TITLE

Comparison of Nebulized Ketamine to Intravenous Sub-Dissociative Dose Ketamine for Treating Acute and Chronic Painful Conditions in the ED: A Prospective, Randomized, Double-Blind, Double-Dummy Clinical Trial.

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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 (1).
Ketamine administration in sub-dissociative doses (SDK) of 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 (2-4).Two commonly utilized routes of of SDK administration in the ED include an intravenous route (intravenous push dose or short infusion) and intranasal route (5-11).

BACKGROUND AND SIGNIFICANCE

In the situation when intravenous access is not readily available or unobtainable, and intranasal route is not feasible, another non-invasive route of ketamine administration such as inhalation via Breath-Actuated Nebulizer (BAN) is coming into the play. The BAN allows a controlled patient-initiated delivery of analgesics in titratable fashion (12). Nebulized administration of ketamine has been studied in the areas of acute postoperative pain management (post-intubational sore throat), in anesthesia (pre-medication for general anesthesia,) and in managing cancer pain, and status asthmaticus therapy (13-14). However, our research team has published a case series of 5 patients receiving nebulized ketamine for a variety of acute painful conditions and has recently completed a randomized double-blind trial of 120 adult patients that evaluated analgesic efficacy and safety of nebulized ketamine at three different dosing regimens for acute pain in the ED.
Currently, we are conducting two additional studies evaluating the role of nebulized ketamine in pediatric ED and pre-hospital arena.

STUDY OBJECTIVES

To compare analgesic efficacy and rates of side effects of sub-dissociative dose ketamine at 0.3 mg/kg dose administered via intravenous route as a short infusion over 15 minutes to a 0.75 mg/kg dose of ketamine administered via breath actuated nebulizer to adult patients presenting to the ED with acute painful and exacerbation of chronic painful conditions.

HYPOTHESIS

In our study we hypothesize that intravenous sub-dissociative-dose ketamine of 0.3 mg/kg will provide better analgesia at 30 min post-medication administration in comparison to nebulized ketamine administered at 0.75 mg/kg. The primary outcome of this trial is the comparative reduction in participant's pain scores at 30 minutes post medication administration.

STUDY DESIGN

Subjects: Patients 18 years of age and older presenting to the ED with acute and chronic painful conditions such as traumatic and non-traumatic abdominal, flank, back, musculoskeletal pain, headache, as well as exacerbation of chronic abdominal, musculoskeletal and neuropathic pain with a score of 5 or more on a standard 11- point (0 to 10) numeric rating scale and requiring parenteral analgesia as determined by the treating attending physician. 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 an ED pharmacist will be available for medication preparation

Eligibility Criteria: Patients 18 years of age and older presenting to the ED with acute and chronic painful conditions such as traumatic and non-traumatic abdominal, flank, back, musculoskeletal pain, headache, as well as exacerbation of chronic abdominal, musculoskeletal and neuropathic pain with a score of 5 or more on a standard 11- point (0 to 10) numeric rating scale. Patients will have to be awake, alert, and oriented to person, place, and time, and will be able to demonstrate understanding of the informed consent process and content. Patients also will have to demonstrate ability to verbalize the nature of any adverse effects they might experience as well as to express their pain severity by using the NRS.

Exclusion Criteria: Altered mental status, allergy to ketamine, pregnant patients, weight greater than 150 kg, unstable vital signs (systolic blood pressure <90 or>180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), inability to provide consent, and past medical history of alcohol or drug abuse, or schizophrenia.

Design: This is a prospective, randomized, double-blind, double dummy trial comparing analgesic efficacy and safety of intravenous SDK administered at 0.3 mg/kg over 15 minutes to nebulized ketamine at 0.75 mg/kg administered via BAN to patients presenting to the ED of Maimonides Medical Center with acute and chronic painful conditions. Upon meeting the eligibility criteria, patients will be randomized into two study groups: IV SDK and Nebulized K-BA

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 language-appropriate consent form will be used and non-investigator, hospital-employed, trained interpreters or licensed telephone interpreter will assist in acquisition of informed consent. 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 either a breath-actuated nebulizer with a dose of 0.75 mg/kg or an infusion dose of IV SDK at 0.3 mg/kg in 100 ml normal saline bag 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. All participants will receive a corresponding placebo in order to maintain double-dummy design: the subjects randomized to receive IV SDK will also receive nebulized saline via BAN, and the subjects receiving K-BAN will also receive an IV infusion of Normal Saline over 15 minutes. The medication will be delivered to the treating nurse in a blinded fashion who will set up an infusion pump with a run time of 15 minutes. The nebulization of active drug and placebo via BAN will have a minimum time of 5 min and maximum time of 15 min.

Study investigators will record pain scores, vital signs, and adverse effects at 15, 30, 60, 90, and 120 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, intravenous morphine at 0.1 mg/kg will be administered as a rescue analgesic.

The preparing ED pharmacist, research manager, and statistician will be the only ones with knowledge of the study arm to which each participant would be randomized. Treating providers, participants, and the data collecting research team will be blind to the medication route received.

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 (Michael Silver), who will work independently 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 120 minutes) by study investigators. Common adverse effects that are associated with sub-dissociative dose ketamine are felling of unreality, dizziness, nausea, vomiting, and sedation.

