Ketamine to Treat Fracture Pain

~~August 1, 2018~~ Jun 23, 2016

12 patients were analyzed as trial stopped early. No safety issues but we could not enroll patients in a fashion that made the data useful.

myIRB: Submitted form approved

myIRB@wusm.wustl.edu

Thu 6/23/2016 9:57 AM

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Your Modification Form for the following project has been approved by the IRB:

IRB ID #: 201501068
PI: Evan Schwarz
Title: Ketamine to treat fracture pain

If you are a PI (If you are not the PI, follow instructions for delegates or contacts below):
1. Go to the link below.
2. Login to myIRB.
3. The link will take you to the Project Summary page for the approved project.
4. Approval letters may be viewed under the "Approval" tab. Stamped Informed Consent Documents and other approved materials may be viewed under the "Attachments" tab. You may begin using any Consent Documents or other materials submitted with this application immediately by printing them from the Attachments tab. (Note - not all documents are stamped, however all materials on the Project Summary Attachments tab are your current approved documents.
5. If the project was reviewed at a full-board IRB meeting, on the Project Summary page under "History", click on the Agenda Date link for the appropriate form to view meeting minutes.

https://myirb.wusm.wustl.edu/summary/projects.page?OID=36026370

If the PI has made you a delegate and you wish to access minutes or approved materials:
1. Login to the regular myIRB website as yourself.
2. Go to the "Personalize" menu and login as a delegate for the PI.
3. Scroll to the listing of "Projects" at the bottom of the PIs Inbox page.

4. Click on the IRB number for the approved project.
5. The link will take you to the Project Summary page for the project. Follow the PI instructions for items #4 and #5 above.

If you are a contact (member of research team) and you wish to access minutes or approved materials:
1. Login to the regular myIRB website as yourself.
2. Scroll to the listing of "Projects" at the bottom of your Inbox page.
3. Change the filter for the Project to show projects where you are a research team member and click "Go" on the filter.
4. Click on the IRB number for the approved project.
5. The link will take you to the Project Summary page for the project. Follow the PI instructions for items #4 and #5 above.

E1 Overview or Design Summary

ED patients will be approached for informed consent if they meet selection criteria. Patients who consent to be in the trial will be randomized to either morphine (0.1mg/kg maximum dose of 10 mg) or ketamine (0.4 mg/kg, maximum dose of 40 mg). During the consent process, patients can be pretreated for pain with fentanyl IV up to 100mcg. Patients will not be given their assigned pain medication until at least thirty minutes after administration of any fentanyl to avoid overlapping effect of fentanyl with ketamine or morphine.

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PHARMACY NOTIFICATION

The research pharmacy will be notified of a potential study participant so they can prepare to randomize the participant using a random number generator. Odd numbered participants will receive ketamine and even numbered participants will receive morphine. Participants in the low dose ketamine arm will receive 0.4 mg/kg IV of ketamine (40 mg maximum). Participants in the opioid arm will receive 0.1 mg/kg of morphine up to 10 mg.

PHARMACY FORMULATION

Upon the completion of consent, the pharmacy will be notified to draw up the appropriate medication and send the medication to the Emergency Department. The study medication will be in identical appearing unmarked syringes, so that neither the study team nor the study subject will no which medication is being administered.

VITAL SIGN COLLECTION

The research coordinator will then complete page one of the Ketamine Data Form. This includes the participant's medical history, including a history of drug abuse, or prior narcotic use, a description of the injury, prior medications given to the subject for this injury either by EMS or in the emergency department, baseline vital signs (prior to study drug administration) and the time of study drug administration. Page 2 includes the baseline (pre study drug administration) visual analog pain scale that the participant will complete.

MEDICATION ADMINISTRATION

If the participant has not yet had an IV placed, one will be placed by the nurse caring for the participant at this time. Study drug will then be administered.

VITAL SIGN COLLECTION

The participant's heart rate, blood pressure, respiratory rate and oxygenation saturation (by pulse oximetry) will be collected every 5 minutes for the first 30 minutes, and every 10 minutes

for the next 30 minutes. The study will terminate at the end of 60 minutes and a final set of vital signs will be recorded at that point on Page 3 of the Ketamine Data Form.

