Ketamine for Acute Painful Crisis in Sickle Cell Disease Patients: Prospective Randomized Control trial

NCT 03431285

Brief Summary:

Investigators hypothesize that administration of ketamine for pain relief in sickle cell patients with vaso-occlusive crisis early on will lead to a more rapid improvement in pain score and less narcotic requirement.

Detailed Description:

Sickle cell disease is an inherited hematological disorder where the shape of red blood cells is altered into a sickle-like cells resulting in red blood cell destruction and therefore anemia and other complications. It's a widely spread condition in African American population as well as the Southern and Eastern Provinces of Arabian Peninsula.

Acute painful episodes are a very common complication of the disease process, mainly thought to be a result of tissue ischemia due to occlusion of the microcirculation with clusters of sickled RBC(1). This usually involves long bones or spine but can involve other areas. Acute painful crises can also be precipitated by cold exposure, dehydration, infection, hypoxia, acidosis or hypercarbia, or in some cases it is not related to a specific trigger. This condition puts the patient in severe pain requiring multiple Emergency Department (ED) visits and sometimes admission to the hospital. Currently the mainstay of therapy for acute painful crises is hydration and IV opioid analgesia (2). This makes pain control challenging for the emergency physician as management of acute painful crises requires multiple doses of IV opioids, a retrospective study of 19 patients and 57 visits showed that accumulative dose of IV morphine ranged between 4 mg and 26.7 (0.05-0.5 mg/kg) during 70% of the visits. 50% of the patients were admitted after less than 3 hours of ED treatment, 28% of the discharged patients returned to the ED within 3 days (3). Moreover, as other chronic pain patients, sickle cell disease patients develop opioid induced hyperalgesia (OIH) leading to activation of N- methyl D Aspartate receptors (NMDA) (1).

The use of ketamine, a non-competitive NMDA receptor antagonist, may have the potential to modulate the OIH through impaired sensitization of spinal neurons to nociceptive stimuli and may, therefore, impede development of and blunt neuropathic pain. Extensive search of the literature database showed few published reports and retrospective studies including few patients which have addressed the use of low-dose ketamine in the management of acute painful crises in SCD (4-6). A retrospective study (5) included 5 children and adolescents received a low-dose ketamine infusion for the treatment of sickle cell-related pain

demonstrated reduced pain scores in 40% of patients and significant reduction in opioid utilization in only 20% of patients. However, that report was retrospective, non-powered, and included few patients. A recent Canadian retrospective study including 9 adult and adolescent patients demonstrated statistically significant reduced cumulative morphine consumption (146±16.5 mg/day vs. 112.±12.2 mg/day) and pain scores after adding intravenous ketamine in patients with painful sickle cell crises (7). Similarly, another American investigators reported decreased opioid consumption with infusing low-dose ketamine as an adjuvant analgesic in 30 patients presented with sickle cell disease with VOC, that study was retrospective (2). Moreover, in year 2017, a prospective, randomized, double dummy trial was done comparing the adverse effects and analgesic efficacy of low-dose ketamine for acute pain in the ED either by single intravenous push or short infusion. This study shows that low-dose ketamine administered as short infusion is related with a significantly lower rates of feeling of unreality and sedation with no difference in analgesic efficacy in comparison to intravenous push (8)

To the best of our knowledge, there is no a large, prospective, comparative, controlled clinical trial investigated the addition of low-dose ketamine in shortening the ER stays and improving the quality of analgesia in patients with VOC.

MAIN RESEARCH QUESTION

Does adding ketamine to the standard acute opiate treatment for pain relief in sickle cell patients with vaso-occlusive crisis at an earlier stage lead to a more rapid improvement in pain score, less narcotics requirement, and help shorten ER stay for pain management?

Hypothesis

We hypothesize that administration of ketamine for pain relief in sickle cell patients with vaso-occlusive crisis early on will lead to a more rapid improvement in pain score and less narcotic requirement.

TRIAL DESIGN

This project is a small scale university hospital prospective, double-blind, RCT of 264 patients that requires opiate treatment to evaluate the effectiveness of Ketamine in managing pain.

- Control Group: Patients will receive standard dose of morphine (0.1mg/kg in 0.9% Sodium Chloride 100ml bag) in addition to standard IV hydration.
- Intervention Group: Patients will receive low dose ketamine (0.3 mg/kg in 0.9% Sodium Chloride 100ml bag) in addition to standard IV hydration. Plus morphine 0.1mg/kg rescue doses.
- Primary Purpose: Treatment

Sample Size

A data obtained from a pilot study included 10 patients who received either morphine or ketamine showed that the mean and SD of pain visual analogue score (VAS) at 1-hour following administering the study drug among patients presented with sickle-cell VOC were (Morphine 6.5 ± 3.41565, Ketamine: 1.6667 ± 1.52753). An a priori power analysis indicated that a sample size of 220 patients is sufficiently large to detect a mean difference in the pain VAS of 1.5 that would have a clinical importance, with a type-I error of 0.05 and a power of 90%. Additional patients (20%) will be added for a final sample size of 264 patients to compensate for those dropping out during the study.

