

TITLE: Analgesic efficacy of orally administered VTS-K (liquid oral ketamine taken simultaneously with VTS-Aspirin) for pain management of adult ED patients presenting to the ED with acute musculoskeletal pain

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INTRODUCTION

Acute Pain is one of the most frequent chief complain and the main reason for visiting the Emergency Department (ED). The acute pain in the ED is largely prevalent across the country with recent literature demonstrating that 61-91% of patients are admitted to the ED due to a variety of acute painful syndromes.(1) Musculoskeletal pain (MSK) affects one out of three adults and it is the most common source of serious long term pain and physical disability (2). Furthermore, studies have demonstrated that the frequency for analgesia for adults who received treatment for musculoskeletal pain in the ED is between 11-29% (3). To complicate the issue of MSK pain management even further, the opioid epidemic spanning over 20 years in the USA and claiming over 400,000 deaths from unintentional prescription opioid overdose, has forced health care systems and hospitals across the nation to reduce the reliance on opioid analgesics and embrace the utility of non-opioid analgesia. Several classes of non-opioid analgesics such as Acetaminophen, NSAID's (aspirin, ibuprofen, diclofenac) and Ketamine have gained great deal of attention as viable alternatives to opioids in management of acute MSK pain in the ED (4-8).

BACKGROUND AND SIGNIFICANCE

The CERTA concept is based on our improved understanding of neurobiological aspect of pain with a shift from symptom-based approach to pain to a mechanistic approach. This targeted, patient-focused analgesic approach allows for a broader utilization of combinations of non-opioid analgesics. These synergistic combinations of different classes of analgesics acting on different target sites have a potential to result in greater analgesia, reduced dose of each individual medication and shorter length of stay. In addition, this concept will allow us to administer non-opioid analgesic modalities as first-line therapies in the ED and utilize opioids as rescue analgesics (9).

A combination of ketamine and aspirin for the treatment of acute MSK pain in the ED would confer multimodal analgesia, with the contributions of aspirin and ketamine to an opioid sparing effect. Research on this multimodal approach is sparse, but the minimal empirical evidence supports a clinical benefit to patients in a post orthopedic surgery setting, both in short term and long term. Remerand et al. evaluated the effect of ketamine in combination with multimodal

analgesia, including non-steroidal anti-inflammatory drugs, like aspirin, on acute and chronic postoperative pain following total hip arthroplasty (THA)(10). All patients were treated perioperatively with NSAIDs, and then randomized to a postoperative treatment of ketamine or opioids. Patients randomized to the ketamine group demonstrated decreased opioid consumption at hour 24 (19 ± 12 mg to 14 ± 13 mg, $P=0.0004$), which is indicative of the opioid sparing effect frequently seen. The ketamine patients also demonstrated improved rehabilitation. From Day 30 to Day 180, the patients randomized to a treatment of ketamine required less assistance walking (56% to 31%, $P=0.0035$), and a smaller proportion of the ketamine-treated patients experienced persistent pain at rest in the operated hip ($P=0.008$). At Day 180, 21% of the control group patients experienced pain at rest, as compared to the ketamine group, in which only 8% experienced this pain ($P=0.036$).

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 (11). 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 (12-14). Two commonly utilized routes of SDK administration in the ED include an intravenous route (intravenous push dose or short infusion) and intranasal route (15-20).

Internationally, oral ketamine wafers/tablets have been used as an alternative to the IV form but are currently unavailable in the United States. Despite the fact that ketamine undergoes extensive first-pass metabolism with an oral bioavailability of approximately 16%, a relatively low orally administered dose of ketamine was required to achieve patient comfort in the study of patients undergoing burn wound dressing changes.(21,22) Oral administration results in decreased ketamine and increased norketamine concentrations in serum.²⁰ Consequently, oral ketamine’s first-pass effect from hepatic metabolism of ketamine to norketamine may help maintain analgesic potency while simultaneously decreasing side effects when compared to the IV form.(23)

