Objective: To use standard meta-analysis techniques to determine the risk of postoperative hemorrhage associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after tonsillectomy.

Data Sources: The MEDLINE database (1966-2001) restricted to the English language was searched using the keywords tonsillectomy, hemorrhage, analgesics, and NSAID in various combinations. Additionally, published articles were cross-referenced. To ensure completeness, the search was rerun using the Science Citation Index database.

Study Selection: Of the 110 articles identified, 7 were selected. Selected studies were prospective trials comparing the effects of an NSAID and a control drug on posttonsillectomy pain and hemorrhage in pediatric and/or adult patients. In all cases, the NSAID or control was administered through an enteric route in the postoperative period. Patients were monitored for early and delayed hemorrhage.

Data Extraction: Data were extracted independently by 2 investigators.

Data Synthesis: A random effects model was used to compute a pooled odds ratio. For the 1368 patients included in analysis, the pooled odds ratio of posttonsillectomy hemorrhage with NSAIDs compared with controls was 1.29 and was not statistically significant (95% confidence interval, 0.85-1.73; \( P = .05 \)). A subgroup analysis revealed an odds ratio of 0.93 (95% confidence interval, 0.44-1.95; \( P = .05 \)) for the nonaspirin NSAID group, while the aspirin group had a statistically significant odds ratio of 1.94 (95% confidence interval, 1.09-3.42; \( P = .02 \)).

Conclusions: There is an increased risk of posttonsillectomy hemorrhage with the use of aspirin after tonsillectomy; however, there appears to be no significant increased risk of bleeding for nonaspirin NSAIDs in this meta-analysis.


Postoperative Hemorrhage With Nonsteroidal Anti-inflammatory Drug Use After Tonsillectomy

A Meta-analysis

Srinivasan Krishna, MD; Larry F. Hughes, PhD; Sandra Y. Lin, MD

Tonsillectomy is the most common major surgical procedure performed on pediatric patients in the United States today.1 Morbidity after tonsillectomy includes pain, bleeding, nausea, vomiting, and dehydration. Potentially life-threatening complications include posttonsillectomy hemorrhage. In most large series, the incidence of posttonsillectomy hemorrhage varies from 1.5% to 5%, with delayed hemorrhage (>24 hours) being more common than primary hemorrhage (≤24 hours).2-5

The increasing trend toward outpatient tonsillectomy dictates a need for adequate postoperative analgesia without added morbidity. Narcotics such as codeine in combination with acetaminophen have been used extensively for posttonsillectomy analgesia. While narcotics are potent pain relievers, they have undesirable adverse effects such as sedation, respiratory depression, nausea, vomiting, and constipation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are proven analgesics and may be potential alternatives for posttonsillectomy pain relief. They have been found to be very effective in postoperative pain relief after wisdom tooth extraction, hip surgery, hysterectomy, and tonsillectomy.6-9 Notably, NSAID therapy is devoid of the adverse effects on the central nervous system that occur with narcotic use. They inhibit cyclooxygenase (COX) and thereby affect prostaglandin synthesis, which gives them useful anti-inflammatory properties. However, NSAID therapy is known to inhibit platelet aggregation and increase bleeding time, thereby potentially increasing the risk of postoperative bleeding. However, the clinical implications of the inhibition of platelet aggregation by NSAIDs in the postoperative setting are still unclear. The literature is replete with articles that both

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support and dismiss the use of NSAIDs for posttonsillectomy pain relief based on the risk of hemorrhage.10-17

The objective of this meta-analysis was to review the current literature and summarize the risk of tonsillectomy hemorrhage associated with the postoperative use of NSAIDs, as evidenced by prospective trials in which an NSAID was administered through an enteric route and compared with a control medication.

**METHODS**

A computerized MEDLINE (1966-2001) literature search limited to the English language was performed using the keywords tonsillectomy, hemorrhage, analgesic, and NSAID. The articles identified based on each keyword search were then combined using all possible combinations. This resulted in a total of 110 articles, the titles and abstracts of which were carefully reviewed. The selection criteria for this study included only prospective trials in which an NSAID or a control drug was administered through an enteric route and compared with a control medication.

