The I-FiBH Trial: Intravenous Fluids in Benign Headaches Trial: A Randomized Single Blinded Clinical Trial

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INTRODUCTION

Migraine headache has a 1-year period prevalence in the US of 11.7% and accounts for approximately 1.2 million migraine visits to US emergency departments per year [1,2]. There are numerous studies that discuss treatment for migraine and other benign headaches within the emergency department, however, there are very few that discuss specifically the use of intravenous fluids (IVF) for headache treatment [3]. Many of these studies look at various options for treating migraine and other benign headaches: treatment options include dopamine antagonists, opioids, non-steroid anti-inflammatory drugs (NSAIDs), triptans, anti-epileptics and ergot derivatives [2]. Comparisons have been done between many of these treatment options with dopamine antagonists appearing to be the most effective, compared to other treatments [4, 5, 6, 7]. The dopamine antagonist with the most evidence and availability for benign headaches is prochlorperazine [6, 7, 8 ,9, 10, 11, 12].

Peripheral IVs and administration are common procedures and treatments within the ED. And while relatively safe, they are not without their own risks [13, 14, 15, 16]. Given that IVF administration is a common part of treatment regimen for benign headache patients in the emergency department and given the lack of randomized trials in adults, we aim to study the use of IVF on pain reduction in headache patients in the adult ED [3]. Given the specific definition of migraine headache, we have chosen to categorize our headaches as benign headaches, avoiding the difficulty of determining if a patient meets the specific criteria for migraine headache [17, 18]. There has been one randomized trial in pediatrics that shows IVF may help in patients with migraines, whereas the adult literature has no randomized control trials and a review of data shows that fluids do not help relieve pain in migraine headache patients [3, 19, 20].

We will design a single blinded randomized trial to study the effects of IVF on benign headaches There are numerous challenges using the International Headache Society guidelines for controlled drug trials in acute migraines, including having a patient population that knows the specifics of migraine headaches and meets the exact definition. In order to facilitate obtaining the necessary number of patients we will include all benign headache patients [17,18].

METHODS

Study Design

This will be a single center, prospective, single blinded randomized controlled trial on a convenience sample of patients presenting to the adult or pediatric ED with a chief complaint of headache. Subjects will only be enrolled when a physician or research assistant who is familiar with the study protocol is available to enroll patients.

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 [7, 8, 11]. Therefore, this study will enroll all patients between the ages of 10 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 10 to 65 years
- Temperature < 100.4° F
- Normal neurologic exam and normal mental status

Exclusion Criteria

- Pregnant.
- 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
- Known allergy to one of the study drugs.
- History of intracranial hypertension.
- Is a prisoner
- Patient declined informed consent
- Non-English speaking patient or parent/guardian for pediatric patients
- Attending provider excludes patient
- Severe dehydration

Informed Consent

Written, informed consent will be obtained from each patient. Consent will include a discussion of the risks and benefits. In addition to parental informed consent in the pediatric population, age appropriate verbal assent will be obtained from pediatric subjects.

Risk/Benefit

The risks are the side effects associated with each drug. For prochlorperazine, this includes drowsiness, blurred vision, xerostomia, congestion, nausea, akathisia, tardive dyskinesia, NMS, and blood dyscrasias. For Benadryl include sedation, tiredness, sleepiness, dizziness, constipation, dry mouth, blurred vision, nausea, and loss of appetite. For normal saline, this

includes injection site swelling, redness, infection, venous thrombosis or phlebitis or hypervolemia. 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 be randomized either to the standard treatment arm to receive prochlorperazine 0.15 mg/kg up to 10 mg IV along with diphenhydramine 1mg/kg (up to 50 mg) IV and normal saline at 5 mL/h IV OR to the study arm to receive prochlorperazine along with diphenhydramine IV and normal saline at 20 mL/kg (up to 1000 mL) given IV over 1 hour. The diphenhydramine will be administered first, and immediately afterward the prochlorperazine will be administered. The patient will then be connected to normal saline on an IV pump and randomized to 5 cc over an hour or 20 cc/kg (maximum 1000 cc) over one hour. The IV bag and pump will be covered so that the patient will not know how much fluid they are receiving. Patients will undergo simple randomization to either the fluid bolus group or the control group. The treating physician will consult a folder that contains a list specifying the group assignment. Each row of the list corresponded to a patient, and will be covered by a small slip of opaque paper that will be removed at the time of enrolment to reveal the group assignment. This list was constructed at the beginning of the study using a random number generator by a research staff. Randomization in the pediatric ED and adult ED will be separate to ensure equal numbers of pediatric patients in both the experimental and control arms (blocking). Emergency providers will be instructed not to administer any rescue medications for at least 30 minutes.

Safety

After 30 minutes, the treating provider will be permitted to administer a “rescue medication” of their choice for further treatment. If there is an untoward event that requires the patient to know which IVF dose was administered, patient will unblinded and 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 30 and 60 minutes. Time zero begins immediately after complete administration of the study drug. Nausea (with a 100 mm VAS) and vomiting 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 if they are currently having a headache (yes or no) and to rate their current pain (0-10). 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 5 cc over an hour and 20 mg/kg (up to 1000 cc) over an hour groups measured as the absolute difference between the means at 60 min. Secondarily, we will measure the difference between the rates of decline in pain scores, rate of admission, nausea scores, rate of vomiting, rate of use of additional medications for headache, and headache resolution with telephone follow up.

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:

Assuming a SD of 22 (based on prior data from our institution), we calculated that we would need 45 patients in each group to find a clinically important difference in pain score reduction (13 mm) between groups at 60 min with at least 80% power and an alpha of 0.05.

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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