I.v. intraoperative ketoprofen in small children during adenoidectomy: a dose-finding study

H. Kokki, E. Nikanne and K. Tuovinen

Summary

We have investigated if a low dose of ketoprofen (0.3 mg kg⁻¹) i.v., provided as good analgesia with less adverse effects than higher doses (1.0 and 3.0 mg kg⁻¹) in 220 children, aged 1–7 yr, undergoing adenoidectomy, in a prospective, randomized, double-blind, placebo-controlled, parallel group study. The postoperative analgesic effect was notable even after the lowest dose of ketoprofen. However, the higher doses seemed to provide better analgesia with no increase in adverse events or intraoperative bleeding. None of the children experienced postoperative bleeding which would have required intervention or delayed discharge from hospital. This study confirms the efficacy and safety of intraoperative ketoprofen in children during adenoidectomy. (Br. J. Anaesth. 1998; 81: 870–874).

Keywords: pain, postoperative; analgesics non-opioid, ketoprofen; analgesia, pre-emptive; analgesia, paediatric; surgery, otolaryngological

After day-case surgery, children need to be free from pain and alert when leaving hospital. Analgesia should be initiated with an effective drug which has the lowest incidence of adverse events after adenoidectomy. Opioids, although potent analgesics, can produce emesis, excessive sedation and respiratory depression. Non-steroidal anti-inflammatory drugs (NSAID) can eliminate the need for opioids after operation in children. However, NSAID can cause gastrointestinal and renal dysfunction. They also prolong the bleeding time and so can increase postoperative blood loss.

Ketoprofen is a NSAID which belongs to the same group of phenylpropionic acid derivatives as ibuprofen and naproxen. It has been in clinical use since 1974. In many countries, ketoprofen is available for i.v. administration; this may be useful during the intraoperative period. Adenoidectomy is one of the most common surgical procedures in childhood and it is frequently carried out as a day-case procedure. In our previous studies, we have proved that intraoperative ketoprofen i.v. provides good background analgesia with a low incidence of adverse effects after adenoidectomy in small children. To date, the optimal dose of ketoprofen for children in the treatment of postoperative pain is unknown.

In this study, we have determined if a low dose of ketoprofen i.v. provided good analgesia with less adverse effects than higher doses in children aged 1–7 yr after adenoidectomy. Doses of ketoprofen 0.3, 1.0 and 3.0 mg kg⁻¹ were compared with placebo; doses of 0.3 mg kg⁻¹ and 3.0 mg kg⁻¹ have not been studied previously. It was of interest to see if this high dose would enhance efficacy without increasing adverse effects.

Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the Declaration of Helsinki. The parents of all patients gave written informed consent. The National Agency for Medicine approved the use of ketoprofen in children less than 20 kg.

We studied 220 ASA I–II patients, aged 1–7 yr, undergoing adenoidectomy (with or without myringotomy, tympanostomy or sinus lavage). Patients were excluded if they had a known allergy to ketoprofen or any other NSAID, asthma, kidney or liver dysfunction, or a haemorrhagic diathesis. We used a prospective, randomized, double-blind, placebo-controlled, parallel group study design. Children were allocated randomly to one of three ketoprofen groups or a placebo group. Fentanyl i.v. was available for rescue analgesia. A block randomization method was used to keep the number of children equal in all groups. After induction of anaesthesia, children in the ketoprofen groups received ketoprofen 0.3 mg kg⁻¹ (group 0.3), 1.0 mg kg⁻¹ (group 1.0) or 3.0 mg kg⁻¹ (group 3.0) dissolved in 10 ml of 0.9% saline, injected i.v. over 5 min. Children in the placebo group received a similar volume of 0.9% saline. The number of children in each group was 55.

A standard anaesthetic technique was used. Each child was premedicated with diazepam 0.5 mg kg⁻¹ orally up to a maximum of 10 mg, 30–45 min before induction of anaesthesia. EMLA cream (Astra, Sweden) was applied to the skin 60 min before venepuncture. Anaesthesia was induced with thiopental (thiopentone) 5–7 mg kg⁻¹ and fentanyl 1 μg kg⁻¹, and tracheal intubation was facilitated with atracurium 0.5 mg kg⁻¹. Anaesthesia was maintained with 1–1.5% isoflurane (inspired concentration) and 65% nitrous oxide in oxygen with IPPV. On completion of the procedure, neuromuscular block was reversed with neostigmine 0.05 mg kg⁻¹ i.v. and atropine 0.01 mg kg⁻¹ i.v. Children were extubated and transferred to the postanaesthetic care unit. Postoperative analgesia was provided with ketorolac 0.5 mg kg⁻¹ i.m. if needed. Fentanyl i.v. was available for rescue analgesia.

