Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery


SUMMARY
In a prospective, double-blind, randomized study, we have compared i.v. ketorolac and morphine in paediatric outpatients undergoing strabismus surgery. Forty-two ASA I or II children, aged 2–12 yr, were allocated randomly to receive either ketorolac 0.75 mg kg\(^{-1}\) i.v. or morphine 0.1 mg kg\(^{-1}\) i.v. and metoclopramide 0.15 mg kg\(^{-1}\). Anaesthesia was induced with propofol and maintained with propofol and nitrous oxide. Pain was assessed at 15-min intervals until discharge, and the incidence of nausea and vomiting was recorded for the first 24 h. There was no difference in pain behaviour scores or recovery times. The incidence of nausea and vomiting during the first 24 h was 19% in the ketorolac group and 71% in the morphine group (P < 0.001). We concluded that ketorolac was an effective analgesic for this type of surgery and that it was associated with less postoperative emesis than morphine and metoclopramide. (Br. J. Anaesth. 1994; 72: 624–628)

KEY WORDS

Postoperative vomiting is common after corrective strabismus surgery in children [1]. Many factors are known to influence the incidence of vomiting in paediatric strabismus surgery, including the use of opioid analgesics [2], administration of antiemetics [3] and anaesthetic technique [2, 4]. Propofol has been shown previously to decrease the incidence of nausea and vomiting in children undergoing corrective strabismus surgery compared with halothane [2, 4, 5], although this effect is less dramatic when opioids are required for pain relief [2]. Previous studies of strabismus surgery have assessed the efficacy of antiemetics in reducing postoperative nausea and vomiting, but have not compared different analgesics for emetic effects. Ketorolac is a non-steroidal anti-inflammatory analgesic that has been shown to be effective in the treatment of postoperative pain in children [6]. When used for non-strabismus surgery, its use was associated with less postoperative emesis than morphine [6]. The aim of this study was to assess the efficacy of i.v. ketorolac as an analgesic and to compare the incidence of postoperative emesis with i.v. morphine and metoclopramide in children undergoing corrective strabismus surgery with propofol anaesthesia.

PATIENTS AND METHODS
We obtained approval from the institutional review body for human research and written informed consent was obtained from the parents of all patients. Patients with a known allergy to ketorolac or non-steroidal anti-inflammatory agents and a history of motion sickness, inner ear or CNS disorders, peptic ulceration or renal insufficiency were excluded. All children were allowed to eat solid food for up to 8 h before operation and clear liquids (up to approximately 4 ml kg\(^{-1}\)) for up to 3 h before operation. Premedication consisted of midazolam 0.75 mg kg\(^{-1}\) orally (to a maximum dose of 20 mg), 15–20 min before operation. An i.v. cannula was inserted after administration of 66% nitrous oxide in oxygen and anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\). Tracheal intubation was facilitated with vecuronium 0.1 mg kg\(^{-1}\) and atropine 10 μg kg\(^{-1}\) was administered for prevention of the oculocardiac reflex. Anaesthesia was maintained with a propofol infusion of 400 μg kg\(^{-1}\) min\(^{-1}\) for the first 10 min followed by 150 μg kg\(^{-1}\) min\(^{-1}\), adjusted to maintain arterial pressure and heart rate to within 20% of baseline values. Ventilation was controlled using 66% nitrous oxide in oxygen adjusted to maintain end-tidal carbon dioxide partial pressure at 4–5.3 kPa.

Patients were allocated randomly to two groups. Group 1 (ketorolac) received ketorolac 0.75 mg kg\(^{-1}\) i.v. before the start of surgery; group 2 (morphine) received morphine 0.1 mg kg\(^{-1}\) i.v. and metoclopramide 0.15 mg kg\(^{-1}\) i.v. before the start of surgery. All children received lactated Ringer’s solution i.v. during the perioperative period. Hourly...
significant. Data were processed using Statview SE +
Apple Macintosh Powerbook 170 computer.

**RESULTS**

There were no differences in patient characteristics
text between the two groups (table III). There was also
no difference in the number of eye muscles operated
on, duration of surgery or anaesthetic, total dose of
propofol infused or i.v. fluids administered, time to
first response to command, additional analgesic and
antiemetic use, time to discharge from hospital or
length of drive home (table IV).

There were no differences in pain scores between
the two groups at any time. Figure 1 shows the
number of children without pain (pain behaviour
score = 0) in the two groups at 15-min intervals.
Figure 2 shows the distribution of maximum pain
scores throughout the hospital stay. No patient in
group 1 had a pain score greater than 3 and only one
patient in group 2 had a score greater than 5
requiring additional morphine; this child did not
vomit or have nausea at any stage. Additional
analgesic requirements (morphine or paracetamol)
were slightly higher in the morphine group (three in
group 1 vs five in group 2) (ns).

