TITLE: Comparison of Nebulized Ketamine to Nebulized Fentanyl for Treating Acute Painful Conditions in the ED: A Prospective, Randomized, Double-Blind Clinical Trial. (The KETAFEN Trial)

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Introduction

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA)/glutamate receptor complex antagonist. It reduces pain by reducing central sensitization, hyperalgesia, and "wind-up" phenomena in 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 Emergency Department (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. Two commonly utilized routes of SDK administration in the ED include an intravenous (IV) route (intravenous push dose or short infusion) and an intranasal (IN) route (2-11).

Fentanyl is a synthetic opioid derivative that is a potent agonist at the μ-opioid receptor. (12) It is widely used in anesthesia and for acute and chronic pain management (13, 14). Fentanyl has a rapid onset and a relatively short duration of action. It is primarily given by the IV route but can also be given transdermally, sublingually, intranasally, intrathecally, and by inhalation. (15) Intranasal fentanyl has been studied as a noninvasive method of fentanyl administration for quick pain relief; however, the maximum volume of fluid that can be administered via the intranasal route limits the dose of fentanyl that can be administered at a time, resulting in the need to administer repeated doses of fentanyl to achieve a therapeutic end point. (16) A systematic review of seven randomized clinical trials assessing the analgesic efficacy and safety of inhaled (nebulized) fentanyl at a dose of 2-4 mcg/kg in ED patients with moderate to severe pain demonstrated that nebulized fentanyl is as effective as IV opioids in the treatment of acute pain with relatively few adverse effects. (17)

Background and Significance

In situations where intravenous access is not readily available or is unobtainable and the intranasal route is not feasible, another non-invasive route of ketamine administration, such as inhalation via breath-actuated Nebulizer (BAN), is becoming a viable alternative. The BAN allows the controlled, patient-initiated delivery of analgesics in a measured and titratable fashion. (18) Ketamine has been studied as a nebulized drug in a lot of different settings and for a lot of different reasons, such as to treat acute pain after surgery (like a sore throat after being intubated), as a pre-medication for general anesthesia, to treat cancer pain, and as a therapy for asthmaticus (18, 19).

Our research team has published two case series of 10 adult patients who were given nebulized ketamine (via BAN) for a variety of acute traumatic and non-traumatic painful conditions. The patients showed a 60% decrease in pain and a small number of side effects (20, 21). Furthermore, our group published a randomized, double-blind trial of 120 adult patients evaluating the analgesic efficacy and safety of nebulized ketamine at three different dosing regimens for acute pain in the ED (0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg), showing similar analgesic efficacy between the three different dosing regimens for short-term (up to 120 minutes)

pain relief (22). Lastly, we recently completed a randomized, double-blind, double-dummy clinical trial comparing the analgesic efficacy and safety of nebulized ketamine and intravenous ketamine in managing acute pain in adult ED patients, with data currently being analyzed.

Nebulized fentanyl given in the ED to adults with acute traumatic and non-traumatic pain syndromes at a dose range of 1.5–4 mcg/kg showed the same or even better pain-relieving effects than IV fentanyl and IV morphine alone. (23-25)

Study Objectives

To compare the analgesic efficacy and rates of side effects of a 0.75 mg/kg dose of ketamine administered via breath-actuated nebulizer (BAN) to a dose of 3 mcg/kg of fentanyl administered via breath-actuated nebulizer (BAN) in adult patients presenting to the ED with acute painful conditions.

Hypothesis

We hypothesized that nebulized fentanyl at 3 mcg/kg per dose would 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 participants' pain scores at 30 minutes post-medication administration.

Study Design

Subjects

Adult patients (18 years and above) presenting to the ED with acute painful conditions such as traumatic and non-traumatic abdominal, flank, back, musculoskeletal pain, headache, etc. with an initial pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale (NRS) and deemed suitable for nebulized analgesia by the treating attending physician. Study investigators and research assistants will perform subjects' screening and enrollment. 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

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

Exclusion Criteria

Patients below 18 years; patients with a painful condition warranting emergent/urgent intervention in the ED; patients with altered mental status allergy to ketamine or fentanyl, pregnant or breastfeeding, weight greater than 100 kg, patients presenting with head injury, unstable vital signs (systolic blood pressure <90 mmHg or >180 mmHg, pulse rate <50 beats/min or >150 beats/min, and respiration rate <10 breaths/min or >30 breaths/min), inability to provide consent, current medical history of alcohol or drug abuse, and administration of opioids or opioid antagonist/agonist within 4-6 hours prior to arrival and NSAIDs 6 hours prior to arrival to the ED.

