Ibuprofen with Acetaminophen for Postoperative Pain Control following Tonsillectomy Does Not Increase Emergency Department Utilization

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No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. To compare the performance of ibuprofen vs codeine for postoperative pain management after tonsillectomy as measured by need for emergency department (ED) treatment for pain and/or dehydration.

Study Design. Retrospective case series with chart review.

Setting. Tertiary children’s hospital.

Subjects and Methods. Consecutive series of patients who underwent tonsillectomy with or without adenoidectomy at a tertiary children’s hospital. Patients were categorized based on the type of postoperative pain management (acetaminophen with codeine vs acetaminophen and ibuprofen). The main outcome measure was the proportion of patients requiring ED visits or inpatient admissions for inadequate pain control or dehydration. Secondary measures included antibiotic use, postoperative hemorrhage, need for return to the operating room, vomiting, and oral diet tolerance.

Results. Patients in the ibuprofen/acetaminophen group were younger than those in the codeine/acetaminophen group (6.2 vs 8.1 years, P < .05). Patients in the codeine/acetaminophen group were more likely to use antibiotics in the postoperative period (50.3% vs 5.9%, P < .05). The proportion of patients requiring ED visits or inpatient admission for dehydration was not significantly different between the groups (5.1% for codeine, 2.7% for ibuprofen, P = .12). Multivariable analysis controlling for age and antibiotic use showed no difference in ED visits or admission for dehydration (P = .09). There was no difference between the groups for any of the secondary measures.

Conclusions. Ibuprofen with acetaminophen represents a safe and acceptable analgesic alternative to codeine and acetaminophen in patients undergoing pediatric tonsillectomy.

Keywords
tonsillectomy, adenoidectomy, pain management, ibuprofen, codeine

Received May 7, 2014; revised July 8, 2014; accepted August 12, 2014.

As a result of reported fatalities and serious adverse events in pediatric tonsillectomy patients, there has been significant attention focused on the optimal medication for postoperative pain control in such patients.1-7 There exists a cohort of patients who are ultra-rapid metabolizers of codeine, which results in higher than expected serum levels of morphine.8 As such, the US Food and Drug Administration (FDA) recently placed a boxed warning against the use of codeine in children following tonsillectomy and/or adenoidectomy.7

Furthermore, in January 2011, the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) published clinical practice guidelines regarding tonsillectomy in children.9 These guidelines assist referring physicians and otolaryngologists in remaining up to date on the optimal management of patients undergoing tonsillectomy. A change from prior recommendations was the inclusion of nonsteroidal anti-inflammatory drugs such as ibuprofen in the medications deemed safe for use postoperatively.

While multiple authors have investigated the safety of using ibuprofen after tonsillectomy with regard to the primary outcome measure of postoperative hemorrhage, there exist only studies with small sample sizes that compare the efficacy of ibuprofen with codeine with regard to adequate postoperative pain control.1-6 We initiated the current study to test the null hypothesis that there was no difference in emergency department (ED) visits for pain or dehydration...
between ibuprofen and acetaminophen vs acetaminophen with codeine for posttonsillectomy patients.

**Methods**

Approval for the study was obtained from the Children’s National Medical Center Institutional Review Board. Charts were retrospectively reviewed of consecutive patients who underwent tonsillectomy with or without adenoidectomy using monopolar electrocautery supervised by one of the 2 senior authors (J.R.B. and R.K.S.) from January 2011 through June 2013. Patients were categorized based on the type of postoperative pain management. One group consisted of patients receiving acetaminophen with codeine. A second group of patients received acetaminophen and ibuprofen. Acetaminophen with codeine was dosed at 0.5 to 1 mg/kg of codeine every 6 hours. Acetaminophen was dosed at 10 to 15 mg/kg every 6 hours. Ibuprofen was dosed at 5 mg/kg every 6 hours. Acetaminophen and ibuprofen were given in an alternating (every 3-hour) fashion. All medications were prescribed as standing doses for the first 3 days and as needed thereafter. Patients were further stratified based on the use of postoperative antibiotic use. In patients who received antibiotics, amoxicillin was used for nonallergic patients, and clindamycin was used for those with penicillin allergies. Early in the study period, patients were routinely prescribed postoperative antibiotics. This practice ended during the study period as a response to the strong recommendation against routine perioperative antibiotic use. In patients who received antibiotics, amoxicillin was used for those with penicillin allergies. Early in the study period, patients were routinely prescribed postoperative antibiotics. This practice ended during the study period as a response to the strong recommendation against routine perioperative antibiotic use in tonsillectomy in the AAO-HNS guidelines.

