Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

Sergey Motov, MD*; Matthew Yasavolian, MD; Antonios Likourezos, MA, MPH; Illya Pushkar, MPH; Rukhsana Hossain, MPH; Jefferson Drapkin, BS; Victor Cohen, PharmD; Nicholas Filk, PharmD; Andrew Smith, PharmD; Felix Huang, MD; Bradley Rockoff, MD; Peter Homel, PhD; Christian Fromm, MD

*Corresponding Author. E-mail: smotov@maimonidesmed.org, Twitter: @PainFreeED.

Study objective: Nonsteroidal anti-inflammatory drugs are used extensively for the management of acute and chronic pain, with ketorolac tromethamine being one of the most frequently used parenteral analgesics in the emergency department (ED). The drugs may commonly be used at doses above their analgesic ceiling, offering no incremental analgesic advantage while potentially adding risk of harm. We evaluate the analgesic efficacy of 3 doses of intravenous ketorolac in ED patients with acute pain.

Methods: We conducted a randomized, double-blind trial to assess the analgesic efficacy of 3 doses of intravenous ketorolac (10, 15, and 30 mg) in patients aged 18 to 65 years and presenting to the ED with moderate to severe acute pain, defined by a numeric rating scale score greater than or equal to 5. We excluded patients with peptic ulcer disease, gastrointestinal hemorrhage, renal or hepatic insufficiency, allergies to nonsteroidal anti-inflammatory drugs, pregnancy or breastfeeding, systolic blood pressure less than 90 or greater than 180 mm Hg, and pulse rate less than 50 or greater than 150 beats/min. Primary outcome was pain reduction at 30 minutes. We recorded pain scores at baseline and up to 120 minutes. Intravenous morphine 0.1 mg/kg was administered as a rescue analgesic if subjects still desired additional pain medication at 30 minutes after the study drug was administered. Data analyses included mixed-model regression and ANOVA.

Results: We enrolled 240 subjects (80 in each dose group). At 30 minutes, substantial pain reduction was demonstrated without any differences between the groups (95% confidence intervals 4.5 to 5.7 for the 10-mg group, 4.5 to 5.6 for the 15-mg group, and 4.2 to 5.4 for the 30-mg group). The mean numeric rating scale pain scores at baseline were 7.7, 7.5, and 7.8 and improved to 5.1, 5.0, and 4.8, respectively, at 30 minutes. Rates of rescue analgesia were similar, and there were no serious adverse events. Secondary outcomes showed similar rates of adverse effects per group, of which the most common were dizziness, nausea, and headache.

Conclusion: Ketorolac has similar analgesic efficacy at intravenous doses of 10, 15, and 30 mg, showing that intravenous ketorolac administered at the analgesic ceiling dose (10 mg) provided effective pain relief to ED patients with moderate to severe pain without increased adverse effects. [Ann Emerg Med. 2016;■:1-8.]

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INTRODUCTION

Background

Ketorolac tromethamine is one of the most commonly used parenteral analgesics in the emergency department (ED) for the treatment of moderate to severe pain, alone or in combination with opioid analgesics.[1] It is a nonsteroidal anti-inflammatory drug that belongs to a group of nonopioid analgesics that primarily inhibit (reversibly) the activity of both cyclooxygenase-1 (constitutive) and cyclooxygenase-2 (inducible) enzymes and block the synthesis of prostaglandins and thromboxanes.[2] Ketorolac is available in oral, intranasal, and parenteral forms. It possesses significant analgesic and antipyretic properties, and it has been widely used to treat a variety of acute painful conditions. It has high cyclooxygenase-1 enzyme selectivity, has a half-life of 2.4 to 8.6 hours, and is extensively metabolized in the liver and eliminated through the kidneys.[2] Ketorolac has multiple drug-drug interactions, many of which arise from the reduction in glomerular filtration

Editor's Capsule Summary

What is already known on this topic

Despite known ceiling effects on nonsteroidal analgesia, many deploy enhanced singular doses, seeking better pain control.