Design

This is a prospective, randomized, double-blind trial comparing the analgesic efficacy and safety of nebulized ketamine administered at 0.75 mg/kg via BAN to nebulized fentanyl administered at 3 mcg/kg via BAN to adult patients presenting to the ED of Maimonides Medical Center with acute painful conditions of moderate to severe intensity. The dosing of nebulized fentanyl at three mcg/kg is based on two randomized, dose-finding clinical trials of acute pain where a one mcg/kg dose was compared to a 3 mcg/kg dose with resultant analgesic superiority of the 3 mcg/kg dose (26, 27). The dose of nebulized ketamine is based on the results of our own randomized clinical trial, which showed that 0.75 mg/kg of nebulized ketamine was as effective at relieving short-term pain in the ED as 1 mg/kg and 1.5 mg/kg. Upon meeting the eligibility criteria, patients will be randomized into two study groups: Nebulized KetaBAN (Ketamine via BAN) and Nebulized FentaBAN (Fentanyl via BAN).

The on-duty ED pharmacist will prepare either a breath-actuated nebulizer (BAN) with 0.75 mg/kg of ketamine or a BAN with 3 mcg/kg of fentanyl, depending on the randomization list, which will be made in SPSS (version 24; IBM Corp., Armonk, NY) with a block randomization of every 10 participants. The medication will be delivered to the treating nurse in a blinded fashion. The nebulization of study drugs via BAN will have a minimum time of 5 minutes and a maximum time of 15 minutes. If a patient requires further analgesia, a second dose of either Ketaban or Fentaban will be offered, or intravenous (IV) fentanyl at 0.75 mcg/kg will be administered as a rescue analgesia.

In addition, study investigators will measure the residual volume of ketamine and fentanyl remaining in the breath-actuated nebulizer after each treatment and document the results on a waste sheet designed by the pharmacy staff. The pharmacist will receive this sheet and use it to determine the actual dose that each study participant received based on their initial randomization group. According to the departmental policy on the waste of controlled substances, a treating nurse will discard the remaining ketamine and fentanyl in the breath-actuated nebulizer.

Data collection procedures

A study investigator will approach each patient for written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization after the treating emergency medicine

physician has evaluated them and they meet the study eligibility requirements**.** 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.

Study investigators will record pain scores, vital signs, and adverse effects at 15, 30, 60, 90, and 120 minutes. If patients report a pain numeric rating scale score of 5 or greater at any of the aforementioned time points and request additional pain relief, intravenous (IV) fentanyl at 0.75 mcg/kg will be administered as a rescue analgesic.

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

All data will be recorded on data collection sheets, including patients' sex, demographics, medical history, vital signs, adverse events, and need for rescue medication, etc., and entered into SPSS (version 24.0; IBM Corp.) by the research manager. The research manager and statistician (Michael Silver) will work independently of any data collection to develop the randomization list, confirm the acquisition of written consent for all participants, and conduct statistical analyses. The randomization will be Bock Randomization every 10 subjects.

Monitoring and Adverse effects

Patients will be closely monitored for any change in vital signs 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 (SDK) are feelings of unreality, dizziness, nausea, vomiting, and sedation. Common adverse effects that are associated with fentanyl are nausea, vomiting, pruritus, dizziness, somnolence, drowsiness, and respiratory depression.

Data Analysis

Data analyses will include frequency distributions, a paired t-test to assess a difference in pain scores within each group, and an independent-sample t-test to assess differences in pain scores between the two groups at various intervals. Mixed-model linear regression will be used to compare changes in the pain numeric rating scale (NRS) across all 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 (e.g., complete resolution of pain), a χ^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 for acute pain in the ED and the comparison of the verbal and visual pain scales, the primary outcome will be a difference of at least 1.3 between the two groups at the 30-minute pain assessment time point that is clinically meaningful. [28,29]

Sample Size

Assuming a greater improvement in pain score in the fentanyl group of 1.3 points over the ketamine group, with a standard deviation (SD) of 3.0 in both groups, we will need to enroll 67 patients per group (134 total) to have 80% power at an 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 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 the numeric rating pain scale (NRS) between recipients of KetaBAN and FentaBAN at 30 minutes post-analgesic administration.

The secondary outcomes will include a need for rescue analgesia and rates of adverse events (AE) in each group up to 120 minutes. With respect to the unique adverse effects of SDK, we will use the Side Effect Rating Scale for Dissociative Anesthetics (SERSDA) and the Richmond Agitation Sedation Scale (RASS) to assess and record such adverse effects (26, 27). Subjects will rate the severity of each side effect on a five-point scale, with "0" denoting the absence of any negative effects and "4" denoting a side effect that is extremely bothersome. The SERSDA Scale includes fatigue, dizziness, nausea, headaches, feelings of unreality, changes in hearing, mood changes, general discomfort, and hallucinations. RASS evaluates the severity of agitation and/or sedation in accordance with the nine-point scale, with scores ranging from "−4" (deeply sedated) to "0" (alert and calm) to "+4" (combative).

