	%	*P* Value
Age, 0-10 y	5023	141	2.8		77	1.5	
Tylenol with codeine	2766	81	2.9	.56	43	1.6	.89
Ibuprofen	2257	60	2.7		34	1.5	
Age, 11-18 y	991	70	7.1		45	4.5	
Tylenol with codeine	551	32	5.8	.084	21	3.8	.22
Ibuprofen	440	38	8.6		24	5.5	

Table 6. Multivariate Linear Regression Comparing Age, Sex, and Analgesic: Reoperation.

Variables	B	SE	*df*	*P* Value	OR	95% CI
Analgesic	–0.120	0.184	1	.513	0.887	0.618-1.272
Sex	–0.187	0.186	1	.312	0.829	0.576-1.194
Age	1.143	0.193	1	.000	3.136	2.148-4.578
Constant	–4.851	0.462	1	.000	0.008	

Abbreviations: 95% CI, 95% confidence interval; B, log of odds ratio; OR, odds ratio.

schedules when providers think that adequate analgesia has not been achieved at 5 mg/kg.

The present study includes 2 defined end points: readmission with a diagnosis of posttonsillectomy bleeding and reoperation for surgical hemostasis. Two end points were selected in our analysis because some patients may present with a complaint of oral bleeding and are admitted with a diagnosis of posttonsillectomy hemorrhage according to patient or parental reports of blood-tinged secretions without evidence of pharyngeal bleeding noted by the provider. It is our opinion that reoperation is therefore a more reliable indicator of significant bleeding events.

Surgical technique and surgeon experience are also independent risk factors for posttonsillectomy hemorrhage and are important variables to consider in tonsillectomy surgery.[25,26] In comparison with large meta-analyses, our results are unique in that surgical technique, as well as the group of surgeons supervising the procedures, remained the same throughout the duration of the study.

Previous studies have indicated that age and sex may be independent risk factors for posttonsillectomy bleeding, making age and sex stratification important study variables.[7,10,27-29] Our review is in agreement with existing studies that illustrate a higher risk of posttonsillectomy bleeding among older individuals. However, multivariate logistic regression demonstrates that age is an independent risk factor and that ibuprofen does not increase the risk of posttonsillectomy bleeding when age is controlled.

Our study includes several limitations. The numbers that we generated were based solely on *CPT* and *ICD* codes in our billing department. No other information from the medical record was reviewed. Therefore, children with bleeding disorders and ibuprofen allergies or intolerances were included in both cohorts, as well as patients who did not experience adequate analgesia with ibuprofen or codeine, and these patients may have received perioperative analgesics other than the study medications. Postoperative day of the reported bleeding event was not elicited from the medical record; therefore,

primary and secondary bleeding events were not delineated. Our results do not account for patients who underwent tonsillectomy at our institution and subsequently presented to other hospitals in our region with posttonsillectomy hemorrhage. On the basis of *CPT* coding and unique medical record numbers, however, we were able to identify patients who presented to our institution with posttonsillectomy bleeding but did not have their initial tonsillectomy surgery performed at our hospital. These patients were eliminated from the data set.

The 2013 Cochrane Collaboration concluded that, despite no clearly established causal relationship between the use of NSAI drug analgesia and posttonsillectomy hemorrhage, there is currently insufficient evidence to exclude an association. This conclusion is largely owing to the fact that many existing studies are based on small populations and thus lacking in statistical power.[10] One study comparing acetaminophen with codeine to ibuprofen demonstrated posttonsillectomy hemorrhage rates of 0% in the codeine group and 12.5% in the ibuprofen group.[13] Closer review of this study reveals that the population size was only 30 patients. In the largest review conducted to date—a meta-analysis of 36 randomized controlled trials—Riggin et al concluded that NSAI drugs are a safe and effective method for achieving posttonsillectomy pain control without an increased risk of bleeding.[12] This study, however, included multiple institutions and various NSAI drug agents. To the best of our knowledge, our review is the largest single institution–based study of its kind and generates significant statistical power in comparison with previous studies examining the effect of ibuprofen on posttonsillectomy hemorrhage.

Conclusion

Based on our review at a high-volume institution, there is no statistically significant difference in the incidence of posttonsillectomy hemorrhage among patients treated with acetaminophen with codeine and those treated with ibuprofen after undergoing tonsillectomy.

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Author Contributions

Julia A. Pfaff, design of the work; acquisition, analysis, and interpretation of data; drafting and critical revision; accountability for all aspects of the work; **Kevin Hsu**, conception of work, acquisition of data, institutional review board approval, revision, approval, accountable for all aspects; **Sri Kiran Chennupati**, design of the work, critical revision, final approval for publication, accountable for all aspects of the work.

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