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Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy†

H. Viitanen[1]*, N. Tuominen[2], H. Vääräniemi[3], E. Nikanne[4] and P. Annila[5]

[1]Department of Anaesthesia, Central Hospital of Seinäjoki, Seinäjoki, Finland. [2]Department of Anaesthesiology and Intensive Care, Tampere University Hospital, Tampere, Finland. [3]Department of Anaesthesia and [4]Department of Otolaryngology, Central Hospital of Central Finland, Jyväskylä, Finland. [5]Department of Anaesthesia, Hatanpää Hospital and University of Tampere, Tampere, Finland

**Corresponding author. E-mail: hanna.viitanen@epshp.fi*

Background. Acetaminophen and non-steroidal anti-inflammatory drugs have different mechanisms of action. We investigated if combining rectal acetaminophen with ibuprofen would provide better postoperative analgesia compared with either drug alone after adenoidectomy in children.

Methods. 160 children, aged 1–6 yr, undergoing day-case adenoidectomy, were randomized to receive either acetaminophen 40 mg kg^{-1}, ibuprofen 15 mg kg^{-1}, their combination, or placebo rectally immediately after anaesthetic induction. A standard anaesthetic method was used and all children received alfentanil 10 μg kg^{-1} i.v. during induction. Meperidine 5–10 mg i.v. was used for rescue analgesia for a pain score (Objective Pain Scale) over 3. Recovery times, sedation scores and the need for rescue analgesia and adverse events during the first 24 h after anaesthesia were recorded. Rescue analgesic at home was ibuprofen 10 mg kg^{-1}.

Results. Total meperidine requirements were significantly less in the groups receiving acetaminophen, ibuprofen, or their combination compared with the group receiving placebo indicating an opioid-sparing effect of 19–28% ($P<0.05$). Children given acetaminophen were more sedated than those given ibuprofen ($P<0.05$). Discharge criteria were fulfilled earlier in the ibuprofen group than in all the other groups ($P<0.05$). At home, less children (49%) needed rescue analgesia in the combination group compared with the other groups (74–77%) ($P<0.02$).

Conclusions. We conclude that prophylactically administered rectal acetaminophen combined with ibuprofen does not improve analgesia after adenoidectomy in the immediate postoperative period compared with either drug alone but does decrease the need for analgesia at home. Ibuprofen results in lesser sedation and faster discharge than when acetaminophen is used.

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Adenoidectomy is a common day-case operation in children.[1] Over 80% of children experience pain on the first day after operation and pain intensity at home correlates with opioid requirements in hospital.[2] Thus, effective pain treatment in the immediate recovery period is essential.

Both non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have been shown to reduce the need for postoperative opioids after surgery in adults[3 4] and children.[1 5 6] Reduced opioid requirements allow for fewer side effects and faster recovery, which is particularly important in day-case surgery. NSAIDs and acetaminophen have different mechanisms of action and their combination could improve pain control after operation. In clinical practice, NSAIDs and acetaminophen are widely used together, but

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whether such a combination actually offers a relevant improvement in analgesia is controversial.[7] In a recent study in children undergoing appendectomy, acetaminophen with diclofenac did not provide additional benefit compared with either drug alone.[6] In contrast, the addition of ibuprofen to acetaminophen reduced the need for early analgesia from 72 to 38% after tonsillectomy in children 3–15 yr.[8]

In infants and small children, rectal acetaminophen or NSAIDs are often used to provide analgesia after operation. However, children generally dislike being given suppositories when awake[9] and it is a common method to administer them at anaesthetic induction. Whether a rectally administered combination of acetaminophen and NSAID improves pain control after adenoidectomy is not known. Therefore, we designed this randomized, double blind, placebo-controlled study to evaluate the analgesic efficacy of pre-treatment with rectal acetaminophen and ibuprofen—alone or in combination—in children undergoing day-case adenoidectomy.

Methods

After obtaining institutional ethics committee approval and written informed parental consent, we studied 160 children, aged 1–6 yr, ASA physical status I, undergoing adenoidectomy with or without myringotomy, according to a randomized, double blind, placebo-controlled protocol. We excluded patients with a known allergy to the drugs being used, asthma, kidney, or hepatic dysfunction or hemorrhagic diathesis.

