

Comparison of ketorolac dosing in an emergency department setting

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Clinical question

Does the analgesic effect of intravenous ketorolac differ if given in doses of 10, 15, or 30 mg to patients presenting to the emergency department with acute pain?

Article chosen

Motov S, Yasavolian M, Likourezos A, et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department: a randomized controlled trial. *Ann Emerg Med* 2017;70(2): 177-84.

Keywords: emergency department, ketorolac, acute pain, analgesia, pain management

OBJECTIVE

Several existing studies have demonstrated that the analgesic efficacy of ketorolac at 10 mg is similar to that of higher doses for the treatment of patients with postoperative or cancer pain.¹⁻⁴ However, limited data exist assessing dosing in patients with acute pain in an emergency department (ED) setting. This was the first randomized, double-blind clinical trial to evaluate the analgesic efficacy of intravenous ketorolac at three different doses in patients presenting to the ED with moderate to severe pain.

BACKGROUND

Ketorolac tromethamine is a common non-steroidal anti-inflammatory drug (NSAID) used in an ED setting for the treatment of acute pain. It works by reversibly inhibiting cyclooxygenase (COX)-1 and COX-2,

thereby decreasing the production of prostaglandins, thromboxane, and prostacyclin. The duration of action is approximately 6 to 8 hours, with a half-life of 5 hours.⁵ The strong analgesic properties of ketorolac make it an effective opioid-sparing medication. Routes of administration include intravenous, intramuscular, oral, ophthalmic, and intranasal forms. However, this medication also has multiple drug-drug interactions and a significant number of side effects ranging from gastrointestinal hemorrhage to nephrotoxicity.⁵

Despite prior studies in the postoperative and oncologic settings suggesting that 10 mg may be as efficacious as higher doses with a lower risk of side effects, ED providers frequently prescribe much higher doses for the treatment of acute pain.^{1-4,6} In fact, one study suggested that as many as 97 % of ED physicians prescribed ketorolac at doses higher than 10 mg, with some prescribing it at doses three to six times higher.⁶ Although existing data have demonstrated efficacy at lower doses in the above-mentioned populations, ED providers may be hesitant to prescribe lower doses because of a lack of trials assessing the efficacy of these doses in an ED setting. This prompted the authors to conduct the following study assessing and comparing the efficacy of 10 mg with that of higher doses in an ED population of patients presenting with acute pain.

METHODS***Population studied***

This study enrolled 240 adults, aged 18 to 65 years, who presented to the ED with acute flank pain, musculoskeletal pain, abdominal pain, or a headache with a

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pain score of five or greater on a zero to ten numeric rating scale. Acute pain was defined as having onset within 30 days or less. Patients who were pregnant or breastfeeding; with active peptic ulcer disease, acute gastrointestinal hemorrhage, a known history of renal or hepatic disease, an allergy to NSAIDs, unstable vital signs (i.e., systolic blood pressure <90 or >180 mm Hg or heart rate <50 or >150 beats per minute); and who already received analgesic medication were excluded.

Study design

This was a randomized, double-blind study conducted at a single-centre 711-bed urban community teaching hospital with an annual ED census of 120,000 visits. Enrolment occurred between March 2014 and December 2015. The screening took place Monday through Friday from 8:00 a.m. to 8:00 p.m. when an ED pharmacist was present. A study pharmacist prepared the 10, 15, and 30 mg doses of ketorolac and placed the solution into an identical-appearing syringe, which was then delivered to the blinded treating nurse.

Outcomes measured

The primary outcome measured was the reduction in the numeric pain score rating 30 minutes after medication administration. The authors determined *a priori* that a difference of more than 1.3 on a pain scale ranging from 0 to 10 would be clinically significant. This was based on prior data suggesting that 1.3 is the minimum clinically significant difference in pain scores.^{7,8} Secondary outcomes included percentages of people experiencing adverse effects and requiring rescue medication. The authors analyzed the data using an intention-to-treat approach.

RESULTS

Between March 2014 and December 2015, 240 subjects were randomly assigned to a 10 mg ($n=80$), 15 mg

($n=80$), or 30 mg ($n=80$) dose of ketorolac. The mean age was 40.1 years, and 36 % of the patients were male. The mean initial pain score was 7.7 out of 10. There was no significant difference in baseline characteristics with respect to age, sex, initial pain score, or vital signs among all three groups.

There was no significant difference in the degree of pain relief at 15, 30, 60, 90, or 120 minutes among all three doses (Table 1). There were no clinically significant differences in adverse events or rates of rescue medication.

Study conclusion

Ketorolac has similar short-term efficacy at the intravenous doses of 10, 15, and 30 mg in ED patients with moderate to severe pain without increased adverse events.

