1) Protocol Title

Subdissociative Dose Ketamine for Treatment of Acute Pain in Subjects with Chronic Pain: A Randomized Controlled Trial

2) HSC Review History

This protocol has not been reviewed by any external HSC.

3) Investigator

David Tanen, MD Timothy Horeczko, MD
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Mark Paulsen, MD
Samantha Cheng
James Archer

4) Objectives*

This is a prospective, randomized, physician and subject blinded controlled clinical trial. This will be conducted to determine whether sub-dissociative dose Ketamine can improve pain control in subjects with chronic pain syndrome presenting to the emergency department with exacerbation of their chronic pain. We also aim to determine whether use of SDDK can reduce the amount of subsequent opioid pain medications required for adequate pain relief in this subject population. We hypothesize that there will be a statistically significant decrease in pain using SDDK versus placebo and subjects will require overall less opioid pain medications for adequate pain relief.

5) Background*

Pain management is a significant issue for many subjects presenting to the Emergency Department (ED) as increasing numbers of subjects present with this complaint. In the ED, treatment of acute pain is a primary concern both for the provider and the subject; recent data suggest that visits for pain-related complaints are rising (1). Subjects with chronic pain account for 12-16% of total ED visits (2,3) with 7% of subjects with chronic pain presenting multiple times (4). Both the Department of Health and Human Services (HHS) and the Institute of Medicine (IOM) have identified pain as a significant public health problem in the United States (5). Currently, the vast majority of painful conditions within the ED are treated with either opioid or non-steroidal anti-inflammatory drug (NSAID) analgesic medications. Treatment of chronic pain syndromes in the ED can be particularly challenging, since many subjects with these conditions are tolerant to the effects of opioids and NSAIDs and it can therefore be difficult to control their pain exacerbations adequately in the emergency department solely with these medications.

Ketamine [2-(o-chlorphenyl)-2-methylamino cyclohexanone] is a phencyclidine derivative with unique analgesic, amnestic, and dissociative properties that acts primarily as a competitive antagonist at the NMDA receptor within the limbic system to modulate autonomic responses to stimuli. Advantages of ketamine include its stable hemodynamic profile and lack of respiratory depression (unlike opioid medications). Ketamine is frequently used for moderate sedation in the ED; recently, it has been suggested that sub-dissociative dose ketamine (SDDK) may be used in the ED for successful primary treatment of acute exacerbations of chronic pain syndromes, or as an adjunct to opioids or NSAIDs. Such treatment has primarily been studied in pain clinic settings and thus far has not been evaluated in

an emergency department setting. We aim to determine whether the use of a sub-dissociative dose of ketamine may be effective in the treatment of acute exacerbations of chronic pain syndromes in subjects presenting to the emergency department.

Although the use of ketamine is currently accepted as standard care in the ED as a moderate sedation agent in both pediatric and adult populations (6-8), it has not been widely utilized for its specific analgesic qualities. While there is extensive evidence on SDDK's safety and efficacy within the anesthesia and palliative care literature, there is very little written about the use of SDDK within the ED setting. Most studies published thus far describe ketamine's use either for procedural sedation or in a palliative care setting, primarily among subjects with cancer-related pain, phantom limb pain, or other pain types (9-12). Indeed, very few studies specifically address SDDK's analgesic uses in the ED. There is promising evidence of SDDK's safe and effective use for the treatment of traumatic pain in the prehospital setting (13), and a randomized, double-blind trial demonstrated that SDDK was safe and reduced opioid consumption in trauma subjects (14-15). One retrospective case series noted SDDK's safe use in subjects presenting to the ED for medical pain (16). A randomized controlled trial compared SDDK to fentanyl as an adjunct to procedural sedation and found its side effect profile and analgesic properties to be superior to standard treatment (17-18). The use of SDDK has also been suggested as effective within wilderness and operational settings, with obvious applications to military populations (19).

6) Setting of the Human Research

This is a prospective, randomized, physician and subject blinded controlled clinical trial, conducted at Harbor UCLA Medical Center Emergency Department

7) Resources Available to Conduct the Human Research

This is a local research study to be conducted in the Emergency Department at Harbor UCLA Medical Center which treats 75,000 patients per year and is located in a brand new facility consisting of 80 beds. This study will include only adult patients and all patients for our study will be identified through triage when they are initially assessed. If they meet inclusion criteria they will be approached for possible enrollment in the study.

