Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children

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Background. The analgesics used for paediatric tonsillectomy may be associated with side-effects such as sedation, respiratory depression and vomiting (opioids) or increased bleeding [non-steroidal anti-inflammatory drugs (NSAIDs)]. In our institution, we employ a combination of paracetamol, NSAID and opioid, although there is no published evidence of analgesic benefit from adding NSAIDs to paracetamol in children.

Methods. This randomized, double-blinded clinical study examined the analgesic effectiveness of combining paracetamol (20 mg kg⁻¹) with rofecoxib (0.625 mg kg⁻¹), ibuprofen (5 mg kg⁻¹) or placebo as premedication for (adenotonsillectomy (n=98) in children aged 3–15 yr. Intravenous fentanyl 1–2 μg kg⁻¹ was given intraoperatively. Regular oral paracetamol (15 mg kg⁻¹, 4 hourly) was given after operation and could be supplemented on request from the child with oral ibuprofen 5 mg kg⁻¹ or oral codeine 1 mg kg⁻¹. The primary outcome variable was need for early supplementary analgesia (within 2 h after surgery).

Results. The addition of ibuprofen to paracetamol reduced the need for early analgesia from 72% to 38% of children (difference 34%; 95% confidence interval 4–64%). The addition of rofecoxib to paracetamol did not significantly alter the need for early analgesia (68 vs 72%). Pain scores were higher in those children who required early analgesia. There were no differences between the groups in operative blood loss or complications, total 24-h analgesic consumption, pain scores at 4 and 8 h, vomiting or antiemetic use.

Conclusion. This study provides evidence to support the combination of ibuprofen (but not rofecoxib) with paracetamol for perioperative analgesia in children.

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and is often used to provide a background of analgesia after surgery, but appears to be insufficiently potent if used alone for tonsillectomy pain.11

The current practice in our unit is to use a balanced approach12 with a combination of regular paracetamol and NSAIDs plus opioid as needed to provide perioperative analgesia for tonsillectomy.13 However, there is no published evidence to support the use of NSAIDs with paracetamol for perioperative analgesia in children. A recent study of children after appendectomy failed to show any additional morphine-sparing effect from combining paracetamol with diclofenac.14 This contrasts with an adult study, which showed the combination of paracetamol and diclofenac to reduce postoperative morphine consumption compared with either drug alone.15

The recently introduced cyclo-oxygenase type 2 (COX-2) inhibitors, such as rofecoxib,16 may have advantages for analgesia in paediatric tonsillectomy. They have analgesic power equivalent to that of NSAIDs for dental extraction pain.17 18 Their COX-2 selectivity produces minimal effect on platelet aggregation. In addition, rofecoxib has a syrup formulation, excellent oral bioavailability and a half-life of 17 h, allowing once-daily dosing. These properties potentially make it a good candidate for perioperative use in paediatrics to help reduce ‘tears at bedtime’.19 Currently, there are no pharmacokinetic or pharmacodynamic data on the use of COX-2 antagonists in children. Rofecoxib 50 mg has been shown to be equianalgesic to ibuprofen 400 mg in the adult dental pain model.17 We have used this measure of the potency of rofecoxib to estimate an equianalgesic paediatric dose (0.625 mg kg⁻¹) as being one-eighth of the paediatric ibuprofen dose (5 mg kg⁻¹).

The aim of our randomized, double-blinded, placebo-controlled pragmatic clinical study was to examine whether combining a NSAID (ibuprofen 5 mg kg⁻¹) or COX-2 antagonist (rofecoxib 0.625 mg kg⁻¹) with paracetamol (20 mg kg⁻¹) before paediatric tonsillectomy would confer analgesic benefits without increasing intraoperative blood loss.

Methods

The study was approved by the hospital ethics committee. A Clinical Trials Exemption certificate was obtained from the Medicines Control Agency of the UK to allow the use of rofecoxib as an analgesic in children. After written informed parental consent and verbal child assent had been obtained, 103 children, ASA I or II, aged 3–15 yr, presenting for elective tonsillectomy or adenotonsillectomy, were entered in the trial. Using a computer-generated random number table, a hospital pharmacist allocated the children randomly to three groups: placebo, rofecoxib or ibuprofen. Both the patients and the investigators were blinded to the study group assignment. Exclusion criteria were sensitivity to NSAIDs, bleeding diathesis, renal or hepatic impairment and severe asthma (requiring recent hospital admission or oral corticosteroid therapy). On enrolment in the study, the children were familiarized with the Oucher visual analogue pain scale, which has been validated in children20 and used previously to score tonsillectomy pain.21