No pre-medication was used. On arrival in the operating room, routine monitoring was applied. An i.v. infusion was started (facilitated by EMLA® cream, AstraZeneca, Södertälje, Sweden) and general anaesthesia was induced by inhalation with sevoflurane, nitrous oxide, and oxygen. Mivacurium 0.2 mg kg^{-1} was used, if needed, to facilitate tracheal intubation. All children received alfentanil 10 μg kg^{-1} at induction and no more opioid was allowed during operation. Children were randomized, according to a computer-generated random numbers program, to receive rectally either ibuprofen 15 mg kg^{-1} (Burana®, Orion, Espoo, Finland), acetaminophen 40 mg kg^{-1} (Panadol®, SmithKline Beecham, Hérouville, France) (a lipophilic suppository), the combination of these two drugs or placebo immediately after tracheal intubation. The suppositories containing either placebo or the analgesics (ibuprofen, acetaminophen) were supplied by a nurse from the ENT surgical ward according to the randomization table. The study drugs were then administered by a nurse in the day-case unit who did not otherwise participate in the assessment or care of the child. Ventilation was controlled and anaesthesia maintained with nitrous oxide 70%, oxygen and sevoflurane adjusted to maintain arterial pressure within 20% of initial readings. Bleeding during surgery was assessed by the ENT surgeon using a scale of 0–2 (0=no bleeding, 1=normal bleeding, 2=more than normal bleeding).

After discontinuation of anaesthesia children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and assessment of pain. Parents were allowed into the PACU as soon as the child had woken up. The recovery of the children and the need for rescue analgesia were assessed by a trained nurse who was blinded to the analgesic treatment used. Pain was assessed every 10 min using a scoring system based on the Objective Pain Scale created by Hannallah and colleagues[10] consisting of 0–2 points (best to worst) for crying, movement, agitation, and verbal response. This scale has been validated in infants and children[11] and has been used previously to score pain after ENT surgery.[12–14] For a pain score of 3 or greater, i.v. meperidine (Pethidin®, Leiras, Turku, Finland) was administered in increments of 5 mg (initial dose for children <20 kg, 5 mg; ⩾20 kg, 10 mg) every 5 min until the child was comfortable. The time to administering the first dose and the total amount of analgesic needed in each study group were recorded. In addition, to assess if the age of the children had any effect on the need for rescue analgesia, we divided the groups into two subgroups: 1–3 yr and over 3yr.

For study purposes all children were kept in the PACU for a minimum of 90 min. Sedation was assessed every 10 min using a scale of 0–3 (0=fully awake, 1=awake, but drowsy, 2=sleeping, but arousable by light touch or speech, 3=sleeping, not arousable). Vomiting and other adverse events were recorded. The children were discharged when they fulfilled the discharge criteria and the time to achieve this goal was recorded. The discharge criteria were: fully awake, stable vital signs for at least 30 min, no bleeding, no signs of excessive pain, no vomiting, and able to ambulate according to age.

At home the rescue analgesic was always rectal or oral ibuprofen, which was supplied to the parents upon discharge (three doses, each 10 mg kg^{-1}). Ibuprofen was given to the child at the discretion of the parent. The parents of the children were asked to record, using a postoperative questionnaire, the well being (pain, use of ibuprofen, vomiting, tiredness, sleep) of the child at home until 24 h after anaesthesia.

Analyses were performed using SPSS™ v. 9.0. Values are presented as mean (SD) and 95% confidence interval (CI) or number (%). Normally distributed data were analysed by using one-way analysis of variance (ANOVA) with Bonferroni corrections. Data not normally distributed were analysed with the Kruskal–Wallis test, and inter-group comparisons were made with the Mann–Whitney *U*-test. For categorical data the χ^2 square test or Fisher's exact test were used, where appropriate. A P value <0.05 was considered significant. Group size was calculated on the basis of detecting a 30% decrease in meperidine consumption in the combination group compared with the groups receiving ibuprofen or acetaminophen alone. A minimum of

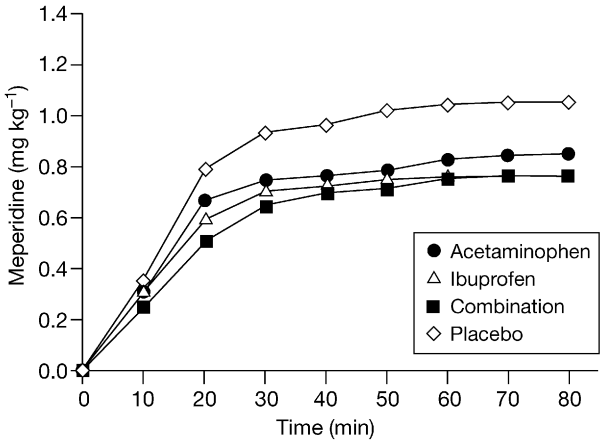

Fig 1 The cumulative amount of mean meperidine consumption (mg kg^{-1}) in the PACU in the four groups. The placebo group had significantly higher meperidine consumption compared with all the other study groups at each time point from 30 min onward (P<0.05). No other inter-group comparisons showed significant differences.

