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Effects of Postoperative, Nonsteroidal, Antiinflammatory Drugs on Bleeding Risk after Tonsillectomy

Meta-analysis of Randomized, Controlled Trials

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TONSILLECTOMY is one of the most common surgical procedures performed on children.[1,2] Postoperative bleeding is rare but can be life threatening. During reoperation for hemostasis, induction of anesthesia is associated with a high risk of pulmonary aspiration and difficult tracheal intubation due to the presence of blood in the upper airway and stomach. The incidence of posttonsillectomy bleeding severe enough to require treatment ranges from 2–10% and that of reoperation for hemostasis ranges from 1–5.5%.[3–6] Many factors are known to contribute to postoperative bleeding, including abnormal preoperative bleeding identified by questionnaire, unusual surgical indications, high postoperative blood pressure, and Sluder technique.[7]

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used in children for their potent antipyretic and analgesic effects. NSAID therapy has been reported to provide effective pain control without opioids after tonsillectomy and other pediatric surgical procedures.[8–10] Tonsillectomy is commonly done on an outpatient basis and is associated with severe postoperative pain.[3] Postoperative pain, nausea, and emesis must be prevented because they cause distress and prolong hospitalization. Vomiting is among the most common reasons for unscheduled readmission after outpatient tonsillectomy.[11,12] NSAIDs are as effective as morphine for pain relief after surgery but are associated with a lower risk of nausea and vomiting. Thus, they are considered the agents of first choice for controlling postoperative pain after pediatric surgery.[8] Two recent postal surveys conducted in the United Kingdom to evaluate pain treatment at home after tonsillectomy for children found that NSAIDs were used in 45–70% of patients.[13,14]

Nevertheless, the ability of NSAIDs to inhibit platelet cyclooxygenase (COX) may be associated with a risk of increased bleeding after tonsillectomy. NSAIDs are widely used in the pediatric population because most children are free of contraindications to these drugs, such as peptic ulcer disease or renal failure. A review of the pediatric literature on bleeding after perioperative NSAID therapy produced inconclusive results.[15] Preoperative NSAID therapy used in prospective studies increased intraoperative blood loss by 70–80% in children undergoing tonsillectomy, requiring additional hemostatic treatment to stop bleeding.[16–19] Moreover, a recent systematic review of preemptive analgesia for postoperative pain relief, including NSAIDs, failed to demonstrate the efficacy of preoperative administration of analgesics.[20] Consequently, there is no evidence to support administration of NSAIDs preoperatively. In retrospective studies, postoperative NSAID therapy increased the incidence of bleeding,[4,21] but this finding was not confirmed in prospective studies.[6,9,10,22–25] We performed a meta-analysis to evaluate the risk of bleeding after tonsillectomy in patients treated postoperatively with NSAIDs.

Materials and Methods

Identification of the Studies

Two electronic databases were searched *via* the Internet for studies published between January 1966 and May 2001: PubMed® (MEDLINE/*Index Medicus*) and the Cochrane Controlled Trials Register published by the Cochrane Library. The medical subject heading terms used for the search were "tonsillectomy," "bleeding," and "NSAIDs." Additional articles were retrieved by clicking on hyperlinks and by manually searching reference lists in original published articles, review articles, and correspondence. Only trials published in English were reviewed. The authors were contacted for addi-

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tional information on the methodology or results for some articles.

Quality Assessment of the Studies

Each study was subjected to a quality assessment by two investigators (E.M. and F.B.), who were not blinded to the authors or results. Disagreements were resolved by discussion. Each article was scored using a five-point scale that evaluates randomization, blinding, and completeness of patient follow-up.[26] One point was given if the study was described as randomized. An additional point was given if the randomization method was described and was appropriate (*e.g.*, computer-generated table of random numbers), whereas one point was subtracted if the randomization method was described and was inappropriate (*e.g.*, alternate allocation or allocation by date of birth). Similarly, one point was assigned to studies described as double-blind, two points were assigned to studies for which the double-blinding method was described and was appropriate (identical placebo, active placebo, double-dummy), and no points were assigned to studies for which the double-blinding method was described and was inappropriate. One point was given if the article specified the numbers of and reasons for withdrawals and dropouts. Thus, the highest possible score was 5. We included studies with a score of 3 or more.

Selection Criteria

Criteria for study selection were as follows: randomized, double-blind design, quality assessment score of 3 or more, population composed of children (age of younger than 16 yr) or adults who underwent tonsillectomy with or without adenoidectomy, NSAID therapy after surgery, report of data on postoperative bleeding, and article in English.

