

CLINICAL PROTOCOL

The CHECK Trial: A Comparison of Headache Treatment in the Emergency Department: Prochlorperazine versus Ketamine

INTRODUCTION

In the emergency department (ED), one of the most common chief complaints is headache [1]. A number of prior 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, non-steroid anti-inflammatory drugs (NSAIDs), triptans, anti-epileptics, and ergot derivatives [2]. Amongst the available options, dopamine antagonists appear to be the most effective, with multiple studies demonstrating their superiority over opioids [3], NSAIDs [4], triptans [5], and anti-epileptics [6]. The dopamine antagonist that we use most frequently, and the one that has the most evidence to support its use for benign headaches, is prochlorperazine [5,6,7,8,9,10]. Although some data suggest that droperidol may be even more effective than prochlorperazine [11], the current national shortage limits its use.

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 by Friedman, 31% of patients still had moderate to severe headaches 24 hours after discharge [12]. Often we resort to opiates in refractory headaches despite evidence to suggest that opiates increase both length of stay and bounce backs [13].

Ketamine is a NMDA receptor antagonist that has both analgesic and dissociative properties [14]. Previous studies have demonstrated the effectiveness of ketamine for post-operative 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 prospective studies that evaluate the effectiveness of ketamine for the treatment of benign headaches in the ED.

We propose a double blind, randomized control study comparing ketamine to prochlorperazine for benign headaches in the ED.

METHODS

Study Design

This will be a multicenter, prospective, double-blinded, randomized controlled trial on a convenience sample of patients presenting to the ED with a chief complaint of headache.

Subjects will only be enrolled when a pharmacist who is familiar with the study protocol is available to prepare medications.

Exempt from FDA IND#

This study meets the requirements in 21CFR312.2(b)Exemptions(1) to exclude this study drug from registration for FDA IND# .

“21CFR312.2(b)Exemptions(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all of the following apply:

“(i) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

Investigators do not intend to report study data to the FDA to support label changes for Ketamine.

“(ii) If the drug that is under investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

Investigators do not intend to provide support for changes in advertising for Ketamine.

“(iii) The investigation does not involve a route of administration or dose level or use in a patient population or other factor that significantly increases the risk (or decreases the acceptability of the risks) associated with the use of the drug product;

Investigators intend to administer Ketamine via the routine IV route at doses lower than typically ordered which will not alter the risk profile of the drug.

“(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 56; and

This investigation will be conducted with UMC IRB approval with Written Informed Consent.

“(v) The investigation is conducted in compliance with the requirements of §312.7.”

Study investigators will be compliant with 21CFR312.7 Which prohibits:

“(a) promotion of an investigational new drug..., (b) Commercial distribution of an investigational new drug..., (c) prolonging an investigation..., (d) charging for and commercialization of investigational drugs...”

Selection of Participants

Previous data have found that patients presenting to the ED with an undifferentiated headache improve with all the above-described headache medications regardless of whether or not they meet the definition of migraine, tension headache, or another primary headache disorder [6,8,10]. Therefore, this study will enroll all patients between the ages of 18 and 65 who meet all of the inclusion criteria and do not meet any of the exclusion criteria, who present to the ED with a benign headache.

Inclusion Criteria

Patients who present to the ED with complaint of a headache with the following criteria:

- Age 18 to 65 years
- Temperature < 100.4° F
- Diastolic blood pressure < 104 mm Hg,
- Normal neurologic exam and normal mental status

Exclusion Criteria

- Pregnant or breastfeeding.
- Meningeal signs are present
- Acute angle closure glaucoma is suspected.
- Head trauma within the previous two weeks
- Lumbar puncture within the previous two weeks
- Thunderclap onset of the headache
- Weight more than 150 kg or less than 40 kg.
- Known allergy to one of the study drugs.
- History of schizophrenia or bipolar disorder.
- History of intracranial hypertension.
- Is a prisoner
- Patient declined informed consent
- Non-English speaking patient.
- Attending provider excludes patient
- Patient received any pain medication prior to enrollment

Written, informed consent will be obtained from each patient. Consent will include a discussion of the risks and benefits. The risks are the side effects associated with each drug. For compazine, this includes drowsiness, blurred vision, xerostomia, congestion, nausea, akathisia, tardive dyskinesia, NMS, and blood dyscrasias. For ketamine, this includes, sialorrhea, nausea/vomiting, elevation in blood pressure or heart rate, nystagmus/diplopia, fasciculations, hallucinations, bradycardia or hypotension, arrhythmias, and respiratory depression. Personal benefits include intended reduction in headache symptoms and the satisfaction that the patient may be assisting investigators in determining a more effective headache treatment.

