Incidence of Surgically Managed Post-Tonsillectomy Hemorrhage Associated With NSAID Prescribing for Postoperative Pain Management

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ABSTRACT

Introduction:
Tonsillectomy ranks high among the most common pediatric surgical procedures in the United States. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as ibuprofen, are routinely prescribed to manage post-tonsillectomy pain, but may carry the risk of hemorrhage.

Materials and Methods:
This retrospective, longitudinal, secondary-data analysis study compared the incidence of surgically managed post-tonsillectomy hemorrhage (sPTH) in pediatric patients prescribed ibuprofen at Brooke Army Medical Center (BAMC) after tonsillectomy compared to a similar cohort of pediatric patients at the Children’s Hospital of Philadelphia (CHOP) not prescribed ibuprofen. Additional regression analysis examined predictors of sPTH at BAMC.

Results:
The odds of sPTH was lower in patients who were prescribed ibuprofen at BAMC, relative to patients who were not at CHOP (OR 0.57, 95% CI, 0.37, 0.87; P < 0.01). In a generalized linear model evaluating BAMC patient data, there was a lack of a relationship between reason for tonsillectomy (tonsillitis versus tonsillar obstruction), primary procedure (tonsillectomy-only versus tonsillectomy with adenoidectomy), and presence of a co-occurring procedure.

Conclusions:
Post-tonsillectomy ibuprofen prescribing practices were not associated with an elevated risk of sPTH, relative to patients at CHOP not exposed to ibuprofen.

INTRODUCTION

Tonsillectomy is among the most common pediatric surgical procedures performed in the United States, with over 250,000 procedures performed in the United States every year.¹ Post-tonsillectomy hemorrhage (PTH) is a serious postoperative complication that occurs at a rate of 0.2% to 2.2% for primary bleeding (within 24 hours of tonsillectomy) and 0.1% to 3.0% for secondary bleeding (>24 hours after surgery).²,³ PTH may cause profound blood loss requiring blood transfusion and/or return to the operating room for surgical hemostasis, and in severe, but rare, cases, death if not managed quickly and appropriately.⁴,⁵

PTH risk is balanced with the need to provide adequate postoperative analgesia, as uncontrolled pain can contribute to post-tonsillectomy complications including oral intake intolerance requiring admission for intravenous hydration and pain control.¹ Per the 2019 Tonsillectomy in Children Clinical Practice Guideline (CPG), non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for postoperative analgesia,⁶ with otolaryngologists commonly prescribing ibuprofen. A Cochrane meta-analysis indicated ibuprofen use was not associated with increased PTH risk, though small sample sizes and large CIs signaled the need for further investigation.⁷ The association between ibuprofen use and PTH severity was further examined in a retrospective cohort single-center study at the Children’s Hospital of Philadelphia (CHOP). Patients prescribed ibuprofen experienced statistically and clinically significant increases in blood product transfusion requirements, a surrogate marker of PTH severity.⁷ Other meta-analyses examining the relationship between PTH and postoperative ibuprofen use are mixed, with conclusions ranging from an increased likelihood toward PTH to a lack of association or no conclusive association.⁸–¹¹
The Tonsillectomy in Children CPG recommends surgeons evaluate their annual incidence of PTH.\(^1\) Additionally, it is important to engage in continual evaluation of not only incidence, but factors associated with PTH. This practice informs surgeons of bleeding complication rates in their patients and provides a useful metric for department and hospital leadership to identify opportunities patient safety improvements. Therefore, the present retrospective cohort study examined the incidence of sPTH in pediatric patients at Brooke Army Medical Center (BAMC), a large academic military treatment facility (MTF), who were prescribed post-tonsillectomy ibuprofen compared to the results of a similar cohort of pediatric patients at CHOP who were not prescribed ibuprofen.\(^2\) Our goal was to evaluate the relative safety of the BAMC routine post-tonsillectomy pain control regimen, as well as benchmark BAMC’s quality and safety against a leading institution.

