

TITLE

Pre-hospital Utilization of Nebulized Sub-dissociative Dose Ketamine for managing acute traumatic extremity pain: a prospective observational study

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

Ketamine administration in sub-dissociative doses (0.1-0.3 mg/kg) in prehospital 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. Two commonly employed strategies of SDK administration in the ED include an intravenous push (IVP) dose (over 2-5 minutes), which is associated with relatively high rates of minor but bothersome psycho-perceptual side effects (feeling of unreality and dizziness), or short infusion (SI) given over 15 minutes with significantly reduced rates of unreality and preserved analgesic efficacy.

BACKGROUND AND SIGNIFICANCE

In the situation when intravenous access is not readily available or unobtainable, or when prehospital delays to obtain intravenous access are not warranted, sub-dissociative dose ketamine can be administered via intranasal (IN) route. The data supporting IN is not set on the optimum intranasal dose (range 0.75-1 mg/kg) and frequencies of administration. In addition, IN administration of SDK for adult patients in the ED requires a highly concentrated solution that is not routinely stock in the ED. Hence, another non-invasive route for analgesia delivery is offered such as nebulization via a Breath-Actuated Nebulizer which allows a controlled patient-initiated delivery of analgesics in titratable fashion.

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 acute pain due to extremity trauma in the prehospital arena.

STUDY OBJECTIVES

To evaluate analgesic efficacy and safety of sub-dissociative dose ketamine administered prehospitally via breath-actuated nebulizer at 1.0 mg/kg for patients with acute traumatic extremity injuries.

HYPOTHESIS

In our study we hypothesize that sub-dissociative-dose ketamine administered as a single agent via breath actuated nebulizer at the dose of 1.0 mg/kg will provide significant pain relief with minimal rates of side effects for patients with acute traumatic extremity injuries and will allow

for alternative administration of effective analgesia especially in those settings for which intravenous or intraosseous routes are difficult or not necessary or when a delay in patient transport to a hospital is not ideal.

The primary outcome of this trial is the percent reduction in participant's pain scores at 30 minutes post medication administration.

STUDY DESIGN

Subjects: Patients 18 years of age and older transported by prehospital care providers to the ED with acute traumatic extremity injuries with a pain score of 5 or more on a standard 11- point (0 to 10) numeric rating scale. Patients will be enrolled by Emergency Medical Services (EMS) providers of Maimonides Medical Center (MMC) who are operating under the New York City 9-1-1 Regional Emergency Medical Advisory Committee (REMAC) auspices. Patient screening, enrollment, and data collection will be performed initially by advanced life support (ALS) paramedics and subsequently completed by study investigators upon arrival to the MMC emergency department. Emergency department pharmacist investigators will prepare PK-BAN packages that will be assigned to every ALS ambulance at the start of shift. They will include a single ketamine 50mg/ml vial, blunt-tip needle and syringe, BAN device/tubing, and data collection sheet.

Eligibility Criteria: Patients 18 years of age and older with acute traumatic extremities injuries with a score of 5 or more on a standard 11- point (0 to 10) numeric rating scale.

Exclusion criteria will include 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), and past medical history of alcohol or drug abuse, or schizophrenia.

Design: This is a prospective, observational study evaluating analgesic efficacy and safety of sub-dissociative dose ketamine of 1.0 mg/kg administered via breath-actuated nebulizer

Data Collection Procedures: Each patient will be approached by advanced life support (ALS) paramedics for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after meeting study eligibility criteria. In case of severe pain (extremis), a verbal consent will suffice the initial administration of the SDK with subsequent signing of the informed consent upon arrival to the ED. 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. An ALS paramedic will record the patient's body weight and baseline vital signs. The PK-BAN package will be opened and weight -based dose of ketamine will be administered to the patient via BAN. The medication will be delivered with a minimum time of 5 min and maximum time of 15 min. An ALS Paramedic record pain scores,

vital signs, and adverse effects at 15 and 30 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, a second (equivalent to the first dose) of SDK via BAN will be administered to the patient in a blinded fashion. In situations when nebulized SDK will fail to achieve acceptable (by patient) pain relief or patient will refuse to continue nebulized SDK treatment, morphine at 0.1 mg/kg IV/IO/IM (not to exceed 5mg) will be administered as a rescue analgesic with an option for one repeat dose (maximum total dose is 10mg).

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. 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 hours) by study investigators after arrival to the ED. Common adverse effects that are associated with sub-dissociative dose ketamine are feeling of unreality, dizziness, nausea, vomiting, and sedation.

Sample Size: To account for possible missing data and patient's dropout, the total sample size will include 50 patients.

Expected Outcomes: The primary outcome will include a percentage of patients achieving a 20% or greater change in pain scores on numeric rating pain scale (NRS) for the baseline to 30 minutes post-analgesic administration. The secondary outcomes will include a need for second or third dose, a need for rescue analgesia at either 15 and 30 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 (SERSDA) and Richmond Agitation Sedation Scale (RASS) (ref) SERSDA 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).