Interim Analysis

An independent safety committee will perform three interim analyses on information time 25% (55 patients), 50% (110 patients) and 75% (165 patients). Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and DeMets, and will employ O'Brien-Fleming Z-test boundaries, which are very conservative early in the trial. For the first interim analysis the efficacy stopping rule would require an extremely low P value ($P< 0.000015$). For the second interim analysis $P< 0.003$ will be taken as efficacy stopping rule. For the third interim analysis $P< 0.02$ will be taken as efficacy stopping rule. Investigators will be kept blind to the interim analysis results.

INCLUSION CRITERIA

We will include patients who signed an informed consent that meets the criteria below:

1) Known diagnosis of SCD based on sickle cell tests and hemoglobin electrophoresis.
2) Age 18 to 60 years

3) Both genders
4) Acute onset of painful crises, defined as having an onset within 7 days

EXCLUSION CRITERIA

1) Pregnancy or breast-feeding
2) Altered mental status
3) Body mass index greater than 40 kg/m2
4) Patients with significant neurological disease
5) Seizures
6) Acute head or eye injury
7) Patients with high intra-cranial tension
8) Patients with known psychiatric disorders
9) Patients with significant cardiac diseases or arrhythmias
10) Patients with significant pulmonary diseases rather than acute chest syndrome
11) Patients with significant renal disease (BUN/creatinine ratio < 25)
12) Patients with significant hepatic disease (Child Pugh class B or C)
13) Patients with significant endocrine disease
14) Known allergy to phencyclidine derivatives, ketamine or morphine
15) Sepsis or septic shock
16) Patients required circulatory or ventilatory supports
17) Alcohol or drug abuse
18) Patients with chronic pain status unrelated to SCD
19) Patients receiving anti-convulsant or anti-psychiatric medications, narcotics, analgesics other than paracetamol and NSAID
20) Patients with communication barriers.

RECRUITMENT AND INFORMED CONSENT

All physicians and nurses at the Emergency Department will be invited to an in-service trial lecture. Pharmacy staff shall likewise be invited to attend this lecture to be conducted by the Principal investigator to encourage screening of patients during their shift. Adult patients with sickle cell disease who will be admitted to the emergency department solely for pain management for severe painful crisis (Numerical Pain rating score (NPRS) greater than 5 on a standard 0: no pain to 10: worst imagined pain (appendix 2) who require opioid analgesia, as will be determined by the attending physician.

Immediately upon identification of patients with chief complaints or visit reasons of sickle cell, study investigators shall screen potentially eligible patients with inclusion/exclusion criteria checklist as per Data Collection instrument. If patient is eligible, study investigators would obtain informed consent and explain potential risks and benefits with receiving study interventions.

RANDOMIZATION

Randomization will be made after a patient is considered eligible and a written informed consent is obtained. Study pharmacist will randomize patients via an electronic pre-generated randomization system. The randomization process will use block randomization stratified by the system thru the previous use of narcotic drug >24 hours prior to randomization and gender. We will use randomly varying block sizes, and will randomize patients in a 1:1 trend to receive low dose ketamine 0.3 mg/kg in 100ml normal saline in addition to standard IV hydration plus morphine 0.1mg/kg rescue doses vs standard dose of morphine (0.1mg/kg) in 100 ml normal saline in addition to standard IV hydration plus rescue morphine doses.

MINIMIZING BIAS

The procedure for randomization warrants confidentiality. All enrolled patients will receive the same designed follow-up. We will use the intention-to-treat principle for all analyses.

TRIAL INTERVENTION

Upon arrival and assessment, all patients shall receive a standard dose of non-narcotic analgesia, either Paracetamol or NSAID. Pain score will then be measured at 0 and 30 minutes; after which, consent procedure and randomization shall be initiated provided that patients rate their pain (NPRS) greater than 5 and the diagnosis of the painful crises had been established.

All health care providers are blinded to the arm. The infusion preparation will be labeled for the patient, with study number from the pharmacy, but without any other identifying marks. The nurse assigned to the patient would administer the intervention.