Adverse Events

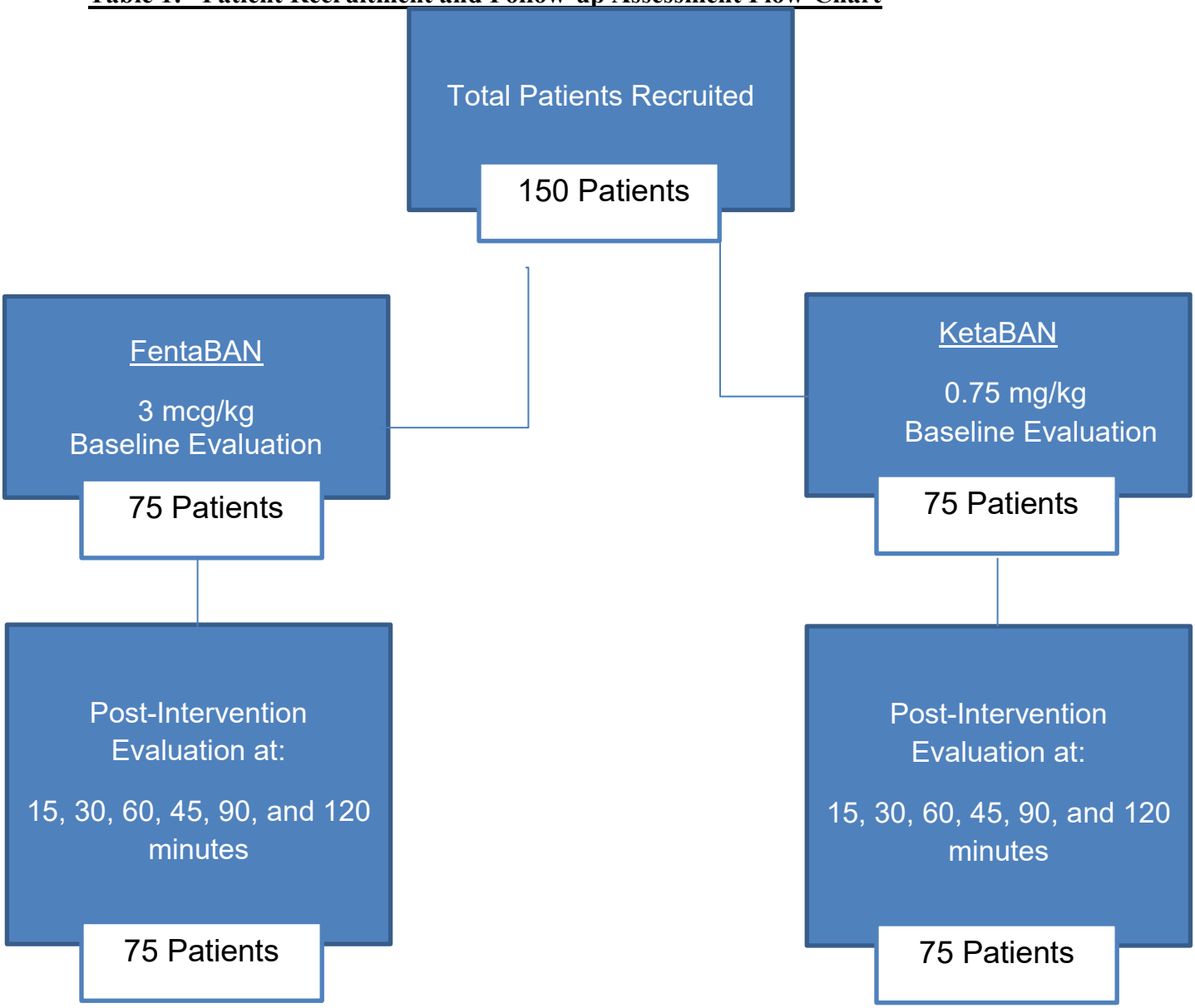
Common Side Effects related to Ketamine:	Dizziness, nausea, vomiting, agitation, weakness or fatigue, feelings of unreality, nightmares, altered mental state, increase in heart rate and blood pressure.
Common Side effects related to Fentanyl:	Nausea, vomiting, pruritus, dizziness, somnolence, drowsiness, relaxation, euphoria, sedation, confusion, urinary retention, pupillary constriction, and respiratory depression.

SAE Reporting

A data and safety monitoring board (DSMB) will be established to review data upon reaching 10 subjects in each arm and/or if there is an SAE. It will consist of: Sergey Motov, MD; Jefferson Drapkin, MPH; Antonios Likourezos, MA MPH; Rukhsana Hossain, MPH; George Fulton, MD.

Within 24 hours of discovery, the research staff will report any serious adverse event that necessitates intervention to the IRB. Less serious adverse events will be reported within a week of discovery. There are known expected outcomes and side effects of the medications being received, and these are the same risks and 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



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