**METHODS**

**Record Identification and Extracted Data**

This study protocol was approved by the BAMC Institutional Review Board (#C.2020.059e) as a retrospective secondary-data analysis study performed at BAMC with comparator study information extracted from the Mudd et al.’s study.\(^3\) BAMC patient data were obtained by querying the local Surgical Scheduling System. Records of patients under 18 years of age who received a tonsillectomy between 2015 and 2019 were included. Additional information included surgical procedures for tonsillar bleed hemostasis, co-occurring adenoidectomy, and preoperative diagnosis (tonsillar obstruction or tonsillitis). Patients who received tonsillectomies for peri-tonsillar abscess and periodic fevers with aphthous stomatitis, pharyngitis, and adenitis syndrome were excluded. Extracted data included age (years), sex assigned in the medical record, primary surgical procedure, and preoperative diagnosis. At BAMC, 1,240 patient records met inclusion and exclusion criteria. Case-specific technique was not evaluated in this study. General anesthesia is typically induced via inhalation of volatile agents in pediatric patients who are unable to receive intravenous catheter placement preoperatively due to their age or high levels of anxiety. The patients’ airways are intubated as the use of laryngeal mask airways for pediatric adenotonsillectomy is not a routine practice at BAMC. General anesthesia is maintained with either intravenous or inhalational agents at the discretion of the anesthesia provider. Postoperatively, the patient is extubated after careful suctioning of the oropharynx in a manner that reduces risk of coughing that might disrupt the surgical repair.

**Clinical Care**

BAMC is a tertiary teaching military hospital with up to 19 otolaryngology surgeons operating during the study timeframe, 3 of whom were pediatric otolaryngology-specialized attending staff. Otolaryngology residents are involved in these surgical cases, mostly in their second and third year of residency training. Monopolar electrocautery tonsillectomy and suction electrocautery adenoidectomy is the most common technique surgeons utilize in this institution. Two surgeons routinely use coblator radiofrequency ablation for their tonsillectomy. The pediatric otolaryngology-specialized surgeons mainly utilize monopolar electrocautery for tonsillectomy. Suture closure of the tonsillar fossa is not routinely completed at this institution. Case-specific technique was not evaluated in this study. General anesthesia is typically induced via inhalation of volatile agents in pediatric patients who are unable to receive intravenous catheter placement preoperatively due to their age or high levels of anxiety. The patients’ airways are intubated as the use of laryngeal mask airways for pediatric adenotonsillectomy is not a routine practice at BAMC. General anesthesia is maintained with either intravenous or inhalational agents at the discretion of the anesthesia provider. Postoperatively, the patient is extubated after careful suctioning of the oropharynx in a manner that reduces risk of coughing that might disrupt the surgical repair.

**Sample Size Calculation**

This study was powered to detect a 2% difference from the 3.5% incidence rate in the no ibuprofen exposure cohort from Mudd et al.\(^7\) A priori power analysis was performed using G*Power for a Fisher’s exact test with an allocation ratio of 4 CHOP to 1 BAMC, an estimated effect size of odds ratio (OR) 1.6, power = 0.8, and two-tailed alpha = 0.05. The calculation yielded a sample size of 4,128 CHOP and 1,032 BAMC patients.

**Analytic Plan**

The cumulative incidence rate of sPTH at BAMC and CHOP was compared using Fisher’s exact test with associated OR and 95% CIs. First, the primary outcome, sPTH incidence between ibuprofen-prescribed (BAMC) and no ibuprofen (CHOP) groups, was compared using Fischer’s exact test and reported with associated OR and 95% CIs. Secondary outcomes included benchmarking of overall institutional incidences of sPTH, also compared using Fisher’s exact test as above, and multivariable regression analysis (generalized linear model) examining the relationship between predictors and sPTH within the BAMC cohort. Predictors included age, sex assigned in the medical record, primary surgical procedure, secondary surgical procedure, and preoperative diagnosis. Regression estimates for each predictor variable are reported as ORs and 95% CIs. Statistical tests with \(P\)-values <0.016, Bonferroni-corrected \(P\)-values for 3 outcomes, and error estimates of 95% CIs that do not cross zero were considered statistically significant. Analyses were completed in Jamovi, an open-source software.

**RESULTS**

At BAMC, 1,240 patient records met inclusion and exclusion criteria. Less than 10 were excluded due to peritonsillar abscess or periodic fevers with aphthous stomatitis, pharyngitis, and adenitis syndrome. The previously published CHOP cohort included 4,588 patient records in the no ibuprofen group. Demographic characteristics for the BAMC and CHOP cohorts are reported in Table I. For the primary outcome, ibuprofen-prescribed BAMC cohort had 25 patients with sPTH and 1,215 without sPTH, for
TABLE I. Demographic Characteristics

