KETOROLAC TROMETAMOL FOR POSTOPERATIVE ANALGESIA AFTER ORTHOPAEDIC SURGERY


SUMMARY

We have compared the postoperative morphine requirements and analgesic efficacy of four doses of i.m. ketorolac 30 mg administered 6-hourly with placebo in a double-blind study of patients undergoing major or minor orthopaedic surgery. During the 24-h postoperative study period which began at the end of surgery, patients were prescribed i.m. morphine 10 mg as required 2-hourly and assessments were made of pain at 4 and 24 h. After major surgery, the median morphine consumption over 24 h was 10 mg in patients who received ketorolac, compared with 30 mg in those who received placebo (P = 0.008). Visual analogue pain scores and verbal pain assessments were better than placebo at 4 h (P = 0.028 and P = 0.008, respectively), but were not statistically different between the groups at 24 h. Overall assessment of pain was similar in both groups who had undergone major surgery. In the minor surgery groups, median morphine consumption was 0 mg in patients who received ketorolac, compared with 10 mg in those given placebo (ns). Visual analogue pain scores at 24 h after surgery were significantly less in patients who had received ketorolac compared with placebo (P = 0.046) and the overall assessment of pain relief was better in the ketorolac group (P = 0.0007). Mandatory administration of ketorolac appeared to be of benefit in both major and minor orthopaedic surgery, although the principal effects were reduction in requirement for supplementary morphine for major surgery and better overall analgesia for minor surgery.

KEY WORDS


Ketorolac trometamol is a new non-opioid analgesic of the non-steroidal anti-inflammatory (NSAID) class [1, 2] which may be administered by the oral, i.v. or i.m. routes and has been shown to have clinically useful morphine-sparing effects after major abdominal surgery [3].

The prescription of opioid analgesics by intermittent, i.m. injections "as required" may result in inadequate analgesia for many postoperative patients [4]. Potentially, administration of an analgesic on a regular basis may improve the quality of postoperative analgesia, but the associated respiratory depression and nausea and vomiting associated with opioids make this strategy unattractive. A non-opioid analgesic might, however, be advantageous.

Ketorolac has been reported to provide useful analgesia after orthopaedic surgery [5, 6]. The present study was undertaken to compare the postoperative morphine requirements and analgesic efficacy of mandatory, intermittent, i.m. ketorolac with placebo in patients who had undergone minor and major orthopaedic surgery.

PATIENTS AND METHODS

Hospital Ethics Committee approval was obtained for the study and all patients gave written informed consent. We studied 75 patients (ages 18–75 yr; weights 45–90 kg) undergoing major or minor elective orthopaedic surgery. Major orthopaedic surgery was defined as an operation which would be expected to fulfill at least two of the following criteria: typical blood loss greater than 100 ml; typical opioid analgesic requirement in the first 24 h of morphine 10 mg every 4 h; requirement for postoperative i.v. fluid administration in the first 24 h.

Patients with significant cardiac, respiratory, hepatic, renal or haematological disorders were excluded from the study. Patients with a history of gastrointestinal bleeding within the previous year or of ulcerative colitis were also excluded, as were patients with allergies to NSAID, psychiatric disorders or a history of drug or alcohol abuse.

A standard anaesthetic technique was used which consisted of premedication with temazepam, induction with i.v. thiopentone and maintenance with enflurane and nitrous oxide in oxygen. Vecuronium was used if neuromuscular block was required. Increments of i.v. morphine were given during...
surgery, as determined by alterations in arterial pressure and heart rate.

Patients were allocated randomly to one of two groups in a double-blind manner. Group 1 received i.m. injections of ketorolac trometamol 30 mg (Syntex Research, Scotland) into the lateral thigh 6-hourly over the 24-h postoperative study period, the first dose being given immediately after surgery. Group 2 received matching placebo injections containing the ketorolac vehicle. All patients were prescribed i.m. morphine 10 mg on demand for pain relief, to a maximum of one administration two-hourly.

Patients were assessed on the evening of surgery and at 24 h after the first dose of study drug. Heart rate, arterial pressure and ventilatory frequencies were noted. Pain scores were assessed using both 100-mm visual analogue scales and a four-point verbal rating scale (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain). Sedation was recorded on a five-point scale (0 = completely awake; 1 = awake but drowsy; 2 = asleep but responds to verbal command; 3 = asleep but responds only to tactile stimulus; 4 = asleep but does not respond to gentle stimulus).

At the 24-h assessment, patients were asked to grade overall pain relief (3 = very good; 2 = good; 1 = fair; 0 = poor). The overall frequency of nausea and vomiting was recorded, with any other adverse effects. The timing and frequency of morphine administration were recorded.

Data were analysed with Minitab v7.1 under DOS 5.0. Patient data were analysed using Student's t test or chi-square test as appropriate. Morphine consumption and pain scores were analysed using the Mann–Whitney U test. A P value of 0.05 or less was taken to indicate significance.

RESULTS

Of the 75 patients studied, 28 underwent major surgery, 14 of whom received ketorolac. One patient in the ketorolac group and two in the placebo group were given oral analgesics during the study and were withdrawn.

