Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Pain relief/management for patients with limb injuries. Specifically intravenous ketorolac and morphine were examined.

Type of intervention
Treatment; Pain relief.

Economic study type
Cost-effectiveness analysis.

Study population
Individuals at least 16 years of age, arriving in an accident and emergency department (A&E) between 9am to 5pm Monday to Friday with isolated painful limb injury. Exclusion criteria included history of substance misuse, dementia, indigestion, peptic ulceration, gastrointestinal haemorrhage, recent anticoagulation, pregnancy, adverse reaction to morphine or ketorolac, renal or cardiac failure, hepatic problems, rectal bleeding, use within previous 24 hours of NSAIDs, asthma, chronic obstructive airways disease, chronic pain syndrome, previous treatment with analgesics, and visual or cognitive impairment.

Setting
Accident and Emergency Department of a University Teaching Hospital. The economic analysis was conducted in Hong Kong, China and Edmonton, Alberta, Canada.

Dates to which data relate
Dates for the collection of effectiveness and resource data were not reported. The base price year used in the analysis was not reported.

Source of effectiveness data
Effectiveness evidence was obtained from a single study.

Link between effectiveness and cost data
Cost data were collected prospectively using the same patient sample as in the effectiveness analysis.

Study sample
The study sample was taken from all eligible patients arriving in the A&E department. Power calculations do not appear to have been used to determine sample size. Initially 182 patients were identified; of these 33 (18%) did not
meet the inclusion criteria and were excluded from the analysis. A further patient, who was initially included, was subsequently withdrawn from the study protocol by his family physician before receiving any treatment. Of the remaining 148 patients, 75 were allocated to the ketorolac group and 73 to the morphine group.

**Study design**
The study was a single-centre, prospective, double blind, randomised controlled trial. Patients were randomised between groups using a random numbers table. A nurse would open a pre-coded envelope indicating details of randomisation number and coded medication. Patients were followed up for up to four weeks following discharge. Those patients with adverse events were encouraged to report these to the study institution within this period. There was no loss to follow up.

**Analysis of effectiveness**
The analysis of effectiveness was based on intention to treat. The primary health outcome used in the analysis was the degree of pain relief, at rest and with activity, measured using a pain relief score, and any adverse events associated with pain relief. At baseline analysis both patient groups had similar demographic and clinical characteristics.

**Effectiveness results**
The effectiveness results were as follows:

Using a hazard ratio where scores greater than 1 favoured ketorolac, at rest pain relief was better in patients receiving morphine, although these results were not statistically significant. For a 50% reduction in pain the hazard ratio was 0.83, (95% CI: 0.60 - 1.15), for 75% reduction 0.84, (95% CI: 0.60 -1.16), and for 100% reduction 0.93, (95% CI: 0.66 - 1.30).

With activity, pain relief was favourable to the ketorolac group, for a 50% reduction the hazard ratio was 1.18, (95% CI: 0.85 - 1.63), not significant, for a 75% reduction this ratio was significant 1.49, (95% CI: 1.05 - 2.12), (p<0.027).

The median rate of decrease in pain was greater with ketorolac than with morphine, for activity in a period of over one-hour, this difference was significant.

The rate of adverse events was significantly different between the two groups; 4 (5%) of the ketorolac group experienced adverse events compared with 65 (89%) of the morphine group, (p<0.0001).

**Clinical conclusions**
Ketorolac appears to be as efficacious as morphine and may offer an advantage over morphine during activity. It also causes fewer adverse events. Morphine may, however, offer a small clinical advantage over ketorolac for patients at rest.

**Measure of benefits used in the economic analysis**
The authors did not introduce a summary benefit measure in the economic analysis. As such a cost-consequences analysis was performed.

**Direct costs**
Costs measured included drug use, pharmacy time, nursing time for both preparation and administration of pain relief, and the treatment of adverse events in the emergency department, emergency room physician costs, inpatient ward costs and re-attendance costs. Costing was undertaken from the perspective of the study institution. A research nurse also recorded procedure times. Resources used in the analysis were reported separately from costs. The costs of drugs used in the analysis were taken from the hospital formulary; a study nurse recorded quantity of drug use. Hospital salary costs were used to estimate costs of nurses, emergency room physicians, pharmacist and dispenser costs.
Inpatient ward costs were based on average daily ward costs at the study hospital. Costs were not discounted, which was appropriate given the short duration of the study. The base price years used do not appear to have been reported.

**Indirect Costs**
Indirect costs were not included.

**Currency**
Hong Kong dollars (HK$).

**Sensitivity analysis**
A one way sensitivity analysis was conducted to test for uncertainty associated with the assumption that all events in the emergency room would be observed within a six-hour period at the study institution. An extra four hours of treatment was included in sensitivity analysis. A threshold analysis was also undertaken to identify how drug costs for ketorolac would have to increase in order to have similar levels of cost-effectiveness to morphine.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The mean costs per patient for pain management in the ketorolac group were HK$43.60 compared with HK$228.80 for the morphine group, (p<0.0001).

The average cost per patient per day (including admissions unrelated to analgesia) in the ketorolac group was HK$11,361.20 compared with HK$7,050.82 for patients in the morphine group.

The difference in overall costs including admissions between the two groups was not significant.

**Synthesis of costs and benefits**
Not applicable as this was a cost-consequences study.

**Authors' conclusions**
Ketorolac is at least as effective as morphine, with improved patient satisfaction and a lower incidence of adverse events. Furthermore it represents a cost-effective alternative to morphine for pain management within an accident and emergency department, as costs of administration and treatment of adverse events are lower than they are for morphine. The authors note that their economic conclusions may not be generalisable outside systems similar to those in Hong Kong.

**CRD COMMENTARY - Selection of comparators**
A justification was provided for the comparator used, namely that morphine represented the gold standard of pain management within an accident and emergency department. You, as a user of the database should decide if this is appropriate within your own setting.

**Validity of estimate of measure of benefit**
The analysis was based on a double blind randomised controlled trial, which was appropriate for the study question. The study sample was representative of the study population. However the authors noted that, as the study only included patients admitted between 9am to 5pm Monday to Friday, it was unclear whether the casemix at the weekend
and other hours would have had an impact on the results of this study. Patient groups were shown to be comparable at analysis. Appropriate statistical analyses were conducted to take account of potential biases in the analysis. In the economic analysis several health outcomes were included and, therefore, this was a cost-consequences study.

**Validity of estimate of costs**
All categories of cost relevant to the perspective adopted appear to have been included in the analysis. The estimate of costs was detailed, although the costs of ordering, delivering and controlling drug stock were not included in the analysis, as it proved impossible to identify costs specific to ketorolac and morphine acquisition. Average staff salaries used in the costing analysis may not reflect the actual staff mix at the study institution. The authors noted that their analysis did not deal with the potential benefits for cost-effectiveness resulting from reduced staff contact time with patients, due to the complex nature of these interactions. The sensitivity analysis demonstrated that these omissions are unlikely to affect the authors’ conclusions. Costs and quantities were reported separately. Resource use data was also taken from the clinical trial. The dates to which prices relate in the analysis do not appear to have been reported.

**Other issues**
This was a well-reported study. The authors did make appropriate comparison of the results of their study with those from other publications and the issue of generalisability to other settings was addressed. The authors did not present their results selectively.

**Implications of the study**
The authors consider their findings relevant to emergency departments in Hong Kong and other systems organised along similar lines. Decision-makers in other settings and countries should consider differences in staff and costs when applying the study results to their own setting.

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