CLINICAL STUDY PROTOCOL

Comparing the Efficacy of Five Oral Analgesics for Treatment of Acute Musculoskeletal Extremity Pain in the ED

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Synopsis

Primary Objective
The primary objective is to compare the efficacy of five oral analgesics for treatment of moderate to severe acute musculoskeletal extremity pain in the ED.

Secondary Objectives
The secondary objective is to compare the incidence of side effects of the oral analgesics.

Primary Outcome Variables
The primary outcome is the between treatment group difference in change in patients' rating of pain intensity one hour after ingestion of the study medication.

Secondary Outcome Variables
Secondary outcomes include: 1) the between treatment group difference in change in patients' rating of pain intensity two hours after ingestion of the study medication; 2) difference in proportion of patients who receive rescue medication; 3) difference in proportion of patients who would choose to take the study medication again if they returned to the ED with similar pain; 4) difference in proportion of patients who are satisfied with pain medication; 5) difference in proportion of patients who experience side effects.

Study Duration
The study will continue until the target enrollment has been achieved. Based upon prior research studies, we anticipate that it will take approximately 15 months to reach our target.

Study Design
This is a double-blind, randomized controlled trial comparing the analgesic efficacy of 5 mg oxycodone + 325 mg acetaminophen, 5 mg hydrocodone + 300 mg acetaminophen, 30 mg codeine + 300 mg acetaminophen, 400 mg ibuprofen + 1000 mg acetaminophen, and 800 mg ibuprofen + 1000 mg acetaminophen.

Study Population
Adult patients (21 through 64 years of age) presenting to the Emergency Department with moderate to severe acute musculoskeletal extremity pain.

Number of Participants
Our target enrollment is 550 patients with complete data (110 in each arm). We anticipate needing to enroll up to 600 patients (120 in each arm) in order to achieve this goal.

Number of Study Sites
This study will be conducted in the acute care areas of the Emergency Departments on the Moses and Einstein campuses of Montefiore Medical Center.

Introduction

According to a recent nationally representative survey of US Emergency Department visits, 23.3 million oral analgesics were prescribed during ED visits in a single year.[1] Approximately 40% of these analgesics contained opioids. The three most commonly prescribed opioid analgesics are hydrocodone + acetaminophen, oxycodone + acetaminophen, and codeine + acetaminophen.

Only a relatively small number of studies have made direct comparisons of these medications for treatment of acute pain.[2-10] They are difficult to compare as they use varying doses of the medications, use different outcomes, and have a variety of methodological limitations including small sample sizes and substantial loss to follow-up.

The Cochrane Collaboration has produced several reviews describing the effectiveness of codeine, both with and without acetaminophen, as well as a review of the efficacy of oxycodone alone or in combination with acetaminophen. Indirect comparisons over a period of 4-6 hours demonstrated greater efficacy of oxycodone compared to codeine.[11-13] Most of the studies included in the reviews were postoperative dental studies utilizing extraction of the third molar as the pain model. There are no Cochrane reviews that describe the efficacy of hydrocodone.

Two randomized controlled trials were found comparing hydrocodone and codeine for chronic pain. Rodriguez et. al. found no significant difference in either analgesia or incidence of side effects in a study of 121 patients using 5 mg of hydrocodone vs. 30 mg of codeine, both in combination with 500 mg of acetaminophen.[14] Palangio et al. in a three armed study design with 469 patients, found greater analgesia in the 15/400 mg hydrocodone/ibuprofen group compared to the 60/600 mg of codeine/acetaminophen.[15]

We have conducted three randomized clinical trials of oral opioids for patients discharged from the ED following presentation for acute musculoskeletal pain. The first compared hydrocodone/acetaminophen against codeine/acetaminophen and found no difference in change in pain intensity when patients were contacted 24-hours post-discharge.[8] The second compared oxycodone/acetaminophen against codeine/acetaminophen and again found no difference at 24 hours.[10] The third trial compared oxycodone/acetaminophen against hydrocodone/acetaminophen and also failed to show a difference in pain control at 24 hours following ED discharge.[9] The design of these studies differed from other studies of oral analgesics in that patients were called 24 hours after they left the ED,

and they were asked to recall their pain intensity just prior to their most recent dose of pain medication and again 2 hours after ingestion of the study medications.

