

Brief Report

Dose-response of flurbiprofen on postoperative pain and emesis after paediatric strabismus surgery

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Purpose: Intravenous flurbiprofen, a non-steroidal antiinflammatory drug (NSAID), has been used recently for postoperative pain relief in adults. The drug is also likely to have antiemetic property. The present study was undertaken to investigate the effect of flurbiprofen on postoperative pain and emesis in children undergoing strabismus surgery, which is well known to produce postoperative nausea and vomiting.

Methods: In a prospective, randomised, controlled clinical trial, 90 children aged 2–11 yr received saline (control), flurbiprofen 0.5 mg·kg⁻¹, or flurbiprofen 1 mg·kg⁻¹. Saline and flurbiprofen were administered *iv* immediately after induction of anaesthesia. Anaesthesia was induced and maintained with sevoflurane and nitrous oxide in oxygen. Postoperative pain was assessed by a blinded observer using an objective pain scale (OPS). No opioids or antiemetics were administered throughout the study. The incidence and frequency of vomiting were compared among groups.

Results: Flurbiprofen 1 mg·kg⁻¹ provided lower OPS (highest) scores during the eight hours after surgery and a reduced requirement for postoperative supplementary analgesic (diclofenac suppository) compared with the other two regimens. The two doses of flurbiprofen failed to decrease the incidence and frequency of vomiting.

Conclusion: These data suggest that preoperative flurbiprofen 1 mg·kg⁻¹ *iv* is a simple and effective approach to postoperative pain relief but not to the prevention of emesis following paediatric strabismus surgery.

Objectif : Le flurbiprofène intraveineux, un anti-inflammatoire non stéroïdien (AINS), est utilisé depuis peu pour le soulagement de la douleur postopératoire chez l'adulte. On pense que ce médicament pourrait en outre avoir des propriétés antiémétiques. La présente étude visait à étudier les effets du flurbiprofène sur la douleur postopératoire et les vomissements chez des enfants opérés pour strabisme, intervention reconnue comme cause de nausées et de vomissements postopératoires.

Méthodes : Au cours d'une étude prospective aléatoire contrôlée, 90 enfants âgés de 2 à 11 ans ont reçu du sol.phys.(contrôle), du flurbiprofène 0,5 mg·kg⁻¹ ou du flurbiprofène 1 mg·kg⁻¹. Le soluté physiologique et le flurbiprofène étaient administrés *iv* immédiatement après l'induction de l'anesthésie. L'anesthésie était induite et maintenue avec du sévoflurane et du protoxyde d'azote en oxygène. La douleur postopératoire était évaluée par un observateur indépendant sur une échelle objective de la douleur (EOD). Aucun morphinique ou antiémétique n'était administré pendant l'étude. L'incidence et la fréquence des vomissements étaient comparées entre les groupes.

Résultats : Le flurbiprofène 1 mg·kg⁻¹ a produit des scores EOB inférieurs pendant les huit heures qui suivaient la chirurgie et a diminué les besoins d'analgésie postopératoire supplémentaire (diclofénac en suppositoire) comparativement aux deux autres alternatives. Les deux posologies de flurbiprofène n'ont pas diminué l'incidence et la fréquence des vomissements.

Conclusion : Ces données suggèrent que l'administration préopératoire de flurbiprofène 1 mg·kg⁻¹ *iv* chez les enfants soulage efficacement la douleur postopératoire mais ne prévient pas les vomissements après la chirurgie du strabisme.

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SEVERAL types of analgesics, including codeine and non-steroidal antiinflammatory drugs (NSAIDs), have been recommended to provide postoperative pain relief for children who undergo corrective strabismus surgery.¹ Ketorolac, a potent NSAID, has been used for this purpose.² The drug is also associated with a decreased frequency of postoperative nausea and vomiting.² Children undergoing strabismus surgery have a high incidence of this complication (54–67%),^{3–6} which is an unpleasant experience leading to delayed discharge from hospital.

Flurbiprofen, another potent NSAID, has been used in the treatment of pain due to osteoarthritis and rheumatoid arthritis.⁷ It effectively produces postoperative analgesia in adults undergoing dental⁷ or abdominal surgery.⁸ Flurbiprofen appears to reduce the incidence of nausea and vomiting in women with dysmenorrhoea.⁸ However, no reports on the effects of flurbiprofen on postoperative pain and emesis in paediatric strabismus surgery have been published. An injectable ampule has recently been made available by emulsifying lipid microspheres containing esterized flurbiprofen. The development of the new drug form has led to some advantages of flurbiprofen over the tablets, characterized by less severe and frequent untoward side effects (e.g. gastric ulcer) and longer duration of action, which are ascribed to the high affinity of the drug for inflammatory tissues.⁹ The peak plasma concentration of flurbiprofen occurs six to seven minutes after a single *iv* injection in adult healthy volunteers, and the half-life ($t_{1/2}$) is 5.8 hr.¹⁰ The onset of analgesic action is obvious within 30 min after *iv* administration with a duration of 5–12 hr.¹⁰ However, no pharmacodynamic or pharmacokinetic data of *iv* flurbiprofen in children are available. We undertook the present study to investigate whether flurbiprofen given *iv* during anaesthesia reduces pain and emesis after corrective strabismus surgery in children in a dose-dependent manner.