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Total#</th>
<th>Patients without sPTH# (%</th>
<th>Patients with sPTH, # (%)</th>
<th>All</th>
<th>Early(thru POD1)</th>
<th>Late(POD2 and beyond)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine post-operative ibuprofen analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP—no post-operative ibuprofen</td>
<td>4588</td>
<td>4428 (96.5)</td>
<td>160 (3.5)</td>
<td>25 (0.5)</td>
<td>135 (2.9)</td>
<td></td>
</tr>
<tr>
<td>BAMC—post-operative ibuprofen</td>
<td>1240</td>
<td>1215 (98.0)</td>
<td>25 (2.0)</td>
<td>2 (0.2)</td>
<td>23 (1.9)</td>
<td></td>
</tr>
<tr>
<td>BAMC cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 12</td>
<td>1086</td>
<td>1064 (98.0)</td>
<td>22 (2.0)</td>
<td>2 (0.2)</td>
<td>20 (1.8)</td>
<td></td>
</tr>
<tr>
<td>12 or older</td>
<td>154</td>
<td>151 (98.1)</td>
<td>3 (1.9)</td>
<td>0 (0.0)</td>
<td>3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Sex assigned in the medical record</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>673</td>
<td>661 (98.2)</td>
<td>12 (1.8)</td>
<td>1 (0.1)</td>
<td>11 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>567</td>
<td>554 (97.7)</td>
<td>13 (2.3)</td>
<td>1 (0.2)</td>
<td>12 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Primary surgical procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>141</td>
<td>139 (98.6)</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Tonsillectomy &amp; adenoidectomy</td>
<td>1099</td>
<td>1076 (97.9)</td>
<td>23 (2.1)</td>
<td>1 (0.1)</td>
<td>22 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Secondary surgical procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>464</td>
<td>457 (98.5)</td>
<td>7 (1.5)</td>
<td>1 (0.2)</td>
<td>6 (1.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>776</td>
<td>758 (97.7)</td>
<td>18 (2.3)</td>
<td>1 (0.1)</td>
<td>17 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Pre-operative diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonsillar obstruction</td>
<td>974</td>
<td>956 (98.2)</td>
<td>18 (1.8)</td>
<td>2 (0.2)</td>
<td>16 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>266</td>
<td>259 (97.4)</td>
<td>7 (2.6)</td>
<td>0 (0.0)</td>
<td>7 (2.6)</td>
<td></td>
</tr>
</tbody>
</table>

Does not include patients who underwent tonsillectomy for Peritonsillar Abscess—4 and PFAFA—2, all without sPTH.

Abbreviations: BAMC—Brooke Army Medical Center; CHOP, Children’s Hospital of Philadelphia; PFAFA, Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis; POD, postoperative day; sPTH, surgically managed post-tonsillectomy hemorrhage.

an incidence rate of 2.0%. Whereas, the CHOP no ibuprofen cohort had 160 patients with sPTH and 4,428 without sPTH, for an incidence rate of 3.5%. Per the Fisher’s exact test, the OR was 0.57 (95% CI, 0.37, 0.87; P < 0.016), indicating the ibuprofen-prescribed sample at BAMC had significantly lower odds of sPTH, relative to the no ibuprofen sample at CHOP.

As an institutional benchmarking comparison, the BAMC sample was compared with the total CHOP study sample of 6,710 patients, of whom, 222 had sPTH (3.3% incidence rate). As such, the odds of experiencing an sPTH at BAMC was lower, relative to CHOP (OR = 0.60, 95% CI, 0.40, 0.91; P < 0.016). In the regression analysis of the BAMC cohort, none of the predictors were significantly associated with sPTH (P > 0.016, Table II).

DISCUSSION

In the present study, BAMC patients prescribed ibuprofen had significantly lower sPTH rates than CHOP patients not prescribed ibuprofen. These findings support the continuation of ibuprofen-prescribing practices in pediatric post-tonsillectomy patients in accordance with the current CPG. Within the BAMC cohort, there was a lack of a relationship between procedure indication, primary procedure, and co-occurring procedures with sPTH incidence. Therefore, sPTH risk was not adequately explained by these variables in the present sample. Previously identified risk factors for

TABLE II. Multivariate Analysis for sPTH: Brooke Army Medical Center Cohort of 1,240 Patients