The children were premedicated 1 h before surgery with paracetamol syrup 20 mg kg⁻¹ and either placebo, ibuprofen 5 mg kg⁻¹ or rofecoxib 0.625 mg kg⁻¹ (syrups 0.25 ml kg⁻¹ to a maximum of 10 ml). Therefore, the maximum dose was ibuprofen 200 mg or rofecoxib 25 mg. Induction of anaesthesia was with propofol or sevoflurane and the airway was secured with a reinforced laryngeal mask (53% of children) or endotracheal tube (47%). Atracurium 0.5 mg kg⁻¹ was used to facilitate intubation. Anaesthesia was maintained with isoflurane in 33% oxygen/67% nitrous oxide and intraoperative analgesia was provided with fentanyl 1–2 μg kg⁻¹. No NSAIDs, paracetamol or prophylactic antiemetic were given in theatre. Intraoperative blood loss was assessed by weighing swabs (assuming 1 g=1 ml blood) and by measuring losses to calibrated suction bottles.

A standardized postoperative analgesic regimen was prescribed of regular paracetamol (15 mg kg⁻¹, 4 hourly) with oral ibuprofen (5 mg kg⁻¹) or oral codeine (1 mg kg⁻¹) to be administered at the child’s request by the ward nursing staff. Pain was scored whenever supplementary analgesia was administered and also 4 and 8 h after premedication, when the first two postoperative doses of paracetamol were given. Children were considered to have required early supplementary analgesia if they received either ibuprofen or codeine within 2 h after surgery. Children were discharged home the day after surgery.

The primary outcome variable was the need for early postoperative analgesia. Secondary outcome variables were intraoperative blood loss, time to first postoperative analgesia, Oucher pain scores, analgesic consumption in the first 24 h, vomiting, antiemetic use and incidence of primary and secondary haemorrhage. The data were collected by the anaesthetist, theatre and ward nurses and subsequently validated by review of the clinical notes.

Differences among groups were compared using the Kruskal–Wallis test for non-parametric data, one-way analysis of variance for parametric data and the χ² test or Fisher’s exact test for nominal data. P<0.05 was considered significant. A sample size calculation based on audit data from our hospital showed that 60% of children premedicated with paracetamol and receiving rectal diclofenac intraoperatively required early postoperative analgesia. Therefore, to show a 50% reduction in the need for early analgesia in the rofecoxib group, we estimated that 42 patients were required per group (power of 80% and P<0.05). To minimize the size of the placebo group, a blinded interim analysis was planned by the statistician at the halfway point. If this showed a greater need for early postoperative analgesia in the placebo group than the ibuprofen group, then recruitment to the placebo group would cease.
Results

Of the 103 children recruited, five were excluded because of protocol violations (two were too young and three received diclofenac in theatre). The patient and surgical characteristics were comparable across the groups (Table 1). There were no differences in the time from premedication to the start of surgery [78 (29) min; pooled mean (SD)], operation type (tonsillectomy or adenotonsillectomy), duration of surgery or dose of intraoperative fentanyl (Table 1).

The interim blinded analysis showed that more children in the placebo group received early postoperative analgesia than in the ibuprofen group (72% vs 38%; difference 34%, 95% confidence interval 24–44%). Therefore recruitment to the placebo group was stopped at 18 children. Significantly more children required early analgesia (within 2 h after surgery) in the rofecoxib group compared with the ibuprofen group (68% vs 43%; difference 25%, 95% confidence interval 14–40%) (Table 2). The pain scores at the time of administration of supplementary analgesia were significantly higher in those children requesting early rescue (Table 2).

There was greater surgical blood loss in children having adenotonsillectomy than in those having tonsillectomy [median (interquartile range) 2.6 (1.6–3.9) vs 0.71 (0.31–1.4); P<0.0001]. There was no significant difference between the treatment groups in blood loss for either tonsillectomy or adenotonsillectomy (Fig. 1), nor was there any difference in the incidence of primary (bleeding requiring intervention within 24 h) or secondary (bleeding requiring readmission) haemorrhage (Table 2). Two of the children required a second operation to achieve adequate haemostasis (one each in the placebo and ibuprofen groups). Both rofecoxib and ibuprofen were well tolerated by the children, with no refusal of medication and no episodes of bronchospasm, pruritis or dizziness. One child in the ibuprofen group developed a mild erythematous, non-itchy rash after surgery, which resolved within 4 h without treatment.

