

# **Investigating the Efficacy of Using Haloperidol vs. Metoclopramide for Treatment of Acute Headaches and Migraines in the Emergency Department: A Prospective Randomized Clinical Trial**

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## **Introduction**

Headaches are a common presenting complaint in the Emergency Department (ED). Over 28 million Americans have migraine headaches, with nearly 15% of these persons seeking ED evaluation and treatment each year. It is also estimated that patients with migraine headaches incur more than 17 billion dollars in the US health care costs annually. ED treatment of patients presenting with headache is challenging because the pathophysiology of migraines is incompletely understood. Due to this, there is no consensus for optimal treatment of patients in the ED setting.<sup>1</sup>

At this time, choice of medications for the treatment of headaches in the ED is still based on personal and patient preferences because no properly constructed trials have been carried out that would allow identification of a superior agent.<sup>2</sup> Metoclopramide (Reglan) is a common agent used for relief of headaches in the ED. Uncontrolled studies have shown successful relief of migraine with metoclopramide of 75%. Further studies have reported success rate of 67% with IV metoclopramide.<sup>3</sup> In this study we seek to explore another option for treatment of headaches in the ED, one that may be more efficacious and efficient. Haloperidol (Haldol), a butyrophenone class of medication, is thought to act by affecting the dopamine 2 receptor in the brain. These receptors are relatively abundant in the brainstem nuclei and sympathetic ganglia and nerves, through which they may regulate autonomic visceral, gastrointestinal, and hemodynamic responses frequently associated with migraine.<sup>4</sup> One study, demonstrated that 4 out of 5 patients felt significant relief in pain intensity with the use of haloperidol, even when other

medications had failed. Relapses were rare, and several patients reported that haloperidol interrupted the prolonged, intractable migraine spiral they had suffered for days.<sup>5</sup> Furthermore, a case series of six cases of migraine treated with 5mg of haloperidol IV after a 500 to 1000ml bolus of IV fluids reported complete or substantial relief within 25 to 65 minutes and side effects were reported as minimal.<sup>4</sup>

The goal of ED therapy is to deliver rapid relief of pain, with a minimum of unpleasant adverse effects and without recurrence of headache after ED discharge.<sup>6</sup> As mentioned previously there is no consensus on the most appropriate treatment for patients presenting to the ED with prolonged headache. By exploring haloperidol as an option for treatment we hope to discover a more efficient and effective medication for the treatment of non-traumatic headaches, thereby decreasing a patient's length of stay in the department and decreasing the rate of return visits for continued discomfort from the same headache. This study could lead to the increased usage of haloperidol as a first line agent in the treatment of prolonged headaches presenting to the ED.

## **Methods**

### *Study Population:*

This study will include 104 patients at least 18 years of age who present to the ED of Doctors Hospital in Columbus, Ohio from January 2014 until June 2016 with an acute headache. To achieve 80% power to detect clinically significant differences between the migraine medication groups, this study needs to enroll a minimum of 90 patients meeting the inclusion criteria. The increase from 90 to 104 will account for such issues as patient study withdrawal and loss to follow-up.

### **Inclusion Criteria**

- Patients 18 or older
- Patients who present with a headache or migraine with onset less than or equal to 72 hours

### Exclusion Criteria

- Known pregnancy
- Breast-feeding women
- Known history of arrhythmias or QT prolongation (450 ms)
- Known adverse effects to haloperidol, diphenhydramine (Benadryl) or metoclopramide
- Subarachnoid hemorrhage
- Headaches caused by trauma, meningitis
- Congestive heart failure
- Parkinson's Disease
- Dementia
- Pheochromocytoma
- History of glaucoma
- History of seizures
- Age less than 18
- Non-English speaking patients

### *Hypothesis:*

Haloperidol is more efficacious than metoclopramide in the treatment of an acute headache or migraine in the ED in regard to a self-reported pain rating scale (Numeric Pain Intensity Scale), need for additional medication, emergency department return rates, and resolution of symptoms.

