I.V. ketoprofen for analgesia after tonsillectomy: comparison of pre- and post-operative administration

A. Salonen[1], H. Kokki[2]* and K. Tuovinen[3]

Departments of [1]Otorhinolaryngology, [2]Anaesthesiology and Intensive Care and [3]Pharmacy, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland

**Corresponding author*

We have evaluated the safety and efficacy of ketoprofen during tonsillectomy in 106 adults receiving standardized anaesthesia. Forty-one patients received ketoprofen 0.5 mg kg^{-1} at induction ('pre' ketoprofen group) and 40 patients after surgery ('post' ketoprofen group), in both cases followed by a continuous ketoprofen infusion of 3 mg kg^{-1} over 24 h; 25 patients received normal saline (placebo group). Oxycodone was used for rescue analgesia. Patients in the ketoprofen groups experienced less pain than those in the placebo group. There was no difference between the study groups in the proportion of patients who were given oxycodone during the first 4 h after surgery. However, during the next 20 h, significantly more patients in the placebo group (96%) received oxycodone compared with patients in the 'pre' ketoprofen group (66%) and the 'post' ketoprofen group (55%) (P=0.002). Patients in the placebo group received significantly more oxycodone doses than patients in the two ketoprofen groups (P=0.001). Two patients (5%) in the 'pre' ketoprofen group and one (3%) in the 'post' ketoprofen group had post-operative bleeding between 4 and 14 h. All three patients required electrocautery.

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Tonsillectomy (with or without adenoidectomy) is the most frequently performed throat surgery in adults. Although generally safe, it is associated with some complications including severe pain, bleeding, protracted vomiting and subsequent dehydration.[1–3] Analgesia after tonsillectomy is often inadequate. The side-effects of opioids, such as emesis, excessive sedation and risk of respiratory depression, can inhibit their use.

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent analgesics and can reduce or even eliminate the need for post-operative opioids.[4] However, they may also cause adverse effects, such as gastric irritation or renal dysfunction. It is also well known that NSAIDs prolong the bleeding time by inhibiting the biosynthesis of thromboxane A_2 and can increase blood loss during and after surgery even in healthy patients.[5]

Ketoprofen, a phenylpropionic acid derivative, has been in clinical use since 1973.[6] It is a widely used analgesic in many countries and has a good safety and efficacy record. A previous study demonstrated the efficacy of ketoprofen after tonsillectomy,[7] but further evaluation of the optimal time of administration and safety of ketoprofen is needed.

The aim of the present study was to evaluate the safety and efficacy of ketoprofen during tonsillectomy. We compared administration of the same dose of ketoprofen, before incision and after surgery, with a placebo group. The main study variables were pain at rest and during swallowing, need for rescue analgesic and the amount of perioperative bleeding.

Materials and methods

This prospective, randomized, double-blind, double-dummy and placebo-controlled study with parallel groups was approved by our Ethics Committee and conducted in accordance with the latest revision of the Declaration of Helsinki. All patients were informed and provided written consent. Patients with a history of severe adverse reactions to NSAIDs, bronchial asthma, kidney or liver dysfunction or bleeding disorders were excluded.

One hundred and six ASA I adult patients undergoing elective tonsillectomy or adenotonsillectomy were studied. Patients were allocated randomly to one of two ketoprofen groups or a placebo group. The allocation was computer

generated and a sealed envelope method was used to ensure blinding. Forty-one patients received ketoprofen at induction ('pre' ketoprofen group) and 40 patients after surgery ('post' ketoprofen group); 25 patients received normal saline (placebo group).