The main outcome measure was the proportion of patients requiring ED visits or inpatient admission for inadequate pain control and/or dehydration. While not a perfect substitute measure for pain control, return to the ED due to uncontrolled pain or dehydration due to pain does give insight into the efficacy of the postoperative analgesic regimen and is an acceptable surrogate for such in retrospective series of post-adenotonsillectomy pain control. Return to the ED demonstrates that the pain threshold was exceeded, resulting in the caregiver seeking higher acuity evaluation for the pain control.

Secondary outcome measures included postoperative hemorrhage, need for return to the operating room, and oral feeding tolerance on postoperative day 1 (as determined by a postoperative routine check-in phone call by recovery room nurses).

Bivariable analysis of continuous variables (ie, age) was performed using a 2-tailed Student t test. The χ² test was used for bivariable analysis of nominal data. Multivariable analysis using logistic regression was performed to examine the effect of the postoperative pain medicine on the primary outcome when controlling for patient age and antibiotic use. Statistical analysis was performed using Microsoft Excel (Microsoft, Redmond, Washington) and SPSS for Mac OS X (SPSS, Inc, an IBM Company, Chicago, Illinois).

**Results**

Of the 666 patients included in the study, 177 were treated with acetaminophen and codeine, and 489 received acetaminophen and ibuprofen. Table 1 summarizes the results of this study. Specifically, patients in the ibuprofen/acetaminophen group were younger than those in the group that received codeine/acetaminophen (6.2 vs 8.1 years, P < .05). Patients in the codeine/acetaminophen group were more likely to use antibiotics in the postoperative period (50.3% vs 5.9%, P < .05).

With regard to the main outcome measure, 9 patients (5.1%) from the codeine/acetaminophen group returned to the ED due to inadequate pain control or dehydration, compared with 13 patients (2.6%) from the ibuprofen/acetaminophen group. This difference was not statistically significant, with P = .12. The effect of antibiotic use on the main outcome measure was not significant: 5.1% of patients in the antibiotic group returned to the ED vs 3% for patients who did not use antibiotics (P = .2). Multivariable analysis using logistic regression showed no significant difference between the codeine/acetaminophen and ibuprofen/acetaminophen groups for the main outcome measure when controlling for patient age and postoperative antibiotic use (P = .09). Age was found to be a significant factor in the multivariable model, with an odds ratio of 0.98 (P < .05), indicating that when controlling for antibiotic and analgesic use, older children were slightly less likely to return to the ED. Table 2 summarizes the findings of the logistic regression analysis.

**Table 1. Summary of Results.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Codeine and Acetaminophen</th>
<th>Ibuprofen and Acetaminophen</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>177</td>
<td>489</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>8.1</td>
<td>6.2</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Postoperative antibiotics</td>
<td>89 (50.3)</td>
<td>29 (5.9)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Emergency room visit</td>
<td>9 (5.1)</td>
<td>13 (2.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (1.7)</td>
<td>17 (3.5)</td>
<td>.23</td>
</tr>
<tr>
<td>Return to operating room</td>
<td>3 (1.7)</td>
<td>7 (1.4)</td>
<td>.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (9.2)</td>
<td>19 (7.1)</td>
<td>.5</td>
</tr>
<tr>
<td>Oral diet intolerance</td>
<td>13 (11.9)</td>
<td>30 (11.2)</td>
<td>.85</td>
</tr>
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</table>

*Values are presented as number (%) unless otherwise indicated.
There were no significant differences between the groups for any of the secondary outcome measures. Three patients (1.7%) from the codeine/acetaminophen group had postoperative bleeding, compared with 17 (3.5%) in the ibuprofen/acetaminophen group ($P = .23$). Need for return to the operating room for control of posttonsillectomy hemorrhage was similar, with 3 patients (1.7%) from the codeine/acetaminophen group vs 7 (1.4%) for the ibuprofen/acetaminophen group ($P = .8$).

Data for vomiting and oral diet tolerance in the first 24 hours postsurgery were available for 376 patients (109 treated with codeine/acetaminophen and 267 treated with ibuprofen/acetaminophen). Among these patients, 10 (9.2%) children treated with codeine/acetaminophen and 19 (7.1%) treated with ibuprofen/acetaminophen reported vomiting ($P = .5$). Of these 376 patients, only 13 (11.9%) among the codeine/acetaminophen group and 30 (11.2%) in the ibuprofen/acetaminophen group were not tolerating an oral diet 24 hours after surgery ($P = .85$).

**Discussion**

The current study tests the null hypothesis that ibuprofen and acetaminophen do not increase ED utilization for pain or dehydration compared with codeine and acetaminophen. Our data demonstrate that a regimen of ibuprofen and acetaminophen performs the same as codeine and acetaminophen for the primary and secondary outcome measures, and the null hypothesis is accepted. However, this conclusion should be met with some caution. The span of the confidence interval for the odds ratio for ED visits suggests that our sample size may be too small to detect significant differences between the groups.