### *Study Design:*

This will be a prospective randomized single-blinded study. Patients will be recruited into the study if they present to the Doctors Hospital ED with a chief complaint of acute headache or migraine.

The investigators or study staff will identify potential subjects by their presenting diagnosis, and verify that they meet all inclusion/exclusion criteria. Once the inclusion/exclusion criteria are met, and the attending physician has agreed to follow the randomization, the patient will be approached by one of the study staff and the study will be thoroughly explained. Once the patient has had all their questions answered and has agreed to participate in the study, informed consent will be obtained. At this point, the study staff will record an initial Numeric Pain Intensity Scale score (0-10), to assess the patient's pain level prior to receiving the treatment.

After the patient is enrolled into the study and the initial information is collected, the investigator or study staff will check the randomization list to determine which treatment the patient will receive. All patients will receive a 1-liter bolus of normal saline (NS) and 25 mg of intravenous (IV) diphenhydramine. In addition, patients will be randomized to receive either 2.5 mg of IV haloperidol or 10 mg of IV metoclopramide following the NS bolus and diphenhydramine. Patients will not know which treatment they receive.

If a CT scan or lumbar puncture is performed after the medication is given indicating meningitis or subarachnoid hemorrhage, the patient will be withdrawn from the study.

One hour after receiving the medication, the study investigator will once again record the patient's pain level. If there is an unsatisfactory pain reduction experienced by the patient, additional medication may be given at the discretion of the clinician. If the patient receives additional medication, their participation in the study will end.

For patients who did not receive additional medication, a chart review will be performed within 48 hours after ED discharge to determine if the patient had to seek further medical care for the same headache/migraine. Once the chart review is performed, the patient's participation in the study will end.

Should an adverse event occur while a patient is enrolled in the study, the investigator or study coordinator obtaining consent will complete an adverse event report and submit this

to the IRB within 24 hours of the event. Events that will require reporting include death, hospitalization, or any life threatening problem that arises prior to discharge from the Emergency Department.

#### *Data Storage and Confidentiality:*

Only de-identified or non-identifiable data will be reported in the study. Only the research investigators will have access to patient information. All resulting data will be stored in electronic format, which will be stored on a password-protected computer, and paper surveys will be collected and filed in a secured facility with limited access. Participants will not be excluded on socioeconomic, racial or religious identity. No form of deception will be used. The data collection and storage processes will follow HIPAA guidelines, in accordance with 21 CFR 46.115 (b); to protect both confidentiality and privacy of each participant. All PHI data will be erased or destroyed per institution protocol.

#### *Study Variables:*

Data to be collected include:

- Demographics (sex, age, ethnicity)
- Treatment Group (haloperidol or metoclopramide)
- Time of headache/migraine onset
- Qualities of headache (location, radiation, associated symptoms)
- Medication use prior to arrival (yes/no, type, time before study drug administration)
- Type of long-term medication
- Number of visits to healthcare provider for same headache/migraine prior to ED visit
- Formal diagnosis associated with headache/migraine (previous diagnosis, during ED visit)

- Numeric Pain Intensity Scale (pre and 1 hour post treatment)
- Need for additional medications used in the ED (yes/no, type, time after study drug administration)
- Whether patient returned to Doctors Hospital ED or other healthcare provider for headache/migraine within 48 hours of ED discharge

#### *Statistical Analysis:*

We will test the hypothesis that clinically significant differences exist in pain perception and need for additional pain medications between metoclopramide and haloperidol.

Descriptive statistics will be produced, using means, medians, ranges and standard deviations for continuous variables, and percentages for categorical variables.

Independent variables will include: gender, age, headache qualities and visual pain scale scores. Inferential statistics will determine statistically significant differences between comparison variables, using Pearson's chi-square test for categorical data. For continuous variables, the paired sample *t*-test will be employed when the data show normality, and the Mann-Whitney U test will be utilized for nonparametric data.

Statistical significance will be evaluated at the 5% ( $\alpha=0.05$ ) level.

#### **References**

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