A standardized anaesthetic technique was used. Each patient was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 15 mg, 60 min before induction of anaesthesia. Fentanyl 2 μg kg^{-1} was given intravenously and anaesthesia was induced with thiopental 5 mg kg^{-1}. Neuromuscular blockade was achieved with *cis*-atracurium 0.1 mg kg^{-1}. Anaesthesia was maintained with 2–3% sevoflurane (inspired concentration) in 65% nitrous oxide in oxygen with intermittent positive pressure ventilation. On completion of surgery, neuromuscular blockade was reversed with neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1}. For intraoperative fluid maintenance, all patients were given 0.9% saline 10 ml kg^{-1} h^{-1} and, after surgery, 5% glucose in 0.3% saline 2 ml kg^{-1} h^{-1} until able to tolerate fluids by mouth.

In the 'pre' ketoprofen group, patients were given ketoprofen 0.5 mg kg^{-1} (Ketorin; Orion, Espoo, Finland) intravenously, mixed with 10 ml of normal saline and injected over 5 min after induction of anaesthesia but before surgical incision, and placebo (10 ml normal saline) injected over 5 min in the postanaesthesia care unit (PACU) followed by a continuous i.v. ketoprofen infusion of 3 mg kg^{-1} over 24 h. In the 'post' ketoprofen group, patients were given placebo (10 ml normal saline) after induction, and ketoprofen 0.5 mg kg^{-1} i.v. in the PACU followed by a ketoprofen infusion of 3 mg kg^{-1} over 24 h. In the placebo group, patients were given normal saline after induction and, in the PACU, normal saline infusion. The drug syringes were prepared by a nurse not otherwise involved in the study, ensuring blinding.

All tonsillectomies were performed between 11 a.m. and 2 p.m. by six surgeons with previous experience of over 50 procedures using an electrodissection technique. Blood loss was assessed by visual estimation of blood volume in sponges and the suction bottle. A study nurse recorded the length of surgery.

Pain intensity after surgery was assessed by asking patients to express their pain on a 100 mm visual analogue scale (VAS; 0=no pain, 100=worst possible pain). Pain scores were recorded at rest and on swallowing 1, 2, 3 and 4 h after surgery in the PACU. Thereafter, on the ward, pain scores were recorded at 8 p.m. and 8 a.m., and just before discharge. At discharge, patients were also asked to rate their worst pain and the average level of pain they had experienced on the ward.

Rescue analgesic medication consisted of oxycodone 0.05 mg kg^{-1} i.v. during the first 4 h after surgery (in the PACU) and thereafter 0.1 mg kg^{-1} i.m. (on the ward). Rescue analgesic was given if the pain score at rest was $\geqslant$30. The oxycodone dose was repeated at 15–30 min intervals until the pain had diminished to slight (pain score at rest <30). All rescue analgesic doses were recorded. No other analgesic medication was permitted during the study. Time to the first voiding, nausea and vomiting and all adverse effects were recorded for each patient. Bleeding was classified as minor if medical attention was required and intravenous fluid or suction of the clot was initiated, and major if electrocautery or reoperation was required.

Patients were discharged 24–30 h after surgery when they had no or mild pain, were able to tolerate clear fluids and soft food, had no bleeding and had no nausea or vomiting. On discharge, all patients received a ketoprofen capsule (2 mg kg^{-1}). For post-operative pain relief at home, all patients were given ketoprofen 50 or 100 mg capsules (Ketorin) and were instructed to take two or three capsules over 24 h (3–5 mg kg^{-1} day^{-1}) for 5–10 days. For rescue analgesia at home patients were prescribed Panacod tablets (Sanofi-Winthrop, Solna, Sweden) containing, per tablet, 500 mg paracetamol and 30 mg codeine.

The sample size was based on detecting a difference of $\geqslant$35% in the need for rescue analgesia between the 'pre' and 'post' ketoprofen groups at a 0.05 significance level with 80% power.

Statistical analysis of continuous variables was performed using the Kruskal–Wallis test. The Mann–Whitney test with Bonferonni correction was used for *post hoc* analysis. The χ^2 test was used for categorical variables**.** Correlation between independent variables was tested with the Pearson correlation coefficient. Differences were considered statistically significant when the P value was <0.05. Results are presented as number of cases (%), mean (SD) with 10th and 90th percentiles, correlation coefficient (R) or mean difference (95% confidence intervals (CI)) as appropriate.