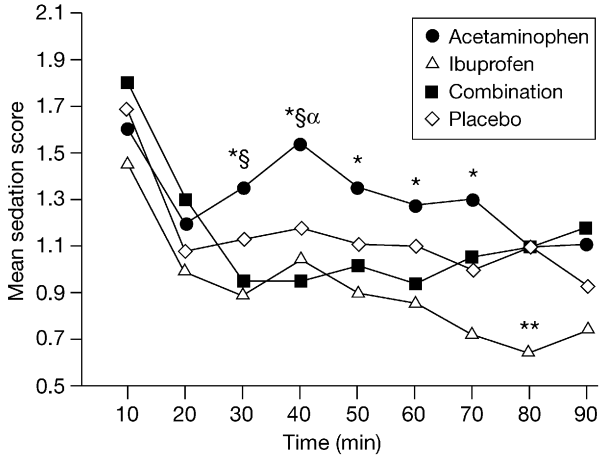

Fig 2 Mean sedation scores throughout the observation period in the four study groups. *P<0.05 *vs* ibuprofen group, $^{\S}P$<0.05 *vs* combination group, $^{\alpha}P$<0.05 *vs* placebo group, **P<0.05 *vs* all other groups (inter-group comparisons at each time point made using the Mann–Whitney *U*-test).

Table 1 Patient characteristics, duration of anaesthesia and surgical details in the study groups. Values are mean (SD), mean (range) for age, or absolute number of patients (%). There were no statistically significant differences between the groups

	Acetaminophen (n=40)	**Ibuprofen (n=41)**	**Combination (n=40)**	**Placebo (n=38)**
Age (yr) (range)	2.7 (1.0–6.4)	3.2 (1.0–6.9)	3.2 (1.0–6.9)	2.6 (1.0–6.3)
Weight (kg)	15 (4)	16 (5)	16 (6)	15 (4)
Duration of anaesthesia (min)	29 (9)	29 (10)	31 (13)	30 (9)
Myringotomy performed (n (%))	31 (80)	25 (63)	30 (77)	29 (78)
Use of electrocoagulation (n (%))	20 (52)	19 (49)	18 (45)	15 (42)

Table 2 Analgesic requirements, adverse events and recovery in the study groups. Data are mean (SD, 95% CI) or absolute number of patients (%). *P<0.05 *vs* all other groups (Mann–Whitney *U*-test)

	Acetaminophen (n=40)	**Ibuprofen (n=41)**	**Combination (n=40)**	**Placebo (n=38)**
Time to first dose of meperidine (min)	11 (11, 7–15)	12 (7, 9–13)	13 (8, 10–15)	10 (5, 8–12)
Total meperidine dose (mg kg^{-1})	0.87 (0.39)	0.78 (0.37)	0.77 (0.45)	1.07 (0.38)*
No. of adverse events in PACU (n (%))				
Retching, vomiting	10 (25)	13 (32)	11 (28)	9 (24)
Abdominal pain	3 (8)	4 (10)	3 (8)	1 (3)
Dizziness	0	0	2 (5)	0
Discharge criteria fulfilled (min)	124 (36, 112–135)	104 (37, 93–117)*	133 (53, 117–151)	124 (42, 111–138)

36 patients was required in each group (α=0.05, power=80%).

Results

Of the 160 children recruited, one was excluded because of protocol violation (received fentanyl instead of meperidine postoperatively). The groups were comparable in their patient characteristics, duration of anaesthesia and surgical data (Table 1). Total and cumulative meperidine consumption was significantly lower in the study groups receiving acetaminophen and/or ibuprofen than in the group receiving placebo (Table 2, Fig. 1) demonstrating an opioid-sparing effect of 19% in the acetaminophen (P=0.03), 27% in the ibuprofen (P=0.001), and 28% in the combination group (P=0.002). The proportion of children requiring more than two doses of meperidine was significantly higher in the placebo group compared with all the other study groups (P=0.008). Other inter-group comparisons in regard to opioid requirement or the time to first analgesia showed no significant differences. Also, there were no differences between the age groups in the total amount of meperidine

consumed (P=0.07) or the distribution of meperidine doses (P=0.22).

There were no differences in the frequency of adverse events between the groups (Table 2). Children receiving acetaminophen alone were consistently more sedated than those receiving ibuprofen alone throughout the observation period (Fig. 2). In addition, children in the ibuprofen group were fit for discharge earlier than children in all the other study groups (Table 2).

There were no differences between the groups in the amount of intraoperative bleeding evaluated by the surgeon. None of the children required surgical intervention or experienced delayed discharge because of bleeding from the operation site.

