Postoperative Bleeding Associated with Ibuprofen Use after Tonsillectomy: A Meta-analysis

William Stokes, MD¹, Robert T. Swanson², Jane Schubart, MBA, PhD³,⁴, and Michele M. Carr, DDS, MD, PhD¹

Abstract
Objective. To better quantify the risk of ibuprofen-associated posttonsillectomy hemorrhage (PTH).

Data Sources. PUBMED/MEDLINE, Web of Science, and Cochrane Clinical Trials Database.

Review Method. Literature searches were performed for English-language publications containing the terms tonsillectomy, ibuprofen, and tonsillectomy from database inception to May 2017. Human clinical trials, prospective cohort studies, and retrospective cohort studies related to tonsillectomy, ibuprofen use, and posttonsillectomy hemorrhage among pediatric patients were selected. Electronic searches revealed 151 studies, of which 12 were deemed eligible for analysis. Studies were weighted according to level of evidence and risk of bias.

Results. Pooling of results across all studies showed a statistically significant increase in PTH among the patients taking ibuprofen (odds ratio, 1.38; 95% confidence interval, 1.11-1.72). The $I^2$ statistic of 20.8% demonstrates overall low study heterogeneity and good comparability of the results.

Conclusion. Our meta-analysis of available cohort studies and randomized controlled trials (RCTs) shows possible increased tendency to PTH with the use of ibuprofen. This has not been demonstrated in other studies and systematic reviews because their analyses were limited by use of multiple nonsteroidal anti-inflammatory drugs and inclusion of studies limited to the perioperative period and low sample size. However, the current analysis is limited due to inclusion of many retrospective cohort studies with unclear follow-up and no blinding. Further RCTs will be required to investigate this trend toward increased PTH.

Keywords
tonsillectomy, hemorrhage, posttonsillectomy hemorrhage, ibuprofen, tonsil, pediatric

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Tonsillectomy is a common procedure in the pediatric population, with indications for surgery, including obstructive sleep apnea, sleep-disordered breathing, and chronic tonsillitis.¹,² Postoperative tonsillectomy analgesia is typically obtained with a combination of acetaminophen, ibuprofen, and opioids.² Deaths have been reported related to respiratory depression after use of codeine in children.³ In particular, young and obese children with a history of sleep apnea are at higher risk of developing serious opioid-related respiratory depression.³ Other children may possess forms of the liver microenzyme CYP2D6, which make them extensive or ultrarapid metabolizers of codeine.³,４In 2013, the US Food and Drug Administration (FDA) issued a Boxed Warning against using codeine in children after tonsillectomy. This warning resulted in many surgeons turning to the use of ibuprofen after tonsillectomy. As a nonsteroidal anti-inflammatory drug (NSAID), ibuprofen use remains an area of debate in postoperative pain management. Ibuprofen is a nonselective inhibitor of cyclooxygenase (COX) and works by limiting the production of proinflammatory cytokines.⁵,⁶ Its nonselective inhibition of COX also leads to blocking of the formation of thromboxane A₂, a component in the platelet aggregation cascade.⁵,⁶ This inhibition may cause a systemic bleeding tendency in patients taking these medications.⁵,⁶

One of the most concerning complications after tonsillectomy is posttonsillectomy hemorrhage (PTH). This can cause significant morbidity and even mortality in this vulnerable population. Typical rates of PTH range from 0.1 to
A systematic review of articles related to PTH, ibuprofen, and tonsillectomy was conducted. The study methodology was based upon the Cochrane Handbook for Systematic Reviews of Interventions. A review protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P), and PubMed/ MEDLINE, Web of Science, and Cochrane Clinical Trials Database were searched from inception to September 2018 for English-language articles using the terms tonsillectomy, ibuprofen, and tonsillectomy and ibuprofen (see Appendix 1, available in the online version of the article).

Human RCTs, prospective cohort studies, and retrospective cohort studies related to tonsillectomy, ibuprofen use, and PTH were reviewed. Inclusion criteria were studies involving pediatric patients, <18 years old, that compared bleeding rates in patients treated with and without postoperative ibuprofen and followed patients past the initial postoperative period to assess for delayed bleeding. Factors such as age, tonsillectomy technique, use of postoperative antibiotics, indication for surgery, and postoperative steroids were considered possible confounding variables when assessing study bias. The primary outcome was PTH. See Table 1 for full PICO statement.

