Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery

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Background. Ketorolac is approved for the relief of postoperative pain but concerns have been raised over a possible risk of serious adverse effects and death. Two regulatory reviews in Europe on the safety of ketorolac found the data were inconclusive and lacked comparison with other non-steroidal anti-inflammatory drugs. The aim of this study was to compare the risk of serious adverse effects with ketorolac vs diclofenac or ketoprofen in adult patients after elective major surgery.

Methods. This prospective, randomized multicentre trial evaluated the risks of death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and allergic reactions, with ketorolac vs diclofenac or ketoprofen administered according to their approved parenteral and oral dose and duration of treatment. Patients were followed for 30 days after surgery.

Results. A total of 11,245 patients completed the trial at 49 European hospitals. Of these, 5,634 patients received ketorolac and 5,611 patients received one of the comparators. 155 patients (1.38%) had a serious adverse outcome, with 19 deaths (0.17%), 117 patients with surgical site bleeding (1.04%), 12 patients with allergic reactions (0.12%), 10 patients with acute renal failure (0.09%), and four patients with gastrointestinal bleeding (0.04%). There were no differences between ketorolac and ketoprofen or diclofenac. Postoperative anticoagulants increased the risk of surgical site bleeding equally with ketorolac (odds ratio=2.65, 95% CI=1.51–4.67) and the comparators (odds ratio=3.58, 95% CI=1.93–6.70). Other risk factors for serious adverse outcomes were age, ASA score, and some types of surgery (plastic/ear, nose and throat, gynaecology, and urology).

Conclusion. We conclude that ketorolac is as safe as ketoprofen and diclofenac for the treatment of pain after major surgery.

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Ketorolac tromethamine (trometamol) is an injectable non-steroidal anti-inflammatory drug (NSAID) approved in 1990 for the treatment of postoperative pain. Despite its widespread use during the past decade, concerns have been repeatedly raised over a possible increased risk of serious adverse effects.\textsuperscript{1-5} Death, severe haemorrhage, and acute renal failure have been reported following the administration of ketorolac.\textsuperscript{3-5} In Europe, the Pharmacovigilance Group of the Committee on Proprietary Medicinal Products (CPMP) has conducted two formal reviews on the safety of ketorolac, but available data were inconclusive and lacked comparison with other NSAIDs approved for use in the postoperative period.\textsuperscript{6} The CPMP recommended that a large population study should be carried out to determine the risks of serious adverse effects associated with the use of ketorolac compared with other injectable NSAIDs. We conducted a prospective, randomized multicentre safety trial of ketorolac vs diclofenac or ketoprofen administered to adult patients for relief of pain after major surgery. The risks of death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions were evaluated.

Patients and methods
Forty-nine hospitals in eight countries in Europe (Belgium, Finland, Ireland, Italy, Portugal, Spain, Switzerland, and UK) provided patients for the trial. The study was conducted in accordance with the Revised Declaration of Helsinki (1996 and 1989). The UK Medicines Control Agency acted as rapporteur to the CPMP, and provided approval for patients to receive anticoagulant drugs while receiving one of the study NSAIDs (which is usually a regulated contraindication in the UK). Informed written consent was obtained from all patients before randomization. Ethics approval was provided by each participating hospital and by the regulatory authorities in each country.

Study population
Adults over 18 yr old, undergoing elective major surgery were entered in the trial. The study procedure defined certain exclusions (patients with known sensitivity to any of the study drugs or other NSAIDs, patients in whom NSAIDs were contraindicated, who were pregnant or lactating, who were to undergo minor, emergency or day-case surgery, or who were ASA physical status class V).

For the purpose of the study, major surgery was defined as a procedure of such complexity as to require admission to hospital for more than 24 h and to require injections of NSAID for relief of postoperative pain. The surgical operation performed was documented and then classified for analysis as orthopaedic (e.g., joint replacement, osteotomy, discotomy); abdominal (e.g., colectomy, small bowel resection, open cholecystectomy); gynaecological (e.g., total hysterectomy, myometrectomy, oophorectomy); urological (e.g., nephrectomy, suprapubic prostatectomy); plastic/ear, nose and throat (ENT) (e.g., extensive skin graft, breast reconstruction, rhinoplasty, faciomaxillary procedures); and others (including cardiac, vascular, and thoracic surgery). Arthroscopic, laparoscopic, and endoscopic procedures were not included.

