Postoperative Hemorrhage With Nonsteroidal Anti-inflammatory Drug Use After Tonsillectomy

A Meta-analysis

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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 post-tonsillectomy 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.

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.

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.

### METHODS

A total of 110 articles were identified. Of these, 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

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*.

### STUDY CHARACTERISTICS

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. 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, ibuprofen, and aspirin. Controls included tramadol hydrochloride, acetaminophen with or without codeine, and placebo. Two of the studies measured preoperative coagulation and excluded patients with abnormal results.

### Table 1. Studies Included in Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Objective</th>
<th>Design</th>
<th>Patients Enrolled, No.</th>
<th>Age, y (Mean)</th>
<th>Coags/Plts</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tawalbeh et al.,2000</td>
<td>Analg eff</td>
<td>PNRT</td>
<td>80</td>
<td>3-14 (NA)</td>
<td>NA</td>
<td>Cautery</td>
</tr>
<tr>
<td>Courtney et al.,2001</td>
<td>Analg eff</td>
<td>SBPRT</td>
<td>64</td>
<td>&gt;11 (17-19)</td>
<td>NA</td>
<td>Cautery</td>
</tr>
<tr>
<td>Harley and Dattolo,1998</td>
<td>Hge rate</td>
<td>DBPRT</td>
<td>30</td>
<td>6-16 (NA)</td>
<td>Normal</td>
<td>Cautery</td>
</tr>
<tr>
<td>St Charles et al.,1997</td>
<td>Hge rate</td>
<td>PRT</td>
<td>113</td>
<td>1.3-14 (6)</td>
<td>Normal</td>
<td>Hot + cold</td>
</tr>
<tr>
<td>Stage et al.,1988</td>
<td>Hge rate</td>
<td>PRT</td>
<td>883</td>
<td>1-62 (15)</td>
<td>NA</td>
<td>Cold</td>
</tr>
<tr>
<td>Dommerby and Rasmussen,1984</td>
<td>Analg eff</td>
<td>DBPRT</td>
<td>142</td>
<td>&gt;12 (19)</td>
<td>NA</td>
<td>Cold</td>
</tr>
<tr>
<td>Reuter and Montgomery,1964</td>
<td>Analg eff</td>
<td>DBPRT</td>
<td>200</td>
<td>4-13 (NA)</td>
<td>NA</td>
<td>Cold</td>
</tr>
</tbody>
</table>

### Table 2. Types of Analgesics Used and Comparison of Hemorrhage Rates (NSAID vs Control) in Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>NSAID</th>
<th>NSAID Dosage</th>
<th>Control</th>
<th>Hemorrhage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tawalbeh et al.,2000</td>
<td>Diclofenac</td>
<td>1-3 mg/kg × 2</td>
<td>Acetaminophen</td>
<td>No difference</td>
</tr>
<tr>
<td>Courtney et al.,2001</td>
<td>Diclofenac</td>
<td>50 mg bid/tid</td>
<td>Tramadol hydrochloride</td>
<td>No difference</td>
</tr>
<tr>
<td>Harley and Dattolo,1998</td>
<td>Ibuprofen</td>
<td>5 mg/kg qd</td>
<td>Acetaminophen + codeine</td>
<td>No difference</td>
</tr>
<tr>
<td>St Charles et al.,1997</td>
<td>Ibuprofen</td>
<td>5-10 mg/kg</td>
<td>Acetaminophen + codeine</td>
<td>No difference</td>
</tr>
<tr>
<td>Stage et al.,1988</td>
<td>Aspirin</td>
<td>1 g qid</td>
<td>Acetaminophen</td>
<td>No difference</td>
</tr>
<tr>
<td>Dommerby and Rasmussen,1984</td>
<td>Aspirin</td>
<td>100, 50, 50 mg</td>
<td>Placebo</td>
<td>No difference</td>
</tr>
<tr>
<td>Reuter and Montgomery,1964</td>
<td>Aspirin</td>
<td>NA</td>
<td>Acetaminophen</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Abbreviations: Analg eff, analgesic efficacy; Coags/Plts, coagulation parameters and platelet counts; DBPRT, double-blinded prospective randomized trial; Hge, hemorrhage; NA, not available; PNRT, prospective nonrandomized trial; PRT, prospective randomized trial; SBPRT, single-blinded prospective randomized trial.
nonaspirin NSAIDs in this series (ibuprofen and diclofenac) did not appear to increase the risk. Nonsteroidal anti-inflammatory drugs are potent analgesics and have been shown to be very effective in postoperative analgesia. 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 prostaglandins including thromboxane A2, a potent platelet aggregator, thereby leading to decreased platelet aggregation and a prolongation of the bleeding time. However, the clinical significance of the increased bleeding risk is not clearly defined. While some studies have shown the risk to be significant, others have not.

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. 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. 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. Therefore, results would be expected to vary from study to study, with differences caused by experimental error and differences in populations.

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). 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 Dattolo19 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 (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). 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 Dattolo19 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 (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). 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 Dattolo19 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 (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). The other NSAIDs studied (ibuprofen and diclofenac) are reversible inhibitors of COX and hence their effects on platelet function are less pronounced.

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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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REFERENCES