Two authors (W.S. and R.T.S.) independently screened titles and abstracts identified from the electronic search and then independently assessed full-text papers for eligibility. Electronic search revealed 151 studies, of which 117 were excluded based on screening of the title and abstract. An additional 19 articles were identified as duplicates. Three studies were excluded because of the use of a control group that could theoretically increase the rate of PTH (2 studies used COX-2 inhibitors for the control group and 1 group used prednisolone15). Finally, 1 study was excluded because it included both adult and pediatric patients. This identified 12 studies eligible for analysis (Figure 1).

The appropriate level of evidence for each study was determined with guidelines established by the Center for Evidence-Based Medicine (http://www.cebm.net/index). A study bias assessment was performed with the 12 eligible studies by 2 separate authors (W.S. and R.T.S.) according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies (NOS) and the Cochrane Collaboration’s tool for assessing risk of bias for RCTs. The NOS involves a star system in which a study is judged based on 3 broad perspectives: the selection of the study group, comparability of the groups, and ascertainment of the outcome of interest. Higher quality studies can be awarded up to 9 stars in the NOS. The risk of bias in RCTs was assessed with the 12 eligible studies (Figure 1).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram.

Table 1. PICO Statement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children &lt;18 years old who underwent tonsillectomy and were followed past the immediate postoperative period</td>
</tr>
<tr>
<td>Intervention</td>
<td>Ibuprofen used for posttonsillectomy analgesia</td>
</tr>
<tr>
<td>Control</td>
<td>No use of NSAID for posttonsillectomy analgesia</td>
</tr>
<tr>
<td>Outcome</td>
<td>Posttonsillectomy hemorrhage</td>
</tr>
</tbody>
</table>

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
sodium and acetaminophen groups were combined into a control group given there is no reported increased rates of PTH with either of these types of drugs. Studies were weighted according to the sample size and estimate of treatment effect. Pooled odds ratios (ORs) of PTH were assessed with the “metan” procedure in Stata/IC 12.1 (StataCorp LLC, College Station, Texas). A random-effects model was constructed using the DerSimonian and Laird method, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Assessment of heterogeneity between studies was performed using the $I^2$ statistic. A funnel plot was performed to assess for general publication bias.

**Results**

Table 2 shows the general demographics for the 12 studies selected for inclusion in the systematic review. Seven of the studies included were retrospective cohort studies $^{7,19,22-27}$ 1 was a prospective cohort study. $^{19}$ 1 was a retrospective database study. $^{28}$ and 3 were RCTs. $^{19,29-31}$ All studies included pediatric patients who underwent tonsillectomy for OSA or chronic tonsillitis. Techniques for tonsillectomy included intra- and extracapsular tonsillectomy performed with cold steel, monopolar cautery, coblator, and bipolar cautery. Although tonsillectomy technique varied widely across all the studies, in each individual study, technique used was consistent and well represented except for 4 studies. $^{22,23,28,29}$ Ibuprofen doses varied across the studies and ranged from 5 to 10 mg/kg. Other possible confounding factors such as indication for surgery were controlled in 3 of the 7 studies. $^{22,26,27}$ Age at time of surgery, a well-documented bleeding risk factor, $^{8}$ was controlled for in only 7 of 12 studies. $^{7,19,27-31}$

Assessment of bias in observational studies and RCTs can be found in Table 3 and Table 4, respectively. Overall, we found a low risk of selection and outcome bias across all observational studies. Comparability of control groups was fair, with 4 of 9 studies $^{7,19,27,28}$ adequately controlling for age and 6 of 9 studies $^{7,19,24-27}$ controlling for surgical technique. Among the RCTs, Kelly et al. $^{29}$ and Harley and Dattolo $^{31}$ showed overall low risk of bias, but no studies reported adequate blinding of participants and patients during the studies’ duration. Kelly et al. $^{29}$ was stopped early because of concerns about oxygen desaturations in the opioid group and therefore suffers from early conclusion bias. St Charles et al. $^{30}$ was subject to possible high selection bias with poor randomization and unclear blinding of patient allocation.

All studies recorded PTH with various reporting mechanisms. Retrospective cohort studies identified PTH by looking at Current Procedural Terminology (CPT) codes for admission and procedures performed $^{7,28}$ or by retrospective chart review of patients returning to the emergency department (ED) after surgery. $^{7,19,22-27}$ RCTs used parental reporting and ED readmissions to identify PTH, and all incidences of bleeding, including blood-tinged saliva, were reported in these studies. $^{19,29-31}$

The overall study heterogeneity was low at 20.8% as assessed by $I^2$ statistic, which resulted in all studies being included in the final analysis (Figure 2). Pooling of results across all studies showed a statistically increased tendency for PTH among the patients taking ibuprofen (OR = 1.38; confidence interval [CI], 1.11-1.72) (Figure 2). Studies were weighted according to sample size and treatment effect. In addition, we performed a funnel plot to assess for publication bias (Figure 3). We found no evidence of publication bias, with most studies lying within the 95% CI of the funnel plot. Secondary analysis was performed, limiting the studies to those that controlled for age.