Results

Patient characteristics are shown in Table 1. No protocol violations likely to interfere with the study variables were recorded. No patients were withdrawn from the study.

Ketoprofen administration before incision did not increase the amount of blood loss or the duration of surgery and there was no difference between the three study groups in these two variables. However, in the whole study population the amount of intraoperative blood loss correlated positively with the duration of surgery (R=0.45, P=0.001) (Table 1).

Thirty-four patients (83%) in the 'pre' ketoprofen group, 34 (85%) in the 'post' ketoprofen group and all 25 in the placebo group received rescue analgesia. There was no difference between the study groups with respect to the proportion of patients receiving oxycodone in the PACU. During the next 20 h, significantly more patients in the placebo group (24 patients (96%)) received oxycodone compared with the 'pre' ketoprofen group (27 patients (66%)) (difference 30%, 95% CI: 14–47%) and with the

Table 1 Patients and surgery characteristics: mean (SD) with 10th/90th percentiles or the number of patients. There were no significant differences between study groups.

	'Pre' ketoprofen group (*n*=41)	**'Post' ketoprofen group (*n*=40)**	**Placebo group (*n*=25)**
Sex (male/female)	17/24	20/20	12/13
Age (yr)	31 (17–59)	29 (17–56)	29 (17–57)
	17–49	18–43	17–51
Height (cm)	172 (9)	173 (9)	172 (11)
	160–186	160–186	158–186
Weight (kg)	72 (14)	74 (15)	70 (14)
	55–92	57–97	53–90
Duration of surgery (min)	24 (15)	23 (13)	24 (9)
	10–50	10–37	15–37
Blood loss (ml)	22 (26)	30 (40)	42 (41)
	2–58	1–100	3–100

Table 2 Number of oxycodone doses during the first 24 h after surgery: mean (SD). *Significantly different from 'pre' ketoprofen (P=0.03) and post-ketoprofen (P=0.036). **Significantly different (P<0.01) from 'pre' ketoprofen and post-ketoprofen (Mann–Whitney test with Bonferroni correction)

	'Pre' ketoprofen (*n*=41)	**'Post' ketoprofen (*n*=40)**	**Placebo (*n*=25)**
Early: 0–4 h	1.5 (1.2)	1.5 (1.4)	2.7 (2.0)*
Late: 5–24 h	1.5 (1.8)	1.5 (2.0)	2.9 (1.7)**
Total	3.0 (2.5)	3.1 (2.9)	5.6 (1.7)**

'post' ketoprofen group (22 patients (55%)) (difference 41%, 95% CI: 24–58%) (P=0.002).

There was no statistically significant difference between the two ketoprofen groups with respect to the mean dose of rescue analgesia, but patients in the placebo group received significantly more oxycodone doses than patients in the two ketoprofen groups (P=0.001). The mean difference between the placebo group and the other two groups was the same ('pre' ketoprofen group, 2.6 (95% CI: 1.3–3.9) doses; 'post' ketoprofen group, 2.6 (95% CI: 1.1–4.0) doses) (Table 2).

Patients in the two ketoprofen groups experienced less pain than those in the placebo group (Figure 1). The occurrence of insufficient pain relief (defined as a VAS score of >30 mm at rest and >50 mm on swallowing) was significantly more common in patients receiving placebo than in those receiving ketoprofen (P=0.001) (Figure 2). The worst pain at rest and on swallowing was less in both ketoprofen groups than in the placebo group (P<0.03). A similar difference was observed in mean pain scores (Figure 3).