Due to the substantial increase in prescription opioid-related overdoses and deaths since the 1990's,[16] the widespread use of oral opioids has been questioned. A potentially efficacious and safer alternative to the opioid combinations prescribed in the ED is a combination of ibuprofen and acetaminophen. The combination of 400 mg ibuprofen and1000 mg acetaminophen has been found to provide superior pain relief to that of 60 mg codeine+1000 mg acetaminophen for pain following third molar extraction,[17] and to the individual components of the combination.[18] The same combination of 400 mg ibuprofen+1000 mg acetaminophen has also been reported to provide superior analgesia when compared to 30 mg codeine+325 mg acetaminophen following micrographic surgery for head and neck skin cancers.[19] In the Oxford League table of analgesic efficacy 800 mg of ibuprofen had the lowest number needed to treat (NNT) of oral analgesics, 1.6 compared with 2.4 for 400 mg ibuprofen.[20] Combining 800 mg of ibuprofen with 1000 mg acetaminophen is a promising strategy to increase analgesic efficacy of non-opioid analgesics. While high doses of ibuprofen are known to cause gastric ulceration when given 3 times daily over 6 weeks[21] there is no evidence that a single dose would be associated with this adverse event.

For this proposed study, we wished to look at the comparative efficacy of a single dose of 5 oral analgesics given while the patient is in the ED and assessed over a two hour period. The aim of the proposed study is to compare the efficacy of five oral analgesics: 5 mg oxycodone + 325 mg acetaminophen, 5 mg hydrocodone + 300 mg acetaminophen, 30 mg codeine + 300 mg acetaminophen, 400 mg ibuprofen + 1000 mg acetaminophen, and 800 mg ibuprofen + 1000 mg acetaminophen. The null hypothesis is that there is no difference in efficacy of the 5 analgesics. The alternate hypothesis is that treatment with at least one of the analgesics is more efficacious than one or more of the other analgesics and that the difference between treatments will meet a standard criterion for clinical significance commonly used in emergency medicine pain research.

The results of the study will help physicians to make evidence-based decisions about oral analgesic treatment of patients with acute extremity pain in the ED.

Methods

Design and Setting: The study will be conducted as a randomized double-blind trial of five oral analgesic combination medications: 5 mg oxycodone + 325 mg acetaminophen, 5 mg hydrocodone + 300 mg acetaminophen, 30 mg codeine + 300 mg acetaminophen, 400 mg ibuprofen + 1000 mg acetaminophen, and 800 mg ibuprofen + 1000 mg acetaminophen. The oral opioids and doses were chosen because they are most commonly used in the ED.[1] We chose to study the non-opioid combination of 400 mg of ibuprofen and 1000 mg of acetaminophen because several studies found them to be superior to codeine.[17, 19] While the combination of 800 mg of ibuprofen and 1000 mg of acetaminophen has not been formally studied, the analgesic efficacy of 800 mg of ibuprofen suggests it may be an improvement over the lower dose combination. Patients will be assessed for eligibility when they present to the urgent care areas of the Weiler and Moses EDs of the Montefiore Medical Center in Bronx, NY. The primary outcome, patient's rating of pain intensity, will be obtained 1 hour after the patients receive the study medication. Secondary outcomes will be assessed 2 hours after ingestion. If the patients leave before 2 hours they will be contacted by mobile phone at that time point by trained research assistants.

Inclusion criteria:

- Patients ages 21 through 64 years of age
- Complaint of acute musculoskeletal pain in one or more extremity, defined as distal to and including the shoulder or hip joints. In the majority of instances this is due to isolated blunt trauma. Blunt trauma is injury caused by the application of mechanical force to the body by a blunt force, object or instrument, or an injury in which the body strikes a surface such as a wall or the ground.
- Pain of less than seven days duration
- Patient speaks Spanish or English
- The clinician plans to treat the patient in the ED with oral analgesics and is willing to treat the patient with opioid analgesics or up to 800 mg ibuprofen and 1000 mg acetaminophen
- Patient is going to receive imaging of the painful extremity. Standard practice is to give patients an oral analgesic while awaiting imaging and subsequent care. This criterion

assures that the majority of patients enrolled will still be in the ED at the time the primary outcome measure is obtained.