Study design
The study was a prospective, randomized multicentre trial of ketorolac vs diclofenac or ketoprofen to evaluate the risks of five primary serious adverse outcomes; these were death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions. They were defined according to standard diagnostic criteria (Appendix 1). Patients were followed for 30 days after their surgery. Randomization was carried out in blocks at each centre to ensure a balanced allocation between ketorolac and the centre’s designated comparator. All patients who were randomized and for whom we had information about outcomes were included in the analysis (intention-to-treat).

Each of the study drugs was administered according to the approved product label for each drug. The maximum daily dose and duration of treatments were: ketorolac, parenteral 90 mg day\textsuperscript{-1} for 2 days followed by oral 40 mg day\textsuperscript{-1} for up to 7 days; diclofenac, parenteral 150 mg day\textsuperscript{-1} for 2 days followed by oral 150 mg day\textsuperscript{-1} for up to 7 days; and ketoprofen, parenteral 200 mg day\textsuperscript{-1} for 2 days followed by oral 200 mg day\textsuperscript{-1} for up to 7 days. If additional analgesia was required, an opioid could be used. Abstracted data were subjected to random audit and tested for inter-observer reliability.

Data analysis
Each of the serious adverse outcomes was analysed by the Mantel–Haenszel test or the Fisher exact test for rare outcomes to test the null hypothesis. Likelihood ratio tests were used to examine heterogeneity of outcomes in different subsets of patients. The Mann–Whitney test was used for continuous variables, and the chi-squared test, or Fisher exact test was used for categorical variables. The only

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stratification used was by study centre. Risk was assessed by multiple stepwise logistic regressions. Data management was performed by Quintiles Scotland Ltd, and the statistical analysis was performed at the London School of Hygiene and Tropical Medicine. The Steering group of principal investigators was responsible for the design, conduct, and interpretation of this study and was blinded until the final analysis was completed. The Study Safety Committee was un-blinded and provided regular status reports to the UK Medicines Control Agency.

Sample size
An estimate of the required sample size was made using data from a retrospective post-marketing surveillance study which reported a rate of 3.6% for a composite outcome (patients who had died, had increased surgical bleeding, or had gastrointestinal bleeding) in a cohort of patients who received ketorolac and opioid. Using this rate, a sample of 16 000 was calculated to provide over 90% power to detect a relative risk of 1.3 for this composite outcome. Interim power calculations were planned after recruitment of 10, 30, and 60% to determine when a power of at least 80% was achieved to detect a relative risk of 1.5 for the composite outcome. The power calculation was based on a one-sided test using the normal approximation to the Poisson with a 0.025 level of significance, equal to 0.05 on a two-sided test. The significance levels for stopping rules that were established a priori by the Safety Committee for death was $P<0.01$ with a relative risk of 3.0, and for serious adverse outcomes was $P<0.001$ with a relative risk of 3.0 separately for increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions. The Safety Committee recommended to stop the study after reviewing the data on the estimated 60% of patients. The time to obtain agreement from the CPMP, and the 30-day observation period resulted in additional patients being entered in the study before the database was closed. A total of 11 302 patients were randomized. This sample provided over 80% power to detect a relative risk of 1.5 at the rate of 1.24%, which was found for the composite outcome.

Results
Fifty-seven of the 11 302 randomized patients were lost to follow-up, leaving 11 245 patients who completed the trial and were entered in the database for the outcome analysis. Of these, 5634 patients received ketorolac, and 5611 patients received one of the comparator NSAIDs. Procedure violations occurred in 33 patients (0.3%) who met an exclusion criterion but were entered into the study. The median number of days in hospital (interquartile range (IQR)) was 6 (4–9) and was no different between ketorolac and the comparators. Ninety-seven per cent of patients received parenteral injections of the assigned study drug, 53% received oral doses of the same drug during the hospital stay, and 32% received oral doses after discharge. The doses of study medication that were administered varied by country. For example, the median (IQR) dose for parenteral ketorolac varied from 40 (40–70) to 100 (70–160) mg, for diclofenac from 75 (75–150) to 150 (75–225) mg, and for ketoprofen from 200 (100–250) to 400 (300–400) mg. In patients who had serious adverse outcomes, the median number of days of parenteral injections was 1 for all three study drugs, and the median number of days of oral administration was 4. The median maximum daily parenteral dose in patients with serious adverse outcomes was 30, 150, and 100 mg for ketorolac, diclofenac, and ketoprofen, respectively. Doses of parenteral study drug in excess of the approved level were administered in only 1.1% of patients who received ketorolac, in 2.2% of patients who received diclofenac, and in 0.7% of patients who received ketoprofen. A chi-squared test for trend between dose categories and the composite outcome was not significant for any of the study drugs. The baseline characteristics of patients were similar in each study drug group (Table 1). There were 766 patients classified as ASA III or IV, and 3208 patients over the age of 60 yr.