REEVALUATION & EXIT SURVEY

The participant will be asked to complete repeat visual analog pain scales at 15, 30, and 60 minutes following study drug administration. The VAS will be administered by a second study coordinator, who has been blinded to the vital sign information, since blood pressure response may allow unblinding to occur. The participant will not have access to their original score for comparison. The study coordinator will then complete the post treatment survey on Page 5. The participant will continue to receive standard care by the emergency department physicians and nurses to ensure adequate relief of pain, appropriate treatment of the underlying pathology, hemodynamic and neuropsychiatric stability, and appropriate diagnostic evaluation, disposition, and follow-up. Any adverse events that occur during the continued treatment of the participant until either admission or discharge will be recorded.

RESCUE MEDICATION

Subjects that do not obtain adequate pain relief within 15 minutes of study drug administration will be offered rescue medication with intravenous morphine sulphate at the same weight-based dose (0.01mg/kg; maximum 10 mg)

TREATMENT OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events and serious adverse events will be noted on the data form and treated by the study physician or the primary treating physician as medically indicated.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Patients over the age of 18 presenting with long-bone fractures are eligible for enrollment. Eligible long-bone fractures include fractures of the shaft of the humerus, radius, ulna, femur, tibia, and fibula.

2.b Exclusion Criteria

Patients with injuries older than 24 hours will be excluded. Patients with avulsion fractures will be excluded. Patients with a history of substance abuse, chronic opioid dependence, pregnancy, intoxication, allergy to ketamine or opioids, and those that cannot consent (e.g. active mental disease preventing them from having capacity to consent) will be excluded. Any patients with hemodynamic instability defined as systolic blood pressure > 180 mmHg or < 100 mmHg, heart rate > 130 bpm, respirations < 10 rpm, or oxygen saturations on room air < 90% shall also be excluded. In addition, any patient that received a narcotic analgesic aside from fentanyl within the last 2 hours will be excluded.

2.c Study Termination

Subjects can terminate their participation in the study at any time. The alternative to continuing in the study is to have the pain treated by emergency physicians and staff as per usual care. The study physician may terminate the study prior to the specified endpoint when deemed medically prudent to do so.

2.d Ethical Considerations

Current research has investigated the effectiveness of ketamine as an analgesic in the Emergency Department. Much of that research is observational which limits the conclusions that can be drawn. While ketamine's mechanism of action would be consistent with an agent that can result in analgesia, we would like to conduct a randomized, blinded trial to determine if ketamine is as effective as an analgesic as morphine. We believe given the pharmacologic properties of ketamine, and prior published research, that ketamine is an effective analgesic so this research is important and ethical. All data will be collected by trained research staff and kept in a locked office to minimize the chance of lost data.

2.e Subject Recruitment Plans and Consent Process

Patients who are identified as potential study participants will be approached by the research coordinators regarding informed consent. The purpose of the study, study procedures, and associated risks and benefits will be explained to the potential subject. Following this, subjects will have 10 minutes to review the consent form on their own and if they agree to participate in the study, the consent form will be completed.

2.f Randomization Method and Blinding

Randomization will occur in the research pharmacy using opaque, sealed envelopes. Twenty participants will be randomized into each arm. Participants in the LDK arm will receive 0.4 mg/kg IV of ketamine (40 mg maximum). Participants in the opioid arm will receive 0.1 mg/kg of morphine up to 10 mg. Medications will be prepared by the pharmacy and delivered to the treating nurse in identical syringes. Study drug will be blinded to the research team and the study participant.

2.g Risks and Benefits

Patient will be exposed to medical risks in both conditions. Patients exposed to morphine will be at risk for hypotension, respiratory depression, altered mental status and possible allergic reaction. Patients exposed to ketamine will be at risk for hypertension, dysphoria and in rare cases laryngospasm and emergence reaction. These side effects are well known by practitioners since both of these drugs are regularly given in the Emergency Department. Patients may also be at risk for inadequate pain control in either condition.