**Discussion**

Our systematic review shows an increased tendency for PTH with the use of ibuprofen (OR = 1.38; CI, 1.11-1.72). This tendency has been demonstrated in a previous systematic review by Cochrane in 2013 that showed a PTH requiring surgical intervention (OR = 1.6 for patients taking NSAIDs). $^{11}$ However, their analysis was limited due to its heterogeneity with the use of multiple NSAIDs, such as ketorolac, and inclusion of studies that looked only at bleeding rates in the immediate postoperative period. Overall, their results were not statistically significant but showed a trend toward increased bleeding.

Ibuprofen’s impact on PTH is difficult to demonstrate in a single institutional study because of the overall low likelihood of PTH (0.1%-5%). $^{7,10}$ Assuming a PTH rate of 5%, it would take ~17,000 patients to detect even a 20% increase in PTH rate with ibuprofen. Therefore, our systematic review and analysis allowed us to see a statistically significant 35% increase in PTH with ibuprofen due to a sample size of 319,305 patients. By including only studies that used ibuprofen and looked at the bleeding rates for the entire postoperative period, we get a better assessment of the typical bleeding rates seen in a clinical setting.

Our study was limited due to the lack of available data on the rate of PTH requiring return to the operating room (OR) and the general severity of PTH. This lack of data makes it difficult to assess the severity and therefore clinical significance of the PTH. This study shows a greater odds of PTH associated with ibuprofen use but does not assess the severity of those bleeds.

A possible limitation of the meta-analysis is the lack of control of age in 5 of 12 studies. This is a well-documented risk factor for bleeding, as noted in previous studies. $^{8,32,33}$ However, it appears that age did not play a significant factor in skewing our data. Restricting the meta-analysis to the 7 studies that controlled for age resulted in similar results (OR = 1.26; CI, 1.04-1.51; $I^2$ = 0.0%). The meta-analysis results were similar (OR = 1.42; CI, 1.12-1.81) and heterogeneity remained of low importance ($I^2$ = 32.1%).

Surgical technique also varied across the different studies. The techniques ranged from extracapsular tonsillectomy performed with harmonic scalpel, monopolar cautery, coblator, or cold knife to intracapsular tonsillectomy performed with coblator. However, the individual surgical technique
Table 2. Study Demographics.

