Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review

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CRD summary
This well-conduced review assessed the incidence of peri-operative bleeding complications attributable to non-steroidal anti-inflammatory drugs (NSAIDs) in patients undergoing tonsillectomy. Although it was unclear whether NSAIDs increased the incidence of bleeding following tonsillectomy, it was suggested that they should be cautiously used until further studies are conducted. The authors’ conclusion and recommendations for further research are appropriate.

Authors' objectives
To determine the incidence of peri-operative bleeding complications attributable to the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients undergoing tonsillectomy.

Searching
MEDLINE (from 1966 to 2001), EMBASE (from 1989 to 2001) and the Cochrane Controlled Trials Register (2001) were searched for published studies. The search terms were provided and no language restrictions were imposed. The reference lists of identified reports and relevant reviews were checked for additional studies. Studies that were unpublished, or were only published in abstract form, were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of systemically administered NSAIDS compared with a non-NSAID, placebo or no treatment were eligible for inclusion. The NSAIDS evaluated in the included studies were diclofenac, ketorolac, ibuprofen, indomethacin, ketoprofen, tenoxicam, naproxen and nimesulide. Comparator non-NSAIDS were opioids (morphine, pethidine, papaveretum, tramadol, tilidine and codeine), acetaminophen and acetaminophen plus codeine. The dose and mode of administering the NSAID and control varied between the included studies.

Participants included in the review
Studies in children or adult patients undergoing tonsillectomy, with or without adenoidectomy, were eligible for inclusion. Further details of the participants in the individual studies included were not given.

Outcomes assessed in the review
The primary outcome of interest was bleeding complications, including the volume of intra-operative blood loss, the incidence of post-operative bleeding, the incidence of readmission and reoperation due to bleeding. The secondary outcomes were the quality of pain relief and post-operative nausea and vomiting (PONV).

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies for inclusion. It was not stated whether the reviewers were blinded, or how any disagreements were resolved.

Assessment of study quality
The validity of each of the included studies was determined using the Jadad instrument. This scale assigns a score between 1 (lowest quality) and 5 (highest quality) to each study based on its adequacy of randomisation, blinding and withdrawals. Four reviewers independently assessed the validity of the included studies. Any discrepancies were
resolved by discussion.

**Data extraction**

One reviewer extracted the data using a standardised form. A second reviewer checked the data extraction. The data collected included information on the NSAID regimens and comparators, surgical technique, observation periods and primary and secondary outcome measures.

Data on the occurrence of rare events (post-operative bleeding, readmission and reoperation) were extracted from individual studies and used to calculate an odds ratio (OR). Data on the occurrence of frequent events (PONV) were extracted from individual studies and used to calculate a relative risk (RR). Data on the mean volume (mL/kg) of blood loss and standard deviations were extracted from individual studies and used to calculate a weighted mean difference (WMD). For pain relief, data were extracted on the reported statistical significance (P<0.05) of the standardised pain assessments used in the individual studies.

**Methods of synthesis**

How were the studies combined?

The results from individual studies were combined using a fixed-effect meta-analysis. For the results of rare events, a pooled OR was calculated with 95% confidence intervals (CIs) applying two models: first, the Peto-modified Mantel-Haenszel (Peto-OR) was used, which did not include studies with no events; second, in studies where no events occurred in the intervention or control group, 0.5 was added to both groups. In this abstract, results of the Peto-OR will be presented unless significant differences were found, in which case the results of both models will be presented. A pooled RR or WMD with 95% CI were calculated for studies evaluating PONV and intra-operative volume of blood loss, respectively, and forest plots were produced to show the relative efficacy of the treatment effects. When statistically-significant pooled OR, Peto-OR or RR were obtained, the numbers-needed-to-treat (NNT) were calculated along with 95% CIs.

How were differences between studies investigated?

L’Abbe plots were used to explore possible heterogeneity between the included studies. The primary data allowed sensitivity analyses to be performed to determine whether studies reporting primary bleeding (within 24 hours of tonsillectomy) differed from those reporting secondary bleeding (after 24 hours); whether the incidence of post-operative bleeding differed when the NSAID was administered before or after surgery; whether the incidence of reoperation differed when the NSAID was administered before or after surgery; and whether the incidence of reoperation differed depending on the administration of a single-dose or multiple-dose NSAID regimen.