The PI and Co-investigators will devote approximately 3 - 4 hours per week conducting the trial during the time period from July 1, 2015 – June 30, 2016 and will should have no problem recruiting the required number of patients since pain is a the most common complaint to the Emergency Department. The Primary Investigator, Dr. Tanen, has conducted numerous research studies in the past. He has completed all required training to conduct research at this institution. He also is well-versed in the Federal regulations as he is a member of one of the institution's IRBs.

The coinvestigators, Drs. Horeczko, Huang and Paulsen have assisted in conducting research studies in the past and will look to Dr. Tanen and the LA BioMed Compliance Monitor for assistance and guidance in carrying out this study. They have also completed the training requirements to conduct research at the institution. Ms Cheng has assisted the investigators in the development of the study and will work directly with the senior investigators in carrying out the study. She has also completed the training requirements to participate in research at this institution.

We will make sure that all persons assisting with the trial are adequately informed about the protocol, research method, and their trial-related duties and functions.

The investigator and study team members will regularly meet to ensure that all persons assisting with the trial are adequately informed about the protocol, research method, and their trial-related duties and functions.

8) Prior Approvals

The study was originally submitted as unfunded and underwent peer review by the institute's Research Committee. Subsequently, Dr. Tanen submitted a request for funding (grant) to the U.S. Air Force to support this research; he was awarded the grant in Aug. 2016.

9) Study Design

a) Recruitment Methods

Screening for eligibility will occur as follows:

Subjects who present to the Harbor UCLA Medical Center Emergency Department(ED) will be screened by the investigator and study team for possible eligibility for this study. Once a subject is identified we will meet with their treatment physician and review their medical record to see if they meet the inclusion criteria. A pregnancy test will be administered, after consent obtained, before the female subject is randomized.

b) Inclusion and Exclusion Criteria*

Inclusion Criteria:

- All adult subjects over the age of 18 with chronic pain* presenting to the emergency department with exacerbation of their chronic pain as their primary complaint
- Subjects who are willing and able to provide informed consent.

* Chronic pain defined as greater > 3 months of symptoms and an initial VAS pain score > 70

Exclusion criteria:

History of overt psychosis, severe HTN as defined by SBP > 180 or DBP > 110, unstable angina, CAD, CHF, porphyrias, thyroid disease, seizure disorder, inability to provide informed consent: dementia, non-English/Spanish speakers, subjects in custody, suicidal, or clinically intoxicated.

c) Local Number of Subjects

We look to enroll a total of 106 subjects meeting the study criteria.

Protocol Modification 4/24/2018:

We are requesting the enrollment of an additional 10 subjects to the protocol. We initially asked to enroll 96 subjects and have thus far enrolled 80 and the recruitment has continued on schedule. In recent discussion with our statistician and co-investigator, Dr Tim Horeczko, the original group size analysis of 96 (32 in each of three groups) did not account for potential loss of data or subjects withdrawing from the study and we should have asked initially for 106 subjects with the expectation of a 10% loss of data due to incomplete records or withdrawal of subjects in the study.

d) Study-Wide Number of Subjects*

This is a single center study done at the Harbor UCLA Emergency Department

e) Study Timelines*

Duration of an individual subject's participation in this study is 1 emergency department visit and one follow-up phone contact 24-48 hours after discharge from Emergency Department.

The estimated date for the start of enrollment of subjects will be September 2015, and it will be continued till the enrolled subjects' number reach the goal of 106.

f) Study Endpoints*

Primary endpoint: To compare pain relief between the 3 treatment groups as measured by the VAS. A decrease of at least 20mm on the VAS will be considered "significant" pain relief (20)

Secondary endpoint:

(a) To compare total dosage of IV hydromorphone needed as rescue therapy to achieved adequate pain relief

(b) To assess the risk for complications of sub-dissociative dose ketamine

g) Procedures Involved in the Human Research*

1. The informed consent process will be initiated by investigators in the emergency department.

2. All potential subjects will be informed that participation in the study could lead to a positive urine drug test that could remain positive for up to a month after the conclusion of the study.

3. Female subjects of child bearing age, will have a pregnancy test performed prior to enrollment; any subjects who are pregnant will be excluded from this project.

