Acetaminophen (APAP) +/- Oxycodone

Protocol ID: 2019-10592

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Background

It is clear that many patients with acute musculoskeletal injury continue to suffer substantial amounts of pain despite optimal therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and even with NSAIDS combined with acetaminophen.(1) In head-to-head studies conducted among patients with acute musculoskeletal injury, oral opioids generally do not outperform NSAIDs or NSAIDs combined with acetaminophen.(2, 3) Similarly, studies of opioids combined with NSAIDs versus NSAIDs alone have not demonstrated increased efficacy of the combination.(4, 5) However, these results belie our clinical experience, in which oral opioids appear to play an important role in a select group of patients. Indeed, one critique of the studies mentioned above is that they generally enrolled a broad population of patients with acute musculoskeletal injury, rather than the population most likely to benefit from oral opioids: the population of patients with substantial persistent pain despite appropriate treatment with NSAIDs. Because of the risks now recognized to be associated with oral opioids, it is imperative to identify specific populations likely to benefit from opioids, so that risk/ benefit assessments among these patients can be evidence based. With this is mind, we propose a clinical trial in which the combination of an oral opioid with an NSAID is compared to NSAID therapy without an opioid among emergency department (ED) patients most likely to benefit from the combination: those patients who report inadequate relief of pain despite use of prescription-strength NSAID. We hypothesize that, among an enriched population of ED patients with acute musculoskeletal pain who request additional analgesia after treatment in the ED with an NSAID, oxycodone/ acetaminophen will provide superior analgesia than acetaminophen alone, as measured by the frequency with which patients report adequate pain control 2 hours after medication ingestion.

Methods

Overview. This will be a randomized, double-blind, two-stage comparative effectiveness study conducted in the Montefiore and Einstein EDs. In stage one, patients with severe acute musculoskeletal pain will be enrolled prior to treatment in the ED and then administered ibuprofen, an NSAID. In stage two, those who request additional analgesia after sufficient time has elapsed after ingestion of the ibuprofen will be randomized to oxycodone 10mg/ acetaminophen 650mg or acetaminophen 650mg alone.

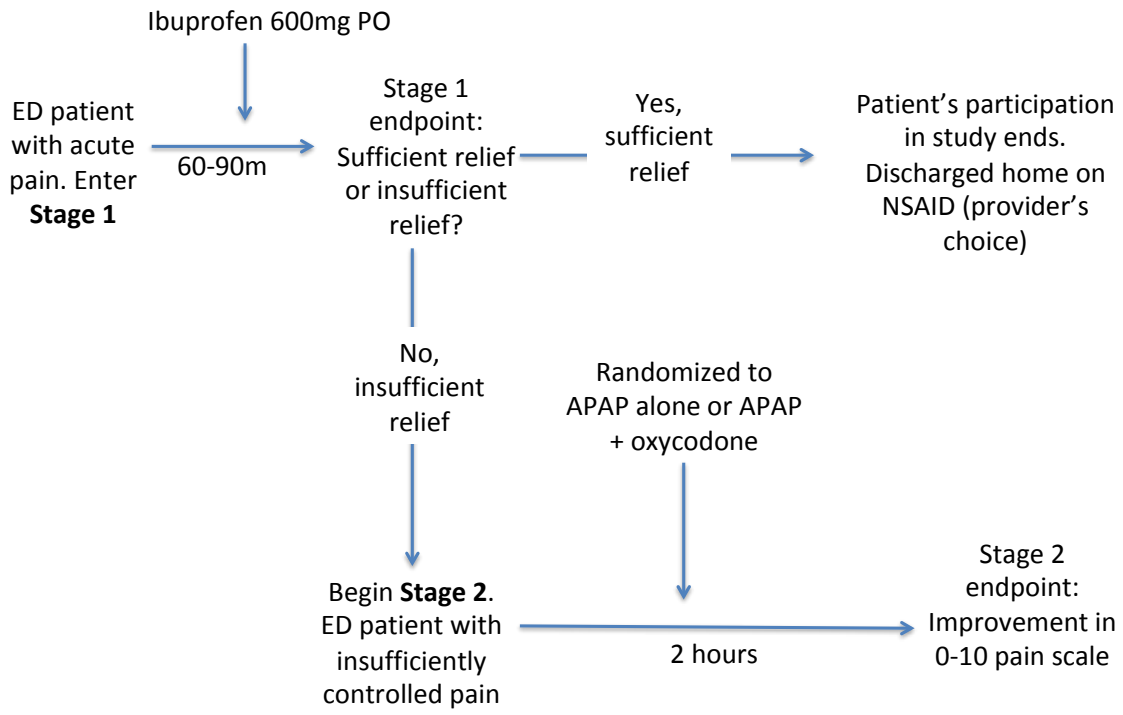

Figure1. Study flow diagram

Population of interest:
--Acute musculoskeletal pain: Any pain attributable to muscles, bones, joints, tendons, ligaments or supporting structures, as determined by the clinical team, of 10 days duration or less. Prior to the onset of acute pain, patients cannot have experienced pain in the same body region during the prior six months
--Pain has to be described as moderate or severe, when the patient is asked if the pain is mild, moderate or severe in intensity

Exclusion criteria are as follows:
--Contraindication to NSAID
--Contraindication to acetaminophen
--Contraindication to oxycodone
--Use of an NSAID within the previous six hours
--Use of acetaminophen within the previous six hours
--Use of an opioid within the previous ten days
--Chronic pain, defined as any pain on ≥50% of days for at least 3 months prior to onset of acute pain
--Gout (a musculoskeletal pain that often requires disease-specific therapy)

Investigational medications

In stage one, all patients will receive ibuprofen 600mg PO.