Discussion

Ibuprofen in combination with paracetamol as premedication reduced the need for early supplementary analgesia by almost 50% after tonsillectomy. The clinical importance of this finding is indicated by the higher pain scores at the time of supplementary analgesia in the children requiring early rescue. This equates to fewer distressed children on the ward.

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Placebo (n=18)</th>
<th>Rofecoxib (n=40)</th>
<th>Ibuprofen (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded (n)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7.0 (5–9)</td>
<td>7.5 (5–11)</td>
<td>7.0 (5–11)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25 (20–31)</td>
<td>29 (21–49)</td>
<td>28 (21–42)</td>
<td></td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>7:11</td>
<td>16:24</td>
<td>21:19</td>
<td></td>
</tr>
<tr>
<td>Asthmatic (%)</td>
<td>4 (22%)</td>
<td>6 (15%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Time from premedication to surgery (min)</td>
<td>81 (33)</td>
<td>73 (28)</td>
<td>82 (28)</td>
<td></td>
</tr>
<tr>
<td>Operation type (T:T&amp;A)</td>
<td>11:7</td>
<td>22:18</td>
<td>22:18</td>
<td></td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>20.1 (8.5)</td>
<td>21.0 (10.0)</td>
<td>21.2 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl dose (µg kg⁻¹)</td>
<td>1.46 (0.6)</td>
<td>1.34 (0.4)</td>
<td>1.37 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Patient characteristics and intraoperative details. Data are median (interquartile range) or mean (SD). There were no significant differences between the groups in any of the variables. T=tonsillectomy; T&A=tonsillectomy and adenoidectomy

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Placebo</th>
<th>Rofecoxib</th>
<th>Ibuprofen</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary analgesic &lt;2 h (n)</td>
<td>72% (13)</td>
<td>68% (27)</td>
<td>43% (17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to supplementary analgesia (min)</td>
<td>62 (35–250)</td>
<td>62 (35–278)</td>
<td>156 (55–300)</td>
<td>0.09</td>
</tr>
<tr>
<td>Pain score at 4 h</td>
<td>20 (0–40)</td>
<td>20 (10–40)</td>
<td>20 (18–40)</td>
<td>0.89</td>
</tr>
<tr>
<td>Vomited (n)</td>
<td>22% (4)</td>
<td>33% (13)</td>
<td>28% (11)</td>
<td>0.71</td>
</tr>
<tr>
<td>Antiemetic administered (n)</td>
<td>22% (4)</td>
<td>20% (8)</td>
<td>20% (8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Primary haemorrhage (n)</td>
<td>5.5% (1)</td>
<td>2.5% (1)</td>
<td>5% (2)</td>
<td>0.83</td>
</tr>
<tr>
<td>Secondary haemorrhage (n)</td>
<td>11% (2)</td>
<td>7.5% (3)</td>
<td>2.5% (1)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 2 Primary and secondary outcomes. Data are percentage (n) or median (interquartile range). ‘Primary haemorrhage’ indicates bleeding requiring intervention within 24 h; ‘Secondary haemorrhage’ indicates delayed bleeding requiring readmission
in the early postoperative period in the ibuprofen group. This analgesic benefit from the combination of paracetamol and ibuprofen lends support to our current practice of using NSAIDs for perioperative analgesia.

Paracetamol 20 mg kg\(^{-1}\) alone provided adequate analgesia for just 24% of the children in this study. This emphasizes the difficulty in providing pain relief in children with contraindications to NSAIDs. A previous study of paediatric tonsillectomy has shown paracetamol (20 mg kg\(^{-1}\)) to be equivalent to diclofenac (1 mg kg\(^{-1}\)), but each drug alone was noted to provide inadequate overall analgesia.\(^{11}\) These results provide some justification for the use of NSAIDs in children with relative contraindications, such as controlled asthmatics, particularly in view of the recent demonstration of the safety of diclofenac in asthmatic children.\(^{22}\) However, it should be noted that, although the dose of paracetamol (20 mg kg\(^{-1}\)) used in this study was our usual oral loading dose, recent studies have demonstrated improved analgesic efficacy with higher doses of oral (40 mg kg\(^{-1}\)) or rectal paracetamol (40–60 mg kg\(^{-1}\)), which achieve higher plasma concentrations.\(^{9,10}\) It is possible that the use of a larger loading dose of paracetamol in our study would have produced an improved analgesic effect. Also of relevance to our study is the observation that the premedication of children having adenotonsillectomies with oral paracetamol elixir (40 mg kg\(^{-1}\)) has been shown to have no effect on the volume or pH of gastric contents at the time of operation.\(^{23}\)