Patients randomized to intervention group will receive low dose ketamine 0.3 mg/kg in 100ml normal saline infused over 30 min in addition to standard IV hydration plus morphine

0.1mg/kg rescue doses based on treating physician discretion while patients randomized to control group will receive standard dose of morphine (0.1mg/kg) in 100 ml normal saline infused over 30 minutes in addition to standard IV hydration plus rescue morphine doses based on treating physician discretion.

Pain score will be checked at 0, 30, 60, 90 and 120 minutes.
If patients rate their pain as lower than 4 at least 2 hours after the administration of either medication, patients can be discharged.
If no pain relief was achieved after 1 dose of therapy, it will be up to the treating physician to resume usual practice of managing painful crises with morphine equivalent or admission.
Patient monitoring includes electrocardiography, non-invasive blood pressure, pulse oximetry and temperature. All patients will receive oxygen supplementation through a face mask or nasal prongs during sleep and when required to maintain oxygen saturation higher than 90%.
Lactated Ringer's or NaCl 0.9 solution will be infused at a rate of 2-3 ml/kg/h.
Normothermia will be maintained with warming air enforced blankets.
Patient's admission to the hospital or home discharge will be left to the discretion of the treating physician. No attempt will be made to expedite this process; the patient will only be discharged from the ER if he/she is alert, oriented to the time and place, conversant, and cooperative, and if vital signs have been stable for at least 2 hours, the patient can sit up without dizziness or nausea, the pain is considered tolerable with an orally administered analgesic and no more parenteral analgesia is required.

TRIAL OUTCOMES

PRIMARY OUTCOME

- Severity of pain scores using NPRS: the patient will be asked to rate his/her pain at the initial assessment, and then the score will be recorded by the ED nurse every thirty minutes until discharge from the ED, as part of the follow-up.
- Length of stay in the ED, defined as the time elapsed from the start of study medication to the readiness for the discharge from the hospital.
- Development of any known Side effect of the drugs used.

SECONDARY OUTCOMES

- The cumulative use of opioid will be recorded during the ED stay

- The rate of hospital admission
- The overall patients' satisfaction using NPRS (0: no pain, 10: the most unimaginable pain).

ADVERSE EVENT REPORTING

We will describe serious adverse events (SAEs) as any manifestation, incident, or response to intervention, whether anticipated or not that needs an in-patient admission or extension of an existing hospitalization that results in disability, life threatening occurrence and death.

DATA ANALYSES

We will analyze patients in the management group to which they are allocated, according to the intention-to-treat principle. We will include all randomized patients in these analyses. We will compare patients allocated to Ketamine and allocated to standard care. The data will be analyzed using SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA) and tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables will be expressed as the mean ± SD or as the median and range or 95% confidence intervals (95% CI) if the assumption of a normal distribution is violated. Categorical variables will be expressed as numbers and percentages. The independent-t-test, Mann–Whitney U test and the Wilcoxon rank-sum test, and the $\chi 2$ test or Fisher's exact test will be used as needed.

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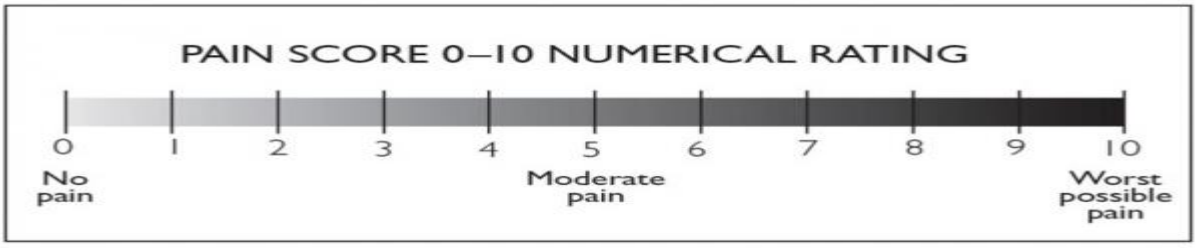
15. APPENDICES:

Appendix 1:

Appendix 2:

a. NPRS=NUMERICAL PAIN RATING SCORE



b. RICHMOND AGITATION SEDATION SCORE (RASS)

+4	**Combative: Combative, violent, immediate danger to staff**
+3	**Very Agitated: pulls or removes tubes or catheters; aggressive**
+2	**Agitated: frequent non-purposeful movement**
+1	**Restless: anxious and apprehensive, but movements not aggressive or vigorous**
0	**Alert and Calm**
-1	**Drowsy: appears sleepy, easily alerts, holds attention for >10s**
-2	**Light sedation: sleeping, but awakens to voice or physical stimulation**
-3	**Moderate sedation: movement or eye opening to voice, no eye contact**
-4	**Deep sedation: arouses to physical stimulation**
-5	**Unarousable**