Forty-seven patients underwent minor surgery, 24 of whom received ketorolac. One patient in the ketorolac group withdrew from the study because he had no pain and refused further medication. Two patients who had received placebo withdrew because of headache and four patients were withdrawn because they had been given additional oral analgesics or were discharged before the final assessments were made. There were no statistically significant differences between the groups in age, weight, sex and duration of surgery for those who completed the study (table I). Intraoperative administration of morphine was not significantly different between the two minor surgical groups or between the two major surgical groups.

Morphine consumption

For patients who had undergone major surgery, morphine consumption over the first 24 h was significantly less in the ketorolac group (median 10.0 mg (95% confidence interval (CI) 10.0–30.0 mg)) than in the placebo group (30.0 mg (95% CI 20.0–40.0 mg)) (P = 0.008). In the minor surgery group, morphine consumption was numerically lower in patients who had received ketorolac (median 0 mg (95% CI 0–10.0 mg)) compared with those given placebo (median 10.0 mg (95% CI 0–20.0 mg)), but the difference was not statistically significant.

Pain scores

Four hours after major surgery, pain scores measured by a visual analogue scale were significantly smaller in the ketorolac group compared with placebo (P = 0.008) (table II) and this was confirmed by pain measured with a verbal rating scale (P = 0.028). At the end of the study, pain in patients who had undergone major surgery and received ketorolac was less than in patients who had been given placebo, but not significantly. Similarly, in patients who had undergone minor surgery, pain scores were consistently smaller in the ketorolac group compared with placebo and were significantly smaller at the 24-h assessment of pain with the visual analogue scale (P = 0.046) (table II). The overall assessment of analgesic therapy made by the patients on the day after surgery was significantly better in the ketorolac group for patients who had undergone minor surgery (P = 0.0007).

There were no significant differences between the groups in the sedation scores or frequency of side effects such as nausea, vomiting and headache.
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TABLE II. Visual analogue scores (VAS), verbal pain assessment (VPA) (0 = none; 1 = mild; 2 = moderate; 3 = severe) and overall analgesic therapy (Overall) (0 = poor; 1 = fair; 2 = good; 3 = very good) (median (95% CI))

<table>
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<tr>
<th></th>
<th>Placebo</th>
<th>Ketorolac</th>
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<td></td>
<td>(n = 12)</td>
<td>(n = 13)</td>
<td>(n = 17)</td>
<td>(n = 23)</td>
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<tr>
<td>VAS (mm) 4 h</td>
<td>39.5 (26.8-51.7)</td>
<td>22.0 (9.48-24.6)</td>
<td>P = 0.008</td>
<td>ns</td>
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<tr>
<td>VPA (0-3) 4 h</td>
<td>1.5 (1.0-2.7)</td>
<td>1.0 (1.0-2.0)</td>
<td>P = 0.028</td>
<td>ns</td>
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<tr>
<td>Overall (0-3)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>P = 0.054</td>
<td>ns</td>
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<tr>
<td>24 h</td>
<td>28.5 (14.9-52.9)</td>
<td>27.0 (7.5-38.3)</td>
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<tr>
<td></td>
<td>2.0 (1.0-2.7)</td>
<td>1.0 (1.0-2.0)</td>
<td>P = 0.054</td>
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<td>1.0 (1.0-2.0)</td>
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DISCUSSION

Ketorolac has the principal advantage compared with the opioid analgesics of not producing cardiorespiratory depression [7, 8]. However, in common with other drugs of this class, it has the potential of causing possible adverse effects on haematological and renal function [9]. While continuous administration of ketorolac may be more effective than regular i.m. injections, a valuable morphine-sparing effect from intermittent i.m. ketorolac has been shown in patients who had undergone upper abdominal surgery [10].

The present study has demonstrated that regular i.m. injections of ketorolac reduce the median consumption of morphine after major orthopaedic surgery to 33% and should also reduce the risk of the dose-related side effects of opioids. Despite i.m. morphine being given on request to both groups, patients in the major surgery ketorolac group had significantly reduced pain scores 4 h after operation. This may indicate that the nursing staff in a busy general ward when patients are returning from surgery do not have adequate time to devote to pain relief. The overall assessment at 24 h of the quality of analgesia by patients who had undergone major surgery was similar for both treatment groups, in spite of the marked reduction in morphine consumption of those who had received ketorolac.

After minor orthopaedic surgery, the overall consumption of morphine was much less than after major surgery and many patients did not require supplementary opioids. The morphine consumption of patients who received ketorolac was less than that of the placebo group, but was not significantly different. However, visual analogue pain scores and the overall assessment at 24 h of the analgesic therapy in the ketorolac group who underwent minor surgery were significantly better compared with the placebo group. The median assessment of patients who had received ketorolac was the maximum possible score of “very good” pain relief.

There would appear to be two modes in which the combination of opioids and ketorolac may be useful, dependent on the degree of surgical trauma. Patients in the major surgery group who were given ketorolac demonstrated a marked reduction in the median 24-h morphine consumption to 30%, but assessed their pain relief as similar to those who had received placebo. In contrast, patients in both treatment groups who had undergone minor surgery had a similar morphine consumption, but those who received ketorolac had a significantly better assessment of their quality of analgesia. Regular i.m. administration of ketorolac may be useful in the provision of postoperative analgesia after major and minor orthopaedic surgery.

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REFERENCES

