

Cost-Effectiveness of Analgesics for Acute Pain Management

Rainer TH, Jacobs P, Ng YC, et al. Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial. *BMJ* 2000;321:1247-51.

Study Overview

Objective. To determine the cost-effectiveness of intravenous ketorolac versus intravenous morphine for acute pain treatment in an emergency department after isolated serious limb injury.

Design. Randomized, double-blind trial. Cost data were collected concurrently with effectiveness data. Analysis was by intention to treat.

Setting and participants. All patients aged 16 years or older who presented with an isolated painful limb injury (ie, limb injury without other injuries) between 9 AM and 5 PM, Monday through Friday, to an emergency department in Hong Kong were considered for the study. Patients were excluded who had a history of substance abuse, dementia, indigestion, peptic ulceration or gastrointestinal hemorrhage, recent anticoagulation, pregnancy, adverse reaction to morphine or ketorolac, renal or cardiac failure, hepatic problems, rectal bleeding, use of nonsteroidal anti-inflammatory drugs, asthma, chronic obstructive pulmonary disease, chronic pain syndromes, or who had previously received analgesia for the same injury. Individuals who could not use a visual analogue scale (VAS) were also excluded.

Intervention. Subjects received either 10 mg of ketorolac or 5 mg of morphine delivered as a loading dose over 60 seconds, followed by half of the loading dose delivered every 5 minutes as needed for up to 20 minutes (maximum doses, 30 mg and 15 mg, respectively). Medications were prepared in the emergency department by a nurse who allocated patients as they were enrolled. It is not clear whether patients could receive additional medication beyond the study drug.

Main outcome measures. The primary outcome measure was costs of care for patients in each group. The primary clinical outcomes were pain relief, as assessed by a VAS when patients were "at rest" and engaged in "activity" (defined as gentle movements such as those necessary to perform radiographs) and adverse events. The authors also measured patient satisfaction. (Information on the instrument used to assess patient satisfaction was not presented in the article.)

Main results. Of 182 patients who presented with appropriate injuries during the study period, 149 were enrolled. A little more than half of those not enrolled declined to participate, and the rest met clinical exclusion criteria. The study cohort comprised roughly equal numbers of men and women, with a mean age of 54 years. Causes of injury included falling (66%), crush injury (23%), and motor vehicle accident (7%). Two thirds of subjects suffered fractures.

No significant differences were observed in the total cost of care or in any pain relief measures except for the likelihood of achieving 75% pain reduction with activity, which favored ketorolac over morphine ($P < 0.05$). In the cost analysis, when expenses related to admissions were excluded, ketorolac showed a statistically significant advantage (U.S. \$5.60 versus \$29.30, $P < 0.001$). Patients receiving morphine demonstrated significantly more adverse effects; drowsiness, sleeping, dizziness, nausea, vomiting, and phlebitis were the most prevalent (total events, 4 in the ketorolac group versus 65 in the morphine group; $P < 0.001$). No serious side effects were noted in either group. Ketorolac patients reported more satisfaction with analgesia (6.0 versus 5.0, $P < 0.001$), although there was no difference between groups in overall satisfaction with emergency department care.

Conclusion

Ketorolac and morphine used to treat pain from isolated limb trauma lead to roughly equivalent costs and clinical outcomes in an emergency department. Patients have fewer minor adverse reactions from ketorolac and may be more satisfied with its analgesic effects.

Commentary

This reasonably well-done study adds interesting, if not definitive, information to the literature on ketorolac's efficacy versus opiate analgesics. Moreover, Rainer and colleagues

"Outcomes Research in Review" is edited by Adam Jonas, MD, MPH, Medical Director for Health Services, Washington State Department of Corrections, Olympia, WA, and Benoit Tonneau, MD, Assistant Professor of Medicine, Department of Medicine, Albany Medical College, Albany, NY. Dr. Jonas prepared reviews 1-3; Dr. Tonneau prepared reviews 4-6.

provide economic data, which are sparse in this area of research. Some irregularities in the study design bear mentioning, however. For financial reasons, patients were only recruited during “regular business hours.” While there is no clear reason why these patients would differ from the total population presenting to emergency department (eg, during evenings, nights, and weekends), this detail does raise questions about the study’s internal—and, in turn, external—validity. It would also be useful to know how truly blinded the study remained. The authors included no assessment of the numbers of subjects and nurses who could have guessed study allocation. Given that study medications were prepared on site (presumably by nurses who could interact with study nurses), it seems likely that the study became largely unblinded before all outcomes were assessed. Furthermore, the fact that many outcomes were evaluated, including several measures of pain relief, suggests a need to examine study results using more rigorous statistical methods. Doing so would eliminate the conclusion of any advantage in terms of efficacy favoring ketorolac.

The question of generalizability is key in determining the significance of Rainer and colleagues’ research, particularly because it was conducted at a single institution in a small, culturally unique location. A sensitivity analysis might have been helpful to assess the generalizability of cost outcomes. In addition, the practical issue of rescue pain medication was

not discussed. The article seemed to indicate that trial patients could receive no more than the maximum dose of their allocated drug. In the “real world,” most physicians would not set an arbitrary limit on doses of pain medication. Often, ketorolac can be best used in combination with opiates to maximize analgesia and minimize side effects [1]. A measure of the total amount of narcotic administered to study patients would have been a useful and practical outcome. Despite these limitations, this study provides important new information for managing acute pain in the emergency department.

Applications for Clinical Practice

Evidence from this trial is not strong enough to support a widespread change in practice. However, it does suggest that physicians who regularly treat patients with moderate to severe acute pain should consider whether ketorolac should play a larger role in therapy. Similarly, designers of protocols and guidelines should examine costs and rates of adverse drug reactions to determine what role ketorolac should play in standard acute pain management.

References

1. Cordell WH, Wright SW, Wolfson AB, et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. *Ann Emerg Med* 1996;28:151–8.

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