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ATTACHMENTS

List any attachments (contracts, participant materials, data collection tools, etc.)

Protocol for analgesic administration via Breath Actuated Nebulizer

**MAIMONIDES MEDICAL CENTER
DEPARTMENT OF EMERGENCY MEDICINE (ED)**

Protocol for ED Analgesics Administration via Breath-Actuated Nebulizers (BAN)

Background

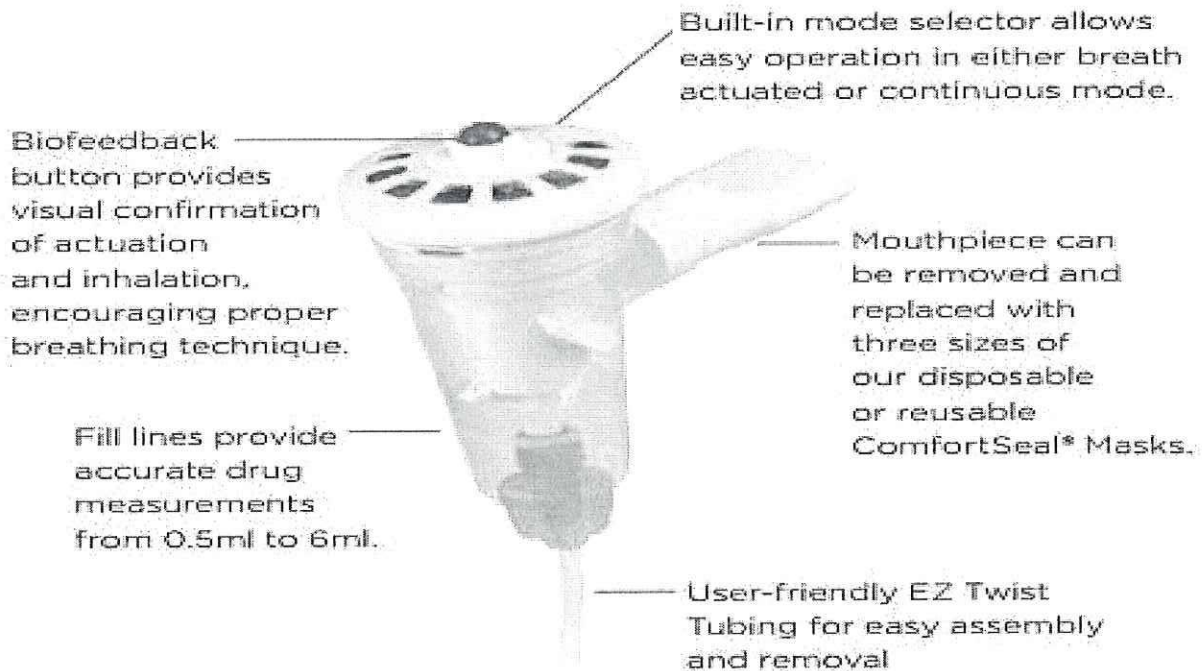
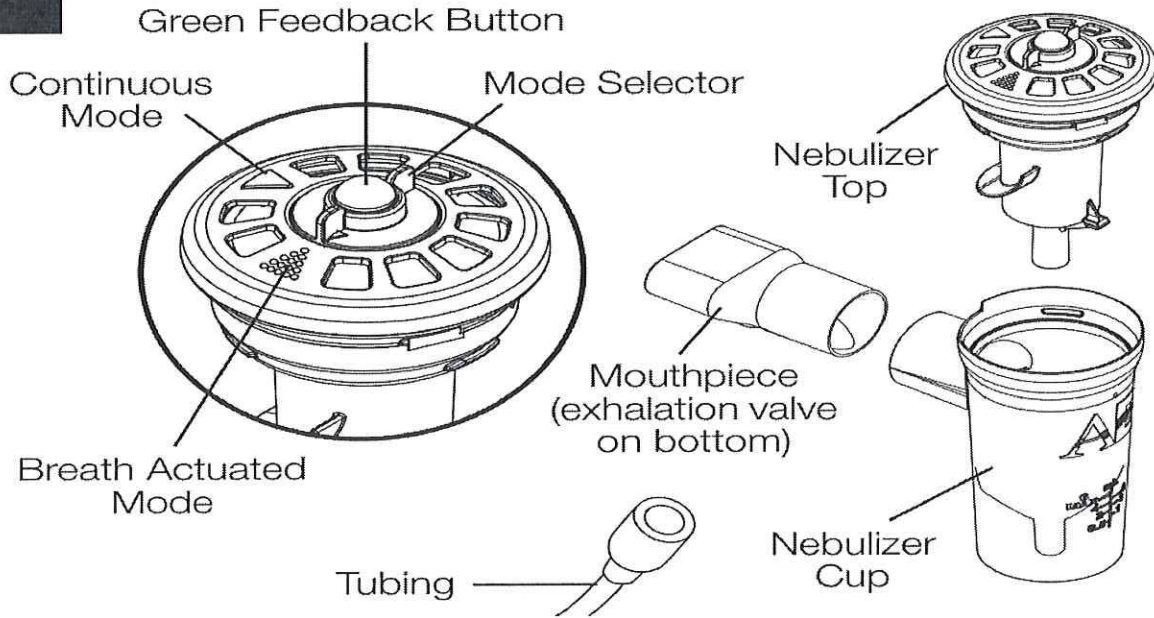
In situations when intravenous access is unobtainable or the desired dose of medications exceeds the maximum allowed dose via IM injections, alternative routes of analgesic administration play an important role in providing timely and effective analgesia in the ED. Nebulized route of analgesic administration (1) provides rapid, effective and titratable analgesic delivery; (2) results in less painful methods of analgesic delivery; (3) minimizes analgesic toxicity and side effects (opioids); and (4) improves overall management of a variety of acute painful conditions in the ED. Data supporting use of nebulized opioids (fentanyl and morphine) in the ED demonstrates comparable analgesic efficacy (overall pain relief, onset of analgesia and a need for rescue analgesia) to intravenous route. To maximize a systemic concentration of nebulized opioids and to prevent iatrogenic exposure of ED staff to opioid vapors, the use of breath-actuated nebulizers (BAN) is strongly recommended.

