DEM Journal Club

Article Appraisal

Article: Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department - A Randomized Clinical Trial

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Background and Study Objective(s):

Increasing overuse of opioids in the United States may be driven in part by levels of physician opioid prescribing. Therefore, changing prescribing practices is an important step in addressing the opioid epidemic. There is growing evidence to support that even short-term opioid use may confer a predisposition to opioid dependence. Wide variation in rates of opioid prescribing exists among physicians, and risk of long-term opioid use is increased when given by a high-intensity prescriber. This study's objective was to compare pain reduction at 2 hours among patient groups receiving 4 different analgesic regimens (three opioid-acetaminophen combinations and one ibuprofen and acetaminophen combination) among adult patients presenting to the Emergency Department (ED) with acute extremity pain.

Study Design:

This was a randomized double-blind trial conducted in both an urban and community ED. The inclusion criteria were adult patients 21-64 years of age who presented to the ED with acute upper or lower extremity pain (defined as pain including or distal to the shoulder or hip) who were clinically judged to require diagnostic imaging. There were multiple exclusion criteria, including chronic pain conditions, past use of methadone or recreational narcotics, and recent opioid, acetaminophen or NSAID use. There were four treatment arms that received the following regimens: 1) 400 mg of ibuprofen and 1000 mg of acetaminophen; 2) 5 mg of oxycodone and 325 mg of acetaminophen; 3) 5 mg of hydrocodone and 300 mg of acetaminophen; and 4) 30 mg of codeine and 300 mg of acetaminophen. Randomization was performed by a research pharmacist using an online randomizer. Patients in each arm were provided three blinded, identical appearing capsules containing the study medications packed with lactose to avoid any pill weight discrepancy. Patients could receive an unblinded 5 mg dose of oral oxycodone at any point during the 2-hour study period as rescue analgesia at the discretion of the ED physician. Additional analgesia could also be administered at the discretion of the ED physician.

The populations at baseline appeared to be similar demographically and had a similar prevalence of fractures. The primary outcome of this study was the mean change in pain scores between treatment groups using a 0 to 10 numerical rating scale (NRS) measured prior to and 2 hours post ingestion. The study was designed with 80% power to detect a change in mean NRS pain score of 1.3, predefined to be clinically significant, and using a within-group

standard deviation of 2.6 based on estimates of variability from a prior study. The analysis was powered for multiple comparisons between each of the treatment arms using a Bonferroni correction. An intention-to-treat analysis was performed using multiple imputation to account for missing data.

Results:

The investigators screened 2302 patients, and after exclusions, a total of 416 patients were enrolled with 104 in each treatment arm. Five patients initially randomized were eliminated from the analysis due to exclusion criteria not initially recognized. Of the remaining 411 patients, full data was collected on all but 4 who were missing a combination of baseline, 1 hour or 2 hours scores.

Pain intensity declined over time in all treatment groups. There were no significant differences between the treatment arms for change in NRS score at 1 or 2 hours and none of the differences between analgesic groups met the a priori definition of a minimally clinically important difference in NRS score of 1.3. The baseline mean NRS pain score was 8.7 and did not differ among groups.

At 2 hours, the mean NRS pain score decreased by 4.3 (95% CI: 3.6 to 4.9) in the ibuprofen and acetaminophen group; 4.4 (95% CI: 3.7 to 5.0) in the oxycodone and acetaminophen group; 3.5 (95% CI: 2.9 to 4.2) in the hydrocodone and acetaminophen group; 3.9 (95% CI: 3.2 to 4.5) in the codeine and acetaminophen group (P = 0.053). 73 patients (17.8%) received rescue analgesics; receipt of rescue analgesia was statistically similar between groups. In a post-hoc sensitivity analysis, the investigators tried to correct for patients who had received rescue analgesia using multiple imputation to estimate these patients' "corrected" pain scores. This analysis did not find a statistically significant difference between the groups' pain responses. Additional post-hoc analysis showed no significant difference in pain score changes for patients who rated their initial pain as a score of 10 or those who had a documented fracture on radiological imaging.

Validity of Results:

The recruitment methods were appropriate for the study, but the well-defined study population was quite narrow and would have excluded many patients in our practice. Patients in all arms received blinded, comparable treatments and blinding was maintained, even in those that required rescue analgesia. Although authors claimed the relatively low dosages of the treatment arms were selected based on studied efficacy, 17.8% of patients required rescue opioid analgesia. This may be a reflection of under-dosing. Physicians in our groups often use twice the doses given in the opioid combination arms. The high rate of administration of rescue analgesia in all treatment arms may have diluted any observable treatment differences and driven results toward the null, though the authors attempted to adjust for this in their post-hoc analysis. Additionally, there is variation between local practice and the described study protocol. In a patient population where a sprain is suspected, rarely would our first choice of analgesia be opioids either alone or in combination with acetaminophen.

Generalizability of Results:

Though the study was applied to a general ED population, 60% of the study cohort identified as Latino and another 31% identified as black, which may limit generalizability to Canadian EDs given that there are potential genetic differences in the pharmacokinetics of these medications. Also, we can't apply this study outside of the treatment of acute extremity pain, and we don't know how effective the treatments were after 2 hours. The study spanned both an urban and community hospital which aids in its generalizability.

The Bottom Line:

For patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at 2 hours between patient groups who were treated with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination regimens. These results align with current practice patterns and provide further evidence to support the use of NSAIDs and acetaminophen in place of opioid combination agents for acute MSK injuries.