Keywords: pain, postoperative; analgesics non-opioid, ketoprofen; analgesia, pre-emptive; analgesia, paediatric; surgery, otolaryngological

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antibiotics the chi-square test was used.

with Bonferonni correction was used. For categorical

variables the Kruskal–Wallis

were not normally distributed, analysis of continuous

post hoc

was performed using the Maunuksela score. 6 The Maunuksela score is an

M/F 55/0 52/3 52/3 52/3

Age (months) 41 (15–79) 40 (18–74) 32 (15–85) 32 (15–72)

Weight (kg) 15 (11–24) 15 (11–25) 14 (11–23) 14 (10–24)

Height (cm) 98 (80–123) 96 (81–120) 92 (78–125) 92 (79–118)

ASA (I/II) 55/0 52/3 52/3 52/3

considered statistically significant. Results are presented as number of cases (%) or median (10th and 90th percentiles), as appropriate.

Results

Sex distribution, age, weight, height and ASA status were similar in the four groups (table 1).

The number of children who needed fentanyl in the PACU was smallest in group 3.0 and significantly different compared with the placebo group ($P=0.01$). In the placebo group, 45 (82%) children were given fentanyl compared with 36 (65%), 34 (62%) and 29 (53%) in groups 0.3, 1.0 and 3.0, respectively. The number of fentanyl doses needed in the PACU was smaller in all ketoprofen groups compared with the placebo group ($P=0.01–0.001$). The number of children who needed more than two fentanyl doses in the PACU was significantly less in all ketoprofen groups compared with the placebo group. There was no significant difference between the ketoprofen groups (fig. 1).

Of those children who were administered fentanyl in the PACU, fewer doses were needed in group 1.0 ($P=0.029$) and group 3.0 ($P=0.003$) compared with the placebo group. The proportion of children who were administered more than two doses of fentanyl was less in group 1.0 ($P=0.033$) and group 3.0 ($P=0.006$) compared with the placebo group.

Time to the first dose of fentanyl in the PACU was longer in the ketoprofen groups than in the placebo group, but this difference was not statistically significant ($P=0.08$): 22 (10th and 90th percentiles 8–57) min in the placebo group and 27 (10–73) min, 33 (13–76) min and 30 (16–82) min in groups 0.3, 1.0 and 3.0, respectively.

Maunuksela pain scores observed during swallowing, 2 h after surgery, were lower in group 3.0 compared with the placebo group ($P=0.046$). The worst pain at rest in the PACU was also lower in group 3.0 compared with the placebo group ($P=0.014$) (table 2).

The surgeon estimated the amount of intraoperative bleeding using a five-point scale. Although children in group 0.3 were estimated to bleed more than children in the placebo group, the difference was not significant ($P=0.055$) (table 3). One child in group 3.0 had epistaxis in the PACU but it stopped without intervention. No child experienced postoperative bleeding which would have required intervention or reoperation, or which would have caused delay in discharge from hospital.

In the PACU, there were no differences in the incidence or distribution of adverse effects between groups (table 4). There were no serious adverse

<table>
<thead>
<tr>
<th>Sex (M/F)</th>
<th>Placebo (n=55)</th>
<th>Ketoprofen Group 0.3 (n=55)</th>
<th>Ketoprofen Group 1.0 (n=55)</th>
<th>Ketoprofen Group 3.0 (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/27</td>
<td>34/21</td>
<td>32/23</td>
<td>33/22</td>
<td></td>
</tr>
<tr>
<td>98 (80–123)</td>
<td>96 (81–120)</td>
<td>92 (78–125)</td>
<td>92 (79–118)</td>
<td></td>
</tr>
<tr>
<td>41 (15–79)</td>
<td>40 (18–74)</td>
<td>32 (15–85)</td>
<td>32 (15–72)</td>
<td></td>
</tr>
<tr>
<td>55/0</td>
<td>52/3</td>
<td>52/3</td>
<td>52/3</td>
<td></td>
</tr>
</tbody>
</table>
events and the medication was not discontinued in any patient.

Administration of fentanyl had an impact on the incidence of adverse effects and episodes of vomiting. Seven children (9%) who did not receive fentanyl in the PACU had adverse effects compared with 30 children (21%) who did (P = 0.012). The number of vomiting episodes was four of 76 children who did not receive fentanyl and 19 of 144 children who did (P = 0.032). Those children who did not receive fentanyl had lower pain scores during swallowing (0(0–1)) on leaving hospital than those who were given fentanyl (0(0–2)) in the PACU (P = 0.035).

Discussion

In this study, we have shown that the use of ketoprofen reduced the number of doses of fentanyl needed in the PACU. The proportion of children who needed fentanyl in the PACU was also smaller if they had received ketoprofen. The differences were statistically significant after a dose of ketoprofen 3.0 mg kg\(^{-1}\) compared with placebo, but the tendency was present after the smaller doses. Further, in those children who required fentanyl, the number of fentanyl doses was smaller if ketoprofen had been administered. Our data suggest that ketoprofen i.v. provides effective background analgesia with all of the doses used in this study. It also has a significant opioid-sparing effect. The analgesic effect was enhanced with the higher doses, but even the smallest dose had a significant effect in reducing the requirement for fentanyl.