There has long been interest in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain relief; this is the largest series to date addressing this question. Following reports of deaths and serious adverse events in children using codeine following tonsillectomy, as well as a subsequent boxed warning by the FDA, it has become even more important to find pain control regimens that are both safe and effective.

Codeine is a prodrug, metabolized via the CYP2D6 pathway to the active drug morphine. Genetic polymorphisms can lead to variation in an individual’s ability to metabolize the drug, with some patients being “extensive” or “ultra-rapid” metabolizers of the medication. Such patients will convert much more codeine to morphine and are more susceptible to adverse reactions such as respiratory depression, even at theoretically weight-appropriate doses. Kelly et al reported on the deaths of 3 children who were administered codeine following adenotonsillectomy and subsequently found to be ultra-rapid metabolizers.

Ibuprofen has the theoretical concern of increasing posttonsillectomy hemorrhage; this assertion is not supported by the literature and was not a primary end point in the present study. This study showed a rate of postoperative hemorrhage of 3.5% in the ibuprofen group, a number near the higher end of reported rates. We attribute this to increased vigilance and parental counseling as we began to use ibuprofen as we had heightened sensitivity to the anecdotes and assertions. Patients were counted as having a hemorrhage even with a parental report of blood-tinted sputum but no evidence of active bleeding or clots on physical examination. Other studies have shown elevated postoperative hemorrhage rates when similar definitions of hemorrhage were used. Notably, in the present study, the operating room return rates for hemorrhages were nearly identical between the codeine and ibuprofen groups (1.7% and 1.4%, respectively).

As a result of the data in the literature regarding ibuprofen and codeine, the guidelines from the AAO-HNS, and the recent FDA boxed warning, there has been a move toward using ibuprofen in pediatric tonsillectomy patients. The senior authors in this study made the switch away from codeine in May 2011 (author R.K.S.) and November 2011 (author J.R.B.). Given the FDA warning, a prospective study comparing these 2 regimens would be ethically dubious.

There is extensive literature investigating and ultimately establishing the safety of ibuprofen use after tonsillectomy. Ibuprofen has been shown to work with at least the same, if not greater, efficacy as codeine in children with musculoskeletal trauma. Evidence for its efficacy after tonsillectomy has not been as robust. Studies by St Charles et al in 1997 and Harley et al in 1998 addressed these questions of safety and efficacy but were limited by the low power of the studies (n = 110 and n = 27, respectively). St Charles et al found no difference in bleeding, pain, or temperature control but did show less nausea in patients receiving ibuprofen. Harley et al found slight differences in favor of codeine in the early postoperative period, but overall, there was no significant difference in pain control or time until return to normal diet.

There was a significant difference in perioperative antibiotic use in our 2 groups. This disparity is due to shifts in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% CI for Odds Ratio</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>0.980</td>
<td>0.965-0.994</td>
<td>.007</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>0.968</td>
<td>0.309-3.037</td>
<td>.956</td>
</tr>
<tr>
<td>Analgesic medication</td>
<td>0.400</td>
<td>0.136-1.170</td>
<td>.094</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
the senior authors’ practice following the strong recommendation in the AAO-HNS guidelines against the routine use of perioperative antibiotics. The use of antibiotics has not been definitively shown to affect postoperative morbidity, specifically pain and hemorrhage. Multivariable analysis in the present study did not find antibiotic use to be a significant predictor of ED return.

The limitations of the present study include the retrospective nature of the study. It is possible that patients may have visited an outside ED, and such events would not have been included in our chart review. This potential is minimized, however, because such information is routinely obtained during the first postoperative visit. Due to the severity of the warning from the FDA, it is unethical to design a prospective study using codeine without screening in some manner for rapid metabolizers. The value of the present study is that it bridges both time periods—prior to the FDA warning and after the FDA warning. Unfortunately, the retrospective nature of the study precludes the use of direct or objective measures of pain control. The rate of return to the ED due to pain and/or dehydration is a suitable surrogate metric and provides useful clinical information on the efficacy of a given postoperative analgesic regimen.

**Conclusion**

There is no difference in the primary and secondary outcome measures in post-tonsillectomy patients based on the use of codeine and acetaminophen or ibuprofen and acetaminophen. Codeine and ibuprofen perform similarly for postoperative analgesia in children after tonsillectomy with or without adenoidectomy with respect to ED utilization. Given the major concerns regarding codeine use in this population, ibuprofen represents an acceptable and safe alternative for pain control.

**Author Contributions**

Joshua R. Bedwell, conceived of and designed the study, analyzed the data, drafted the initial manuscript, and approved the final manuscript as submitted; Matthew Pierce, collected the data, performed initial data analysis, assisted in drafting the initial manuscript, and approved the final manuscript as submitted; Michelle Levy, collected the data, performed initial data analysis, and approved the final manuscript as submitted; Rahul K. Shah, designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

**Disclosures**

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.

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