Breath-actuated nebulizer

The breath-actuated nebulizer (BAN, AeroEclipse, Trudell Medical International, London, Ontario, Canada) has been available as an aerosol delivery option for several years as a viable alternative to analgesic administration. This small-volume disposable nebulizer is primarily designed to generate aerosol during inspiration in response to the patient's inspiratory flow triggering the opening valve. BAN provides smaller particles and greater dose delivery efficiency than continuous jet nebulizers. This increased drug efficiency is associated with decreased release of aerosol to the atmosphere. In addition, BAN possesses dual modes of action: (1) continuous aerosol generation; and (2) breath-actuated (in response to the patient's inspiratory flow) ensuring virtually that no drug is lost to the environment. It provides better compliance, a safer patient environment, and impacts clinical outcomes such as Length of Stay in the ED as well as better patient outcomes and reduced costs.

For ED purposes, the BAN should be placed on Breath Actuated Mode only.

Breath Actuated Nebulizer (BAN)



Instructions for Use:

1. The equipment should be set to Breath Actuated Mode only.
2. Ensure mouthpiece is inserted into side opening of the nebulizer with the exhalation valve facing down.
3. Inspect the tubing for fray, wear or loose particulates, and ensure nothing is blocking the air supply pathway of the nebulizer
4. Unscrew and remove top of nebulizer. Place prescribed medication into nebulizer cup (maximum cup volume 6 mL). Reattach top and gently hand tighten. Medication to be prepared by the ED RN.
5. Secure the top of the nebulizer with a strip/tape that is dated and initialed by the ED RN to prevent tampering by a patient.
6. Attach one end of the supplied tubing to the fitting in the bottom of the nebulizer and the other end to the Air Source
7. Ensure both ends are securely engaged.
8. Set the flowmeter to 7 to 8 liters per minute (lpm) with an air source capable of delivering 50 PSI (344.7 kPa).
9. Instruct the patient to place mouthpiece in mouth, and inhale slowly and deeply. As patient inhales, the green feedback button on top of the nebulizer will move into the fully down position, indicating that the AEROECLIPSE* II BAN is producing aerosol in response to inhalation.
10. Patient should exhale normally: a valve on the mouthpiece opens allowing passive exhalation, as the green feedback button returns to the up position indicating no aerosol is being produced.
11. Instruct the patients to not place the lips over the exhalation valve on the bottom of the mouthpiece. Doing so will prevent the valve from functioning properly.
12. The BAN can be used for multiple rounds of medications per one patient. Once entire treatment regimen is completed, the nebulizer is to be discarded. The BAN stays with the patient for multiple doses of medications and gets discarded after the patient leaves the ED.

Indications:

Pain syndromes requiring opioid analgesia in the ED in the absence of intravenous access

Contraindications:

1. Allergy to medications
2. Altered mental status
3. Hemodynamic instability
4. Contraindications to opioids
5. Inability to follow directions
6. Patients with aberrant drug-related behaviors

Medications to be used:

1. Fentanyl:
 - a. Adults: 4 mcg/kg dose titrated q 10 min up to three doses
 - b. Pediatrics: 2-4 mcg/kg titrated q 10 min up to three doses
2. Morphine:
 - a. Adults: 10-20 mg titrate q 10-15 min up to three doses
 - b. Pediatrics: 0.2 mg/kg titrated q 10-15 min up to three doses

3. Sub-dissociative Dose Ketamine:
 - a. Adults: 0.75-1.5 mg/kg titrated q15 min up to three doses
 - b. Pediatrics (Age: older than 5): 0.75-1.5 mg/kg titrated q15 min up to three doses

Notes:

- No need for continuous cardiac and SpO2 monitoring.
- Patients should be reassessed at 10-15 minute intervals.
- Although opioid overdose using the BAN is rare, intranasal Naloxone may be used to reverse opioid overdose if it happens.