There was no difference between the study groups in the time to first voiding after surgery (data not shown). Thirty-seven patients (35%) developed adverse effects, none of which were serious. The incidence was similar in the three groups (Table 3). Clinically significant bleeding occurred in two patients (5%) in the 'pre' ketoprofen group, one (3%) in the 'post' ketoprofen group, and none in the placebo group. All three patients needed electrocautery under local anaesthesia to stop bleeding. Bleeding was observed 4 and 8 h after surgery in the 'pre' ketoprofen group and 14 h after surgery in

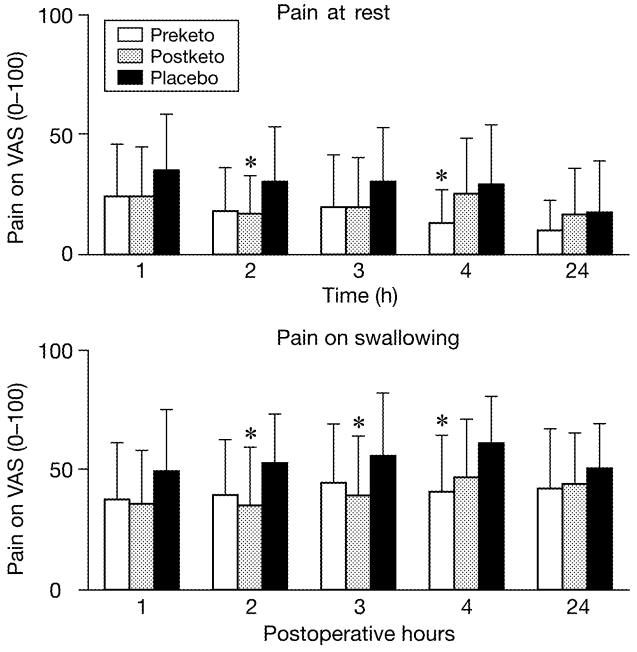

Fig 1 Mean (SD) VAS pain scores at rest and on swallowing for the study groups at various times after surgery. *Placebo group significantly different (P<0.05) from both ketoprofen groups (Mann–Whitney test with Bonferroni correction).

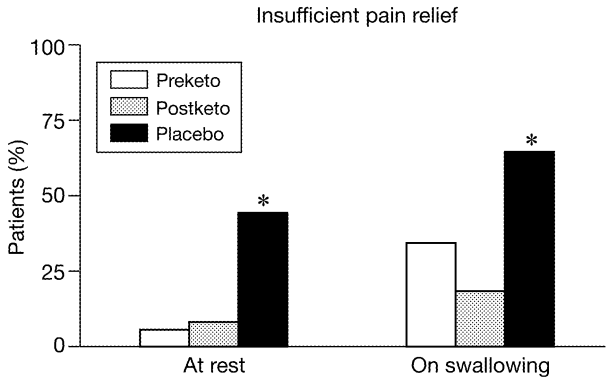

Fig 2 The proportion of patients with insufficient pain relief, defined as a VAS pain score >30 mm at rest and >50 mm on swallowing, in the study groups. *Placebo group significantly different (P=0.001) from both ketoprofen groups (χ^2 test).

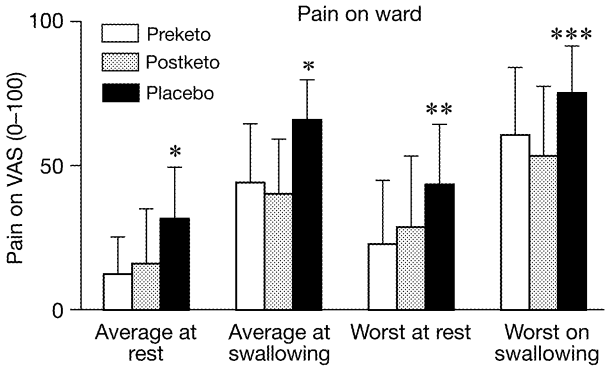

Fig 3 Mean (SD) VAS pain scores for average and worst pain at rest and on swallowing on ward during the first 24 h after surgery in the study groups. *Placebo group significantly different (P=0.001) from both ketoprofen groups; **placebo group significantly different from 'pre' ketoprofen group (P=0.001) and 'post' ketoprofen group (P=0.03); ***placebo group significantly different from 'pre' ketoprofen group (P=0.02) and 'post' ketoprofen group (P=0.001) (Mann–Whitney test with Bonferroni correction).

the 'post' ketoprofen group. No blood transfusions were required.