Methods

After institutional approval and parental informed consent, 90 children (2–11 yr, inpatients of ASA class 1) were randomly divided into three groups using an envelope method: saline (control), flurbiprofen 0.5 mg·kg⁻¹, and flurbiprofen 1 mg·kg⁻¹. Children with renal or gastrointestinal disease, obese patients, those taking medication known to affect gastric fluid composition or gastric emptying, and those who had undergone any operation before were excluded. Flurbiprofen and saline were prepared and administered *iv* immediately after induction of anaesthesia by the fourth author, who did not anaesthetize the patients or collect data of pain and emesis. The ratio-

nale for the dose of flurbiprofen was based on the following reports. Oral flurbiprofen 50 mg produces superior pain relief to aspirin⁹ or acetaminophen¹⁰ in 60 kg adults undergoing oral surgery. Intravenous flurbiprofen 50 mg provides postoperative analgesia in adult abdominal surgery.⁹

No preanaesthetic medication was prescribed. All children were prohibited from eating solid food or drinking milk products after midnight but were instructed to ingest clear fluid (10 ml·kg⁻¹) three hours before anaesthesia. Anaesthesia was induced and maintained with sevoflurane and nitrous oxide. Shortly after tracheal intubation, gastric contents were aspirated using an oro-gastric tube. The trachea was extubated in the operating room after residual neuromuscular blockade by vecuronium had been antagonized with neostigmine 0.05 mg·kg⁻¹. All children were then transferred to the ophthalmological ward. The degree of recovery from anaesthesia was assessed by an independent observer using the Aldrete score¹¹ 10–15 min after anaesthesia. Oral intake of clear fluid (up to 5 ml·kg⁻¹·time⁻¹) was required or offered a minimum of one hour after surgery if the children felt thirsty. Until then, postoperative infusion was continued. The times of fluid ingestion were not limited. No children received opioids or antiemetics throughout the study. All children were discharged two days after surgery without sequelae.

Pain was rated by an independent observer using an objective pain scale (OPS) consisting of five items¹² postoperatively on awakening, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hr thereafter. "Pain-free" denotes those children who scored zero throughout the study period. Children with OPS score 5 received a diclofenac suppository (12.5 or 25 mg) as a "rescue" analgesic. Rectal diclofenac is our routine regimen for pain control after paediatric surgery.^{13,14} This route of diclofenac provides postoperative analgesia and is a useful alternative to caudal blockade in children undergoing inguinal herniotomy.¹⁵ Diclofenac suppository has more potent analgesic effects than rectal acetaminophen in paediatric adenoidectomy.¹⁶ Postoperative diclofenac and acetaminophen provide similar pain relief.¹⁷ The analgesic effect of flurbiprofen was assessed with the highest OPS score, the percentage of "pain-free" children, and the overall number of patients requiring diclofenac. Vomiting was recorded by ward nurses, who were unaware of the group allocation. Retching and nausea were discounted. The observation period was eight hours.

Parametric data (e.g. age, weight) among the groups were compared using one-way analysis of variance with Tukey correction for post-hoc comparison. Nonparametric data (e.g. the number of children

requiring "rescue" analgesic, incidence of vomiting) were analyzed using the χ^2 test and Fisher's exact test. The highest OPS scores and Aldrete recovery score were compared using the Kruskal-Wallis test. $P < 0.05$ was deemed statistically significant.

Our previous reports^{13,14} indicated that approximately 90% of children in the placebo group required a rescue analgesic and 37% of children vomited. Power analysis¹⁸ based on the proportion revealed that sample size ($n=30$ each) in the present study was sufficient to detect analgesic effect of flurbiprofen provided that the power is 80%. It is possible to detect antiemetic effect of the drug in this small sample size, if the effect is potent.

Results

Demographic and operative data, and recovery in the ward were comparable (Table I). The highest OPS score was lower in children receiving flurbiprofen 1 mg·kg⁻¹ than in those receiving the other regimens

TABLE I Clinical Characteristics of the Study Groups.