What question this study addressed

Does increasing the dose of intravenous ketorolac improve analgesia in emergency department (ED) patients with a wide variety of pain syndromes?

What this study adds to our knowledge

In a single-site, controlled, randomized trial with 240 subjects, pain reduction at 30 minutes postdosing for 10, 15 and 30 mg of ketorolac was not different and adverse effects did not differ.

How this is relevant to clinical practice

There is no benefit to using higher doses of ketorolac for pain relief in unselected ED patients.

induced by ketorolac or by competitive displacement of the second drug from protein-binding sites. Coadministration of ketorolac with warfarin leads to worsening of gastrointestinal hemorrhage; with steroids, to peptic ulcer disease; with diuretics, to nephrotoxicity and hyperkalemia; and with lithium and digoxin, to toxicity of these agents.[2,3]

Importance

Nonsteroidal anti-inflammatory drugs may commonly be used at doses above their analgesic ceiling, although this may not offer an incremental analgesic advantage and potentially adds risk of harm. Analgesic ceiling is the dose of a drug beyond which any further dosage increase results in no additional analgesic effect.[4] The ketorolac analgesic ceiling dose of 10 mg is lower than both the dosing regimen recommended in emergency medicine textbooks[5] and the recommended Food and Drug Administration–approved doses: 30 mg intravenously and 60 mg intramuscularly for patients younger than 65 years.[6] Ketorolac is the only analgesic whose parenteral dosing is 3 to 6 times higher than the oral regimen based on the Food and Drug Administration–recommended oral regimen of 10 mg every 6 hours for no more than 5 days.[6]

Like all nonsteroidal anti-inflammatory drugs, ketorolac has several potentially serious adverse effects: gastrointestinal hemorrhage, nausea, vomiting, dyspepsia, dizziness or lightheadedness, and somnolence. Of these, gastrointestinal hemorrhage is the most concerning because it also appears to be dose dependent. Of all nonsteroidal anti-inflammatory drugs, the risk of gastrointestinal hemorrhage is highest for ketorolac and increases with higher doses.[7] In healthy volunteers, single doses of parenteral ketorolac have been demonstrated to interfere with platelet function by prolonging bleeding time, inhibiting platelet aggregation, and reducing platelet thromboxane production.[8-10] Likewise, single doses of ketorolac at 15 and 30 mg intravenously and 60 mg intramuscularly have been shown to worsen hemorrhage in postoperative patients.[11,12]

Several studies have demonstrated that ketorolac analgesic efficacy at 10 mg is similar to that at higher doses (15 to 90 mg) for treatment of postoperative and cancer pain while minimizing the adverse effects typical of higher dosages.[13-16] Despite this, Food and Drug Administration recommendations and the majority of studies of parenteral ketorolac in the ED advocate the use of doses that are higher than 10 mg.

Goals of This Investigation

We hypothesized that the standard dosing of ketorolac is supra-analgesic and that higher doses are superfluous. We conducted a clinical trial comparing the analgesic efficacy of 3 doses of intravenous ketorolac for acute pain in the ED.

MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind trial to determine the analgesic equivalency of intravenous administration of ketorolac at 10 mg for the treatment of acute pain compared with higher doses of 15 and 30 mg.

We conducted this study at a 711-bed urban community teaching hospital with an annual ED census of greater than 120,000 visits. Patient screening, enrollment, and data collection were performed by study investigators (S.M., M.Y., I.P., R.H., J.D., and C.F.). The Maimonides Medical Center Institutional Review Board approved the trial. We report this trial in accordance with the Consolidated Standards of Reporting Trials statement.[17]

Selection of Participants

Patients considered for inclusion comprised adults aged 18 to 65 years who presented to the ED primarily for management of acute flank, abdominal, musculoskeletal, or headache pain with an intensity of 5 or greater on a standard 0 to 10 numeric rating scale and who would routinely be treated with intravenous ketorolac in our ED as determined by the treating attending emergency