Outcome Measures

The primary evaluation criterion was the need for surgical electrocautery to stop the bleeding. The secondary evaluation criterion was postoperative bleeding requiring a change in postoperative management—*i.e.*, admission to the emergency department, readmission to the hospital, or blood transfusion. Minor postoperative bleeding such as minimal oozing or blood-tinged mucus was not considered clinically relevant and was not examined in this meta-analysis. Bleeding was defined as primary if it occurred within 24 h after surgery and as secondary if it occurred later.

Statistics

When not reported in the article, an intention-to-treat analysis was performed based on the original data. The Mantel–Haenszel procedure was used to pool odds ratios that were assigned weights proportional to the inverse of the within-study odds-ratio variance.[27] We used the heterogeneity statistics as a chi-square (k-1 degree of freedom) following the Armitage formula. Analyses were performed with Microsoft Excel 97 (Microsoft, Redmond, WA). The primary and secondary evaluation criteria were analyzed separately.

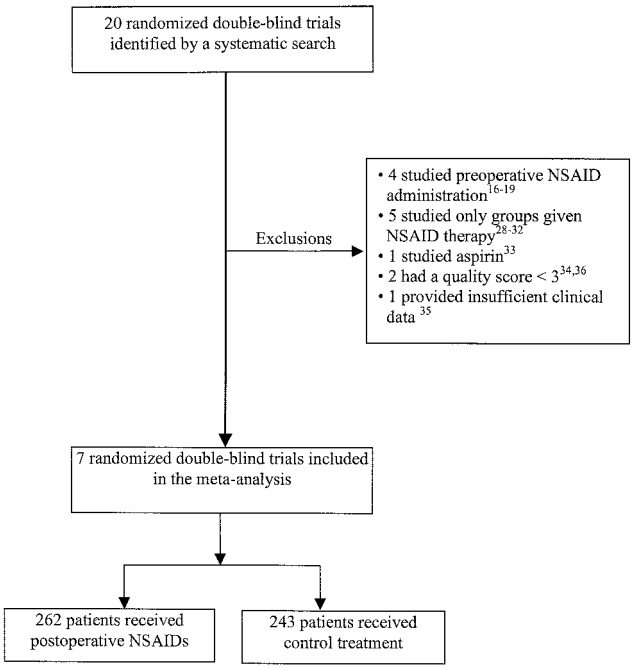

Fig. 1. Flowchart of controlled trials selected for the meta-analysis. NSAID = nonsteroidal antiinflammatory drug.

For the primary evaluation criterion, we computed the number needed to harm as the inverse of the difference of the proportion of patients who required reoperation in the NSAID groups and the control groups. CIs were constructed by inverting and exchanging the limits of the 95% CI for the absolute risk reduction. All tests were two-sided, and *P* values of less than 0.05 were considered statistically significant.

Results

Thirty-seven articles were identified by the MEDLINE search. Of these articles, 30 were excluded for the following reasons: 4 were not in English and were published before 1977; 6 were retrospective; 8 were letters, editorials, or literature reviews; and 12 were randomized, controlled trials (fig. 1) of which 9 involved preoperative NSAID therapy and/or had no control group managed without NSAIDs,[16–19,28–32] 1 reported the effects of aspirin on postoperative bleeding,[33] 1 had a quality score of less than 3,[34] and 1 reported insufficient clinical data.[35] Finally, the MEDLINE search identified seven trials that met our selection criteria[6,9,10,22–25] (fig. 1 and table 1). A manual search of cross-references from the articles identified an additional study, which was excluded because its quality score was less than 3[36] (fig.

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Table 1. Summary of Data from the Seven Studies Included in the Meta-analysis

Study	Age Range (yr)	Patients* (n = 505) NSAID Group	Patients* (n = 505) Control Group	Surgical Dissection Technique	NSAID Type, Dosage or Dose	Route of Administration	Duration of Treatment or No. of Doses	Onset of NSAID Treatment
Bailey et al., 1997[6]	Adults 19–37	37, 29/8	43, 26/17	Electrocautery	Ketorolac, 30 mg	Intramuscularly	First 24 h	Patient's request
Gunter et al., 1995[9]	Children 1–12	49, NR	47, NR	Electrocautery dissection	Ketorolac, 1 mg/kg	Intravenously	One dose	At completion of surgery
Harley and Dattolo, 1998[22]	Children 6–16	16, NR	11, NR	Electrocautery	Ibuprofen, 5 mg · kg^{-1} · 6h^{-1}	Orally	2 wk	At child's discharge to home
Romsing et al., 1998[23]	Children 5–15	20, 6/14	20, 6/14	Electrocautery dissection	Ketorolac, 1 mg/kg	Intravenously	One dose	At completion of surgery
St Charles et al., 1997[10]	Children 1–14	55, 33/22	55, 33/22	Electrodissection (n = 98) or cold dissection-and-snare technique	Ibuprofen, 5 mg · kg^{-1} · 6h^{-1}	Orally	2 wk	In the postanesthesia care unit
Salonen et al., 2001[24]	Adults 17–57	40, 20/20	25, 12/13	Electrodissection	Ketoprofen, 3.5 mg/kg	Intravenously	First 24 h	In the postanesthesia care unit
Sutters et al., 1995[25]	Children older than 7	45, 26/19	42, 22/20	NR	Ketorolac, 1 mg/kg	Intramuscularly	One dose	At completion of surgery