Groups	Saline (control)	Flurbiprofen 0.5 mg·kg ⁻¹	Flurbiprofen 1 mg·kg ⁻¹
Age (yr)	5±2	6±2	6±2
Weight (kg)	20±3	22±4	23±4
Clear fluid ingested (ml·kg ⁻¹)	9.2±0.3	8.9±0.3	9.4±0.3
Surgical time (min)	84±21	80±17	78±18
Anaesthesia time (min)	111±25	106±23	103±24
Time to extubation (min)#	9±3	8±3	9±4
Time to obeying commands (min)#	19±6	17±6	20±7
Postoperative recovery score on returning to the ward	9 (7-10)	9 (7-10)	9 (7-10)
Number of muscles repaired	2 (1-4)	2 (1-4)	2 (1-4)

Values are expressed as mean (SD) or median (range).

Anaesthesia time: from induction of anaesthesia until extubation of the trachea; Extubation time: from the end of surgery to tracheal extubation; Obeying commands time: from the end of surgery to response to commands which was evaluated by asking the child to "squeeze my hand" at 30-60 sec intervals.

#These times are in minutes from the end of surgery unless otherwise stated. For any variables, $P > 0.05$.

TABLE II Number of patients requiring postoperative analgesic "Rescue" therapy and the highest Objective Pain Scale (OPS) scores and incidence and frequency of postoperative emesis.

	Saline (control)	Flurbiprofen 0.5 mg·kg ⁻¹	Flurbiprofen 1 mg·kg ⁻¹
ANALGESIC EFFECT			
Number Requiring "Rescue" (%)	28/30 (93%)	29/30 (97%)	15/30*# (50%)
Highest OPS (median (range))	7 (3-10)	7.5 (3-10)	4.5 (2-10)*#
ANTIEMETIC EFFECT			
Oral intake time (min) (mean±SD)	163±57	174 (63)	159 (61)
Incidence	9/30 (30%)	9/30 (30%)	7/30 (23%)
Frequency (median (range))	1 (1-3)	2 (1-3)	1 (1-3)

OPS: maximum and minimum possible scores are 10 (= severe maximum pain) and 0 (= no pain), respectively.

Oral intake time: from the end of surgery to oral intake.

*Lower score than the control group ($P < 0.05$). #Lower score in the flurbiprofen 1 mg·kg⁻¹ group than in the 0.5 mg·kg⁻¹ group ($P < 0.05$).

(Table II). However, there were no "pain-free" children. The overall number of children requiring postoperative "rescue" analgesics was lower in the flurbiprofen 1 mg·kg⁻¹ group than in the other two groups. Oral intake time was similar among the three groups. No children vomited before surgery. The overall incidence and frequency of vomiting was comparable in the three groups (Table II).

Discussion

Flurbiprofen 1 mg·kg⁻¹ provided postoperative analgesia in 50% of children after strabismus surgery. Because NSAIDs and opioids act at different sites, a combination of these drugs may provide additive pain relief. The absence of severe untoward effects has encouraged us to conduct a coming trial of flurbiprofen in children undergoing day-surgery. Further studies are also required to compare the effects of flurbiprofen and ketorolac in strabismus surgery, because comparative data on postoperative pain control are unavailable.

We have also shown that flurbiprofen failed to reduce vomiting following strabismus surgery. This failure may be attributed to the small sample size of the study, the relatively lower incidence of this complication (30%) in the control group, or poor pain control even in the flurbiprofen group. The number of children enrolled in our study may be insufficient to detect a slight difference (7%) in the incidence of vomiting between the control and flurbiprofen groups. The low incidence of postoperative emesis may be related to our routine duration of hospitalization (two days) after surgery. This period may provide helpful postoperative rest (e.g. lack of body movement, avoidance of passive transfer). A primary antiemetic effect of flurbiprofen may have been counteracted by poor pain control (success rate of 50%). Opioids with potent analgesic and emetic effects are often used to reduce pain after strabismus surgery. Use of a larger sample size or opioids would have elicited a different result concerning postoperative emesis.

Flurbiprofen (50 mg ampule: ¥351=US\$3.25) and acetaminophen (120 mg suppository: US\$1.34) are less expensive than ketorolac (30 mg ampule: US\$6.84). However, the two former drugs may need antiemetics such as droperidol (1 ml ampule: US\$3.54), since they seem to have little or no antiemetic effect following strabismus surgery unlike ketorolac. Prophylactic droperidol is more cost-effective than metoclopramide (US\$1.50) and ondansetron (4 mg ampule: US\$22.51) for antiemetic therapy.¹⁹ Although acetaminophen costs less than flurbiprofen, the cost-benefit ratio of the drugs cannot be simply compared because the latter is more potent analgesic. Cost-effectiveness of these analgesics/antiemetics including the expense of treatment for drug-related side effects should be compared in the same setting.

In conclusion, preoperative intravenous flurbiprofen 1 mg·kg⁻¹ reduced pain but not vomiting after paediatric strabismus surgery. These data suggest that flurbiprofen *iv* is a simple approach for postoperative pain relief in this setting.

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Footnotes

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