Efficacy of rectal ibuprofen in controlling postoperative pain in children

Eeva-Liisa Maunuksela MD PhD, Pauli Ryhänen MD PhD, Leena Janhunen MD

The efficacy of ibuprofen with scheduled administration, starting preoperatively, for postoperative pain was studied in 128 boys and girls, 4 to 12 yr old, having elective surgery. In a double blind placebo-controlled study, rectal ibuprofen (40 mg · kg^{-1} · day^{-1} in divided doses) or placebo was given for up to three days. For two hours after surgery heart rate, blood pressure and respiratory rate were recorded every 15 min together with sedation scores and pain scores, as assessed by an observer and the patient. Morphine was given to all children, 0.1 mg · kg^{-1} iv or 0.15 mg · kg^{-1} im according to clinical needs. Every morning on the ward the patients were interviewed about the efficacy of the analgesic treatment. All unwanted effects were registered. In the recovery room the heart rate was lower ($P < 0.05$) and the patient's pain scores were less ($P < 0.05$) in the ibuprofen group. After orthopaedic operations children needed more opioid than after ophthalmic or general surgical procedures ($P < 0.001$). However, after all operations the need for additional morphine was less in the recovery room ($P < 0.05$), during the day of operation ($P < 0.01$) and during the three-day study period ($P < 0.01$) in children receiving ibuprofen. On the day of operation the analgesic therapy was considered to be good or very good by 44/53 and 32/49 of the children in ibuprofen and placebo groups, respectively ($P < 0.05$). Later, their assessments did not differ. The incidence of unwanted effects was similarly low in all groups. It is concluded that the scheduled administration of ibuprofen decreased the need for opioid analgesic, improved the pain relief during recovery and on the day of operation and did not cause additional side-effects.

L'efficacité de l'ibuprofen administré de façon régulière, débutant dans la période préopératoire, pour le contrôle de la douleur postopératoire, a été étudiée chez 128 garçons et filles de 4 à 12 ans subissant une chirurgie élective. Dans une étude à double insu avec contrôle placebo, de l'ibuprofen par voie rectale (40 mg · kg^{-1} · jour^{-1} en doses divisées) ou du placebo était administré pour des périodes allant jusqu'à trois jours. La fréquence cardiaque, la tension artérielle et la fréquence respiratoire étaient notées toutes les quinze minutes pendant deux heures après la chirurgie, de même que les pointages de sédation et de douleur tel qu'évalués par un observateur et par le patient. De la morphine était administrée à tous les enfants à raison de 0,1 mg · kg^{-1} iv ou 0,15 mg · kg^{-1} im selon les besoins cliniques. Chaque matin à l'étage, les patients étaient questionnés sur l'efficacité du traitement analgésique. Tous les effets indésirables étaient notés. A la salle de réveil, la fréquence cardiaque était moins rapide ($P < 0,05$) et les pointages de douleur des patients étaient moindres ($P < 0,05$) pour le groupe ibuprofen. Les enfants ont eu besoin de plus d'opiacés après les chirurgies orthopédiques qu'après les interventions ophtalmiques ou de chirurgie générale ($P < 0,01$). Cependant, après toutes les interventions, le besoin de morphine additionnelle était moindre à la salle de réveil ($P < 0,01$), le jour de l'intervention ($P < 0,01$) et pendant les trois jours de l'étude ($P < 0,01$) chez les enfants recevant de l'ibuprofen. Le jour de l'intervention, la thérapie analgésique était considérée comme bonne ou très bonne par 44/53 et 32/49 enfants dans les groupes ibuprofen et placebo respectivement ($P < 0,05$). Par la suite, leurs évaluations ne différaient pas. L'incidence d'effets secondaires non désirables était faible et semblable dans tous les groupes. En conclusion, l'administration régulière d'ibuprofen diminuait le besoin d'analgésie avec les opiacés, améliorait le soulagement de la douleur pendant le réveil et le jour de l'intervention, et ne causait pas d'effets secondaires additionnels.

Key words
ANAESTHESIA: paediatric;
ANALGESIA: postoperative;
ANALGESICS: ibuprofen.

From the Department of Ophthalmology, Helsinki University Central Hospital, Department of Anesthesiology, Oulu University Central Hospital and Jorvi Hospital, Finland.