**STUDY CHARACTERISTICS**

Of a total of 110 articles, only 7 met all the inclusion criteria, 6 of which were from the MEDLINE database. The seventh article, which was published in 1964, had been quoted as a reference and was not included in the computerized MEDLINE database. Six of the articles were published in otolaryngology journals, and 1 article was published in the Saudi Medical Journal.

**RESULTS**

The details of the individual trials are summarized in Table 1 and Table 2. Of the 7 studies, 3 were performed at institutions in the United States. While all the studies chosen were prospective trials, only 2 were double-blinded, randomized prospective trials, and 1 was single blinded. In 3 of the studies, the primary objective was to assess postoperative hemorrhage risk, while the others were designed to assess analgesic efficacy. The study subjects ranged in age from 1 to 62 years, but most were children. Tonsillectomy techniques included both electrocautery and cold dissection. The NSAIDs used in the various studies were diclofenac (3), ibuprofen (2), or aspirin (2). Controls included tramadol hydrochloride, acetaminophen with or without codeine, and placebo. Two of the studies measured preoperative coagulation and excluded patients with abnormal results. Of the 1368 subjects from the 7 studies, 1083 received aspirin and 289 received either ibuprofen or diclofenac as the NSAID.

**SEARCH RESULTS**

Of a total of 110 articles, only 7 met all the inclusion criteria, 6 of which were from the MEDLINE database. The seventh article, which was published in 1964, had been quoted as a reference and was not included in the computerized MEDLINE database. Six of the articles were published in otolaryngology journals, and 1 article was published in the Saudi Medical Journal.
The individual ORs were variable, ranging from 0.77 to 1.98 (Table 3). The mean±SD (SE) pooled OR, which amounts to the relative risk of any postoperative hemorrhage with NSAID use compared with controls, was 1.29±0.55 (0.22), with 95% confidence limits ranging from 0.85 to 1.73 (95% confidence interval, 0.44). An OR could not be calculated for the study by Harley and Dattolo,19 since the incidence of bleeding in the control group was zero. Despite the fact that the pooled sample size was 1368 patients, the overall pooled OR of 1.29 was not statistically significant (95% confidence interval, 0.85-1.73; P=.05). A subgroup analysis was performed to determine the pooled ORs for aspirin vs nonaspirin NSAIDs. The pooled OR for nonaspirin NSAIDs was 0.93 (95% confidence interval, 0.44-1.95; P=.05). However, the pooled OR for the aspirin subgroup was 1.94 (95% confidence interval, 1.09-3.42; P=.02). An additional subgroup analysis was performed to compare primary vs delayed hemorrhages. However, the sample sizes were too small to achieve adequate statistical power to draw any conclusions from this subgroup analysis.

There is a need for adequate analgesia after tonsillectomy without unwanted adverse effects. Nonsteroidal anti-inflammatory drugs are potent analgesics and have been shown to be very effective in postoperative analgesia.6-9 They have several advantages over narcotics, the most significant being the lack of adverse effects on central nervous system. In addition, NSAIDs have a longer half-life (6-10 hours). Their mechanism of action is by inhibiting the COX enzyme, which in turn inhibits the synthesis of prostaglandins24 including thromboxane A2, a potent platelet aggregator, thereby leading to decreased platelet aggregation and a prolongation of the bleeding time.25 However, the clinical significance of the increased bleeding risk is not clearly defined. While some studies have shown the risk to be significant,19,21,23 others have not.17,18,20,22

In an effort to clarify this controversy, we undertook this meta-analysis. Meta-analysis is defined as a systematic review that uses statistical methods to combine and summarize the data from several studies.26 Although strict selection criteria were applied in this study, the diversity in study design and methods made the process of pooling data from several studies challenging. Since the studies analyzed had different sample sizes and populations, and thereby differing sampling errors, the information gathered from each study was weighted for the sample size.27 The final result was expressed as a pooled OR, which in our case was the risk of bleeding in the treatment group (NSAID) compared with the control group. In our study, a random effects model was used to compute the pooled OR. This model assumes that there is a population of true effect sizes, with each source article representing 1 member of this population.28 Therefore, results would be expected to vary from study to study, with differences caused by experimental error and differences in populations.28