<table>
<thead>
<tr>
<th>Article</th>
<th>Study Type</th>
<th>No.</th>
<th>Ibuprofen Group (No. with PTH)</th>
<th>Control Group (No. with PTH)</th>
<th>Control Used</th>
<th>Possible Confounders Addressed</th>
<th>Ibuprofen Dose</th>
<th>Bleed Identification Technique</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfaff et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>6014</td>
<td>2697 (98)</td>
<td>3317 (113)</td>
<td>Acetaminophen with codeine</td>
<td>Age, surgical technique</td>
<td>10 mg/kg</td>
<td>Retrospective analysis of CPT for tonsillar hemorrhage</td>
<td>Extracapsular tonsillectomy with harmonic scalpel performed in all cases. Follow-up in clinic, time not reported</td>
</tr>
<tr>
<td>D'Souza et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>2180</td>
<td>449 (17)</td>
<td>1731 (19)</td>
<td>Acetaminophen with codeine</td>
<td>Surgical technique, indication for surgery</td>
<td>Not stated</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Intracapsular tonsillectomy performed in all cases. Cases from 2002 to 2005 received control medication and cases from 2011 to 2013 received ibuprofen. The control group was significantly younger (age = 6) than the ibuprofen group (9.5 years) at the time of surgery. Follow-up in clinic, time not reported</td>
</tr>
<tr>
<td>Bedwell et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>666</td>
<td>177 (3)</td>
<td>489 (17)</td>
<td>Acetaminophen with codeine</td>
<td>Surgical technique</td>
<td>5 mg/kg</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Extracapsular tonsillectomy with monopolar cautery or coblator. Ibuprofen used as rescue medication in ibuprofen group. Part of the ibuprofen group received codeine, and the other part did not. It was not clear how often ibuprofen was dosed. Four- to 6-week follow-up</td>
</tr>
<tr>
<td>Mattos et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>1065</td>
<td>783 (66)</td>
<td>282 (23)</td>
<td>Acetaminophen ± opioid</td>
<td>Indication for surgery</td>
<td>10 mg/kg q6hp</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Extracapsular tonsillectomy with cold technique. Only 1 week of follow-up</td>
</tr>
<tr>
<td>Yaman et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>171</td>
<td>62 (3)</td>
<td>109 (4)</td>
<td>Acetaminophen</td>
<td>Surgical technique</td>
<td>Not stated</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Surgical technique not noted. Study performed at 2 separate institutions with the ibuprofen group coming from institution B and the control group coming from both institutions A and B. One month of follow-up</td>
</tr>
<tr>
<td>Jeyakumar et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>1148</td>
<td>480 (5)</td>
<td>668 (5)</td>
<td>Acetaminophen with codeine</td>
<td>None</td>
<td>5 mg/kg</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Extracapsular tonsillectomy with monopolar cautery or cold technique. Technique for tonsillectomy not noted; medications for control group not tracked</td>
</tr>
<tr>
<td>O'Connell et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Retrospective database cohort</td>
<td>306,536</td>
<td>1206 (46)</td>
<td>305,330 (8224)</td>
<td>Not ibuprofen</td>
<td>Age</td>
<td>Unknown</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Database study; tracked medications by dates filled at pharmacy. Technique for tonsillectomy not noted; medications for control group were not tracked</td>
</tr>
<tr>
<td>Swanson et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>773</td>
<td>504 (44)</td>
<td>269 (16)</td>
<td>Acetaminophen ± opioid</td>
<td>Age, surgical technique, indication for surgery</td>
<td>Unknown</td>
<td>Retrospective analysis of ED admission for tonsillar hemorrhage</td>
<td>Extracapsular tonsillectomy with monopolar cautery performed in all cases. Two-week follow-up</td>
</tr>
<tr>
<td>Harley and Dattolo&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Randomized controlled trial</td>
<td>27</td>
<td>16 (2)</td>
<td>11 (0)</td>
<td>Acetaminophen with codeine</td>
<td>Age, surgical technique, antibiotic, steroids (none given)</td>
<td>5 mg/kg q6h</td>
<td>Parental report, readmission to the ED</td>
<td>Extracapsular tonsillectomy with monopolar cautery or cold technique. Two-week follow-up</td>
</tr>
<tr>
<td>St Charles et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Randomized controlled trial</td>
<td>110</td>
<td>55 (4)</td>
<td>55 (5)</td>
<td>Acetaminophen with codeine</td>
<td>Age, surgical technique, antibiotic, steroids (none given)</td>
<td>10 mg/kg</td>
<td>Parental report, readmission to the ED</td>
<td>Extracapsular tonsillectomy with monopolar cautery performed in all cases. Follow-up in clinic, time not reported</td>
</tr>
</tbody>
</table>
Table 2. (continued)

<table>
<thead>
<tr>
<th>Article</th>
<th>Study Type</th>
<th>No.</th>
<th>Ibuprofen Group (No. with PTH)</th>
<th>Control Group (No. with PTH)</th>
<th>Control Used</th>
<th>Possible Confounders Addressed</th>
<th>Ibuprofen Dose</th>
<th>Bleed Identification Technique</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al</td>
<td>Randomized controlled trial</td>
<td>86</td>
<td>41 (3)</td>
<td>45 (2)</td>
<td>Acetaminophen with morphine</td>
<td>Age, antibiotics (none given), steroids (none given)</td>
<td>10 mg/kg</td>
<td>Parental report, readmission to the ED</td>
<td>Surgical technique was not noted. Study was stopped early due to increased rate of early postoperative desaturations in the morphine group (however, there was no change in mean desaturation rate and lowest saturation level in the study). Follow-up at least 5 days</td>
</tr>
<tr>
<td>Ozkiris et al</td>
<td>Prospective cohort</td>
<td>340</td>
<td>115 (6)</td>
<td>225 (8)</td>
<td>Metamizole sodium/acetaminophen</td>
<td>Age, surgical technique, antibiotic, steroids (none given)</td>
<td>5 mg/kg q4h</td>
<td>Parental report, readmission to the ED</td>
<td>Extracapsular tonsillectomy with bipolar cautery. RCT with 3 arms (ibuprofen, metamizole sodium, and acetaminophen). Metamizole sodium and acetaminophen groups were combined for analysis. One-week follow-up</td>
</tr>
</tbody>
</table>

Abbreviations: CPT, Current Procedural Terminology; ED, emergency department; PTH, posttonsillectomy hemorrhage; RCT, randomized controlled trial.