2.h Early Withdrawal of Subjects

Participants will be told they have the right to withdraw from the study at anytime for any reason. Participants will also be taken out of the study early if the physician, nurse or research coordinator decides that the participant is at risk for a life-threatening event. Since this study does not include any outpatient follow-up, we do not anticipate early withdrawal to be a problem.

2.i When and How to Withdraw Subjects

The research coordinator will continually monitor the participant, and the nurses and physicians will be able to remotely monitor the participant's vital signs at the telemetry station. If a life-threatening event is identified, the participant will be resuscitated as deemed appropriate by the physician caring for the participant.

2.j Data Collection and Follow-up for Withdrawn Subjects

Due to the short duration of the study (60 minutes), we do not anticipate early withdrawal to be a problem. Participants who have inadequate pain relief and require rescue medication, or who have adverse events that require other treatment will have their data included, even if study personnel are unable to complete the follow-up VAS scores at 15, 30, or 60 minutes.

Study Drug

2.k Description

Ketamine is a dissociative agent that is thought to modulate pain by binding to NMDA receptors. Participants assigned to the ketamine arm will be given 0.4 mg/kg IV of ketamine (40 mg maximum).

Morphine is an opioid that acts on opioidergic receptors to modulate pain. Participants in the opioid arm will receive 0.1 mg/kg IV of morphine (10 mg maximum).

2.l Treatment Regimen

The study is designed to compare a one-time dose only. Therefore study medication administration will occur once following the baseline pain and vital sign assessment.

Assignment of Subjects to Treatment Groups

Participants will be assigned to either the ketamine arm or the morphine arm in the pharmacy by random number generator. Participants and all study personnel will be blinded to the assignment.

2.m Preparation and Administration of Study Drug

Once participants are in the process of being consented, the pharmacy will be notified to prepare the drug. The drug will then be sent to the Emergency Department for administration.

2.n Subject Compliance Monitoring

Participants will be given the drug intravenously by the emergency department staff nurse assigned to their care. The research coordinator will monitor the participant's vital signs, pain relief, and any side effects during the duration of the study. Since medication is only given one time, non-compliance will not be an issue.

Prior and Concomitant Therapy

Participants will be excluded from the study if they are found to be chronic users of either prescribed or illicit opioids or opiates.

2.o Packaging

Study drug will be packaged by the pharmacy in identical looking syringes so as to maintain blinding. This is a question for the pharmacy. I will email Craig about this.

2.p Blinding of Study Drug

As above

2.q Receiving, Storage, Dispensing and Return

The pharmacy will transport the study medication to the emergency department. If the patient withdraws from the study, the medication can be returned to the pharmacy.

F Study Procedures

F1 Screening for Eligibility

Participants will be identified in the Emergency Department waiting room as a potential candidate for the study by nurses, physicians and the research coordinator on duty. If a long bone fracture is deemed highly likely or if a long bone fracture has been identified by X-ray, the injury occurred within 24 hours, and the patient is conscious and alert and hemodynamicaly stable they will be approached for consent.

F2 Schedule of Measurements

Participants will have vital signs collected immediately prior to administration of the medication to which they are assigned. Vital signs (heart rate, respiratory rate, blood pressure, and pulse oximetry) will be recorded every 5 minutes for the first 30 minutes following the administration of study drug, and then every 10 minutes until study

completion (60 minutes post medication administration). Pain severity will be assessed immediately prior to administration of medication via the VAS and at 15, 30 and 60 minutes following medication administration..

F3 Visit 1

The participant will only be treated on the first encounter in the Emergency Department.

F4 Visit 2 etc.

N/A

F5 Safety and Adverse Events

We will monitor and record for changes in vital signs including hypotension, hypertension, tachycardia, bradycardia, respiratory depression. We will also monitor for nausea and vomiting, laryngospasm, and emotional and psychological effects (emergence reactions).

5.a Safety and Compliance Monitoring

Participants will receive only one dose of study drug, thus compliance will not be an issue. Participants will be monitored continuously for alterations in vital signs, or any other adverse events during the entirety of the study.