The incidence of both nausea and vomiting and
vomiting alone was divided into that occurring in
hospital, on the drive home, while at home and
during the first 24 h after operation (table V). No

<table>
<thead>
<tr>
<th>Table I. Pain behaviour score (each of five categories is scored 0, 1 or 2, giving a maximum score of 10)</th>
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<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Cry</td>
</tr>
<tr>
<td>Face</td>
</tr>
<tr>
<td>Body position</td>
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<td>Legs</td>
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<td>Consolability</td>
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<th>Table II. Discharge criteria</th>
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<tr>
<td>Airway: unobstructed</td>
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<td>Respiratory effort: unlaboured</td>
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<tr>
<td>Level of consciousness: awake or easily aroused</td>
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<tr>
<td>Vital signs (heart rate, arterial pressure, pulse oximetry): stable</td>
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<td>Comfort level: according to pain behaviour score</td>
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<td>Operative site: dressing dry and intact</td>
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fluid requirements were calculated from the child's
body weight as follows: 4 ml kg⁻¹ for children up to
10 kg; an additional 2 ml kg⁻¹ for each kilogram
above 10 kg, up to 20 kg; and an additional 1 ml kg⁻¹
for each kilogram above 20 kg. The total volume
given was calculated to provide fluids for a 12-h
period. The propofol infusion was discontinued
10 min before the end of surgery and residual
neuromuscular block was antagonized with atropine
20 µg kg⁻¹ and edrophonium 1 mg kg⁻¹. Stomach
contents were aspirated with an orogastric tube and
the patients were extubated when awake. The
patients were then transferred to the recovery unit.

The postanaesthetic recovery unit (PARU) at our
institution is divided into phases 1 and 2; initial
recovery from anaesthesia occurs in phase 1, the
average length of stay being approximately 1 h. Pain
was assessed at 15-min intervals until discharge
using a pain behaviour score (table I) by a recovery
room nurse blinded to the analgesic given.

Time to first response to command and the
incidence of nausea and vomiting were also noted.
Vomiting was defined as the forceful expulsion of
stomach contents. If additional analgesia was
required, as indicated by a score greater than 5,
morphine 0.05 mg kg⁻¹ i.v. was administered. If the
score was between 3 and 5, a paracetamol suppository
of 15 mg kg⁻¹ was prescribed. Oral paracetamol was
prescribed for analgesia at home. Persistent nausea
and vomiting (greater than twice while in recovery)
was treated with droperidol 50 µg kg⁻¹ i.v. Patients
were discharged when our standard post anaesthesia
care unit criteria had been met (table II). The family
was contacted by telephone within 24 h of surgery to
determine the length of drive home, the incidence of
nausea and vomiting on the drive and while at home,
and the use of analgesics and antiemetics.

Results were analysed using the unpaired t test,
chi-square test or Mann–Whitney U test, as
appropriate. P < 0.05 was considered statistically
significant. Data were processed using Statview SE+
graphics, version 1.04 (Abacus Concepts, Inc.) on an
Apple Macintosh Powerbook 170 computer.
Corrective strabismus surgery in children is associated with both pain and vomiting. Several studies have shown the advantage of propofol infusion compared with an inhalation technique in reducing postoperative emesis [2, 5], but if opioid analgesia is administered, the beneficial effect of propofol anaesthesia is reduced. The present study showed that by using the non-opioid analgesic, ketorolac, analgesia comparable with that of morphine was achieved with a lower incidence of nausea and vomiting in the first 24 h after operation (less than 20%). This low rate of emesis is similar to that of a previous study from our institution using propofol anaesthesia, in patients who did not receive morphine after operation [2].

Pharmacokinetic studies of i.v. ketorolac 0.5 mg kg\(^{-1}\) in children suggested that, because of the greater volume of distribution and clearance of the drug, a larger dose per weight may be required than in adults [7]. Ketorolac 10 or 30 mg i.v. has been used successfully as an alternative to morphine 2 or 4 mg in the treatment of moderate to severe postoperative pain in adults undergoing gynaecological, abdominal or orthopaedic surgery [8]. Watcha and colleagues demonstrated, in children undergoing elective surgery, that an intraoperative dose of ketorolac 0.9 mg kg\(^{-1}\) i.v. provided postoperative analgesia similar to that of morphine 0.1 mg kg\(^{-1}\) and that ketorolac was associated with significantly less emesis. We chose a dose of 0.75 mg kg\(^{-1}\) as it has been suggested that ketorolac may have a "ceiling" analgesic effect and that doses between 0.5 and 0.9 mg kg\(^{-1}\) may produce a similar degree of pain relief [6]. The present study showed that ketorolac 0.75 mg kg\(^{-1}\) provided analgesia comparable with that of morphine 0.1 mg kg\(^{-1}\) for this type of surgery, as assessed by a pain behaviour score.