The postoperative questionnaires were returned by 142 (90%) parents. During the first 24 h at home, ibuprofen was administered to fewer children in the combination group (18 (49%)) than in the acetaminophen (26 (74%)), ibuprofen (29 (76%)), or placebo (21 (77%)) groups (P<0.02). Before bedtime pain relief was required by 24 (67%), 26 (68%), 17 (46%), and 22 (71%) children (P=0.1), and during the night by 10 (28%), 10 (27%), four (11%), and four (13%) children in the acetaminophen, ibuprofen, combination and placebo groups, respectively (P=0.15). Ten (28%) children in the acetaminophen, six (16%) in the ibuprofen, three (8%) in the combination and four (13%) children in the placebo group needed two or more doses of ibuprofen (P=0.13). Vomiting occurred in six (17%), three (8%), five (14%), and two (7%) children in the acetaminophen, ibuprofen, combination, and placebo groups, respectively (P=0.49). No differences occurred in drinking ability, tiredness, bad temper, or quality of sleep.

Discussion

We undertook this study in order to investigate the efficacy of a very commonly used analgesic regimen in children—rectal use of NSAID and/or acetaminophen at anaesthetic induction—for pain after adenoidectomy. Our results show that both ibuprofen and acetaminophen and their combination were significantly more effective than placebo in reducing meperidine requirement during recovery. However, combining rectal acetaminophen with ibuprofen did not offer improved pain control in the immediate postoperative period compared with either drug alone although it resulted in less analgesic use at home during the first 24 h after operation. Interestingly, we also found that children receiving ibuprofen alone were less sedated and fit for dicharge sooner than those receiving acetaminophen.

Differences in type of surgery, patient characteristics, and the dosage and route of medication used can affect the analgesic efficacy of acetaminophen and NSAIDs.[7 15] We used rectal doses of analgesics proven to be efficacious for postoperative pain in children.[5 16] All study drugs improved analgesia significantly compared with placebo after operation. However, nearly all children needed rescue analgesia confirming previous findings that NSAIDs and acetaminophen alone are often unable to provide sufficient analgesia after ENT surgery.[1 17 18]

Why no additional benefit from the concurrent use of ibuprofen and acetaminophen was demonstrable may relate to the unpredictable and variable bioavailability of rectally administered drugs, especially acetaminophen. Although detectable plasma concentrations[17 19] and a clear decrease in pain[5] as early as 35–45 min after rectal administration of acetaminophen have been demonstrated, substantial evidence show that acetaminophen is associated with highly variable, erratic and slow absorption with peak plasma levels occurring 2–3 h after administration.[20–22] In adults, peak plasma levels after rectal ibuprofen have been detected approximately 1.14 h after administration.[23] Given the short duration of anaesthesia in the present study, plasma concentrations of either drug most probably did not attain their peak concentrations at the time of awakening. This may explain why there was no difference in the time to first rescue analgesia between groups. However, all study drugs improved subsequent pain control compared with placebo, which speaks for a clinically relevant amount of absorption occurring later on.

In the present study, acetaminophen demonstrated equal analgesic efficacy to ibuprofen after adenoidectomy confirming that acetaminophen is a viable alternative to NSAIDs in children undergoing ENT surgery.[17 18 24] The use of NSAIDs for analgesia in ENT surgery has been a matter of concern as NSAIDs have been associated with increased postoperative bleeding.[17 24] However, several studies have demonstrated the safety of the perioperative use of NSAIDs both after tonsillectomy[4] and adenoidectomy.[1 2 25] Likewise, we did not find perioperative bleeding to be increased with the use of ibuprofen. We used a crude estimation by the operator for evaluating bleeding during surgery and found no difference between groups. Also, none of the patients needed re-operation for haemostasis.

An unexpected finding was the difference between ibuprofen and acetaminophen in sedation scores and time to discharge. Sedation scores were consistently higher in the acetaminophen group compared with the ibuprofen group and the time to achieve discharge criteria was shortest in the ibuprofen group. Sedation reached its peak level at approximately 40 min after arrival in the PACU in all study groups probably reflecting the sedative effect of meperidine, which was given shortly before this time. The deeper level of sedation in the acetaminophen group may have been a result of an interaction between meperidine and acetaminophen. Substantial data suggest that acetaminophen exerts its anti-pyretic and anti-analgesic effect through a central mechanism of action involving the serotonergic and nitric oxide systems and the inhibition of prostaglandin release in the central nervous system.[26–28] Acetaminophen may possibly potentiate the sedative effect of meperidine via this interaction. Curiously enough, the level of sedation

in the combination group resembled the level observed in the ibuprofen group. The combination group received less meperidine than the acetaminophen group thus perhaps suffering from a decreased amount of opioid-mediated sedation.

Only 49% of children in the combination group needed rescue analgesia at home compared with 74–77% of children in the other study groups. Korpela and colleagues[5] also found a long-lasting dose-related analgesic effect with acetaminophen which extended into the first 24 h after operation, stating that a single large dose of acetaminophen has a beneficial effect far beyond its pharmacokinetic profile. In this respect, although combining acetaminophen with ibuprofen did not offer improved pain control in the immediate postoperative period, it may be useful in improving well-being at home.

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