TITLE: **A comparison of Oral VTS-K (combination of VTS-Aspirin and oral ketamine) to Nurtec (Rimegepant) for managing acute headache in the ED: randomized, open-label, clinical trial.**

NCT#:

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INTRODUCTION

Headaches affect over 50% of patients annually, with close to 4% of ED visits for headache. Most headaches managed in the ED are benign, with 90% of these headaches classified as tension, migraine, or cluster. At present, the satisfaction with ED treatment of headache is low, and despite the multitude of available medications, the evidence- based treatment options are often quite limited. There are over twenty different types of medications available to the ED clinicians for managing headache, many with different routes of administration (parenteral, intranasal, subcutaneous, and oral). Many of these medications are provided in so-called "headache cocktail", which varies based on the physician, institution, and patient preferences.

STUDY OBJECTIVES

To compare analgesic efficacy and rates of side effects of a proprietary formulation of orally administered aspirin and ketamine (AOK) to a Nurtec ODT (Rimegepant) for pain management in adult ED patients presenting to the ED with acute headache.

HYPOTHESIS

We hypothesize that the administration of AOK will provide similar analgesia at 60 minutes post-administration in comparison to Nurtec (Rimegeapant) in adult patients presenting to the ED with acute headache. The primary outcome of this trial is the difference in participant's pain scores at 60 minutes post-medication administration.

STUDY DESIGN

Subjects: Patients 18 years of age and older presenting to the ED with acute headache (defined as HA lasting no more than 1 week) and an initial pain score of 5 or more on a standard 11- point (0 to 10) numeric rating scale and requiring oral 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 headache (<7 days) and an initial pain score of 5 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: Patients with altered mental status, allergy to aspirin, ketamine, rimegepant, pregnant patients, 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, consumption of Aspirin/NSAID's within 6 hours of arrival to the ED, or acetaminophen within 4 hours of arrival to the ED, active PUD, history of GI Hemorrhage, history of renal and hepatic insufficiency, past medical history of alcohol or drug abuse, or schizophrenia, as well as clinical findings concerning for acute intracranial process, acute infections process, or vascular catastrophe, pregnant patients and breastfeeding patients.

Design: This is a prospective, randomized, open-label, equivalence trial comparing analgesic efficacy and safety of AOK and Nurtec (Rimegepant) in patients presenting to the ED of Maimonides Medical Center with acute headche. Upon meeting the eligibility criteria, patients will be randomized into one of the two study arms: Group I will receive AOK, and Group II will receive Nurtec

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. 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 statistician, who will work independently of any data collection.

Data Analysis: Data analyses will include frequency distributions and independent-sample t-test to assess differences in pain scores at the various intervals. Mixed-model linear regression will be used to compare changes in pain numeric rating scale across time points.
For categorical outcomes (eg, complete resolution of pain), a X^2 or Fisher's exact test will be used to compare outcomes at 60 and 120 minutes. 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 2 points between two groups at the 60-minute and 120-minute pain assessment.[28,29]

Sample Size: Assuming the minimum statistically significant difference of 2 points on NRS, with Standard deviation of 3.0, alpha=0.05, and power of 80%, the sample size will require 40 patients per group. To account for potential loss to follow up (discharge form the ED before 120 minutes), we will enroll 45 patients in each group.

Expected Outcomes: The primary outcome will include a comparative reduction of pain scores on numeric rating pain scale (NRS) at 60 minutes from the baseline. The secondary outcomes will include a need for rescue analgesia, rates of adverse effects, and change in pain score up to 120 minutes.

Adverse Events:
With respect to unique adverse effects of ketamine, 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 with the nine-point scale with scores ranging from "−4" (deeply sedated) to "0" (alert and calm) to "+4" (combative).