Recent restrictions on dose and duration of treatment with ketorolac have been recommended by the Committee on Safety of Medicines following reports of fatalities associated with the use of this drug [9]. Contraindications to ketorolac include history of peptic ulceration or gastrointestinal haemorrhage, haemorrhagic diathesis or antico-
agulant therapy, operations associated with a high risk of bleeding, asthma, hypersensitivity to aspirin or non-steroidal anti-inflammatory agents, renal impairment, hypovolaemia and pregnancy or lactation.

In a pilot study, pain scoring was attempted initially using the “Oucher” scale [10] which requires children to point to a graded set of faces in order to rate their pain. We found a reluctance by the children to open their eyes in the immediate postoperative period and therefore used the more objective pain behaviour score. The use of supplementary analgesia (either morphine or paracetamol) was lower in the ketorolac group, although this was not significant.

There have been several studies demonstrating beneficial effects of infusions of propofol compared with conventional inhalation techniques in reducing the incidence of postoperative emesis in paediatric strabismus surgery [2, 4, 5]. The role of nitrous oxide as an emetic stimulus is not defined clearly, although the incidence of emesis is clearly increased when opioids are used. The routine use of opioids in strabismus surgery remains controversial. In a previous study [2], we found that despite the use of paracetamol suppositories during operation, nearly 50% of patients required opioids after operation for additional analgesia. We felt that routine analgesia was justified for this type of surgery and therefore used the morphine group as a control.

The influence of premedication on postoperative vomiting is unclear. We used midazolam 0.75 mg kg$^{-1}$ orally, as suggested by Feld, Negus and White [11]; this provided good sedation, easy parental separation, ready acceptance of the face mask and minimal reaction to i.v. cannulation. Some authors have reported restlessness on emergence from a propofol-based technique [2, 4]. This was not seen in the present study; patients were noticeably sedated for the first 30 min of recovery. Hospital stay was not prolonged as a result of premedication with midazolam. In similar studies of strabismus surgery using propofol anaesthesia, Larsson, Ageirsson and Magnusson [4] used rectal midazolam for premedication but did not report discharge times, while Watcha and colleagues [5] omitted premedication and reported a mean discharge time of 4.7 ± 2 h. Discharge time was 2.2 ± 1 h in the group premedicated with midazolam 0.75 mg kg$^{-1}$ in the study by Feld, Negus and White [11]; this is similar to our discharge times of 1.8 ± 0.5 h.

Several drugs have been used to reduce the incidence of vomiting after strabismus correction, including droperidol [12], metoclopramide [3, 13], promethazine [1], dicyazine [14], hyoscine [15] and even acupressure [16]. Broadman and co-workers [13] used metoclopramide 0.15 mg kg$^{-1}$ i.v. and showed a reduction in both emesis and recovery room times, while Lin, Furst and Rodarte [3] showed that metoclopramide 0.25 mg kg$^{-1}$ i.v. was as effective as droperidol 75 μg kg$^{-1}$ i.v. in reducing the incidence of emesis and patient discharge time after strabismus surgery. A pilot study at our institution compared ketorolac with morphine alone in strabismus surgery and found an unacceptably high incidence of vomiting in the morphine group (> 85%). It was decided therefore, to add metoclopramide to the morphine group; by omitting metoclopramide in the ketorolac group, any antiemetic effects would be biased towards the morphine group.

The pattern of nausea and vomiting was interesting. We divided this into vomiting occurring in hospital, on the trip home and while at home. It is important to assess symptoms for the first 24 h, as vomiting occurs frequently on the trip home or while at home [17]. In the ketorolac group, the incidence of vomiting during the three time intervals was 10%, while in the morphine group, a relatively low incidence of vomiting in hospital (19%) increased while at home (33%). Morphine appeared to be more of an emetic stimulus on the trip home and resulted in delayed vomiting. It has been known for some time that morphine and other opioid analgesics exert their effects on both the chemoreceptor trigger zone and the sensitivity of the labyrinthine system [18, 19]. This latter effect may explain the increasing incidence of emesis seen with morphine during travel home, particularly in those children whose sight was impaired at the same time. The overall incidence of vomiting during the first 24 h was 52% in the morphine group compared with 19% in the ketorolac group. Relatively rapid discharge times, which is the practice of this institution, may have contributed to this pattern.

Relatively few studies have observed an incidence of vomiting of less than 30% in the first 24 h after strabismus surgery. In three recent studies using propofol anaesthesia, there was a low incidence of postoperative emesis in several situations. Larsson, Ageirsson and Magnusson used fentanyl 2 μg kg$^{-1}$ at the beginning of operation and paracetamol after operation, resulting in only 1 of 33 patients vomiting [4]. Watcha observed an incidence of postoperative emesis of 23% using morphine 0.1 mg kg$^{-1}$ but avoided nitrous oxide; when nitrous oxide was used, postoperative vomiting increased to 60% [5]. Weir and colleagues reported a 24% incidence of emesis when opioids were not required for postoperative pain relief [2].

REFERENCES