- Clinician judges patient to have capacity to provide informed consent

Exclusion criteria:

- Patient does not have cell phone or cannot receive a verification phone call on their cell phone while in the ED
- Any use of methadone currently or previously
- Chronic condition requiring frequent pain management such as arthritis, sickle cell disease, fibromyalgia, or any neuropathy
- History of an adverse reaction to any of the study medications
- Opioids taken in the past 24 hours
- Ibuprofen or acetaminophen taken in past 24 hours
- Any other prescribed or over the counter topical or oral analgesics taken in past 24 hrs
- Pregnancy by either urine or serum HCG testing
- Breastfeeding per patient report
- History of peptic ulcer disease
- Medical condition that might affect metabolism of opioid analgesics, acetaminophen, or ibuprofen such as hepatitis, renal insufficiency, hypo- or hyperthyroidism, Addison's, or Cushing's disease
- Lacerations,
- Multiple injuries
- Taking any medicine that might interact with one of the study medications, such as antidepressant SSRI's or tricyclics, antipsychotics, anti-malaria medications quinidine or halofantrine, amiodarone or dronedarone, diphenhydramine, celecoxib, ranitidine, cimetidine, ritanovir, terbinafine, or St John's Wort.

Measures: Pain intensity will be assessed on a reliable and validated 11-point numerical rating scale (NRS) where 0 indicates no pain, and10 indicates the worst possible pain.[22, 23] Upon discharge, patients will be asked: "The next time you come to the emergency room with acute pain, do you want to be given the same pain medication?" Patients will also be asked if they experienced any of the

following side effects after taking the study medication in the ED: nausea, vomiting, stomach pain, heartburn, gas, constipation, diarrhea, itch, rash, dizziness, and drowsiness.

Baseline information including age, sex, weight, diagnosis, procedures performed, and pain scores using the NRS will be obtained. RAs will obtain documentation of administration of rescue medications and timing of administration from the medical record.

Outcomes

Primary outcome: The primary outcome is the between-group difference in change in patients' NRS rating of pain intensity 1 hour after ingestion of the study medication.

Secondary outcomes: Secondary outcomes include: 1) the between-group difference in change in patients' NRS rating of pain intensity 2 hours after ingestion of the study medication; 2) difference in proportion of patients who receive rescue medication during the study; 3) difference in proportion of patients who would choose to take the same study medication to which they were randomly allocated on a later occasion if they returned to the ED with similar pain; 4) difference in proportion of patients who experience side effects.

Protocol

Patients will be referred to the study by the attending physician only after the clinician has determined that the patient meets inclusion criteria and has the capacity to provide informed consent. Further patient screening for both inclusion and exclusion criteria will be performed by our team of trained bilingual (Spanish and English) salaried research associates who staff both study EDs 24 hours a day, 7 days a week. The research associates receive training and periodic refreshers in the ethical and practical aspects of data collection and a practicum with a senior research associate. The PI will orient the research associates to the specific details of the protocol and monitor data collection. The attending physician will conduct a final review of eligibility prior to enrollment in the study. The research associates will obtain written informed consent and perform all data collection.

Randomization will be performed in blocks of 10 determined by a sequence generated at http://www.randomization.com. The pharmacist working in an area inaccessible to ED staff will ensure proper blinding of the study by masking the medication and inserting it into unmarked gel capsules, filling any void with small amounts of lactose. In order to ensure that the capsules are small enough for

all patients to comfortably swallow, the dosage will be divided into fifths and 5 identical capsules will be filled. The pharmacist will make up numbered research packets based on the random allocation list, each with 5 tablets containing the masked investigational medication. Research packets will be removed sequentially by the nurse from the Pyxis automated medical dispensing system and administered to the study patients in the ED. Based on the allocation list patients will be randomized to one of the five experimental arms using the randomization schedule as described above: 5 mg oxycodone + 325 mg acetaminophen, 5 mg hydrocodone + 300 mg acetaminophen, 30 mg codeine + 300 mg acetaminophen, 400 mg ibuprofen + 1000 mg acetaminophen, and 800 mg ibuprofen + 1000 mg acetaminophen.

While the patients are in the ED, the RAs will collect background information and will instruct them on the use of the verbal NRS pain measure. Outcome data will be obtained 1 and 2 hours after ingestion of the study drug for patients who remain in the ED through 2 hours. If patients receive rescue medication they will be asked to rate their pain immediately before they received the rescue medication. Since radiologic imaging is required for study entry, it is anticipated that the majority of patients will have the second pain score assessed while still in the ED. Patients who leave the ED before 2 hours will be called at the appropriate time after patients took the medication by the RA. Cell phone numbers will be validated before the patients leave the ED. To minimize loss to follow-up, a minimum of two phone numbers will be recorded for each patient. During the follow-up phone call the RA will ask the patients to rate their pain intensity and respond to structured queries about side effects.