The addition of rofecoxib to paracetamol failed to confer any additional analgesic benefit compared with paracetamol alone. This was a surprising finding, which questions the role of COX-2 antagonists for perioperative analgesia. Previous perioperative studies in adults have demonstrated rofecoxib to have an analgesic efficacy equivalent to that of ibuprofen\(^{17,18}\) and it has been shown to be opioid-sparing after spinal surgery.\(^{24}\) When designing our study, in the absence of paediatric pharmacokinetic data, we calculated the dose of rofecoxib (0.625 mg kg\(^{-1}\)) such that a 40-kg child would receive the current UK maximum adult dose of 25 mg. Our rofecoxib dose calculation was based on the finding that, in adults, a dose of rofecoxib 50 mg is equianalgesic to 400 mg ibuprofen.\(^{17}\) As the usual paediatric dose of ibuprofen is 5 mg kg\(^{-1}\), we expected a dose of rofecoxib 0.625 mg kg\(^{-1}\) to be equianalgesic. This dose also allowed us to give equal volumes of the ibuprofen and rofecoxib drug syrups (0.25 ml kg\(^{-1}\)), which assisted with study blinding.

The study drugs were given more than 60 min before surgery, allowing approximately 100 min for rofecoxib absorption and the onset of analgesic action before arrival in the recovery unit. Data from dental extraction studies have indicated that the time to onset of analgesia for rofecoxib is similar to that of ibuprofen\(^{18}\) and has been quoted by the manufacturer as 45 min. We have no evidence of a delayed analgesic effect of rofecoxib as the total analgesic consumption in the first 24 h was similar across the groups. In seeking to explain our failure to demonstrate any benefit, it is unlikely that our study was under-powered, as we have been able to show the beneficial analgesic effect of ibuprofen.

This study looked for an additive analgesic effect of the combination of rofecoxib and paracetamol. The sites of action of both drugs may be relevant: paracetamol inhibits brain cyclo-oxygenase\(^{25}\) and rofecoxib inhibits COX-2, which is expressed constitutively in the brain as well as being inducible in the periphery.\(^{16}\) If both drugs were acting to inhibit the same brain cyclo-oxygenase, we could perhaps explain the lack of additive effect (if we assume that paracetamol is producing nearly maximal antagonism of brain COX). Alternatively, it is possible that inducible
COX-2 does not play a major role in nociception in the early recovery period after tonsillectomy. Our findings suggest that central cyclo-oxygenase and peripheral COX-1 are involved in mediating early pain after tonsillectomy.

The surgical blood loss seen during this study was similar to that reported previously from our institution. There were no significant differences in blood loss or in bleeding complications between the three groups. In designing the study, we wished to reflect our normal clinical practice so no restriction was placed upon surgical grade or technique employed for tonsillectomy. A retrospective power analysis showed that the study had limited power (23%) to demonstrate the largest difference seen between the groups because of the large variation in blood loss. That the observed distributions were so wide suggests that there are factors other than the perioperative use of NSAIDs that determine surgical bleeding.

The incidence of postoperative vomiting was 29% in the first 24 h. This was without prophylactic antiemetic and is lower than that previously reported in this surgical population. Previous studies of tonsillectomy have correlated postoperative vomiting with opioid use and pain. In our study, there were no significant differences between the groups in vomiting or in the need for rescue antiemetic. In conclusion, this clinical study emphasizes that paediatric tonsillectomy is a painful procedure requiring proactive analgesic strategies to provide a good quality of postoperative recovery. We have shown analgesic benefit without increased risk of complications by combining ibuprofen with paracetamol for premedication. We failed to show an analgesic effect of rofecoxib in combination with paracetamol, suggesting that the COX-2 antagonists will require careful evaluation before their role in perioperative analgesia can be defined clearly. In particular, studies that compare COX-2 antagonists with paracetamol (which, coincidentally, also has a low incidence of gastric and haemostatic complications) will be particularly valuable. There is further scope for improving analgesia after tonsillectomy but we can commend the perioperative combination of ibuprofen with paracetamol as a useful strategy in children.

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