Interventions

After enrollment, each patient will randomized either to the standard treatment arm to receive prochlorperazine 10 mg IV along with diphenhydramine 25 mg IV, OR to the

study arm to receive ketamine 0.3 mg/kg along with ondansetron 4 mg IV. The diphenhydramine or ondansetron will be administered first, and immediately afterward the prochlorperazine or ketamine will be administered. The prochlorperazine or ketamine will be diluted in saline so that the total volume is 5 mL, and will be administered over 2 minutes. The diphenhydramine will be diluted in saline so that it is 2 mL (the same volume as the ondansetron). Both groups will also receive a 500 mL normal saline bolus after the study medications are administered. The ED pharmacist will be responsible for preparing the medications, using a double-blind protocol. He or she will record which arm the patient was randomized to. Only the pharmacist will have access to the randomization records and will not reveal the randomization until the end of the study. Emergency providers will be instructed not to administer any rescue medications for at least 30 minutes. The electronic medical record order will read “randomized study medication” (for the ketamine or prochlorperazine) and “randomized add-on medication” (for the ondansetron or diphenhydramine).

Safety

After 30 minutes, the treating provider will be permitted to administer any medication they would like for further treatment. If there is an untoward event that requires the treating provider to know which medication was administered, the pharmacist will unblind the randomization for that individual patient and the patient will not continue in the study.

Reportable Events

Anticipated side effects are those listed on the manufacturer’s package insert and are treated as routine non-urgent or non-emergent events are not reportable events.

Adverse Events are those unanticipated side effects that require interventions or anticipated side effects that do not respond to intervention.

Serious Adverse Events are those side effects that require Advanced Life Support measures to control symptoms.

AEs and SAEs will be reported to the IRB within 5 days of the event.

Methods of Measurement

Enrolled patients will fill out a brief data collection form to include age, sex, race, phone number, and baseline headache severity using a 100-mm visual analog scale (VAS). Repeat headache severity scores will be measured at 15, 30, 45, and 60 minutes. Time zero begins immediately after complete administration of the study drug. Nausea (with a 100 m VAS), vomiting, anxiety, restlessness (akathisia), heart rate, and blood pressure will also be assessed at these time intervals. The need for rescue medications will be extracted from the patient’s chart at a later time.

Trained research assistants will call the patient 24-48 hours post-discharge by phone to ask them to rate their satisfaction with the drug they received on a scale of 0-10, and to

ask if they are currently having a headache (yes or no). If the patient is admitted, the patient will be approached in the hospital by an investigator or research assistant for follow up.

Outcome Measures

The primary outcome measure will be the difference in pain scores between the prochlorperazine and ketamine groups, measured as the absolute difference between the means at 60 min. Secondly, we will measure the difference between the rates of decline in pain scores, rate of admission, nausea scores, rate of vomiting, rate of development of akathisia, rate of use of additional medications for headache, heart rate and blood pressure changes, headache resolution with telephone follow up, and patient satisfaction.

Privacy and Security

In order to protect the privacy of the research subjects and to maintain the confidentiality of data, all data will be managed only by trained research assistants or investigators and will be stored in the locked Emergency Medicine research offices and electronic data will be stored on a password protected computer in the locked Emergency Medicine research office. All research assistants and investigators are HIPAA- trained, CITI trained and credentialed by UMC IRB, and oriented to the study protocol.

Data Analysis:

A couple prior studies have used a 25-mm difference in mean VAS score reduction between groups to show a clinical benefit [6,9]. We define significant pain relief as an absolute decrease in the mean VAS score of 25 mm.

Thirty-two patients will be needed in each group to find a 25-mm difference between the group means on the VAS at 60 min, with a power of 0.80 and an alpha of 0.05. We will aim for 35 patients per group to account for about a 10% dropout rate. The groups will be compared using a *t*-test on gender, race, and age; and a chi (with Yates correction)-squared test on severity of presenting headache, to determine if they are similar. The individual VAS measurements will be compared using a repeated measures analysis of variance (ANOVA) test.

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