# A Comparison of Headache Treatment in the Emergency Department: Prochlorperazine Versus Ketamine

Tony Zitek, MD*; Melanie Gates, MD; Christopher Pitotti, MD; Alexandria Bartlett, BS; Jayme Patel, PharmD; Aryan Rahbar, PharmD; Wesley Forred, RN; Joseph S. Sontgerath, MD; Jill M. Clark, MBA/HCM, CCRP

*Corresponding Author. E-mail: zitek10@gmail.com.

**Study objective:** Intravenous subdissociative-dose ketamine has been shown to be effective for pain management, but has not been specifically studied for headaches in the emergency department (ED). For this reason, we designed a study to compare standard treatment (prochlorperazine) with ketamine in patients with benign headaches in the ED.

**Methods:** This study was a multicenter, double-blind, randomized, controlled trial with a convenience sample of patients presenting to the ED with benign headaches. Patients were randomized to receive either prochlorperazine and diphenhydramine or ketamine and ondansetron. Patients' headache severity was measured on a 100-mm visual analog scale (VAS) at 0, 15, 30, 45, and 60 minutes. Nausea, vomiting, anxiety, and the need for rescue medications were also tracked. Patients were contacted at 24 to 48 hours posttreatment to rate their satisfaction and to determine whether they were still experiencing a headache.

**Results:** There were a total of 54 subjects enrolled. Two patients in the ketamine group and one in the prochlorperazine group withdrew because of adverse effects of the medications. In regard to the primary outcome, at 60 minutes, the prochlorperazine group had a mean improvement in VAS pain scores of 63.5 mm compared with 43.5 mm in the ketamine group, corresponding to a between-groups difference of 20.0 mm (95% confidence interval [CI] 2.8 to 37.2 mm) and a *P* value of .026. At 45 minutes, the prochlorperazine group had a mean improvement in pain scores of 56.1 mm compared with 38.0 mm in the ketamine group, a difference of 18.1 mm (95% CI 1.0 to 35.2 mm). At 24- to 48-hour follow-up, the mean satisfaction score was 8.3 of 10 for prochlorperazine and 4.9 of 10 for ketamine, a difference of 3.4 (95% CI 1.2 to 5.6). There was not a statistically significant difference in the percentage of patients who had a headache at follow-up or in other secondary outcomes.

**Conclusion:** Prochlorperazine appears to be superior to ketamine for the treatment of benign headaches in the ED. [Ann Emerg Med. 2017;■:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2017.08.063

## INTRODUCTION

### Background

In the emergency department (ED), one of the most common chief complaints is headache.[1] A number of previous studies have demonstrated the efficacy of a variety of medications for migraines and other benign headaches.[2] Some of the options for treating these types of headaches include dopamine antagonists, opioids, nonsteroidal anti-inflammatory drugs, triptans, antiepileptics, and ergot derivatives.[2] Among the available options, dopamine antagonists appear to be the most effective, with multiple studies demonstrating their superiority over opioids,[3] nonsteroidal anti-inflammatory drugs,[4] triptans,[5] and antiepileptics.[6] A commonly used dopamine antagonist, and one that has a great deal of evidence to support its use for benign headaches, is prochlorperazine.[5-10] Although some data suggest that droperidol may be even more effective than prochlorperazine,[11] the current national shortage limits its use.

### Importance

Despite the general effectiveness of dopamine antagonists and the variety of options for benign headache treatment, many patients who present to the ED still have headaches 24 hours after treatment. In one study, 31% of patients still had moderate to severe headaches 24 hours after discharge.[12] Often, emergency physicians resort to opiates for refractory headaches despite evidence to suggest that the drugs increase both length of stay and rate of return ED visits.[13]

**Editor's Capsule Summary**

*What is already known on this topic*

Ketamine has analgesic properties and is gaining popularity as a treatment for acute pain.

*What question this study addressed*

Does ketamine with ondansetron relieve acute, benign headache pain better than standard treatment with prochlorperazine and diphenhydramine?

*What this study adds to our knowledge*

In this 54-patient randomized trial, the ketamine and ondansetron regimen was less effective and associated with more adverse effects than standard first-line therapy.

*How this is relevant to clinical practice*

Ketamine and ondansetron is unlikely to be better than standard treatments for acute benign headache.

*Research we would like to see*

Because headache is among the most common adverse effects of ondansetron, further headache research should omit this component. Ketamine alone or with alternative adjuvant agents may be helpful, but future prospective randomized trials are needed.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that has both analgesic and dissociative properties.[14] Previous studies have demonstrated the effectiveness of ketamine for postoperative pain,[15,16] pain in burn patients,[17] and chronic pain.[18] New studies have also shown ketamine to be useful for acute pain in the ED by both the intranasal[19] and intravenous routes.[20] To our knowledge, there are no published prospective studies that evaluate the effectiveness of intravenous ketamine for the treatment of benign headaches in the ED.

### Goals of This Investigation

We performed a double-blind, randomized, controlled study comparing ketamine with prochlorperazine to assess the efficacy of ketamine for benign headaches in the ED.

## MATERIALS AND METHODS

### Study Design and Setting

This was a multicenter, prospective, double-blind, randomized, controlled trial performed in Las Vegas, NV, with a convenience sample of patients presenting to the ED with a chief complaint of headache. The primary site for the study was a county, academic, tertiary care facility and the secondary site was a military hospital. Subjects were enrolled only when a pharmacist who was familiar with the study protocol was available to prepare medications. (This was generally 2 PM to 2 AM.)

Each of the 2 hospitals involved in the study received approval for it from their respective institutional review boards. This was an investigator-initiated study without any pharmaceutical company involvement.

### Selection of Participants

Previous data have shown that patients presenting to the ED with an undifferentiated headache improve with all the above-described headache medications regardless of whether they meet the definition of migraine, tension headache, or another primary headache disorder.[3,7,9,21] Therefore, this study enrolled patients who presented to the ED with a "benign headache," which was defined as a headache that was thought to likely be a primary headache without signs or symptoms of serious intracranial pathology. In particular, patients who presented to the ED with complaint of a headache could be included if they met the following criteria: aged 18 to 65 years, temperature less than 100.4°F (38°C), diastolic blood pressure less than 104 mm Hg, and normal neurologic examination result. Patients were excluded if they were pregnant or breastfeeding, were a prisoner, had meningeal signs, had signs of acute angle closure glaucoma, had head trauma within the previous 2 weeks, had a lumbar puncture within the previous 2 weeks, had a thunderclap onset of their headache, weighed more than 150 kg or less than 40 kg, had a known allergy to one of the study drugs, had a history of schizophrenia or bipolar disorder, had a history of intracranial hypertension, did not speak English, or had received pain medication in the ED before enrollment.

Written, informed consent was obtained from each patient.

### Interventions

After enrollment, each patient was randomized either to the standard treatment arm to receive prochlorperazine 10 mg intravenously along with diphenhydramine 25 mg intravenously, or to the study arm to receive intravenous ketamine at 0.3 mg/kg along with intravenous ondansetron at 4 mg. The diphenhydramine or ondansetron was administered first, and immediately afterward the prochlorperazine or ketamine was administered. The prochlorperazine or ketamine was diluted in saline solution so that the total volume was 5 mL and was administered during 2 minutes. The diphenhydramine was diluted in