Table 1 Baseline characteristics of 11 302 randomized patients for ketorolac and comparator NSAIDs. Fifty-four patients were lost to follow-up leaving 11 245 patients entered in the database

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ketorolac vs comparator</th>
<th>Ketorolac vs diclofenac</th>
<th>Ketorolac vs ketoprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD) [range]</td>
<td>49 (17), 49 (16) [19–94]</td>
<td>48 (17), 47 (17) [19–90]</td>
<td>49 (16), 50 (16) [19–94]</td>
</tr>
<tr>
<td>Females (%)</td>
<td>3429 (61), 3382 (60)</td>
<td>1456 (56), 1467 (57)</td>
<td>1973 (64), 1915 (63)</td>
</tr>
<tr>
<td>ASA I</td>
<td>3505 (62), 3505 (62)</td>
<td>1602 (62), 1589 (62)</td>
<td>1903 (62), 1916 (63)</td>
</tr>
<tr>
<td>ASA II</td>
<td>1769 (31), 1750 (31)</td>
<td>760 (29), 771 (30)</td>
<td>1009 (33), 979 (32)</td>
</tr>
<tr>
<td>ASA III</td>
<td>364 (6), 373 (7)</td>
<td>210 (8), 211 (8)</td>
<td>154 (5), 162 (5)</td>
</tr>
<tr>
<td>ASA IV</td>
<td>15 (&lt;1), 14 (&lt;1)</td>
<td>13 (&lt;1), 11 (&lt;1)</td>
<td>2 (&lt;1), 3 (&lt;1)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Orthopaedic</td>
<td>1670 (30), 1687 (30)</td>
<td>1224 (40), 1229 (40)</td>
</tr>
<tr>
<td></td>
<td>Abdominal</td>
<td>724 (13), 774 (14)</td>
<td>516 (17), 564 (18)</td>
</tr>
<tr>
<td></td>
<td>Plastic/ENT</td>
<td>844 (15), 784 (14)</td>
<td>232 (8), 208 (7)</td>
</tr>
<tr>
<td></td>
<td>Gynaecology</td>
<td>1067 (19), 1055 (19)</td>
<td>548 (18), 515 (17)</td>
</tr>
<tr>
<td></td>
<td>Urology</td>
<td>335 (6), 333 (6)</td>
<td>36 (1), 40 (1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1026 (18), 1028 (12)</td>
<td>518 (17), 511 (17)</td>
</tr>
</tbody>
</table>
The number and per cent of patients with serious adverse outcomes are summarized in Table 2A for ketorolac vs comparator, Table 2B for ketorolac vs ketoprofen and Table 2C for ketorolac vs diclofenac. There were 155 patients (1.4%) with at least one serious adverse outcome but no difference was found for any outcome between ketorolac and the comparators.

There were 19 deaths (0.17%); the causes of death were cardiac arrest (10 patients), sepsis (three patients), pulmonary embolism (two patients), intraoperative haemorrhage (one patient), renal failure secondary to peritonitis (one patient), metastatic carcinoma (one patient), and respiratory failure (one patient). None were considered to be related to the use of a study drug. Twelve patients had a severe allergic reaction (0.11%), 10 patients had acute renal failure (0.09%), and four patients had gastrointestinal bleeding (0.04%).

The most frequent outcome was increased surgical site bleeding in 117 patients (1.04%) of whom 61 received ketorolac, and 56 received one of the comparators. The risk of surgical site bleeding was 3.05 times higher with the use of postoperative anticoagulants. Forty-one per cent of patients received an anticoagulant after surgery including fractionated low-molecular-weight heparin (LMWH) in 2929 patients (26%), and low-dose unfractionated heparin (UFH) in 1552 patients (13.8%). The risk of surgical site bleeding was generally higher with low-dose UFH than with fractionated LMWH. More patients received anticoagulants after orthopaedic (55%), gynaecological (55%), abdominal (47%), and urological (34%) surgery than after plastic/ENT surgery (14%). Patients who received ketorolac (odds ratio=2.65, 95% CI=1.51–4.67) or comparator NSAID (odds ratio=3.58, 95% CI=1.93–6.70) were equally likely to experience a higher risk of surgical site bleeding when an anticoagulant was administered (Table 3).

Other risk factors for serious adverse outcomes were age, ASA score, history of regular alcohol use, plastic/ENT surgery, gynaecological surgery, and urological surgery (Table 4). However, none of these risks were any different between ketorolac and diclofenac or ketoprofen.

