Sub-dissociative Dose Ketamine Dosing Study

NCT03714620

Date 10/17/2018

I. Study Protocol

Patient screening, enrollment, and data collection will be performed by the study investigators. All adults ≥18 years of age and < 60 years of age and weighing between 45-115 kg with acute abdominal, flank, back, musculoskeletal pain, or headache, with a score of 5 or more on a standard 11-point (0 to 10) VAS pain rating scale requiring intravenous analgesia, as determined by the treating attending physician, will be screened for inclusion. Exclusion criteria are as follows: pregnancy, breast-feeding, altered mental status rendering the patient unable to consent to the study, allergy to ketamine, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/minute, and respiration rate <10 or >30 breaths/minute), and medical history of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, history of alcohol or drug abuse, and psychiatric illness. Only the first admission will be included if patients present multiple times during the study period.

i. Recruitment procedures

1. Where will recruitment occur?

Recruitment will occur in the LUMC ED upon patient's arrival and once physician has deemed it necessary that the patient receive intravenous pain medication.

2. Where and when will consent be obtained?

Consent will be obtained in the Emergency Department once it is determined that the patient meets inclusions criteria for enrollment if the patient is able to provide it.

3. Who will obtain consent?

The treating attending physician, or one of physician members of the research team, will obtain consent from the patient in the ED.

ii. Screening procedures

Patients will be screened as a convenience sample during daytime hours Monday – Friday when any of the study investigators are working and the ED clinical pharmacist is available to prepare the study drug and randomize the patients. Patients presenting to the ED with acute moderate to severe abdominal, flank, back, musculoskeletal pain, or a headache will be screened for inclusion criteria and asked to consent prior to enrollment. Consent must be obtained prior to enrollment.

b. Randomization procedures (if applicable)

The study will be double-blinded and randomized. Patients meeting inclusion criteria who consent for participation will be randomized in a 1:1 fashion to either Ketamine 0.15 mg/kg IVBP or Ketamine 0.3 mg/kg IVBP. Dosing will be based on actual body weight. Both drugs will be administered over 15 minutes. Physicians will obtain consent from the patient, but will not be aware of dose that the patient receives. Treatment will be prepared and blinded by the ED clinical pharmacist. ED Pharmacist will maintain the randomization list, which was generated before commencement of the study, prepare the medication, and deliver it to the nurse caring for the study participant in a blinded manner.

c. Study Intervention

i. For Drug/device studies:

1. Active study agents

Ketamine 0.15 mg/kg IVBP administered over 15 minutes
Ketamine 0.3 mg/kg IVBP administered over 15 minutes

2. Placebo study agents

No placebo

3. Blinding/labeling/preparation of agents

Patients will be randomized in a 1:1 fashion to receive either 0.15 mg/kg of Ketamine IVPB or 0.3 mg/kg of Ketamine IVBP. The ED clinical pharmacist will prepare and label the study treatments, and ensure blinding of the patient, research team, and clinical staff.

4. Storage

Storage of the study medication will be kept in the ED pyxis to facilitate rapid use.

5. Administration

0.15 mg/kg or 0.3 mg/kg dose of Ketamine administered intravenously over 15 minutes

6. Toxicities and guidelines for adjustments

No dosage adjustment will be necessary.

ii. For Other types of intervention studies: n/a

1. Active intervention description
2. Control group

d. Study Assessments and Activities

i. Describe all study procedures, assessments, and subject activities

Patients will be consented for participation by one of the study investigators or the treating ED attending physician. The ED pharmacist will prepare the medication, and ensure blinding of the patient, research team, and clinical staff. The nurse caring the patient will administer the IV medication and give the patient a survey to fill out regarding pain relief and side effects at 15 minutes, 30 minutes, and 60 minutes post initiation of administration of the ketamine. Time zero will be time the drug administration is initiated. The survey will ask the patient to rate their pain using the VAS pain rating scale. Additionally, it will have a list of adverse effects, and the patient will need to rate each adverse effect using a 5 point SERSDA scale (rating each adverse event from “absent” to “very bothersome”). At the same time intervals (15, 30, and 60 minutes post initiation of drug administration), the nurse will rate the patient using the RASS scale. Vital signs will be monitored per ED protocol. Rescue analgesia will be offered at 30 minutes.

ii. Provide a schedule of all study assessments and subject activities, including a tabular representation or timeline as applicable

-Patient presents to the emergency department with acute pain
-Emergency treatment will not be delayed for the purposes of this study
-Patient seen by physician and screened for inclusion/exclusion criteria
-Patient consented for participation by research team member or physician treating the patient
-Patient randomly assigned to treatment group
-Drug prepared by ED pharmacist, administered by blinded nurse
-Time zero (0) is when nurse initiates administration of the ketamine
-Ketamine infuses over 15 minutes, ending at 15 min time mark

-Survey administered to the patient to be filled out at 15 min, 30 min and 60 min post administration of the ketamine (nurse to alert patient at specified time intervals)
-Nurse to score patient using RASS scale at 15 min, 30 min, 60 min post initiation of drug administration

II. Safety Monitoring Plan

a. Definition of adverse events, serious adverse events

Adverse effects include dizziness, disorientation, dysphoria, nausea. Adverse events include hypoxia (<90%), hypotension (<90 systolic), vomiting, or life-threatening events.

b. What procedures will be used to monitor subject safety?

Ketamine is currently being used in sub-dissociative doses in the ED at LUMC to treat acute pain utilizing doses between 0.1 mg/kg- 0.3 mg/kg. The procedures to monitor safety are consistent with the ED guidelines used in current practice at LUMC. Subjects will have continuous telemetry monitoring including heart rate, respiratory rate and oxygen saturation. Vital signs (including but not limited to blood pressure measurements) will be measured and documented per standard protocol in the ED. Documented adverse side effects of sub-dissociative ketamine have included dizziness, dysphoria, and disorientation, but no serious adverse events have been noted.

c. Who (list names) will identify, document, and report adverse events?

The blinded physician, nurse caring for patient, or one of the research team members, will identify, document, and report adverse events.

d. What is the frequency for review of summarized safety information and who will perform the review (e.g., safety monitoring board)?

The research team will review safety information weekly.

e. What are the stopping rules with regard to efficacy and safety?

As the target enrollment is 49 subjects per group, and we see hundreds of adult patients monthly for acute pain, we do not anticipate needing to stop the trial early. All adverse events will be reviewed and the study will be stopped immediately if we determine the AE was directly related to the subject's participation in the study.

III. Analysis Plan

Describe statistical analysis methods as appropriate. For example, will intention-to-treat methodology be used in the analysis? Will there be any sample stratification?

Descriptive statistics, including means, standard deviations, medians, interquartile ranges and percentages will be calculated for baseline variables. Comparisons of continuous parametric variables will be done using a t test. Non-parametric data will be expressed as a median and analyzed using the Mann–Whitney test. A Chi-square test or Fischer's exact test will be used to compare categorical variables as appropriate. A bivariate analysis will be performed to assess differences between SDK regimens. A P value < 0.05 will be considered significant. Microsoft Excel software and STATA version 12 will be used for data analysis.