TITLE: Comparison of Analgesic Efficacy of Morphine Sulfate Immediate Release (MSIR)/Acetaminophen vs. Oxycodone/Acetaminophen (Percocet) for Acute Pain in Emergency Department Patients

Unique Protocol ID: 2017-01-05

Identifier #: NCT03088826

Document Date: December 22, 2016

Introduction: The non-medical use of prescription opioids is a major public health crisis in the United States. In 2014, a total of 10.3 million persons reported using prescription opioids non-medically (i.e. using medications that were not prescribed for them or were taken only for the experience or feeling that they produced). In 2014, U.S. retail pharmacies dispensed 245 million prescriptions for opioid analgesics, which is 4 times higher when compared to 1999. Emergency department visits involving misuse or abuse of prescription opioids increased 153% between 2004 and 2011, and admissions to substance-abuse treatment programs linked to prescription opioids more than quadrupled between 2002 and 2012. More troubling is that between 2000 and 2014 the rates of death from prescription-opioid overdose nearly quadrupled (from 1.5 to 5.9 deaths per 100,000 persons). The pattern of nonmedical use of prescription opioids varies, from infrequent use once or twice per year to daily or compulsive heavy use and addiction. A key underlying characteristic of the epidemic is the association between the increasing rate of opioid prescribing and increasing opioid-related morbidity and mortality. Oxycodone is the most commonly prescribed opioid in the ED and it has the highest rates of abuse, misuse, diversion and fatalities related to overdose. Moreover, it has been shown that a single opioid prescription from the ED has been associated with subsequent opioid abuse.

This public health crisis calls for immediate interventions to identify safe and effective ways to control pain. One potentially powerful safety intervention is to identify an opioid that is effective for managing pain in the ED while at the same time having the least potential for recreational abuse, misuse and diversion. Therefore, our project is designed to investigate analgesic efficacy of Morphine Sulfate Immediate Release Tablets (MSIR) and consider its use in the ED as the alternative to commonly prescribed Oxycodone/Acetaminophen (Percocet). Our hypothesis is that MSIR is as effective as Percocet in treating pain in the ED and that it has far less potential for abuse based on the level of "likeability" and “attractiveness". The results of our investigation have the potential to be of great benefit to the safety of patients as well as for the education of providers and policy makers. By identifying a safer alternative to oxycodone, our study may influence opioid prescribing practices nationwide, which has the potential to reduce the considerable morbidity and mortality related to misuse and abuse of prescription opioids.

Aim: We expect our study results to show that Morphine Sulfate Immediate Release (MSIR) possesses similar analgesic efficacy in comparison to Percocet in adult ED patients presenting with moderate to severe acute pain. The magnitude of the national opioid health crisis has reached unprecedented levels and our faculty and patients frequently express concern about what is being prescribed to them in the ED. Frequently, patients raise questions about the safety of prescribed analgesics and demonstrate significant fears about developing addiction. It is not uncommon to hear patients complain about receiving pain medications that induce a high feeling of drunkenness and euphoria. Patients present to the ED with an expectation that physicians can manage their pain without prescribing medications that are highly addictive. The goal of our project is to investigate if Morphine Sulfate Immediate Release combined with Acetaminophen can serve as an opioid analgesic alternative to Oxycodone combined with acetaminophen. Oxycodone, the active opioid ingredient in Percocet, is both the most widely prescribed and the most diverted and misused oral opioid, and it is responsible for more overdose related deaths than any prescription opioid. We believe that if we prove our hypothesis we will increase safety

for all our patients who require opioid prescriptions by reducing the likelihood of misuse and abuse, which has the potential to make an impact nationwide by influencing future prescribing practices, thereby helping to address the opioid epidemic with safer alternatives to current practice standards.

Hypothesis: Is there a difference in the analgesic efficacy between oral analgesics Oxycodone combined with acetaminophen versus MSIR combined with acetaminophen for acute pain in the in ED setting?

Our hypothesis is that MSIR coupled with acetaminophen will have similar if not better analgesic efficacy at 30 minutes and 1 hour than oxycodone coupled with acetaminophen for acute painful conditions in the emergency department.

To compare the analgesic efficacy of two oral opioid analgesics potentially used in the inpatient emergency department setting to change the practices of emergency department physicians. The goal being to provide an alternate oral analgesic option and increase utilization of MSIR in a patient with acute pain. As there is a reported decreased likability in MSIR, the option of using MSIR in the ED may lead to decrease drug seeking and abuse if proven to have equal analgesia to Percocet.

Study Design: We will conduct a double-blind, randomized, clinical trial comparing analgesic efficacy of MSIR and Percocet in the ED for adult patients presenting with moderate-to-severe pain. The study site is a 711-bed community teaching hospital with a Level 1 trauma center and an annual ED census of greater than 120,000 visits. Three research coordinators will be assigned to screen and enroll patients. All participants will be randomized to receive 15mg PO morphine sulfate immediate release combined with 650mg of Acetaminophen or 1 tablet 10mg Oxycodone combined with 650 mg Acetaminophen. Patients, physicians, nurses and research assistants will be blinded to drug assignment throughout the study. Medications will be prepared by the ED pharmacist.

The study enrollment will proceed as follows. The study team will screen for eligible patients from 8 am to 8pm from Monday to Friday. After being evaluated by the treating adult ED physician, each patient will be approached by a member of the research team (other than the pharmacists or research manager) for assessment of eligibility criteria and acquisition of written informed consent and HIPAA authorization. To assess pain, we will use an 11-point Numerical Pain Rating Scale to evaluate the analgesic effectiveness of each medication.
To assess "likeability" a Visual Analog Scale Questions will be used to evaluate the severity of the patient’s subjective effects. (Table 1)

TABLE 1
Questions:
“Do you feel any DRUG EFFECT?”
“Do you LIKE the drug?”
“How HIGH are you?”
“Does the drug have any GOOD EFFECTS?”
“Does the drug have any BAD EFFECTS?”
“How much do you DESIRE the medication?”
" Does the drug make you have UNPLEASANT THOUGHTS?”
“Does the drug make you have UNPLEASANT BODILY SENSATIONS?”
“Does the drug make you feel IRRITATED?”
“Does the drug make it DIFFICULT TO CONCENTRATE?”

The patients will respond by positioning an arrow along
a 100-point line labeled with “not at all” at one end and “extremely” at the other

ED pharmacy investigators will maintain the randomization list which will be generated prior to commencement of the study, prepare the medication, and deliver it in a blinded manner to the nurse caring for the study participant. The study coordinators will screen for patients who qualify to be in the study. Patients will be included if upon evaluation by their treating physicians they warrant prescribing of oral narcotic analgesia. Painful conditions may include but are not limited to acute traumatic musculoskeletal pain including fracture and dislocations, renal colic and dental pain.

Patients’ pain intensity will be assessed at 30, 45 and 60 minutes. The clinically significant pain outcome is reduction in pain score at 60 minutes. Secondary outcomes will include the rate of reportable adverse effects and the requirement of additional analgesia.

The minimum clinically significant difference in generalized likability and chance for repeated use is by 2 mm for each question by using VAS.

Statistical Analyses: Data will be analyzed by intention to treat and will include frequency distributions, and Student’s T-test to assess a difference in pain scores and vital signs. The chi-square test will assess the presence or absence of side effects between the two groups. $P<.05$ will denote statistical significant difference between the groups.

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