NR = not reported, NSAID = nonsteroidal antiinflammatory drug.

* Data are no. of patients, no. of males/no. of females.

1). The Cochrane Controlled Trials Register search retrieved 53 studies. Only 16 of these trials reported the use of NSAIDs; all 16 had been identified by the MEDLINE search. Thus, a total of 20 randomized, controlled trials studying the effects of NSAIDs after tonsillectomy were identified by our systematic search of the two databases and the manual search of cross-references from the articles (fig. 1). Seven of these 20 trials met our selection criteria and were included in the meta-analysis.

Study Designs, Patients, and Surgical Techniques

All seven randomized, double-blind studies were published in or after 1995 (table 1).[6,9,10,22–25] All patients were screened for preoperative coagulation or bleeding disorders. Two studies were placebo-controlled; they compared preoperative NSAID therapy, postoperative NSAID therapy, and a placebo.

Of the 505 patients in these seven studies, 71% were younger than 16 yr of age. Two trials[6,24] studied the analgesic effect of NSAIDs used as the only pain reliever in 145 adults. Intention-to-treat analysis was done in all seven studies, but surgery was not completed on one patient scheduled for both tonsillectomy and adenoidectomy. Two hundred sixty-two patients received posttonsillectomy NSAID therapy, which consisted of IV or intramuscular ketorolac (151 patients), IV ketoprofen (40 patients), or oral ibuprofen (71 children) (table 1). For the 243 control patients, the agent to which NSAID therapy was compared was saline (n = 87),[23–25] paracetamol plus codeine (n = 66),[10,22] or either morphine or meperidine (n = 90).[6,9] Treatment duration ranged from 24 h to 2 weeks (table 1).

Outcomes

The overall incidences of postoperative bleeding treated medically or surgically and of postoperative bleeding treated surgically were 7.3 and 2.6%, respectively. None of the patients required blood transfusion. The most common consequence of postoperative bleeding was admission to the emergency department. Cases of postoperative bleeding were evenly divided between primary and secondary bleeding. Tests to assess heterogeneity between the seven studies were not significant (figs. 2 and 3). Therefore, trials were considered comparable and combined in a meta-analysis.

Of the 243 patients who did not receive NSAID therapy, 13 had primary or secondary postoperative bleeding (5.3%; range, 0–25%) (fig. 2). In 7 of these 13 controls, the bleeding was secondary. Of the 262 patients who received NSAID therapy postoperatively, 24 (9.2%; range, 0–25%) had postoperative bleeding (odds ratio, 1.8; 95% CI, 0.9–3.4). The bleeding was primary for nine patients in the NSAID group.

Of the 262 patients given NSAID therapy postoperatively, 11 required reoperation for hemostasis. The bleeding was primary in five patients and secondary in six patients (four children and two adults). Two control patients required reoperation for hemostasis. The bleeding was primary in one patient and secondary in one patient. These figures translate into a significant difference in the rate of reoperation for hemostasis, with 0.8% for the controls and 4.2% for the NSAID-treated patients (odds ratio, 3.8; 95% CI, 1.3–11.5; $P = 0.02$) (fig. 3). This indicates a 425% increase in the odds ratio. The number needed to harm was 29 (95% CI, 17–144).