Patients who require rescue medications will receive oxycodone 5 mg (without acetaminophen). This will be determined subjectively (i.e. if the patient requests additional pain medication or the treating physician decides that additional pain medication is needed). Decisions about discharge medication and follow-up will be at the discretion of the treating provider as per his/her usual care.

Safety Monitoring

Patients will be enrolled in the urgent care area of the ED and will stay there for the duration of the study where they can be observed by medical and nursing staff. All the Research Associates have substantial experience with interacting with patients in pain studies and recognizing adverse events. They will receive refresher training by the Co-PI in recognizing serious adverse events and the need of reporting them immediately to the treating physician and the Co-PI. As part of the informed consent the patients are asked to tell their doctor if they do not feel well and to report all symptoms, reactions

and other complaints to the research personnel. This will be emphasized by the Research Associates during the informed consent process. Any adverse events observed by the RAs will be immediately reported to the clinical staff.

Data Collection, Processing

The research associates will collect data electronically through REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data capture for investigational purposes. The PI will review the data collected and informed consent documents weekly for accuracy and completeness. The data when downloaded from REDCap will be kept in backed-up, password-protected files on the PI's computer kept in a secure location.

Data analysis

We will calculate descriptive statistics for all variables, expressed as: frequencies, means and standard deviations, medians and IQR, and proportions as appropriate. The primary analysis is an analysis of variance (ANOVA) of the mean difference in pain from immediately before the medication was taken to 1 and 2 hours later. A significant ANOVA at a significance level of 0.05 will be followed by pairwise comparisons of medication. We will apply the Bonferroni method to adjust the overall significance level of 0.05 to avoid inflation of type 1 errors for the primary analysis. As there are 10 pairwise tests the actual significance level is 0.005. The main analyses will be intention-to-treat. However, it is likely that some patients will require and receive rescue medication. Therefore we are asking patients to rate their pain before taking the rescue medication. That rating will be used as the pain rating at 1 hour, for those who receive rescue medication before 1 hour, and at 2 hours for those who receive pain medication between 1 and 2 hours. This will be done because the effect of the study medications could be obscured by the effect of the rescue medicine.

We will use chi-square tests to compare secondary categorical outcomes. In order to reduce the number of comparisons of side effects, they will be grouped into upper GI (nausea, vomiting, abdominal pain, heartburn,), lower GI (constipation, diarrhea), dermatologic (itchiness, rash), and CNS (dizziness,

drowsiness, confusion). We will also conduct multi-variate analyses if there are differences between the groups at baseline. SPSS version 24 (Chicago, IL.) will be used to conduct all data analyses.

Sample Size Calculation

The following parameters were used to calculate the sample size: an overall 2-sided significance level of 0.05 (0.005 for each t-test using the Bonferroni correction), power of 80%, delta of 1.3 NRS unit change in pain between groups, based on a validated and reliable standard definition of the minimal clinically significant difference in pain between different analgesic treatments,[22, 23] and a within group standard deviation of 2.6, based on estimates from previous work of variability of change in pain in response to oral opioid analgesics.[8-10] Using these parameters 110 patients are needed in each group for a total of 550 patients. We propose enrolling up to an additional 50 patient in order to be sure of having at least 550 patients with analyzable data i.e., a total of 600 patients.

Data safety and monitoring

The monitoring plan will be executed by a Data Safety Monitoring Committee. The DSMC will be comprised of Dr. Adrienne Birnbaum and Dr. Benjamin Friedman, both Emergency Medicine physicians and experienced researchers. They both have Masters of Science degrees in Clinical Research. The DSMC will make the final decision about continuation, revision or discontinuation of the research project following reports of adverse events, unanticipated problems, or protocol deviations. They will decide if they need to convene a meeting in addition to the regularly scheduled meetings, review the data, discuss it with each other and the PI and will make a decision based on these discussions. The committee will meet twice a year. We feel the committee does not need to meet more frequently because the oral analgesics studied are all routinely used in the ED, there are few serious adverse events associated with these medications, the patients only receive the medication one time in the ED, and there is an opportunity for rescue medication if patients want more pain relief.