Although our meta-analysis suggested that there was a trend toward an increased risk of posttonsillectomy hemorrhage with the use of NSAIDs for postoperative pain relief, the overall risk was not statistically significant. There may be several reasons for this. Although all the studies met the inclusion criteria, there was considerable variability in their methods. The studies with the larger sample sizes (ie, Reuter and Montgomery23 [1964] and Stage et al21 [1988]) had more influence. Both studies concluded that NSAID use increased hemorrhagic risk. However, both used aspirin as the NSAID, and it is well-known that aspirin use inhibits platelet function irreversibly and lasts for the life of the platelet (8-11 days).29 The other NSAIDs studied (ibuprofen and diclofenac) are reversible inhibitors of COX and hence their effects on platelet function are less pronounced. Another study by Harley and Dattolo20 using ibuprofen showed an increased risk of bleeding, but had a small sample size of 30. The studies that showed no difference in the hemorrhagic risk tended to have smaller sample sizes.17,18,20,22 In an effort to address this variability between aspirin and the nonaspirin NSAIDs, we performed a subgroup analysis. The OR for the aspirin group was 1.93, which was statistically significant (P=.02). This demonstrated that aspirin was associated with an increased risk of posttonsillectomy bleeding. However, the nonaspirin NSAID group had a pooled OR of 0.93. The nonaspirin NSAIDs in this series (ibuprofen and diclofenac) did not appear to increase the risk.

**Table 3. Odds Ratios for Each Individual Study**

<table>
<thead>
<tr>
<th>Source</th>
<th>NSAID</th>
<th>Control</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tawalbeh et al,17 2000</td>
<td>Yes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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<td>39</td>
</tr>
<tr>
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<td>Yes</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Harley and Dattolo,19 1998</td>
<td>Yes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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<td>11</td>
</tr>
<tr>
<td>St Charles et al,20 1997</td>
<td>Yes</td>
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<td>5</td>
</tr>
<tr>
<td></td>
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<td>51</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Stage et al,21 1988</td>
<td>Yes</td>
<td>18</td>
<td>9</td>
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<tr>
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<tr>
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<td>89</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; NSAID, nonsteroidal anti-inflammatory drug.

**STATISTICS**

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**COMMENT**

There is a need for adequate analgesia after tonsillectomy without unwanted adverse effects. Nonsteroidal anti-inflammatory drugs are potent analgesics and have been shown to be very effective in postoperative analgesia.6-9 They have several advantages over narcotics, the most significant being the lack of adverse effects on central nervous system. In addition, NSAIDs have a longer half-life (6-10 hours). Their mechanism of action is by inhibiting the COX enzyme, which in turn inhibits the synthesis of prostaglandins24 including thromboxane A2, a potent platelet aggregator, thereby leading to decreased platelet aggregation and a prolongation of the bleeding time.25 However, the clinical significance of the increased bleeding risk is not clearly defined. While some studies have shown the risk to be significant,19,21,23 others have not.17,18,20,22

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Other variables such as the variations in technique (electrocautery vs cold), the actual dosage of NSAID consumed by the patient, and the definition of bleeding may have influenced the results. This further emphasizes the need for larger prospective randomized trials to answer this important question.

The studies analyzed in this meta-analysis have all used NSAIDs that were nonselective COX inhibitors. Cyclooxygenase has 2 known isoforms, COX-1 and COX-2. Nonsteroidal anti-inflammatory drugs that are selective COX-2 inhibitors, such as celecoxib and rofecoxib, have been shown to have an improved adverse effect profile and do not inhibit platelet function. These agents may be ideal for posttonsillectomy analgesia, and further research with these drugs is needed.

Also, a combination of an opioid agent (hydrocodone) with an NSAID (ibuprofen) has been shown to be superior to ibuprofen alone for postoperative analgesia. This combination may be an area for further research in the setting of posttonsillectomy analgesia. The synergistic effect of the combination and the resulting decrease in the need for each individual agent may obviate some of the adverse effects of each drug when taken alone.

In conclusion, NSAID use appears to have varying effects on the risk of posttonsillectomy hemorrhage. In our meta-analysis, when considering all studies that met inclusion criteria, there was no statistically significant increase in hemorrhage risks when using NSAIDs. However, it was clear that studies using aspirin had an increased risk of posttonsillectomy hemorrhage. Use of nonaspirin NSAIDs does not appear to have the same effect. Larger randomized, prospective trials are warranted to study this issue further.

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