Nebulized Sub-dissociative Dose Ketamine at Three Different Dosing Regimens for Treating Acute Pain in the Pediatric ED

**STUDY DESCRIPTION**

**Brief Summary**

In the situation when intravenous access is not readily available or unobtainable, sub-dissociative dose ketamine can be administered via intranasal route (IN). The data supporting intranasal route in pediatric patients is somewhat conflicting with regards to the optimum intranasal dose (range 0.75-1 mg/kg) and frequencies of administration. Hence, another non-invasive route such as nebulization via Breath-Actuated Nebulizer which allows a controlled patient-initiated delivery of analgesics in titratable fashion might be considered in the ED. Administration of fentanyl via BAN for pediatric patients presenting to the ED with acute traumatic musculo-skeletal injuries was found to be safe and effective and comparable to intravenous fentanyl and intravenous morphine. Nebulized administration of ketamine however, has only been studied in the areas of acute postoperative pain management, cancer palliation, and status asthmaticus therapy (ref). To our knowledge, there are no prospective randomized trials that evaluated a role of nebulized SDK role in managing a variety of acute and chronic painful conditions in the ED.

**Condition or Disease:** Pain

**Intervention/treatment:**

- Drug: Nebulized Sub-dissociative Dose Ketamine at either 0.75 mg/kg
- Drug: Nebulized Sub-dissociative Dose Ketamine at 1 mg/kg
- Drug: Nebulized Sub-dissociative Dose Ketamine at 1.5 mg/kg.

**Phase:** Phase 4

**DETAILED DESCRIPTION**
STUDY DESIGN
Subjects: Pediatric patients aged 7-17 years presenting to the ED with acute painful conditions such as traumatic and non-traumatic abdominal, flank, back, musculoskeletal pain, vaso-occlusive painful crisis of sickle cell disease, and lacerations with a pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale and requiring sub-dissociative dose ketamine analgesia as determined by the treating attending physician. Eligible patients will be identified by the primary evaluation of the treating physician, who believes that the patient will benefit from the non-invasive route of Breath Actuated Nebulized (BAN) Sub-Dissociative Dose Ketamine rather than other methods (Intravenous, oral etc.) The treating physician will inform the research team of the potential patient to begin the consenting and enrollment process.

Patients’ screening and enrollment will be performed by study investigators and research assistants. All patients will be enrolled at various times of the day when study investigators will be available for patient enrollment and ED pharmacists will be available for medication preparation.

Eligibility Criteria: Patients with ages between 7 and 17 presenting to the ED with acute painful conditions such as traumatic and non-traumatic abdominal, flank, back, musculoskeletal pain, vaso-occlusive painful crisis of sickle cell disease, and lacerations with a score of 5 or more on a standard 11-point (0 to 10) numeric rating scale. Patients receiving oral acetaminophen and/or ibuprofen at triage prior to SDK administration will be eligible for the study.

Exclusion criteria will include altered mental status, GCS<15, allergy to ketamine, pregnant patients, weight greater than 100 kg, heart rate >180, airway abnormalities (congenital or acquired), absence of parent(s) at the time of consent, closed head injury, seizure disorder, use of opioid analgesics, schizophrenia or bipolar disorder.

Design: This is a prospective, randomized, double-blind trial comparing analgesic efficacy and safety of nebulized SDK administered at three different doses to pediatric patients presenting to the ED of Maimonides Medical Center with acute painful conditions. Upon meeting the eligibility criteria, patients will be randomized into one of three study arms based on the dosing of the SDK: 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg.

Data Collection Procedures: Each patient will be approached by a study investigator for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after being evaluated by the treating emergency physician and determined to meet study eligibility criteria. When English will not be the participant’s primary language, a staff interpreter or licensed telephone interpreter would be used. Baseline pain score will be determined with an 11-point numeric rating scale (0 to 10), described to the patient as “no pain” being 0 and “the worst pain imaginable” being 10. A study investigator will record the patient’s body weight and baseline vital signs. The on-duty ED pharmacist will prepare a breath-actuated nebulizer with doses of 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg according to the predetermined randomization list, which will be created in SPSS (version 24; IBM Corp, Armonk, NY) with block randomization of every 10 participants. The medication will be delivered to the treating nurse in a blinded fashion and will be administered via breath-initiated nebulization for duration of treatment of 10 minutes.

Study investigators will record pain scores, vital signs, and adverse effects at 15, 30, and 60 minutes. In addition, study investigators will record a residual amount of medication (ml) in the nebulizer after the treatment. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief at 15 minutes mark post-ketamine administration, intravenous morphine at 0.1 mg/kg will be administered as a rescue analgesic.

All data will be recorded on data collection sheets, including patients’ sex, demographics, medical history, and vital signs and entered into SPSS (version 24.0; IBM Corp) by the research manager. Development of the randomization list, confirmation of written consent acquisition for all participants, and statistical analyses will be conducted by the research manager and statistician, who would work independent of any data collection.

Patients will be closely monitored for any change in vital sings and for adverse effects during the entire study period (up to 2 h) by study investigators. Common adverse effects that are associated with sub-dissociative dose ketamine are feeling of unreality, dizziness, nausea, vomiting, and sedation.

Data Analysis: Data analyses will include frequency distributions, paired t-test to assess a difference in pain scores within each group, and independent-sample t-test to assess differences in pain scores between the 3 groups at the various intervals.

Mixed-model linear regression will be used to compare changes in pain numeric rating scale across time points. This will compensate for participants lost to follow-up and allow all patients’ data to be analyzed on an intention-to-treat principle.