Discussion

In this study, ketoprofen was associated with an opioid sparing effect and patients receiving it were in less pain, as shown by others.[7] However, no pre-emptive effect was found: recovery was similar when ketoprofen was administered before or after surgery.

Pre-emptive or proactive administration of NSAIDs is justified because of the delayed action of these drugs. However, in this study, ketoprofen administered after surgery performed as well as the same dose administered before incision. This is consistent with assumptions that, in addition to its peripheral action, ketoprofen has a rapid central analgesic action.[8]

Table 3 Adverse effects after tonsillectomy in the study groups (number (%))

	'Pre' ketoprofen (n=41)	'Post' ketoprofen (n=40)	Placebo (n=25)
Vomiting			
Early: 0–4 h	3 (7%)	1 (3%)	1 (4%)
Late: 5–24 h	11 (27%)	7 (18%)	5 (20%)
Recurrent: ⩾3 episodes	2 (5%)	2 (5%)	1 (4%)
Total	12 (29%)	7 (18%)	5 (20%)
Nausea without vomiting	3 (7%)	5 (13%)	2 (8%)
Headache	–	–	1 (4%)
Pruritus	1 (2%)	–	–
Excessively sedated	–	–	2 (8%)
Patients with one or more adverse effects	15 (37%)	13 (33%)	9 (36%)

NSAIDs increase bleeding time but usually within normal limits.[9] The reduction in thromboxane A_2 biosynthesis produced by NSAIDs prevents platelet aggregation and therefore inhibits haemostasis. Whether or not the increase in blood loss during surgery is clinically significant is controversial. Ketoprofen has been used successfully in children undergoing adenoidectomy without any major peri-operative bleeding.[10] The safety of ketoprofen during throat surgery may be supported by the present study, as no significant differences were found between the study groups in the amount of peri-operative bleeding. Post-tonsillectomy haemorrhage continues to pose serious problems. Over the years, the incidence of significant bleeding has decreased, but it still occurs in approximately 2–3% of patients.[11–16] In contrast to two recent studies where peri-operative use of ketoprofen did not cause post-operative bleeding,[7 17] three cases of haemorrhage occurred 4–14 h after surgery in our study. Most studies have investigated small numbers of patients, introducing a large risk of type II error. However, some conclusions may be drawn. (i) Studies suggest that the risk of bleeding varies between different NSAIDS. In many studies, ketorolac has been associated with a higher incidence of bleeding than propionic acid derivatives (ibuprofen, naproxen or ketoprofen).[7 10 15 18–25] (ii) Post-tonsillectomy bleeding seems to occur with a similar incidence when paracetamol (with or without codeine) is used instead of propionic acid derivatives.[20 26–31] (iii) When opioids are used alone, bleeding still occurs.[7 21–24] Moreover, when opioids are used without background analgesia, post-operative nausea and vomiting are common. This may delay discharge.[24 29] (iv) Nerve blocks and periotonsillar infiltrations with local anaesthetics have not improved anaesthesia after tonsillectomy and studies have shown that post-operative bleeding occurs as often as with other analgesic techniques.[27 28 31] (v) Unlike Stoeckli and colleagues,[32] we supposed that fibrin glue did not decrease post-operative pain and bleeding.

Vomiting is common after tonsillectomy and may be induced not only by swallowed blood and oropharyngeal irritation but also by opioids.[7 33] We did not find any

difference between the groups with respect to the incidence of vomiting, but overall it was less than reported previously.[33] Opioids may have different emetic properties. We have found that fentanyl induces less vomiting than morphine.[34] The present study suggests that oxycodone is also associated with a fairly low incidence of vomiting, as only 23% of our patients vomited, compared with 41% in a previous study.[33]

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