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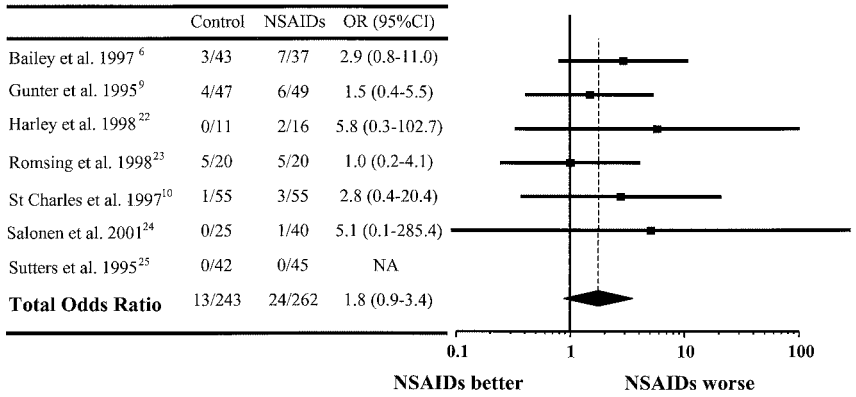

Fig. 2. Effects of postoperative administration of nonsteroidal antiinflammatory drugs (NSAIDs) after tonsillectomy on the relative risk for severe postoperative bleeding. NS = not significant.

OR: Odds ratio. NA: not applicable

Test for heterogeneity χ^2_6=3.07 (p = 0.7; NS)

Discussion

This meta-analysis of seven randomized, controlled trials showed that postoperative NSAID therapy increased both the risk of postoperative bleeding requiring treatment and the risk of reoperation for hemostasis. Several retrospective studies suggested that postoperative NSAID therapy was associated with a greater likelihood of reoperation for hemostasis, but the small prospective studies done to evaluate this point found no significant difference.[6,10,22–25] Six of the seven trials that met our quality criteria for inclusion in this meta-analysis yielded odds ratio of greater than 1 for reoperation for hemostasis, although the differences were not statistically significant (figs. 2 and 3). Moreover, one of these studies suggested an increase in immediate postoperative bleeding.[9] This study was stopped prematurely because the incidence of major immediate bleeding was 10%, as compared with none among the control group. However, the overall incidence of bleeding was similar in the two groups.[9]

Publication bias with underpublication of studies that show no significant difference can limit the validity of meta-analyses.[37] However, it seems reasonable to assume that absence of increased bleeding with NSAID therapy is just as important to clinicians as increased bleeding. Therefore, we assumed that publication bias would be minimal. Support for this assumption came from a careful manual search of abstracts presented at American and European meetings (American Society of Anesthesiology, European Society of Anaesthesiology, and Société Française d'Anesthésie Réanimation) during the study period (1995–2001), which identified no additional studies without increased bleeding in patients given NSAIDs. Furthermore, the aim of many of the studies included in this meta-analysis was to examine the analgesic efficacy of NSAIDs, not their effect on bleeding risk. Four studies concluded that NSAIDs were effective in relieving pain after tonsillectomy. Another potential limitation may be failure to report rare drug-related adverse events. However, our primary evaluation criterion, the need to reoperate for hemostasis, is a major event associated with a high risk of morbidity. This explains why all seven studies described the incidence of reoperation for hemostasis in the NSAID and control groups.

The quality of trials included in a systematic review may alter the results.[38] Moher *et al.*[38] demonstrated that

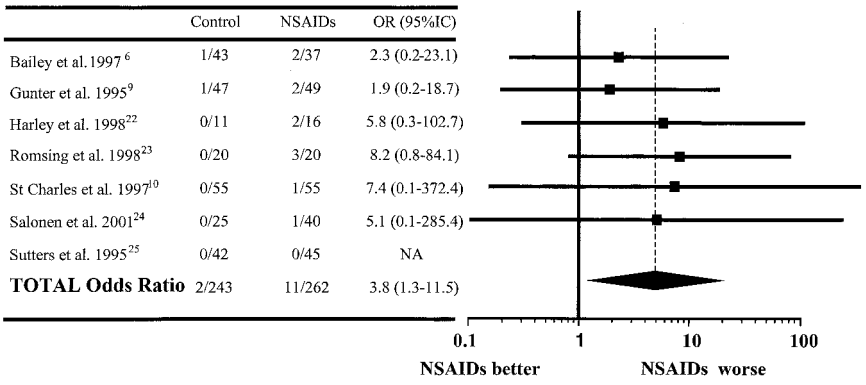

Fig. 3. Effects of postoperative nonsteroidal antiinflammatory drug (NSAID) administration after tonsillectomy on the relative risk for reoperation. NS = not significant.