Standard reporting of all adverse events using the WHOART terminology was done in our study. There were 254 patients (2.3%) with these adverse events of which 123 patients received ketorolac and 131 patients received one of the comparators (Table 2A−C).

**Discussion**

This study was designed to answer the concerns of the CPMP of a possible increased risk of serious adverse outcomes with ketorolac compared with other NSAIDs. The addition of a placebo group or other treatment group, such as an opioid, was not considered relevant as there was no concern over safety in patients not receiving an NSAID. Of
particular interest was any increased risk in elderly patients and in those with serious systemic disease who had undergone major surgery. We found the risk of serious adverse outcomes was very low in this study and did not identify any difference between ketorolac and diclofenac or ketoprofen for any outcome.

Gastrointestinal effects

Gastrointestinal perforations, ulceration, and bleeding (PUBs) have been reported with all NSAIDs after chronic use. However, the risk of serious gastrointestinal adverse effects with NSAIDs, including ketorolac, is very low after short-term perioperative use. A review of 15 postoperative placebo-controlled trials reported only one case of serious gastrointestinal bleeding in 1520 patients, of whom 927 had received an NSAID. Several studies have reported an increased risk of serious gastrointestinal bleeding in patients over 60 yr old, in women, in patients with a history of peptic ulceration, in smokers, and in patients who consume excessive amounts of alcohol.

A retrospective postmarketing surveillance study in over 20,000 patients who received ketorolac or opioid, reported a small increased risk of gastrointestinal bleeding with ketorolac (odds ratio=1.30, 95% CI=1.11–1.52) but no significant increased risk of surgical bleeding (odds ratio=1.02, 95% CI=0.95–1.10). These risks were significantly increased further in patients over 70 yr, and in patients who received excessive doses of ketorolac for more than 5 days. In our study, there were only four patients (0.04%) who had gastrointestinal bleeding. None of these patients received ketorolac.

### Postoperative surgical site bleeding

The use of NSAIDs after surgery may increase the risk of bleeding by their antiplatelet effects; however, the evidence of increased bleeding is conflicting. Some studies have reported no increased bleeding with ketorolac or diclofenac when administered after transurethral prostatectomy, a procedure that is commonly associated with postoperative bleeding. In contrast, aspirin or other NSAIDs taken preoperatively increased the risk of postoperative bleeding after prostatectomy. Bleeding time is increased with NSAID therapy and for ketorolac this increase is 312–468 s (normal ~600 s). However, the antiplatelet effects of NSAIDs do not appear to significantly alter postoperative coagulation and may be protective for myocardial infarct and thromboembolism.

In our study, the risk of postoperative surgical site bleeding was increased when anticoagulant drugs were used for thromboprophylaxis after surgery, but was no different between ketorolac and the two other NSAIDs. Low-dose UFH was associated with a higher risk of bleeding (2.5%) than fractionated LMWH preparations (1.3%). A recent meta-analysis of randomized trials in general surgery has reported that low-dose LMWH was safer than low-dose UFH, but at higher doses there was an increased risk of major haemorrhage with both preparations. A possible interaction between NSAID and anticoagulant drugs cannot be ruled out, but this does not appear to involve a clinically important increase in bleeding time. Some types of surgery in our study were associated with a higher risk of surgical site bleeding, independent of the use of postoperative anticoagulants. Plastic/ENT surgery increased the risk by 3.5 times, gynaecological surgery increased the risk by 2.7 times, and urological surgery increased the risk by 2.5 times. A recent study in 215 patients after breast reconstruction found no increased

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Risk of postoperative surgical site bleeding with ketorolac and comparator with and without anticoagulant. POB=postoperative surgical site bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Ketorolac n (%) with POB</td>
</tr>
<tr>
<td>Any anticoagulant</td>
<td>39 (1.7)</td>
</tr>
<tr>
<td>No anticoagulant</td>
<td>21 (0.6)</td>
</tr>
<tr>
<td>Anticoagulant vs no anticoagulant</td>
<td>2.65 (1.51–4.67)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Risk factors for the composite outcome (death, surgical site bleed, or gastrointestinal bleed). *Odds ratio is for 10-yr increase. *Odds ratio is for one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Age*</td>
<td>1.18 (1.04–1.34)</td>
</tr>
<tr>
<td>ASA score²</td>
<td>1.48 (1.10–1.98)</td>
</tr>
<tr>
<td>History of regular alcohol use</td>
<td>1.50 (1.04–2.17)</td>
</tr>
<tr>
<td>Postoperative anticoagulant</td>
<td>2.52 (1.69–3.76)</td>
</tr>
<tr>
<td>Surgery: plastic/ENT</td>
<td>3.45 (2.02–5.89)</td>
</tr>
<tr>
<td>Surgery: gynaecology</td>
<td>2.65 (1.72–4.10)</td>
</tr>
<tr>
<td>Surgery: urology</td>
<td>2.46 (1.28–4.71)</td>
</tr>
</tbody>
</table>
incidence of haematoma with ketorolac, and in our study we found no difference for increased surgical site bleeding between ketorolac and the two comparators in patients who had undergone plastic/ENT surgery or other types of surgery. Whereas the absolute risk of increased surgical site bleeding appears to be small, further studies are needed to evaluate the potential interaction and increased risk with concomitant NSAID and anticoagulant use in specific types of surgery.

