

## **TITLE**

### **Comparison of Nebulized Sub-dissociative Dose Ketamine at Three Different Dosing Regimens for Treating Acute Pain in the Pediatric ED: A Prospective, Randomized Double-Blind Trial**

## **INTRODUCTION**

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA)/glutamate receptor complex antagonist that decreases pain by diminishing central sensitization, hyperalgesia, and “wind-up” phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system.

Intravenous ketamine administration in sub-dissociative doses (0.1-0.3 mg/kg) in pre-hospital settings and in the ED results in effective pain relief in patients with acute traumatic and non-traumatic pain, chronic non-cancer and cancer pain, and in patients with opioid-tolerant pain by virtue of providing anti-hyperalgesia, anti-allodynia, and anti-tolerance.

## **BACKGROUND AND SIGNIFICANCE**

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.

## **STUDY OBJECTIVES**

To compare analgesic efficacy and rates of side effects of sub-dissociative dose ketamine administered via breath-actuated nebulizer at three different doses (0.75mg/kg, 1 mg/kg and 1.5 mg/kg) for pediatric ED patients presenting with acute painful conditions.

## **HYPOTHESIS**

In our study we hypothesize that sub-dissociative-dose ketamine administered as a single agent via breath actuated nebulizer at the dose of 1.5 mg/kg will provide better analgesia at 15 min post-administration with similar rates of side effects in comparison to 0.75 mg/kg and 1 mg/kg for pediatric ED patients presenting to the ED with acute painful conditions. The primary outcome of this trial is the comparative reduction in participant’s pain scores at 15 minutes post medication administration.

## **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 signs 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  $X^2$  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.<sup>28,29</sup>

**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.

## REFERENCES

- [1] Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. *Anesth Essays Res.* 2014;8(3):283–9.
- [2] Ahern TL, Herring AA, Anderson ES, et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. *Am J Emerg Med.* 2015;33(2):197-201.
- [3] Beaudoin FL, Lin C, Guan W, et al. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. *Acad Emerg Med.* 2014;21(11):1193-20
- [4] Motov S, Rockoff B, Cohen V, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. *Ann Emerg Med.* 2015;66(3):222–9.

- [5] Goltser A, Soleyman-Zomalan E, Kresch F, et al. Short (low-dose) ketamine infusion for managing acute pain in the ED: case-report series. *Am J Emerg Med.* 2015;33(4):601. e5-7.
- [6] Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing intravenous push dose of low dose ketamine to short infusion of low dose ketamine for treatment of moderate to severe pain in the emergency department. *Am J Emerg Med.* 2017;35(8):1095-100
- [7] Schulz KF, Altman DG, Moher D; for the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials.*
- [8] Miner JR, Kletti C, Herold M, et al. Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* 2007;14:895–8.
- [9] Furyk JS, Grabowski WJ, Black LH. Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: a randomized controlled trial. *Emerg Med Australas* 2009;21:203–9.
- [10] Eide Stubhaug A, Oye I, Breivik H. Continuous subcutaneous administration of the N-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine in the treatment of post-herpetic neuralgia. *Pain.* 1995;61(2):221–8
- [11] Ahuja V, et al. Nebulized ketamine decreases incidence and severity of postoperative sore throat. *Indian J Anaesth.* 2015 Jan;59(1):37-42.
- [12] Goyal S, et al. Ketamine in status asthmaticus: a review. *Indian J Crit Care Med.* 2013 May-Jun;17(3):154-161.
- [13] Ahuja V, et al. Nebulized ketamine decreases incidence and severity of postoperative sore throat. *Indian J Anaesth.* 2015 Jan;59(1):37-42.