Address correspondence to: Dr. Eeva-Liisa Maunuksela, Texas Tech University Health Sciences Center, Department of Anesthesiology, 3601 4th Street, Room 1C-272, Lubbock, Texas 79430, USA

Accepted for publication 18th November, 1991.

There is increasing interest in the use of non-steroidal anti-inflammatory drugs (NSAID's) as analgesics for the treatment of postoperative pain in adults and in children.[1–3] The

common paediatric surgical procedures are minor operations after which pain often can be controlled by the judicious, prophylactic use of NSAIDs. In adults, ibuprofen reduced the need for opioid analgesics following gynaecological operations and when treating cancer pain.[1,4] It is also known to be an effective antirheumatic and antipyretic in children and produces minimal side effects.[5,6] To our knowledge, ibuprofen has not been studied as a scheduled postoperative analgesic in paediatric patients.

Methods

The study was carried out on paediatric surgery wards of two university hospitals and one regional teaching hospital. The study protocol was accepted by the ethical committee of each hospital. One hundred twenty-eight boys and girls, aged 4 to 12 yr, participated in the study after informed parental consent. The children were ASA physical status I or II, and scheduled for operations after which the need for analgesia was expected. Children with mental or neurological disorders interfering with feeling or communicating about their pain, or with asthma or allergy to acetylsalicylic acid or any severe health problems were excluded.

Premedication and anaesthesia

The children were visited by an anaesthetist on the day before operation. Informed consent was obtained, the pain scoring system was explained to the child and it was checked that he understood it. Premedication was with oral flunitrazepam 0.07–0.1 mg · kg^{-1} (maximum 2.0 mg). Local anaesthetic cream, EMLA, was used for venous cannulation sites.

Anaesthesia was induced with thiopentone (3–5 mg · kg^{-1}). If intubation was needed it was facilitated with succinylcholine 1.0–1.5 mg · kg^{-1}. Maintenance of anaesthesia was with halothane or isoflurane in N_2O/O_2 7/3. Muscle relaxation for longer operations was achieved with pancuronium or atracurium and the degree of neuromuscular blockade was monitored by a transcutaneous neurostimulator. At the end of the operation relaxation was reversed with neostigmine 0.04 mg · kg^{-1} and glycopyrrolate 0.01 mg · kg^{-1}. During anaesthesia no analgesics, except for the study drug, were administered.

The study drug

The children were divided into weight groups. The daily dose was aimed to be 40 mg · kg^{-1} of ibuprofen or placebo, divided in three or four doses (Table I). The first dose was given after induction of anaesthesia. The study suppositories were produced, packed and randomized by Medipolar (Oulu, Finland). The suppositories and the analgesic pack looked identical within a weight group. A personal pack was assigned to each child in numerical order according to his weight.

TABLE I Dosage schedule, daily doses and dose ranges according to the patients' weight

Weight kg	*Single dose mg*	*Number of doses · day^{-1}*	*Daily dose mg*	*Dose range mg · kg^{-1}*
10.0–12.0	100	4	400	40–33
12.5–14.5	125	4	500	40–34
15.0–18.0	200	3	600	40–33
18.5–19.5	250	3	750	40–38
20.0–24.5	200	4	800	40–33
25.0–29.5	250	4	1000	40–34
30.0–37.0	400	3	1200	40–32
37.5–39.5	500	3	1500	40–38
40.0–49.0	400	4	1600	41–33
50.0–60.0	500	4	2000	40–33

Monitoring and measurement

In the recovery room the children were continuously observed by nurses trained in pain assessment. Systolic and diastolic blood pressure, heart rate and ventilatory rate together with sedation (0 = no sedation, 1 = slight sedation, awake, 2 = moderate sedation, asleep but easily arousable, 3 = heavy sedation, arousable, 4 = asleep, not arousable) and observer's pain score (0–9) were assessed at arrival and every 15 min. After that, the child was asked to rate the pain on a scale 0–3, 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain. The observer's pain score was based on several items such as moisture and colour of the skin, mimic, vocalisation, movements or rigidity of the limbs and body, response to handling and the measured cardioventilatory variables. In an earlier paper we described the method thoroughly and the observer's assessment was shown to correlate well with the child's own assessment.[7] The assessments were continued for two hours. If the pain was assessed as moderate or severe or if the child requested an analgesic, 0.1 mg · kg^{-1} of either morphine (HUCH, Jorvi Hospital) or oxycodone (OUCH) was given *iv*. The same analgesic dose was repeated every 5 to 15 min until the child was assessed to be free of pain or said he was comfortable.