4. Each subject will be asked to grade his/her pain severity on a 100mm non-hatched visual analog scale (VAS) ranging from 0 (no pain) to 100 (worst, maximum pain).

5. Each subject will be asked to fill out a baseline pain questionnaire

6. Each subject will be placed on monitors for continuous pulse oximetry, Heart Rate, Respiratory Rate, and blood pressure every 5 minutes for the duration of the study of one hour and longer for any patient who needs continued care. The patients temperature will be taken prior to the start of the protocol..

7. Each subject will have an intravenous catheter placed.

8. Each subject will be sequentially assigned to one of three treatment groups, based on a computer-generated randomization schedule, to receive an intravenous infusion of sub-dissociative Ketamine (0.25mg/kg), sub-dissociative dose Ketamine (0.5mg/kg), or an equal amount of normal saline.

9. All medications will be prepared by an emergency department pharmacist and all study medication IV bags will be identical in appearance and will be administered by the emergency

department nurse caring for the patient who will be blinded to the study drug.

10. Each subject will receive lightly tinted sunglasses to wear during the duration of the study to minimize bias as ketamine can evoke a tell-tale short-lived nystagmus

11. Each subject will receive the study medication over a 20 minute period via an automated pump. At this point, the subjects will be asked to rate their pain on a VAS and asked if they need additional pain medication that will consist of intravenous hydromorphone with the dose and frequency determined by the discretion of the treating physician and documented on the data collection sheet.

12. After 1 hour the subject will again be asked to grade his/her pain on a VAS. Additionally, they will be asked if they experienced any other adverse effects over the treatment period, specifically: rash, hallucinations, anxiety, disorientation, burning at the injection site.

13. Subjects will be asked if they require additional pain relief. Those who request further pain relief will be administered hydromorphone IV, the dosage and frequency will be at the discretion of the treating physician. Total hydromorphone administration will be documented on the data collection sheet.

14. All subjects will receive a follow-up phone call from one of the investigators between 24 – 48 hours after their visit to the Emergency Department to gauge the extent of their continued pain through the use of a Pain Rating Scale. They will also be asked if they suffered any untoward effects and if so, will be asked to detail them.

15. Any study patient returning to the Emergency Department for any reason will be fully evaluated and the study team will be notified. If there is evidence of any psychotic reaction (persistent or delayed presentation after the administration of the medication, the patients will be treated with benzodiazepines (shown to be effective in the emergence reaction sometimes seen after dissociative doses of ketamine are used) and a psychiatric consult will be obtained. The medical monitor will also be notified because this would be an adverse event.

h) Data and Specimen Banking*

No data collected for banking purposes.

i) Data Management *

Descriptive statistics will be used. Tests for significance will be conducted using the t test for continuous variables and chi-squared test or Fisher's exact test for categorical variables.

We estimated the sample size needed for the primary end point of significant pain relief as defined by a decrease in the VAS of 20mm. A power analysis based indicated that a sample size of 106 subjects would be required to detect a statistically significant difference with a power of 90% (α = 0.05).

Data from the patient examinations will be stored in an excel spreadsheet or compatible REDCAP database after being de-identified of all unique information to the subject. The study source documents (including consent forms, etc.) will be stored in a locked filing cabinet in a locked office only accessible by study investigators. It will be stored until this

study completes. The data will be shared among the principal investigator and co-investigators. Principal investigator will be responsible for receipt or transmission of the data.

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j) Confidentiality

Confidentiality will be maintained by use of coded data sheets and an enrollment logbook. Data will be stored in a password locked excel data sheet s/REDCAP database. The study source documents (including consent forms, etc.) will be stored in a locked filing cabinet in a locked office only accessible by study investigators. It will be stored until the completion of this study. Only research investigators and research associates will have an access to this data or the room where the data sheets and enrollment logbook is kept.

k) Provisions to Monitor the Data to Ensure the Safety of subjects*

Dr Yadav, an Emergency Physician not associated with the study but who has an expertise in procedural sedation in emergency department patients will be a Safety Monitor who will review all patient information whether they received placebo or ketamine for both harm and benefit on a monthly basis to determine if the study is safe to continue. Dr Yadav, is an LAbiomed investigator with significant experience in the conduct of research and possesses the expertise to serve as the Safety Monitor.

l) Withdrawal of Subjects*

Subjects will be withdrawn from the study if they don't complete their Ketamine or normal saline infusion and they will continue to be monitored and treated as necessary if they experience any untoward or unexpected effects from the medication.

