DEM Journal Club

Article Appraisal

Article: Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial (Annals Emerg Med, 2016, S Motov et al).

Date of Journal Club: September 7, 2017

Resident Reviewer Name(s) and Residency Affiliation: Dr. Jennifer Chao, PGY-3, RCPS-EM Residency

Faculty Methodology/Bio-statistics Resource Person: Dr. Riyad B. Abu-Laban

Background and Study Objective(s):

Ketorolac is a widely used NSAID in the ED because it can be administered IM and IV. However, ketorolac has been shown to have the highest relative risk profile for gastrointestinal bleeding, and the benefit of parenteral over oral administration is poorly defined. Although IV ketolorac is routinely dosed at 30 mg, previous studies in the perioperative setting have found that lower doses have equivalent analgesic effects. This equivalence study sought to compare 3 different dose regimens of IV ketorolac for treating acute pain in the ED.

Study Design:

This was a single-centre, double blind, randomized controlled trial. A convenience sample of healthy and stable ED patients, age 18 to 65 years, who presented with acute, moderate to severe pain and had not yet received analgesic medication were enrolled. Participants were randomized to receive either 10mg, 15mg, or 30mg of IV ketorolac. A pharmacist was responsible for randomization, and participants, providers and researchers were blinded to the allocation. Data gathered included pain scores (from 1-10), vital signs, and adverse effects (all recorded at baseline, 15, 30, 60, 90, and 120 minutes post study drug administration). Rescue analgesia involving a single dose of 0.1mg/kg of IV morphine was available at 30 minutes. The primary outcome was the mean reduction in pain score at 30 minutes. Secondary outcomes included rates of adverse effects and rescue analgesia use. Data were analysed on an intention to treat principle, and multiple imputation was applied to deal with any missing data. The investigators hypothesized that there would be no difference in the primary outcome between the 3 groups, and a sample size calculation indicated that to detect a clinically significant pain score difference (deemed a priori to be 1.3 or greater) with 80% power at an alpha of 0.05, 78 participants in each group were required.

Results:

The study enrolled 240 participants (80 in each group), and all were included in the analysis. The 3 study groups had similar baseline demographics, vital signs, and pain characteristics. At 30 minutes, the pain score of 10 mg group improved from 7.7 to 5.2; the 15 mg group improved from 7.5 to 5.1, and the 30 mg group improved from 7.8 to 4.8. There was no statistically significant difference in the reduction of pain scores at 30 minutes between the groups. Pain scores remained similar between the groups throughout the 2 hour data collection period. Rates of rescue

analgesia were similar, and no serious adverse effects were found.

Validity of Results:

This study was tightly performed regarding randomization, blinding and data collection, and it is noteworthy that there were only two missing data points in the primary outcome. However, as an equivalence trial the study was arguably underpowered at 80% power (meaning a 20% chance exists that the study would fail to detect a significant difference between the groups). Most equivalence trials are powered at 90% or even 95%. Furthermore, given that the rate of rescue analgesic use was common, and that the 30 minute pain scores were approximately 5/10 in all groups, the results illustrates that ketorolac should be viewed as an adjunctive rather than sole analgesic agent. It was noted by Journal Club attendees that the sample size enrolled was insufficient to detect rare but potentially important adverse effects. How patients were selected via the "routinely treated with IV ketorolac" enrolment criterion is subject to selection bias, however it was noted that this would not necessarily undermine the validity of the results as they relate to the equivalence of the various ketorolac doses. Finally, it is difficult to determine if participants were all treated equally because data collection ended at 120 minutes and what happened after this time, such as whether or not patients were still in pain and able to be discharged, is unknown. All of this prompted significant discussion among the Journal Club attendees regarding whether or not this paper was truly "practice changing". These centred around two competing perspectives: (1) "there is no evidence the status quo dosing is problematic"; and (2) "it is axiomatic that we should always use the lowest dose possible of any drug to reduce side effects, and there is no evidence the status quo dosing is required". When Journal Club attendees were informally polled, the room appeared evenly split on prescribing the 10 mg vs 30 mg dose as a result of this study.

Generalizability of Results:

As a single-centre US study, with subjective criteria for who received ketorolac, it was felt that the results would not necessarily be generalizable to all EDs worldwide. However the general sentiment was that this study provided information that was potentially applicable to patients in Canadian EDs.

The Bottom Line:

Journal Club attendees felt that this study supports physicians who choose to administer IV ketorolac at a 10 mg dose rather than the status quo 30 mg dose. However, it was felt that this study does not provide irrefutable evidence that such a shift in standard practice is warranted. It seems likely a significant proportion of EPs will choose to continue the status quo, given the lack of evidence that a single 30 mg dose is detrimental, and the continued possibility it may be beneficial. Ultimately, it was concluded that the best application of the study results arise from the concept of "personalized medicine" and the resulting support for those who chose to use IV ketorolac at lower doses in smaller patients, the elderly, or those deemed to be at increased risk for GI or renal side effects.