On the surgical ward the study suppositories were administered according to the schedule, every six or eight hours. If the child was considered to have moderate or severe pain or if he requested an analgesic *im* morphine (oxycodone) 0.15 mg · kg^{-1} was administered. During every shift the nurses recorded all medication given and unwanted effects. Postoperative bleeding was assessed as mild, moderate or severe. When the patient had drains the volume of blood loss was measured (ml · day^{-1}). The next morning the children were interviewed by an anesthetist. The child was asked if the pain relief was very good, good,

TABLE II Characteristics of the patient groups (number of patients and mean ± SD)

	M/F	*Age yr*	*Height cm*	*Weight kg*	*Operation min*	*Ophthalmic/ general surgery/ orthopaedic*
Ibuprofen	43/21	7.7	125.5	26.7	48.0	26/26/12
SD		2.7	16.8	8.3	40.8	
Placebo	33/31	7.4	124.1	25.3	50.1	23/22/19
SD		2.7	16.4	8.9	39.4	

P = NS.

satisfactory, poor or very poor. If the answer was poor or very poor the reason was asked: inadequate effect, too short effect, side-effects or other reasons.

Statisical analysis

Differences in demographic data were assessed with Student's t test or in the case of categorical data with Fisher's exact test. Sequences of data collected in the recovery room were analyzed with repeated measures analysis of variance (ANOVA) with two grouping factors (treatment and hospital) and one within factor (time). A ln-transformation was used for the cardiorespiratory data due to skewed distributions.

For sedation and pain scores non-parametric procedures (Friedman's ANOVA, Mann-Whitney U test) were applied. The number of patients using analgesic was compared with log-linear model (factors: treatment, hospital) and the amount of analgesic used with two-way ANOVA (factors: treatment, hospital). Pain relief on the operation day and the data of postoperative side-effects were analyzed with Fisher's exact test, again.

All statistical work was performed with BMDP-programs (BMDP Statistical Software Inc, USA). Results are given as mean ± SD or median and range. P values <0.05 were considered to be statistically significant.

Results

The characteristics of the study groups and the mean duration and type of operations are presented in Table II. The data of the three hospitals and different types of operations was first analyzed separately but then combined because the results did not differ. During the two-hour stay in the recovery room the systolic and diastolic blood pressures and ventilatory rate did not differ between the study groups. The mean heart rate of the ibuprofen group was lower during the whole period ($P < 0.05$, repeated measures of ANOVA).

In the recovery room the sedation scores (median and range) in both groups were similar. The first, last and maximum pain scores of the observer and the patient were compared between groups. In the patient's assessments the first, the last and the maximum scores were higher in the placebo group than in the ibuprofen group. Only the maximum pain score by the observer was higher in the placebo group (Table III).

TABLE III Pain scores by the observer (0–9) and the patient (0–3) during the two-hour recovery room observation (median and range, Mann-Whitney U-test)

	First	*Last*	*Maximum*
Observer (0–9)			
Ibuprofen	0.0 (0–5)	0.0 (0–3)	2.0 (0–8)
	$n = 63$	$n = 64$	$n = 64$
Placebo	0.0 (0–7)	0.0 (0–5)	3.0 (0–7)
	$n = 64$	$n = 64$	$n = 64$
	NS	NS	$P < 0.05$
Patient (0–3)			
Ibuprofen	0.0 (0–3)	0.0 (0–3)	1.0 (0–3)
	$n = 48$	$n = 52$	$n = 52$
Placebo	1.0 (0–3)	1.0 (0–3)	2.0 (0–3)
	$n = 54$	$n = 58$	$n = 58$
	$P < 0.05$	$P < 0.01$	$P < 0.001$

The administration of additional opioid analgesic in the recovery room, during the operative day, and during the whole study period is presented in Table IV. Thirty-six percent of the patients in the ibuprofen group and 19% in the placebo group did not receive any rescue analgesic during the study period. When the need for additional opioid analgesic was analyzed by type of operation, more opioids were used after orthopaedic operations than after ophthalmic or general surgical operations (two-way ANOVA model).