10) Risks to Subjects*

Risk of Ketamine

Incidence unknown*:* Bloody or cloudy urine, bluish lips or skin, blurred vision, chest pain or discomfort, confusion, disorientation, convulsions, cough, increased secretions, dizziness, syncope, tachycardia, hives, itching, facial edema, hallucinations, rash, agitation, anxiety, fatigue, unmasking psychosis

Risk of Sodium Chloride

Common: None
Uncommon: Edema
Rare: Congestive Heart Failure from fluid overload

Risk of intravenous catheter insertion

Uncommon: bruise at the puncture site, inflamed vein
Rare: Infection

The study involves the collection and recording of information including protected health information. There is a slight risk of a breach of confidentiality.

Subjects will be asked to rate their pain throughout the study which may cause them some anxiety.

11) Potential Benefits to Subjects*

Possible pain relief. If randomized to placebo (saline solution) subjects pain is monitored and pain relief provided if pain is not subsiding.

12) Provisions to Protect the Privacy Interests of Subjects

Data confidentiality is maintained as above. Only research investigators will have an access to this data.

The enrollment will be performed at emergency department.

We will not discuss private medical information in a setting with other than a health care provider or in other than a private clinical setting.

For the follow up phone call, we will ascertain from the subject, that they are willing and able to any questions and that they feel they have adequate privacy to do so.

We will limit the information being collected to only the minimum amount of data necessary to accomplish the research purposes.

13) Compensation for Research-Related Injury

There is no commitment to provide any compensation for research-related injury. In the event that subjects are injured as a result of participating in this research, emergency care will be available. But subjects will, however, be responsible for the charges for the emergency care.

14) Economic Burden to Subjects

The cost for the care provided during the emergency department visit is the responsibility of the subject. The subject will not be charged for the study medication (ketamine or saline).

15) Consent Process

Consent process will take place in the Emergency Department. Patients will be presented with the risks and benefits of participating in the study when being introduced to the study. During the consent process, patients will be asked to explain to the investigator or research associates the following aspects of the study, based on the UC San Diego Brief Assessment of Capacity to Consent (UBACC): What is the purpose of the study? What makes you want to participate in the study? Do you have to be in the study if you do not want to participate? If you withdraw from the study, will you be able to receive regular treatment? Please describe some of the risks and discomforts for being part of this study? If patients are unable to answer the questions with an appropriate, or correct response, they will be informed of the correct response, and will not be able to proceed unless they are able to express, in their own words, the correct, or appropriate, response.

If subjects require some time for the information to be absorbed and appreciated, the researcher allow a period of time to elapse between imparting the information and requesting a signature on the consent form.

We are following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

Other than English, we expect Spanish speaking population to be participated in the study. In such case, consent form written in Spanish will be provided, and we will provide oral information using language line or by Spanish speaking investigators.

Subjects who are not yet adults (infants, children, teenagers)

Only subjects over the age of 18 will be included in this study.

Cognitively Impaired Adults

Only subjects capable of consent will be included in this study. The UBACC will utilized as described above.

Adults Unable to Consent

Only subjects capable of consent will be included in this study.

16) Process to Document Consent in Writing

We have reviewed and will follow "SOP: Written Documentation of Consent (HRP-091)."

17) Vulnerable Populations

Adults unable to consent, individuals who are not yet adults, pregnant women, and prisoners will be excluded in this study.

Other vulnerable subjects, such as students, subjects with limited or no treatment options, and socially and economically disadvantaged, may be included in this study. This study does not involve more than minimal risk to the subject.

18) Drugs or Devices

Unlabeled fluid (either normal saline, 0.25mg/kg Ketamine, or 0.5mg/kg ketamine) will be obtained and prepared by the emergency department pharmacist in conjunction with the investigator but the investigator will remain blinded to the study medication. The investigator and the emergency department pharmacist will have a coded list for the randomization but only the pharmacist will be aware of the medication given to each subject.

19) Multi-Site Human Research*

This research is a single center research trial at Harbor UCLA Emergency Department

20) Community-Based Participatory Research

This is not a community-based participatory research.

21) Sharing of Results with Subjects

There are no results to be shared with the subjects

22) Bibliography

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