5.b Medical Monitoring

Both of these medications are commonly used in the emergency department setting, and have a good safety record. Nonetheless, AEs, and SAEs may occur. Any adverse event directly linked to administration of either ketamine or morphine that results in permanent disability or death will result in the cessation of the entire study.
Further, after every 10 patients are enrolled, all AE's will be reviewed by an independent expert. If there is a high frequency of adverse events that cause great distress to participants or that results in many participants ending their participation, the study will be terminated.
If five or more serious adverse events (SAE's) occur, we will have an institutional Data and Safety Monitoring Board perform an interim analysis to determine if there is a safety issue.

i Independent expert to monitor

We will perform an interim analysis on the AE's after every 10 patients. If we identify five or more SAE's, we will suspend the study until we have an institutional Data and Safety Monitoring Board perform an interim analysis to determine if there is a safety issue.

ii Institutional Data and Safety Monitoring Board

We will assign 3 independent experts to an institutional DSMB.

iii Independent Data and Safety Monitoring Board

We do not plan to have an independent DSMB

5.c Definitions of Adverse Events

Any untoward medical occurrence (signs, symptoms, lab abnormalities) associated with the use of study drug, whether or not considered drug related.

Serious Adverse Events (SAE's):
Any Adverse Event that in the opinion of the Investigator or Sponsor results in:
Death or is life-threatening (immediate risk of death)
Hospitalization or prolongation of existing hospitalization
Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability)
In addition, we have defined the following vital sign and behavioral abnormalities as SAE's:

Apnea: period of no respirations for greater than 20 seconds

Hypotension: systolic blood pressure < 90 mmHg

Hypertension: systolic blood pressure > 180 mmHg

Laryngospasm: Reflexive closure of the vocal cords that results in inability to ventilate.

Emergence Reaction: Anxiety, agitation, disorientation

Respiratory depression: respiratory rate < 8 breaths/min or sats < 92%

Bradycardia: Heart rate < 50 bpm

5.d Classification of Events

i Relationship

We will review each adverse event to see if it is associated with study drug. The relationship of the AE to study drug will be based on temporal association, and other clinical information such as concomitant medications, pre-existing conditions, and the natural history of the disease process.
Investigator causality assessment (relationship of AE to study drug) will be categorized as: 1) Probably related 2) Possibly related 3) Unlikely related and 4) Not related.

ii Severity

Severity of the AE will be documented using the FDA categories of 1) mild, 2) moderate, 3) severe, and 4) potentially life threatening.

Expectedness
Based on past research, we believe adverse events will be rare and severe events are unlikely to occur.

5.e Data Collection Procedures for Adverse Events

The research coordinator will write down all adverse events on the data form in the designated spot. They will also report the events to the treating team.

5.f Reporting Procedures

The research coordinator will report all adverse events to the principal investigator (PI) investigator during the study. The PI will determine severity and causality.
The PI will keep track of adverse events to determine if the study needs to be stopped.

5.g Adverse Event Reporting Period

This is an acute treatment trial, with a duration of one hour following study drug administration. However, any AEs that occur at any time during the entire ED stay of the study participant will be reported.

Post-study Adverse Event

The duration of the drugs used in this study will not exceed the time the participant is monitored.

F6 Study Outcome Measurements and Ascertainment

Study outcomes involve change in participants' pain as measured by the VAS, significant changes in any vital signs collected, a list of adverse events that the participant experienced, as well as questions included in the data form assessing whether the participant would consider using the drug given to them for pain relief in the future.

G Statistical Plan

G1 Sample Size Determination and Power

Sample size for this study is based on limited funding and will serve as a pilot study looking for trends in the efficacy of morphine and ketamine to treat pain as well physiologic effects and adverse events. If the results appear promising, further funding will be requested and a full power analysis will be performed.

G2 Interim Monitoring and Early Stopping

All adverse events will be promptly reviewed by the primary research team following the participant's completion of the study. Any adverse event directly linked to administration of either ketamine or morphine that results in permanent disability or death will result in the cessation of the entire study. After every 10 patients are enrolled, adverse event information will be reviewed by an independent expert. If there is a high frequency of