The patient's opinion of pain relief differed on the operative day: in the ibuprofen group the number of children considering the pain relief good or very good was 44/53, in the placebo group 32/49 ($P < 0.05$, Fisher test). On the second and third days the groups did not differ, on the second (ibuprofen 10/17, placebo 9/17) and third days (ibuprofen 6/9, placebo 8/11) respectively.

There were no differences in the incidence of unwanted

TABLE IV The need for additional opioids ($mg \cdot kg^{-1}$) in the ibuprofen and placebo groups after orthopaedic (Ortho) and ophthalmic or general surgical (others) operations (mean ± SD). The statistical assessment was performed with two-way ANOVA model

	Recovery room n = 128	*Operative day n = 128*	*1–3 days n = 128*
Ibuprofen			
Ortho ($n = 12$)	0.13 ± 0.06	0.27 ± 0.20	0.46 ± 0.52
Others ($n = 52$)	0.07 ± 0.08	0.09 ± 0.11	0.09 ± 0.14
Placebo			
Ortho ($n = 19$)	0.19 ± 0.11	0.42 ± 0.23	0.82 ± 0.67
Others ($n = 45$)	0.10 ± 0.08	0.12 ± 0.10	0.12 ± 0.10
P values			
Ibuprofen vs placebo	<0.05	<0.01	<0.01
Ortho vs others	<0.001	<0.001	<0.001
Interaction	NS	NS	<0.05

TABLE V Percent of patients suffering from unwanted effects in the ibuprofen (Ibu) and placebo (Pl) groups. None of the frequencies differed between the groups (Fisher's exact test)

	Operation day n = 128		*Second day n = 86*		*Third day n = 29*	
	Ibu	*Pl*	*Ibu*	*Pl*	*Ibu*	*Pl*
Nausea/vomiting	26	34	25	14	8	0
Abdominal pain	10	19	16	17	8	0
Diarrhoea	0	0	3	0	16	0
Headache	3	6	5	7	0	0
Dizziness	5	3	5	2	0	0
Disturbed vision	2	0	0	0	0	0
Rash	3	3	0	0	0	0
Other	4	4	3	11	0	0
Bleeding						
– mild	6	8	5	5	0	13
– moderate	3	3	0	2	0	0

effects during any study period between the ibuprofen and placebo groups (Table V).

On the operative day approximately 10% of the patients had mild or moderate postoperative bleeding in both groups. There were ten children in the ibuprofen and 11 in the placebo group with drainage. The mean (±SD) measured blood loss was 34 ± 59 ml and 50±69 ml on the operative day, 23 ± 57 and 52 ± 109 ml on the second day and 0 and 37 ± 84 ml on the third day in the ibuprofen and placebo children, respectively. In no case was the bleeding unexpectedly high necessitating any interventions or interruption of the study.

Discussion

The study groups were very similar with regard to age distribution and type of operation. No unwanted haemodynamic effects were seen following the prophylactic administration of ibuprofen. The lower heart rate in the ibuprofen group was an expected effect of a drug inhibiting prostaglandin synthesis which was also seen in other studies.[8] In no patient did the slow heart rate raise clinical concern or require therapy.

In the recovery room, as expected, there were no differences in the sedation scores since ibuprofen has no sedative effect.[9] However, the pain scores by the observer and by the patient were lower in the ibuprofen group. Also the administration of additional opioid analgesic was lower in the ibuprofen group in the recovery room and throughout the study period. The difference in the need for opioids was most clearly seen following extensive orthopaedic operations where more pain could be anticipated and all patients needed some analgesic. This opioid saving effect has been shown in adults with the use of rectal ibuprofen[1] and in children with intravenous indomethacin.[3]

Oxycodone was used as a rescue opioid analgesic in Oulu University Hospital and morphine in the other hospitals participating in the study. In Finland, oxycodone is probably the most commonly used postoperative analgesic and the opioid used routinely in Oulu. There are only a few comparative studies on the analgesic efficacy and pharmacodynamics of oxycodone[10,11] which indicate that its analgesic effect and side-effects are similar to those of morphine.

The assessment of pain used in this study in the recovery room has been validated and correlates with the child's own assessment.[7] In our experience, the nurse on the ward does not have the possibility to evaluate reliably every patient. Therefore, we have relied on the patient's interview. When this study was performed there were no patient-controlled analgesia (PCA) devices available on our paediatric wards. In adults, this device is an excellent measure of pain. Although today we know that school-age children usually can use a PCA device, its adequacy as a measure of pain in children has not been proven.