Specific Procedures: The research assistants (RAs) who collect the data will notify the PI immediately if any serious adverse event occurs whether anticipated or not. The PI will report all serious adverse events to the DSMC within 24 hours of occurrence. The RAs will also be asked to report any protocol violations and deviations to the PI. The PI will analyze the data weekly for the first month and biweekly after that to look for systematic errors in data collection, participant enrollment, missing data, and the occurrence of non-serious adverse effects (e.g., nausea, vomiting, stomach pain). The PI will report all

adverse events, unanticipated problems, and protocol deviations to the IRB as specified in the Reportable Events Policy of the IRB.

We plan to conduct an interim analysis after half the data are collected, i.e. 50 patients in each arm of the study. With a target p-value of 0.005 (all pairwise comparisons with a Bonferroni adjustment), we calculated the p-value for the interim analysis to be 0.00004 using the Lan-Demets1approach with O'Brien-Fleming alpha spending. The p-value for the comparisons at the end of the study is 0.00496. This translates into a mean difference of 2.1 NRS units between any pair of means. Thus if the mean difference between any arm of the study and one or more of the other arms is 2.1 or more (indicating worse pain control) that arm will be dropped so that patients are not exposed to a markedly less effective treatment. Dr. Friedman will conduct the interim analysis.

Risks and Benefits

Potential benefits: Determining the relative efficacy and side effect profile of both opioid and non-opioid oral analgesics will help the clinician choose effective therapies for the treatment of acute pain. If the efficacy of ibuprofen and acetaminophen is similar to or greater than that of the oral opioid analgesics with the same or fewer side effects, and if this is replicated in other settings, this study may contribute to addressing the increasing problems of overuse and abuse of oral opioids.

Potential risks: While all five treatments have been found to provide analgesia, some research subjects may experience less analgesia if there is a difference in efficacy.

Oral opioid analgesics combined with acetaminophen are known to cause several non-serious adverse events including nausea, vomiting, constipation, dizziness, drowsiness, headache, blurred vision, ringing in ears, and dry mouth. Rare serious adverse events that may occur include: severe allergic reactions (rash; hives; itching; difficulty breathing; chest tightness; swelling of the mouth, face, lips, or tongue); extreme weakness, shallow breathing, uneven heartbeat, sweating, or cold or clammy skin; dark-colored urine or pale stools, difficulty urinating, jaundice; confusion, fear, anxiety; hypotension, bradycardia, respiratory depression, oxygen desaturation, and addiction to opioids. Physicians who enroll eligible patients in this study must consider the oral opioid analgesic combination drugs as a possible treatment for the patient, so these risks are likely not to be any greater than those of patients who are not enrolled in this trial who also commonly receive these drugs in the ED.

Ibuprofen is known to cause several non-serious adverse events including abdominal pain, heartburn, gas, nausea, and rash. Serious adverse events in addition to those associated with opioid analgesics (e.g., allergic reaction) include stomach pain, heartburn, gastrointestinal bleeding. Physicians

who enroll eligible patients in this study must consider ibuprofen as a possible treatment for the patient, so these risks are likely not to be any greater than those of patients who are not enrolled in this trial who also receive ibuprofen.

The combination of ibuprofen and acetaminophen is not commonly used in the ED but they are commonly used separately. There is no evidence that the combination of these two analgesics are associated with a higher incidence of adverse events than the opioid combination medications.[17]

Potential non-medication risks to study subjects include breach of confidentiality although this is considered to be unlikely given the limited access to the data and the secure electronic means of acquiring it.

Data Safety Monitoring Plan

The Principal and Co-Principal Investigators will be responsible for closely monitoring patient safety and data integrity. The Research Associates will be instructed to report any serious AEs, UAs and PDs as soon as they occur to the investigators who will decide if they need to be reported to the IRB and/or if any procedures need to changed. The PI will review the data every week for the occurrence of all AEs, UAs and PDs. The PI will maintain a log with all the serious AEs, UAs and PDS. She will also review the data weekly for completeness of data collection, and any indication that the study is not being conducted as intended. The PI will maintain the key file that links the code number assigned to each patient and the patient's identifying information and will de-identify the data as they accumulate.

Conclusion

This 5-arm randomized, double-blind clinical trial is expected to further our understanding of the relative efficacy of three commonly prescribed oral opioids (oxycodone, hydrocodone, and codeine, each combined with acetaminophen) and two novel non-opioid combinations of ibuprofen and acetaminophen, thereby improving the physician's ability to manage acute musculoskeletal extremity pain in the ED.

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