For categorical outcomes (eg, complete resolution of pain), a x2 or Fisher’s exact test will be used to compare outcomes at 30 minutes. Percentage differences and 95% confidence intervals between the treatment groups will be calculated for all time points with P<.05 to denote statistical significance. Based on the validation of a verbally administered rating scale of acute pain in the ED and the comparison of verbal and visual pain scales, we will use a primary outcome consisting of a minimal clinically meaningful difference of 1.3 between three groups at the 30-minute pain assessment.28,29 Sample Size: Assuming an SD of 3.0, a power analysis determined that a repeated-measures ANOVA with a sample size of 34 patients per group (102 total) will provide at least 80% power to detect a difference of at least 1.3 at 30 minutes (as well as at any other interval post-baseline), with an alpha=0.05. To account for possible missing data the total sample size will be 120 patients (40 per group). A pre-planned interim data analysis will occur upon reaching a total of 60 patients (20 patients per group).

Expected Outcomes: The primary outcome will include a comparative reduction in pain scores on numeric rating pain scale (NRS) between recipients of nebulized SDK given at three different doses at 15 minutes after analgesic administration. The secondary outcomes will include a need for rescue analgesia at 15, 30 or 60 minutes and adverse events in each group. With respect to unique adverse effects of SDK, we will use Side Effect Rating Scale for Dissociative Anesthetics (SERDSA) and Richmond Agitation Sedation Scale (RASS) (ref SERDSA Scale includes fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, mood change, general discomfort, and hallucinations with severity of each graded by patients on a five-point scale, with “0” representing the absence of any adverse effects and “4” representing a severely bothersome side effect. RASS evaluates the severity of agitation and/or sedation in accordance to the nine-point scale with scores ranging from “-4” (deeply sedated) to “0” (alert and calm) to “+4” (combative).
Active Comparator: 0.75 mg/kg
The on-duty ED pharmacist will prepare a breath-actuated nebulizer with doses of 0.75 mg/kg sub-dissociative dose ketamine (SDK) to give to ED pediatric patients with moderate to severe pain based on a score of 0 to 10 on a Visual Analog scale where 0 is no pain, 5 is moderate pain and 10 is very severe pain.

Drug: Nebulized Sub-dissociative Dose Ketamine at either 0.75 mg/kg
Nebulized Sub-dissociative Dose Ketamine at 0.75 mg/kg

Active Comparator: SDK: 1 mg/kg
The on-duty ED pharmacist will prepare a breath-actuated nebulizer with doses 1 mg/kg sub-dissociative dose ketamine (SDK), to give to ED pediatric patients with moderate to severe pain based on a score of 0 to 10 on a Visual Analog scale where 0 is no pain, 5 is moderate pain and 10 is very severe pain.

Drug: Nebulized Sub-dissociative Dose Ketamine at 1 mg/kg
Nebulized Sub-dissociative Dose Ketamine at either 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg.

Active Comparator: SDK: 1.5 mg/kg.
The on-duty ED pharmacist will prepare a breath-actuated nebulizer with doses of 1.5 mg/kg sub-dissociative dose ketamine (SDK), to give to ED pediatric patients with moderate to severe pain based on a score of 0 to 10 on a Visual Analog scale where 0 is no pain, 5 is moderate pain and 10 is very severe pain.

Drug: Nebulized Sub-dissociative Dose Ketamine at 1.5 mg/kg.
Nebulized Sub-dissociative Dose Ketamine at 1.5 mg/kg.

OUTCOME MEASURES

Primary Outcome Measures: 1. Pain Score reduction from baseline [ Time Frame: 15 minutes ]
The primary outcome will include a comparative reduction in pain scores on numeric rating pain scale (NRS) between recipients of nebulized SDK given at three different doses at 15 minutes after analgesic administration. The Visual Analog Scale Ranges from 0 (no pain) to 10 (very severe pain) with 5 being moderate pain

ELIGIBILITY CRITERIA

Ages Eligible for Study: 7 to 17 Years (Child)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria
Inclusion Criteria:
Patients with ages between 7 and 17 presenting to the ED with acute painful conditions; score of 5 or more on a standard 11-point (0 to 10) numeric rating scale. traumatic and non-traumatic abdominal pain flank pain back, pain musculoskeletal pain, vaso-occlusive painful crisis of sickle cell disease, and lacerations

Exclusion Criteria:
altered mental status, GCS180, airway abnormalities ( congenital or acquired), absence of parent(s) at the time of consent, closed head injury, seizure disorder, use of opioid analgesics, schizophrenia or bipolar disorder

CONTACTS AND LOCATIONS

Contacts
Contact: Antonios Likourezos, MPH 7182836896 alikourezos@maimonidesmed.org
Contact: Sergey Motov, MD 7182838693 smotov@maimonidesmed.org

Locations
United States, New York
Maimonides Medical Center
Brooklyn

Sponsors and Collaborators
Antonios Likourezos

Investigator
Study Chair: John Marshall, MD
Maimonides Medical Center

MORE INFORMATION

Responsible Party: Antonios Likourezos
ClinicalTrials.gov Identifier: NCT03950817
Other Study ID Numbers: 2019-01-05
First Posted: May 15, 2019
Last Update Posted: April 8, 2022
Last Verified: April 2022
Individual Participant Data (IPD) Sharing Statement: Plan to Share IPD: No
<table>
<thead>
<tr>
<th>Studies a U.S. FDA-regulated Drug Product:</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies a U.S. FDA-regulated Device Product:</td>
<td>No</td>
</tr>
<tr>
<td>Product Manufactured in and Exported from the U.S.:</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional relevant MeSH terms:</td>
<td>Acute Pain</td>
</tr>
<tr>
<td></td>
<td>Neurologic Manifestations</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
</tbody>
</table>