Table 3. Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.

<table>
<thead>
<tr>
<th>Article</th>
<th>Representativeness</th>
<th>Selection of Control</th>
<th>Ascertainment of Exposure</th>
<th>Outcome of Interest Not Present at Start</th>
<th>Comparability of Controls</th>
<th>Assessment of Outcome</th>
<th>Follow-up Long Enough</th>
<th>Adequacy of Follow-up</th>
<th>Overall Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfaff et al</td>
<td>*</td>
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<td>*</td>
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<td>*</td>
<td>******** (8)</td>
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<tr>
<td>D’Souza et al</td>
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<td>******** (7)</td>
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<tr>
<td>Bedwell et al</td>
<td>*</td>
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<td>*</td>
<td>*</td>
<td>******** (7)</td>
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<tr>
<td>Mattos et al</td>
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<td>*</td>
<td>*           (5)</td>
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<tr>
<td>Yaman et al</td>
<td>*</td>
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<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>******** (5)</td>
</tr>
<tr>
<td>Jayakumar et al</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
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<td>*</td>
<td>*</td>
<td>*</td>
<td>*           (5)</td>
</tr>
<tr>
<td>O’Connell Ferster et al</td>
<td>*</td>
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<td>*</td>
<td>*</td>
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<td>*</td>
<td>*</td>
<td>******** (5)</td>
</tr>
<tr>
<td>Swanson et al</td>
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<td>*</td>
<td>******** (7)</td>
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<tr>
<td>Ozkiris et al</td>
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<td>*</td>
<td>*</td>
<td>*           (6)</td>
</tr>
</tbody>
</table>

*Studies with ≥7 asterisks were considered high quality. Studies with ≤4 asterisks were considered low quality.
was controlled for in 8 of 12 studies. The wide variation in techniques makes it hard to relate one study to another; however, our results are strengthened once again due to the low heterogeneity between the groups.

A further limitation is that no studies can state that the patients received the prescribed ibuprofen, as there are no third-party medication diaries or drug blood levels available. The dosing regimen in these studies varies; giving ibuprofen as a multidrug pain control regimen may result in fewer doses being taken as patients have other options. Also, many studies used a lower dose of ibuprofen, 5 mg/kg, than is typically prescribed in clinical practice. Both these factors could further reduce the rates of PTH associated with ibuprofen that we have seen in our study.

Two previous meta-analyses did not prove an increased rate of PTH with NSAID use. Their findings were not significant due to low power and study heterogeneity, but by including cohort and RCT studies that used ibuprofen and looked for delayed bleeding throughout the posttonsillectomy period, we were able to improve on previous meta-analysis heterogeneity and show an increase in PTH in patients prescribed ibuprofen. Yet, a major limitation of our analysis is the lack of large RCTs assessing PTH. We await the RCTs adequately powered to detect an increased rate of PTH with ibuprofen use and that compares PTH to opioid-based therapy and its inherit risk of respiratory depression.

**Conclusion**

Interest in using ibuprofen after tonsillectomy is high currently. This study suggests that caution may be indicated when doing so. Under the Clinical Practice Guideline for Tonsillectomy in Children, ibuprofen is recommended for postoperative analgesia after tonsillectomy. This meta-analysis demonstrates an increased rate of delayed hemorrhage after tonsillectomy. However, this study cannot assess the severity and clinical relevance of increased PTH due to limitations in the available data. We need an adequately powered, likely multi-institutional, RCT that adequately assesses the risk of ibuprofen-associated PTH vs the risk of opioid-related respiratory depression after tonsillectomy. Data in the literature suggest an increased rate of PTH in older children with chronic tonsillitis and increased rate of respiratory depression in younger children who typically have OSA. This does open the possibility of using different medications for different age groups/indications, but additional studies will be required to further assess these risks.

**Author Contributions**

William Stokes, obtained data, drafted the work, approved final work, accountable for all aspects; Robert T. Swanson, obtained...
data, revised the work for important intellectual content, approved final work, accountable for all aspects; Jane Schubart, data analysis, revised the work for important intellectual content, approved final work, accountable for all aspects; Michele M. Carr, performed study design and oversaw execution, revised the work for important intellectual content, approved final work, accountable for all aspects.

Disclosures
Competing interests: None.
Sponsorships: None.
Funding source: None.

Supplemental Material
Additional supporting information is available in the online version of the article.

References
30. St Charles CS, Matt BH, Hamilton MM, Katz BP. A comparison of ibuprofen versus acetaminophen with codeine in the