Patients eligible for stage 2 will be randomized to oxycodone 10mg/ acetaminophen 650mg or acetaminophen 650mg alone.

The ibuprofen will not be blinded. The research pharmacist will mask the medication for stage 2 by placing it in unmarked capsules. Randomization will occur using a sequence generated at http://randomization.com. Research personnel will be presented with consecutive medication packets, which are to be dispensed to consecutive patients in sequential order.

The study will be stratified by study site.

Measures.
--Pain scales. We will use two complementary pain scales. The primary scale will be an 11-point numerical scale, on which patients assign their pain an integer between 0 and 10. This scale, the numerical rating scale for pain, is commonly used in ED acute pain research We will also assess pain using a four-item ordinal scale, on which patients describe their pain using the descriptors severe, moderate, mild, or none.
--Adequacy of analgesia.
Patients will be asked the following questions:
1) Did the medication we gave you control your pain? Answer choices: Yes (it did); No (It did not); and Not sure.
2) The next time you have the same type of pain, do you want a stronger medication? Answer choices: Yes (I want a stronger medication); No (I do not want a stronger medication); and Not sure
--Medication induced side effects. Patients will be asked if they developed any new symptoms they believe were caused by the investigational medications. An affirmative response will trigger an open-ended follow-up question eliciting details
--Satisfaction with medication. Patients will be asked if they would want to take the same medication during a subsequent episode of pain.

If study participants are discharged from the ED prior to completion of the study, they will be followed by telephone.

Outcomes.
This study will be conducted in two stages, the first stage will be non-randomized and open label. The second stage will be randomized and blinded. Each stage will have a primary outcome. Stage one will commence at the time of enrollment and conclude when the patient determines whether or not he or she has experienced sufficient analgesia.

The second stage will commence after the patient has determined whether or not he or she has experienced sufficient analgesia and conclude two hours later.

The primary outcome of the open-label stage is the patient's determination of whether or not they have experienced adequate analgesia. This will be assessed 60 minutes after receipt of the NSAID in the ED. If at this 60 minute time point the patient is unable to determine whether or not they have experienced adequate analgesia, they will be permitted to defer the decision for an additional 30 minutes.

Secondary outcomes of the open-label stage will be an assessment of medication induced side effects, which will be determined 60 minutes after medication ingestion, and at 90 and 120 minutes as well if the patient is still in the ED

The primary outcome of the blinded stage is improvement on the 0-10 pain scale between the time of medication ingestion and 2 hours later. Secondary outcomes include pain levels, adequacy of analgesia, satisfaction with the medication, and medication-induced side effects.

Baseline variables.
--Severity of pain, duration of pain, pain region and discharge diagnosis.
--We will also ask the provider to predict whether or not the patient will opt for second stage treatment.

Analysis.
For the open-label stage, outcomes will be reported as n/N (%) with 95%CI. Similarly for the blinded stage, outcomes will be reported as mean improvement between baseline and two hour with 95%CI. Between group differences will be reported as mean difference with 95%CI. The results will be considered statistically significant if the 95%CI of the between group difference does not cross 0. Missing primary outcome data will be managed by carrying forward pain scores closest to the primary outcome, which we anticipate will bias the results slightly towards the null hypothesis.

Sample size calculation.
We calculated a sample size of 146 (73 per group) based on the following parameters: alpha = 0.05, power = 0.8, minimum clinically important difference of 1.3 numerical rating scale (NRS) units, and standard deviation of 2.8 NRS units. We wish to enroll an additional 8 subjects (approximately 5%) in order to account for potential protocol violations and missing data. Thus, our final sample size for stage 2 is 154 subjects.
We predict that the frequency with which patients request additional analgesia after completing stage 1 will be between 20 and 33%. Therefore, we may need to enroll 770 patients in stage 1 to obtain a sufficient number of patients for stage 2, although

we will continue enroll patients in stage 1 only until 154 patients have been randomized in stage 2.

Data Monitoring Plan.
Dr. David Esses, the director of the Moses ED and Dr. Polly Bijur, Ph.D, head of the Division of Research of the Department of Emergency Medicine, will meet monthly with the PI. This meeting will aim to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

Data Collection.
All data will be entered directly into REDCap.

Process for enrollment and consent.
Participants will be approached for participation in the study after initial evaluation by the attending physician in the emergency department. The recruitment and consent process will be performed by the department's research associates, with supervision from the study investigators.

References

1. Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J**.** Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. JAMA. 2017;318(17):1661-7.
2. Gong J, Colligan M, Kirkpatrick C, Jones P**.** Oral Paracetamol Versus Combination Oral Analgesics for Acute Musculoskeletal Injuries. Ann Emerg Med. 2019.
3. Jones P, Dalziel SR, Lamdin R, Miles-Chan JL, Frampton C**.** Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. Cochrane Database Syst Rev. 2015(7):CD007789.
4. Friedman BW, Dym AA, Davitt M, Holden L, Solorzano C, Esses D, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015;314(15):1572-80.
5. Graudins A, Meek R, Parkinson J, Egerton-Warburton D, Meyer A**.** A randomised controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury. Emerg Med Australas. 2016;28(6):666-72.