<table>
<thead>
<tr>
<th>sPTH predictor variable</th>
<th>Odds ratio*</th>
<th>95% CI Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (with increasing interval of 1 year)</td>
<td>1.03</td>
<td>0.94</td>
<td>1.13</td>
</tr>
<tr>
<td>Sex assigned in the medical record: male versus female</td>
<td>0.80</td>
<td>0.36</td>
<td>1.77</td>
</tr>
<tr>
<td>Primary surgical procedure: tonsillectomy versus tonsillectomy &amp; adenoidectomy</td>
<td>0.55</td>
<td>0.12</td>
<td>2.48</td>
</tr>
<tr>
<td>Secondary surgical procedures: yes versus no</td>
<td>0.68</td>
<td>0.28</td>
<td>1.67</td>
</tr>
<tr>
<td>Pre-operative diagnosis: tonsillitis versus tonsillar obstruction</td>
<td>1.48</td>
<td>0.58</td>
<td>3.75</td>
</tr>
</tbody>
</table>

*Odds ratio of sPTH versus no sPTH. Abbreviation: sPTH, surgically managed post-tonsillectomy hemorrhage.
sPTH in pediatric patients include patients with von Willebrand disease, hemophilia, and recurrent tonsillitis in patients ages 12 years and older.7 Taken together, further investigation regarding sPTH risk and risk mitigation strategies, in addition to post-tonsillectomy prescription practices, is required.

Celecoxib, a cyclooxygenase-2 (COX-2) isoenzyme selective NSAID, may be an option treating post-operative pain in pediatric patients undergoing tonsillectomy, as it does not appear to impair platelet function like other non-selective NSAIDs.12 While an initial study indicated celecoxib resulted in modest improvements in pediatric post-tonsillectomy pain,13 a more recent randomized placebo-controlled trial of children ages 3 to 11 years showed significant clinical benefits without increased risk of hemorrhage, albeit at twice the normal pediatric dose.14 Additionally, meta-analyses also support the safety of celecoxib in patients with stable mild-to-moderate asthma who experience aspirin-exacerbated respiratory symptoms,15 for which non-selective NSAIDs such as ibuprofen are contraindicated. However, as a large portion of tonsillectomies are performed as outpatient surgeries, post-operative administration of celecoxib would be challenging as no commercial oral solution is currently available. While an oral solution formulation can be compounded,13,16 the associated pharmacy cost of compounding at-scale versus using generic, commercially available ibuprofen would likely restrict this treatment option to only specialized centers.

Limitations
It is unclear whether patients who were prescribed ibuprofen in the BAMC cohort also used this medication. It is also unclear whether patients who were not prescribed ibuprofen had the medication at home and used it. As such, the present study is limited to conclusions regarding patients who were prescribed ibuprofen. Many factors that could be associated with sPTH were not included in this study, such as the extent to which patients prescribed ibuprofen had adequate pain control and hydration, which may have lowered sPTH risk. Surgeon technique is not a likely factor associated with sPTH, as multiple studies have shown monopolar electrocautery and coblation to be equivocal.17–19 There was a lack of sample size to evaluate transfusion rates in a manner similar to the Mudd et al.’s study.7 The overall number of pediatric surgical cases performed at BAMC is low due to its primary mission as an adult Level 1 trauma surgical institution. The pediatric patient population who receive care at BAMC are primarily TRICARE beneficiaries. TRICARE is the health care program for active duty service members, military retirees, and their enrolled family members. Therefore, generalizability may be limited. As such, there are benefits from benchmarking comparisons with higher-volume pediatric surgical institutions to evaluate safety practices when adhering to CPGs. This information is useful to department and hospital leadership as they determine whether current CPGs are meeting their goals for patient care and safety.

CONCLUSION
Pediatric patients prescribed ibuprofen had a lower incidence of sPTH, relative to prior reported incidence of patients not prescribed post-tonsillectomy ibuprofen. Reasons for the lower incidence could be multifold, to include outpatient medication compliance and other factors that contribute to sPTH such as hydration status and pain control, requiring further research to optimize post-tonsillectomy pathways and subsequent CPGs recommendations.

ACKNOWLEDGMENTS
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CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to disclose.

DATA AVAILABILITY
The data are sourced from the Department of Defense and cannot be made available directly to the public or individual researchers by the authors. Any request for data would need to go through the appropriate procedures (e.g., data sharing agreements) and authorities (Defense Health Agency).

CLINICAL TRIAL REGISTRATION
Not applicable.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)
This study was approved as Exempt Research by the Brooke Army Medical Center Institutional Review Board (#C.2020.059e).

EXEMPT STUDIES:
The Brooke Army Medical Center Institutional Review Board approved this study as Exempt Research.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
Not applicable.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT
All authors contributed equally on this project.

INSTITUTIONAL CLEARANCE
Institutional clearance approved.

REFERENCES