Postoperative pain management has traditionally relied on the patient's request for analgesia when he feels too much pain. This treatment has been satisfactory in adults but one of the difficulties of paediatric analgesia is the child's inability to request medication. In paediatric practice, the assessment of pain is more difficult, partly because of the child's withdrawal. The nurses' attitudes about analgesic administration to children vary. There are reports that "when needed" medication is often not given.[12,13] Thus, children may benefit from prophylactic and scheduled administration of postoperative analgesics. Although the children in the placebo group received about one-third more opioid analgesics than the children in the ibuprofen group on the operation day they did not consider the *iv* analgesic therapy as good as children with scheduled

ibuprofen. The lack of difference in the child's assessment of analgesia on the second and third days might reflect a better ability to attract the attention of the caregivers being more alert. More frequent doses of opioid produced analgesia equal to ibuprofen and fewer doses of opioid.

The incidence of unwanted effects did not differ between the study groups. The most common side-effect on the day of operation was nausea and vomiting but the incidence was lower than in adult studies.[1,2] This might have been due to different operations performed on adults and children or it could reflect children's better gastrointestinal tolerance of NSAIDs. Side-effects were generally mild and there were no differences between the groups. Bleeding did not cause clinical interventions in any patient. Also other studies with continuous or scheduled NSAID administration have not reported bleeding problems.[1,8]

It is concluded that the scheduled administration of ibuprofen is effective in alleviating postoperative pain in children and decreases the need for opioid medication in several types of surgery. It does not cause bleeding or other side-effects and therefore prophylactic administration is considered safe.

Acknowledgements

We wish to thank Farmos Oy (Oulu, Finland) for producing and randomizing the study drugs. The statistical analysis was done by Mr. Jouni Vuorinen M.Sc. We are grateful for his expertise and co-operation. Our gratitude is due to the nurses in the recovery rooms and paediatric surgical wards and anaesthesiology colleagues in the Department of Ophthalmology, University of Helsinki, Oulu University Children's Hospital and Jorvi Hospital. Their cooperation made the study possible.

References

1 *Owen H, Glavin RJ, Shaw NA.* Ibuprofen in the management of postoperative pain. Br J Anaesth 1986; 58: 1371–5.

2 *Slavic-Svircev V, Heidrich G, Kaiko RF, Rusy BF.* Ibuprofen in the treatment of postoperative pain. Am J Med 1984; 77: 84–6.

3 *Maunuksela E-L, Olkkola KT, Korpela R.* Does prophylactic intravenous infusion of indomethacin improve the management of postoperative pain in children? Can J Anaesth 1988; 35: 123–7 .

4 *Ferrer-Brechner T, Ganz P.* Combination therapy with ibuprofen and methadone for chronic cancer pain. Am J Med 1984; 77: 78–83.

5 *Mäkelä AL, Lempiäinen M, Yrjänä T.* Ibuprofen in the treatment of juvenile rheumatoid arthritis: metabolism and concentration in synovial fluid. Br J Clin Pract 1979; Suppl 6: 23.

6 *Walson PD, Galletta G, Braden NJ, Alexander L.* Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989; 46: 9–17.

7 *Maunuksela E-L, Olkkola KT, Korpela R.* Measurement of pain in children with self-reporting and with behavioral assessment. Clin Pharmacol Ther 1987; 42: 137–41.

8 *Maunuksela E-L, Olkkola KT, Korpela R.* Intravenous Indomethacin as postoperative analgesic in children: acute effects on blood pressure, heart rate, body temperature and bleeding. Ann Clin Res 1987; 19: 359–63.

9 *Adams SS, McCullough KF, Nicholson JS.* The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. Arch Int Pharmacodyn 1969; 178: 115–29.

10 *Beaver WT, Wallenstein SL, Rogers A, Houde RW.* Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. J Pharmacol Exp Ther 1987; 207: 92–100.

11 *Pöyhiä R, Kalso E, Onnela P, Tigerstedt I, Tammisto T.* Oxycodone and morphine in postoperative pain treatment. Pain 1990; Suppl 5: S143.

12 *Mather L, Macie J.* Incidence of postoperative pain in children. Pain 1983; 15: 271–9.

13 *Sechter NL, Allen DA, Hanson K.* Status of pediatric pain control: a comparison of hospital analgesic usage in children and adults. Pediatrics 1986; 77: 11–5.