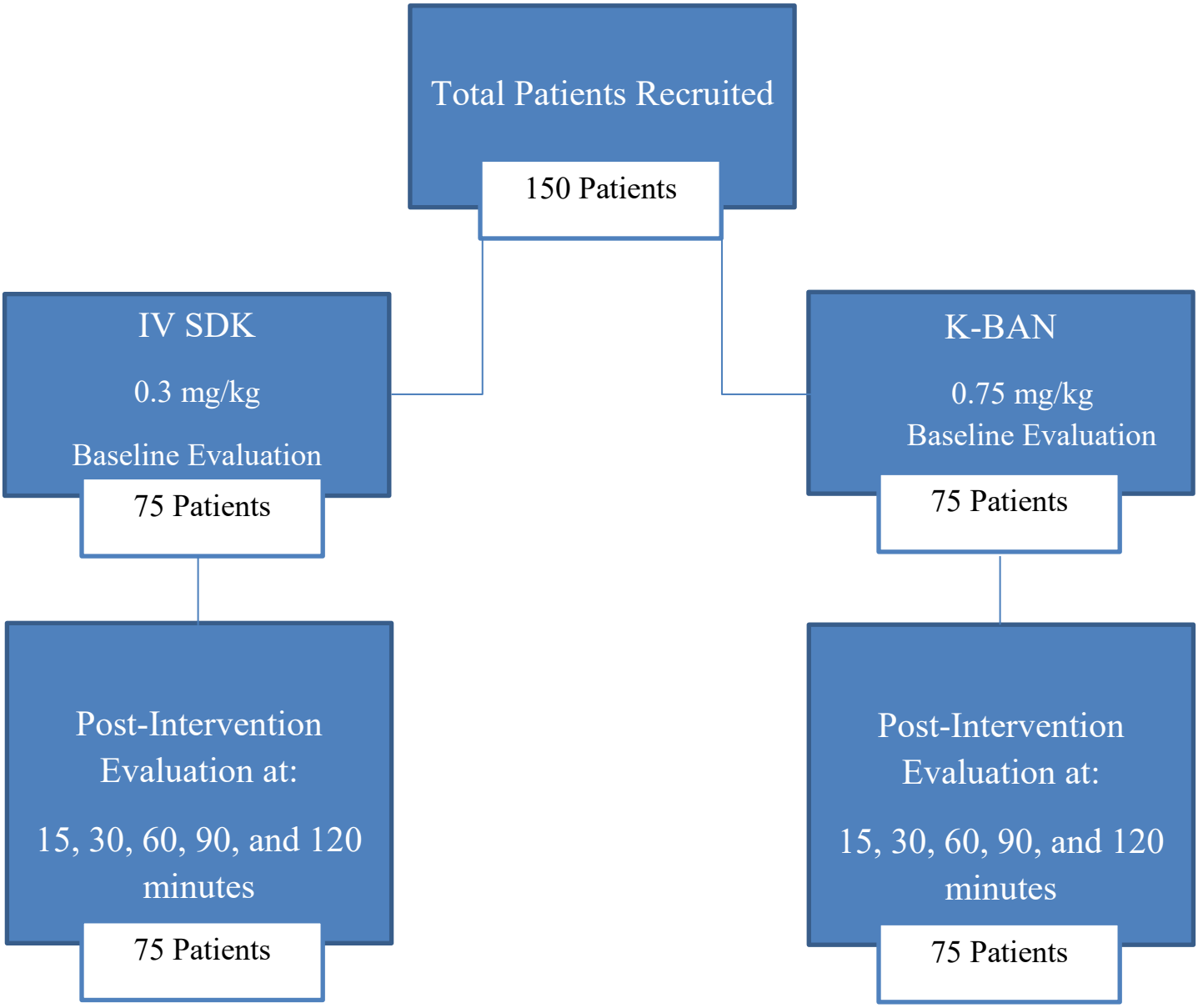
Data Analysis: Data analyses will include frequency distributions, paired t-test to assess a difference in pain scores within each group, and independent-sample t-test to assess differences in pain scores between the 2 groups at the various intervals.
Mixed-model linear regression will be used to compare 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.[28,29]

Sample Size: Assuming a greater improvement in pain score in the IV group of 1.3 points over the nebulized group, with a SD of 3.0 in both groups, we will need to enroll 67 patients per group (134 total) to have 80% power at alpha = 0.0465, for a one-sided z-test. To account for possible missing data the total sample size will be 150 patients (75 per group). A pre-planned interim data analysis will occur upon reaching a total of total of 60 patients (30 patients per group), and alpha = 0.0035 will be used to maintain overall power, this will make the overall alpha of the study 0.05.

Expected Outcomes: The primary outcome will include a comparative reduction of pain scores on numeric rating pain scale (NRS) between recipients of IV SDK and K-BAN at 30 minutes post-analgesic administration.

SAE Reporting: Any serious adverse event, requiring intervention, will be reported to the IRB within 24 hours of discovery by the research staff. Less serious adverse events will be reported within a week of discovery. There are known expected outcomes and side effects to the procedures and medications being received and these are the same risks/side effects as the standard of care – these will be reported if they are serious and require intervention.

Table 1: Patient Recruitment and Follow-up Assessment Flow-Chart



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*. 2010;11:32.

[8] Ahern T, Herring A, Stone M, et al. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. *Am J Emerg Med*. 2013;31:847-851

[9] Ahern TL, Herring AA, Miller S, et al. Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Med.* 2015;16(7):1402–9

[10] Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med*. 2007;25(4):385–90.

[11] 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

[12] Ahuja V, et al. Nebulized ketamine decreases incidence and severity of postoperative sore throat. Indian J Anaesth. 2015 Jan;59(1):37-42.

[13] Goyal S, et al. Ketamine in status asthmaticus: a review. Indian J Crit Care Med. 2013 May-Jun;17(3):154-161.

[14] Ahuja V, et al. Nebulized ketamine decreases incidence and severity of postoperative sore throat. Indian J Anaesth. 2015 Jan;59(1):37-42.