COMMENTARY

Motov et al. conducted a well-designed, double-blind, and randomized study to evaluate the analgesic effect of intravenous ketorolac in a convenience sample of patients presenting to a busy urban ED. The primary outcome was a reduction in the numeric rating scale pain score at 30 minutes, and the authors demonstrated that ketorolac had a similar efficacy at the intravenous doses of 10, 15, and 30 mg. This is an important finding, as this suggests that ED patients may experience an equal benefit from a lower dose that could reduce the potential for adverse events. Since ketorolac has been marketed, there have been many reports of death because gastrointestinal and operative site bleeding have been associated with it.^{9,10} Consequently, it is imperative to use the lowest possible dose to achieve the ceiling analgesic effect particularly in preoperative patients, the elderly, or those with renal impairment.^{10,11} Strengths of this study include the use of a patient-centred outcome and excellent pain reassessment, as well as an evaluation of ketorolac in isolation.

Table 1. Pain scores for the 10, 15, and 30 mg doses of ketorolac over time

Dosage	Baseline (95 % CI)	15 min (95 % CI)	30 min (95 % CI)	60 min (95 % CI)	90 min (95 % CI)	120 min (95 % CI)
10 mg	7.73 (7.36–8.09)	6.04 (5.48–6.59)	5.14 (4.54–5.74)	4.60 (3.99–5.21)	4.09 (3.50–4.69)	3.74 (3.13–4.35)
15 mg	7.54 (7.18–7.90)	5.76 (5.22–6.30)	5.05 (4.48–5.62)	4.11 (3.53–4.68)	3.84 (3.28–4.41)	3.54 (3.03–4.04)
30 mg	7.80 (7.46–8.14)	5.87 (5.31–6.44)	4.81 (4.18–5.45)	4.14 (3.50–4.78)	3.56 (2.93–4.19)	3.46 (2.85–4.08)

CI = confidence interval.

While no difference was noted in the adverse event rate, this was a secondary outcome, and the study might have been underpowered to detect this important aspect.

It is also important to consider several limitations with respect to this study. First, this study was conducted at a single-centre, urban community teaching hospital during daytime hours, Monday through Friday. It is possible that this study sample might not represent patients presenting during weekends or off-hours or in a different setting, as such patients may have different proportions of underlying aetiologies for their pain. The study also excluded patients older than 65 years who may experience a higher rate of side effects with a higher dose, so it is unclear how this would apply to that patient population. Additionally, this study assessed the effect in patients presenting with only four specific pain locations, and it is possible that other conditions or pain locations may have a different response. It is also possible that some pain syndromes (e.g., flank pain) may respond differently to certain doses of ketorolac, though more studies would be needed to evaluate this. Moreover, there was a significant number of patients with abdominal or flank pain, while headache was underrepresented in the studies. It is difficult to determine from the current study whether a headache has an equal analgesic response to different doses. Of note, ketorolac has been suggested to have similar efficacy to oral NSAIDs (e.g., ibuprofen), with a higher rate of adverse events.^{12,13} The primary benefit of ketorolac is that it is a parenteral NSAID. However, many patients can be administered oral NSAIDs in the ED, and it is unclear whether similar results would have been found if oral NSAIDs were used in place of a parenteral NSAID.

There were also a number of patients across each group who were missing pain assessments (i.e., 15 % in the 10 mg group, 18.8 % in the 15 mg group, and 10 % in the 30 mg group). For the missing data, the authors created an imputation model using the pain assessment at 90 minutes plus factors related to the missing pain assessment. While there was no difference in the pattern of missing pain assessments across the groups, it is possible that the missing values may have altered the results if a significant difference had been identified in only one of the groups. Furthermore, the analgesic effect of ketorolac occurs within 30 minutes, with its maximum effect occurring between 1 and 2 hours and a duration of 6 to 8 hours.^{5,14,15} Pharmacokinetic studies have suggested that ketorolac is metabolized in a linear

manner, meaning that higher doses may have a longer duration of action.¹⁶ While the primary outcome was appropriate given the time of onset, it is unclear if there would have been a difference in prolonged pain relief beyond 120 minutes. Finally, this study was underpowered to detect a significant difference in adverse events. However, the results suggest a similar analgesic effect at lower doses, suggesting that providers can use lower doses of ketorolac that may theoretically reduce the risk of adverse events.

CONCLUSION

Ketorolac was demonstrated to have a similar short-term analgesic efficacy at the intravenous doses of 10, 15, and 30 mg in ED patients presenting with acute pain, suggesting that 10 mg is an effective ceiling dose for this medication.

Competing interests: None declared.

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