In this study, we used a placebo-controlled method. The use of a placebo group was ethical as all children in pain were administered fentanyl for rescue analgesia, and before discharge all children receive a ketoprofen tablet (2 mg kg\(^{-1}\)). The worst pain at rest in the PACU was assessed as less in those children who had received a high dose of ketoprofen. These children also experienced less pain during swallowing 2 h after operation. This difference was not seen 1 h after operation. The relatively slow onset of analgesic effect has also been shown in previous studies with ketoprofen and other analgesics which act via inhibition of prostaglandin synthesis.\(^{1,3,7}\)

NSAID are known to prolong bleeding time by inhibiting cyclo-oxygenase which leads to inhibition of platelet thromboxane A2 production and platelet aggregation.\(^{2}\) Perioperative ketorolac has been studied widely in the treatment of postoperative pain in children. Increased perioperative bleeding has been shown to occur with ketorolac 1 mg kg\(^{-1}\).\(^{8,9}\) In our previous studies with ketoprofen, only one child experienced postoperative bleeding.\(^{4,5}\) This child received ketoprofen 2.0 mg kg\(^{-1}\) and was observed for a few hours before discharge. In none of our three studies of 491 children has postoperative bleeding occurred which would have required intervention or overnight admission to hospital. These results may indicate the

![Figure 1](image-url)  
**Figure 1** Number of fentanyl doses during the first 2 h in the post-anaesthesia care unit in the ketoprofen groups (ketoprofen 0.3 mg kg\(^{-1}\) (group 0.3), 1.0 mg kg\(^{-1}\) (group 1.0) and 3.0 mg kg\(^{-1}\) (group 3.0)) and in the placebo group. Placebo vs group 0.3, P = 0.01; placebo vs group 1.0 and group 3.0, P = 0.001 (Mann–Whitney test with Bonferroni correction).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Maunuksela pain scores in the post-anaesthesia care unit (PACU) (median (10th and 90th percentiles)).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>Placebo ((n=55))</td>
</tr>
<tr>
<td>After 1 h</td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>1 (0–8)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>4 (0–8)</td>
</tr>
<tr>
<td>After 2 h</td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>0 (0–6)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>1 (0–7)</td>
</tr>
<tr>
<td>On leaving the PACU</td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Worst pain in the PACU</td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>4 (0–8)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>5 (0–8)</td>
</tr>
</tbody>
</table>
different effects of NSAID on platelet function and are worthy of further study. Inhibition of maximal platelet aggregation and platelet thromboxane synthesis has been shown to be dose related with ketoprofen and ibuprofen. In our previous study, intraoperative bleeding was estimated to be greater in children who received ketoprofen 2 mg kg\(^{-1}\) than in those who received placebo. In the present study, only children who received ketoprofen 0.3 mg kg\(^{-1}\) had slightly more intraoperative bleeding compared with those who received placebo. This difference was not seen after ketoprofen 1.0 or 3.0 mg kg\(^{-1}\). Therefore, the tendency to dose related intraoperative bleeding was not seen in our studies. However, in our studies, intraoperative bleeding was estimated by the surgeon using a five-point scale. Obviously, this method may neglect minor differences in intraoperative bleeding and more exact methods should be used in future studies.

In previous studies with ketoprofen, the incidence of adverse effects varied from 0% to 50%. In our study, 14% of children receiving ketoprofen and 16% of children receiving placebo had one or more adverse effects. There were no serious adverse events. The incidence and scale of adverse effects in our study were comparable with earlier reports of short-term use of NSAID in children. Based on this study and earlier studies, we can confirm the safety of i.v. ketoprofen in children during adenoidectomy.

In day-case surgery in children, it is necessary that parents feel safe to leave hospital with their child. Children should therefore be painfree and alert. Pain and nausea and vomiting are common problems after adenotonsillar surgery in children and can delay discharge. In this study, children had less vomiting and fewer adverse effects if they were not given fentanyl in the PACU. Pain scores were minimal in all groups by discharge. However, on leaving hospital, children who were not given fentanyl had even lower pain scores during swallowing. These results support the use of NSAID in day-case surgery in children because of their opioid-sparing effect.

In our studies, we have used intraoperative ketoprofen i.v. doses of 0.3–3.0 mg kg\(^{-1}\). For routine use, we recommend a dose of 1 mg kg\(^{-1}\). The higher ketoprofen doses seem to provide better analgesia without any increase in adverse effects or perioperative bleeding. Hence when severe postoperative pain is expected after surgery, higher doses or repeated doses can be used safely. On the other hand, even the lowest doses seem to provide effective background analgesia. This finding should be considered in children undergoing surgery accompanied by a higher risk of intraoperative bleeding and in children who are expected to have any reduction in haemostatic function. In children with a high risk of bleeding, it is appropriate to use alternative agents (e.g. paracetamol).

In our opinion, based on this and our previous studies, ketoprofen i.v. is a potent analgesic for use in children undergoing day-case surgery. It provides effective background analgesia after adenoidectomy without any adverse effects or perioperative bleeding.

### References

5. Nikanne E, Kokki H, Tuovinen K. Comparison of a dose of 2.0 mg kg\(^{-1}\) with a dose of 0.5 mg kg\(^{-1}\) i.v. perioperative ketoprofen in small children during adenoidectomy. *British Journal of Anaesthesia* 1997; 79: 606–608.