**Results of the review**

Twenty-five RCTs (n=1,853) involving 33 comparisons were included in the analysis, of which 21 were double-blind.

Methodological quality: the median quality score assigned to included studies was 4 (range: 1 to 5).

Intra-operative blood loss: based on 9 RCTs (12 comparisons), no statistically-significant difference between the NSAID (2.1 +/- 0.91 mL/kg) and control (1.8 +/-0.9 mL/kg) groups was found; the WMD was 0.38 (95% CI: -0.81, -0.06).

Incidence of post-operative bleeding: based on 1,304 patients in 16 RCTs (19 comparisons), no statistically-significant difference between the NSAID and control groups was found, with event rates ranging from 0 to almost 30% (Peto-OR 1.30, 95% CI: 0.89, 1.89). This result was independent of the OR model used and no significant difference was found between studies that reported primary compared with secondary bleeding.

Number of readmissions due to bleeding: based on 506 patients in 8 RCTs (9 comparisons), no statistically-significant difference between the NSAID and control groups was found (Peto-OR 2.10, 95% CI: 0.85, 5.19). This result was
independent of the OR model used.

Reoperation due to bleeding: based on 1,626 patients in 21 RCTs (27 comparisons), the likelihood of requiring reoperation due to bleeding was significantly higher in the NSAID group than in the control group (Peto-OR 2.33, 95% CI: 1.12, 4.83, P-value not given). However, when studies with no cases of reoperation due to bleeding were included, there was only a trend towards a statistically-significant difference between the NSAID and control groups (OR 1.92, 95% CI: 1.00, 3.71, P-value not given). The resulting NNT was 60 (95% CI: 34, 277). Sensitivity analyses found the likelihood of reoperation due to bleeding was only statistically significant in patients administered NSAID treatment after surgery (Peto-OR 4.3, 95% CI: 1.69, 11.26); the NNT was 40 (95% CI: 23, 123). This was independent of the OR model used. No statistically-significant difference was found between single- and multiple-dose NSAID regimens.

Pain relief: in 10 of the 11 studies, NSAIDs were associated with statistically-significant improvements in pain relief compared with placebo or no treatment. Compared with opioids, NSAIDs were associated with statistically-significant improvements in pain relief (2 studies) or were no different (5 studies); one study found that opioids were associated with a statistically-significant improvement in pain relief over NSAIDS. No statistically-significant difference in pain relief was found between NSAIDs and acetaminophen (3 studies). Compared with acetaminophen codeine, NSAIDs were associated with statistically-significant improvements in pain relief (1 study) or were no different (1 study); one study found that acetaminophen codeine was associated with a statistically-significant improvement in pain relief over NSAIDS.

PONV: based on 11 RCTs, the risk of PONV was significantly higher in patients receiving an opioid than a NSAID (RR 0.73, 95% CI: 0.63, 0.85); the NNT was 9 (95% CI: 5, 19).

**Authors' conclusions**
It was unclear whether NSAIDs increased the incidence of bleeding following tonsillectomy. However, there was evidence to suggest that the likelihood of reoperation due to bleeding increases when NSAIDs are administered, particularly in the post-operative period. NSAIDs were equianalgesic in comparison with opioids, and they reduced the risk of PONV in this surgical setting.

**CRD commentary**
This is a well-conducted review guided by a clear review question and appropriate inclusion criteria. Several sources were searched to identify potential studies and an attempt was made to reduce language bias. However, the exclusion of abstracts and unpublished work means that publication bias cannot be ruled out. The quality of the included studies was assessed systematically and appropriate procedures were used to minimise bias in the study selection, data extraction and quality assessment processes. The method used to combine the studies was appropriate given that the outcome of interest was rare and the authors considered zero-event studies. The authors performed several sensitivity analyses and acknowledged that shortcomings in the data reported in primary studies prevented analyses (e.g. to differentiate between adults and children). The authors’ conclusion and recommendations for further research are appropriate given the results presented.

**Implications of the review for practice and research**
Practice: The authors stated that NSAIDs should be cautiously used in patients undergoing tonsillectomy until further studies are conducted.

Research: The authors stated that further research is required to compare NSAIDs with cyclo-oxygenase type 2 inhibitors in tonsillectomy, and to evaluate the risk of bleeding associated with NSAIDs in other types of surgery. They recommended that future studies use standard definitions when recording the incidence of peri-operative bleeding.

**Bibliographic details**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.