TITLE

Comparison of Nebulized Sub-dissociative Dose Ketamine at Three Different Dosing Regimens for Treating Acute and Chronic Painful Conditions in the ED: A Prospective, Randomized 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
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. 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, sub-dissociative dose ketamine can be administered via intranasal 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 solutions that are not routinely stock in the ED. Hence, another non-invasive route such as nebulization via a Breath-Actuated Nebulizer which allows a controlled patient-initiated delivery of analgesics in titratable fashion (ref).
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 ED patients presenting with acute and chronic 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 30 min

post-administration with similar rates of side effects in comparison to 0.75 mg/kg and 1 mg/kg for ED patients presenting to the ED with acute and chronic painful conditions. 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, or musculoskeletal pain 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 sub-dissociative dose ketamine 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, or musculoskeletal pain 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.

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 trial comparing analgesic efficacy and safety of nebulized SDK administered at three different doses 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 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 with a minimum time of 5 min and maximum time of 15 min up to three doses.

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, 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 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 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 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.[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=.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 total of 60 patients (20) patients per group.

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

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

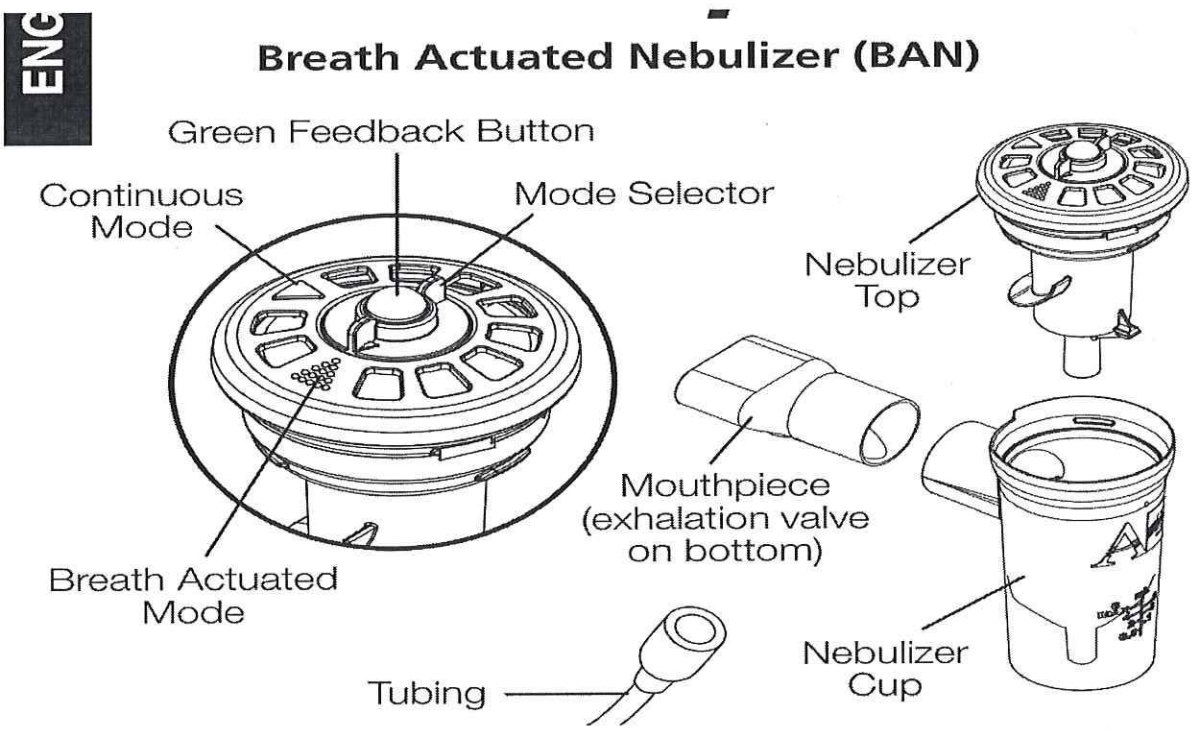
In situations when intravenous access is unobtainable or the desired dose of medications exceeds the maximum allowed dose via IM injections, alternative routes of analgesic administration play an important role in providing timely and effective analgesia in the ED. Nebulized route of analgesic administration (1) provides rapid, effective and titratable analgesic delivery; (2) results in least 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.

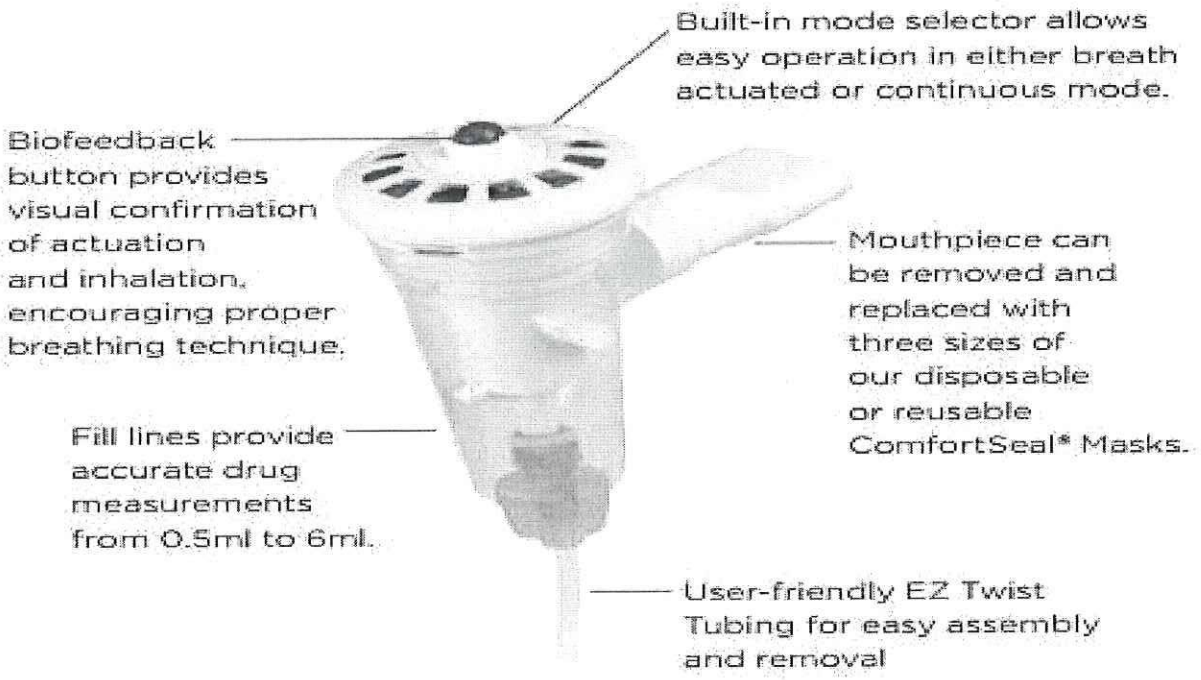
Breath-actuated nebulizer

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.





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.