Aspirin is a prototype of non-steroidal anti-inflammatory drugs (NSAIDs), and member of the family of salicylates that have in common salicylic acid as the active agent. The pharmacological properties of aspirin are similar to those of salicylates, but also to the biological actions attributed to salicylate itself, and it has other independent effects due to its reactive acetate group. Both components, salicylate and acetate groups, are biologically active and act independently of each other at different sites (24). Aspirin is a safe and well-understood non-steroidal anti-inflammatory drug (NSAID). It has certain and clinically accepted analgesic properties. It is a non-selective and irreversible NSAID that inhibits an activity of both cyclooxygenase-1 and 2 and blocks the synthesis of prostaglandins and thromboxanes. (25)

Vitalis Pharmaceuticals (New York, NY) has developed a proprietary formulation of aspirin, VTS-Aspirin that may deliver faster and stronger pain reduction than traditional aspirin. Preliminary research indicates that combinations of VTS-Aspirin with analgesics may confer greater benefit in pain management than some current standards of care (26).

An oral combination drug of VTS-Aspirin and ketamine (VTS-K) would facilitate the shift from IV opioids to a non-IV therapy for patients presenting to the ED with acute MSK pain. This formulation has a potential to provide effective analgesia in the ED with reduced side effects. VTS-K's proprietary oral formulation of established, safe, and well-understood APIs, makes it uniquely appropriate for use in the ED. VTS-K is administered orally, which is suitable for resource-poor environments in which the healthcare setting may be inadequate as well as suitable to improve the throughput of ED Patients by reducing their length of stay. This is especially pertinent given the alternative of IV opioids for pain management of acute MSK pain, which requires both clinical monitoring and equipment, whereas VTS-K promotes weaning off opioids, alleviating the resource consumption.

STUDY OBJECTIVES

To evaluate analgesic efficacy of orally administered VTS-K (liquid oral ketamine taken simultaneously with VTS-Aspirin and oral ketamine (in a liquid form)) for pain management of adult ED patients presenting to the ED with acute musculoskeletal pain

HYPOTHESIS

In our pilot study we hypothesize that the VTS-K combination will result in analgesia with a change in pain score at least of 1.3 points on NRS. The primary outcome of this trial is the reduction 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 musculoskeletal painful conditions (traumatic and non-traumatic) with 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 musculoskeletal painful conditions (traumatic and non-traumatic) with 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 and ketamine, 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 or NSAID's within 6 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.

Design: This is a prospective observational pilot trial evaluating analgesic efficacy and safety of VTS-K in adult patients presenting to the ED of Maimonides Medical Center with acute musculoskeletal painful conditions. Upon meeting the eligibility criteria, patients will be offered to participate in the study.

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 an oral dose of ketamine by using a formulary for parenteral use. The oral dosing regimen of ketamine is 0.5 mg/kg that will be placed in the syringe or a medication cup. The research associate will deliver both medications (VTS-Aspirin and Oral Ketamine) to the patient. Study investigators will record pain scores and adverse effects at 15, 30, 60, and 90 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, an oral immediate release morphine tablet of 7.5 mg will be given

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.

Patients will be closely monitored for adverse effects during the entire study period (up to 90 minutes) by study investigators. Common adverse effects that are associated with oral ketamine are feeling of unreality, dizziness, nausea, vomiting, and sedation. Common adverse effects are associated with VTS-Aspirin are nausea, dyspepsia, epigastric discomfort.

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 χ^2 or Fisher's exact test will be used to compare outcomes at 60 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 1.3 between three groups at the 60-minute pain assessment.^{28,29}

Sample Size: Assuming a minimal clinically meaningful difference of 1.3 in change of pain score from the baseline until 60 minutes, given a standard deviation of 3.0, with a one-side 97.5%

confidence interval, we will need 21 subjects for this pilot trial. We would enroll 25 patients to account for any loss to follow-up.

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