Renal effects
Cyclo-oxygenase-1 and -2 are important components of the control of glomerular filtration and excretion of urine. NSAIDs can interfere with renal function through the inhibition of both forms of cyclo-oxygenase. There are four toxic effects of NSAIDs on the kidney: acute ischaemic renal insufficiency, acute interstitial nephritis, analgesic-associated nephropathy, and progressive hypertensive nephropathy. Reports of acute renal failure after ketorolac and other NSAIDs are mainly the result of acute ischaemic effects. Other factors that increase the risk of acute renal failure include hypovolaemia, cardiac failure, ascites, and liver cirrhosis. A large retrospective cohort found no significant association with ketorolac in patients who developed postoperative acute renal failure. A meta-analysis of eight randomized trials of NSAID effects on postoperative renal function reported only a minor transient decrease in creatinine clearance after ketorolac, diclofenac, indomethacin, or ibuprofen. Ten patients (0.1%) had acute renal failure in our study, three cases were reported after ketorolac and seven cases after the comparator NSAIDs. There was no significantly increased risk of acute renal failure in 42 patients with a history of renal insufficiency, or 72 patients with a history of congestive heart failure.

Allergic reactions
Allergic reactions to NSAIDs are uncommon and include skin rash, bronchospasm, and anaphylaxis. It has been estimated that between 5 and 10% of asthmatics are sensitive to aspirin and acidic NSAIDs. Ketorolac has been reported to cause acute bronchospasm in aspirin-intolerant patients. Systemic anaphylaxis associated with NSAID is very rare but is often fatal. There were 12 patients who experienced severe allergic reactions in our study. None of these patients died and no difference was found between ketorolac and the comparator NSAIDs.

The overall risk of serious adverse effects with ketorolac and the comparator NSAIDs was very low in this study. We found no evidence that the risk of serious adverse effects with ketorolac was any different to that with ketoprofen or diclofenac. It should be noted that these drugs were administered according to their approved dose and duration of treatment. We conclude that parenteral and oral ketorolac, ketoprofen, and diclofenac are equally safe for the treatment of pain after major surgery when administered according to the approved product label.

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Appendix 1
Criteria for serious adverse outcomes
Death
Patients who were randomized and entered into the trial and who died from any cause during the 30 days after surgery. The cause of death and all related medical information was documented.

Increased surgical site bleeding
An overt or covert loss of blood from the operative site that requires medical intervention and/or is excessive and/or is unexpected. For internal bleeding, evidence of shock, hypotension (<100 mm Hg systolic, <60 mm Hg diastolic), decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine. For external bleeding, evidence of excessive bleeding into surgical drains and/or wound dressings, shock, hypotension, hypovolaemia, decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine.

Gastrointestinal bleeding
An overt loss of blood from the gastrointestinal tract (haematemesis and/or melaena and/or blood per rectum) that requires medical intervention including endoscopy, transfusion of blood and/or i.v. fluids, or surgical reoperation to control bleeding, with evidence of shock, hypotension, decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine.

Acute renal failure
Renal impairment that results in 100% increase in serum creatinine and/or oliguria, and/or dialysis, with evidence of increased blood urea and increased potassium, i.v. pyelogram, renal biopsy, x-rays, and/or ultrasound.

Severe allergic reaction
An allergic reaction that requires inhaled and/or i.v. medication, and/or intubation, and/or ventilation, with evidence of bronchospasm, dyspnoea, anapnoea, angioedema, laryngeal oedema, shock, hypotension, anaphylaxis, skin rash, inotropic drugs, adrenergic drugs, antihistamines, and/or i.v. corticosteroids.
Appendix 2

The Investigators


References

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