OR: Odds ratio. NA: not applicable

Test for heterogeneity χ^2_6=1.32 (p = 0.95; NS)

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meta-analyses with low-quality trials (Jadad assessment scale, less than or equal to 2) compared with high-quality trials (assessment scale, more than 2) were associated with an increased estimate of benefit of one third. Similarly, trials using inadequate allocation concealment may also overestimate as much as 37% the benefit of treatment.[38] Therefore, multiple scales have been proposed to assess the quality of trials included in a meta-analysis to decrease bias due to the inclusion of low-quality trials. We used the Jadad composite scale to assess quality using factors such as randomization, double-blinding, and patient withdrawals.[26] Meta-analysis of trials with low quality as evaluated with this scale significantly exaggerate benefits.[38,39] Consequently, all seven trials selected for our systematic review were double-blind and randomized and had a scale reflecting high quality.[38] Different NSAIDs (ketorolac, ketoprofen, and ibuprofen) were used in trials in our systematic review. Ketorolac has been proposed to cause more frequent hemorrhagic complications than other NSAIDs.[40] However, the POINT study, which included 11,245 patients randomized in 49 centers, did not show any statistical difference for surgical site bleeding between patients receiving ketorolac *versus* another NSAID (ketoprofen or diclofenac).[41] Administration of NSAIDs during plastic or ear, nose, and throat surgery significantly increased the risk of surgical site bleeding by 3.45 times in comparison with other types of surgery in this multicenter study.

The risk of gastrointestinal and operative site bleeding, which is the main complication of NSAID therapy, has generated controversy about the use of these agents for postoperative pain relief.[15] However, in a postmarketing study comparing 9,900 patients given ketorolac and 10,247 patients given an opioid, the only risk factors for operative site bleeding were age older than 75 yr, dose higher than 100 mg, and treatment duration longer than 5 days.[42] A subsequent subgroup analysis found no increase in the risk of clinically serious operative site bleeding among the patients operated on by otorhinolaryngologists.[43]

After tonsillectomy, the rate of reoperation for hemostasis ranged from 1–5.5% in cohort and retrospective studies.[3–6] Results for the control groups in the current meta-analysis were in accordance with these figures. In the NSAID groups, in contrast, the risk of bleeding was increased nearly fourfold. In retrospective studies, the rate of reoperation increased from 2.4–7% after a single intraoperative ketorolac dose[44] and from 0.7–5.5% after diclofenac administration at anesthesia induction.[45] Thus, the rate of reoperation for hemostasis was comparable in these retrospective studies and in our meta-analysis. Moreover, in large series, secondary bleeding contributed to most cases of posttonsillectomy bleeding.[3,4,21] In our meta-analysis, 6 of 11 reoperations for hemostasis were in patients with secondary bleeding, although in some NSAID groups the patients received a single NSAID dose. Of the two control patients who underwent reoperation for hemostasis, one had primary bleeding, and the other had secondary bleeding. In the NSAID-treated patients, we also found an increase in medical interventions related to primary and secondary bleeding. Taken together, these data suggest that NSAID-related bleeding occurred both within the first 24 h and later on. Tonsillectomy is frequently performed on an outpatient basis; therefore, analgesic therapy is often given at home.[13] The results of this meta-analysis suggest that use of NSAID therapy after tonsillectomy should be abandoned both at the hospital and at home. Consequently, additional strategies—*e.g.*, local anesthetic infiltration[46] or dissection with high-frequency ultrasound[47,48] that may decrease postoperative pain—should be investigated and may facilitate recovery after tonsillectomy.

We found a number needed to harm of 29 for reoperation for hemostasis, although some patients received a single NSAID dose. The number needed to harm incorporates the side effects of a drug, and the number needed to treat incorporates the benefit of therapy. Our results suggest that use of NSAIDs in 29 patients after tonsillectomy for relief of pain would be accompanied by a hemorrhage severe enough to require reoperation in at least one patient. Reoperation for active tonsillectomy-site bleeding is associated with a high risk of morbidity related to pulmonary aspiration and difficult tracheal intubation. NSAIDs inhibit the enzyme COX, thereby reducing prostaglandin synthesis and inhibiting platelet aggregation.[49,50] Two COX isoenzymes have recently been identified, the constitutive COX-1 isoform expressed in gastric mucosa and platelets and the COX-2 isoform, which is up-regulated during inflammation. However, selective COX-2 inhibitors do not inhibit platelet aggregation *in vitro*.[51] Available studies of NSAID therapy for relieving pain related to tonsillectomy evaluated nonselective COX inhibitors. COX-2 inhibitors may provide similar pain relief without the risk of increased bleeding associated with nonselective COX inhibitors. This, however, will require further investigation to establish. Thus, studies of COX-2 inhibitors after tonsillectomy may be in order.

In conclusion, postoperative use of conventional NSAIDs such as ketorolac, ibuprofen, or ketoprofen increases the risk of reoperation for hemostasis after tonsillectomy. These drugs should not be used after tonsillectomy.

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