Intravenous fluid therapy for the treatment of emergency department patients with migraine headache: a pilot randomized controlled trial

Abstract:

Headache is one of the most common reasons patients visit the emergency department (ED), with migraines accounting for over one million annual US ED visits. While intravenous fluid (IVF) has not been prospectively studied in migraine patients, there is evidence that intravascular volume status affects central pain processing, and dehydration can trigger migraines. We propose a pilot, randomized controlled trial assessing the impact of an IVF bolus on patients with migraine headache. We hypothesize that patients who receive IVF will experience greater improvement in pain one hour after treatment as compared to controls. Adults treated in the Cooper ED with migraine headache will be randomized to receive normal saline at either 1000 ml/hr (treatment) or 10 ml/hr (control) for one hour, with a comparison in pain scores before and after treatment. Our first specific aim will establish the feasibility of successfully enrolling patients with migraine in the study and adhering to the study protocol. Our second specific aim will examine the efficacy of a normal saline bolus for relieving pain among patients with migraine headache. The data collected during this pilot study will support a competitive, larger-scale external grant application further investigating the efficacy of IVF for migraine.

Research plan

I. Project statement

Patients commonly present to the emergency department due to migraine headache. While some patients receive intravenous fluids as a method of controlling pain, the effectiveness of this intervention has not been prospectively studied. Our long-term objective is to determine the effect of an intravenous fluid bolus on pain among patients treated in the emergency department for migraine headache. The purpose of this pilot study is to obtain feasibility and preliminary outcome data in support of a future trial.

II. Specific aims

Migraine headache exacerbation is one of the most common reasons that people seek emergency department (ED) care.[1] Common treatments in the emergency department include phenothiazines,[2] serotonin receptor agonists,[3] and corticosteroids.[4] Because severe headache exacerbation is often refractory to these interventions, approximately 50% also end up receiving opioids,[5, 6] despite the fact that these medications are contraindicated in migraine headache, can cause headache recurrence, and can contribute to drug abuse and addiction.[7-11]

One commonly used but little-studied treatment for migraine headache is IV fluid (IVF). Using a nationally representative staged probability sampling survey we recently found that approximately 40% of patients treated in US EDs for headache received IV fluid therapy.[12] Theoretical reasons to suggest that IVF may be useful in painful conditions such as migraine headache include data from healthy volunteers suggesting that IV fluid administration may reduce headache pain by correcting dehydration,[13-15] and by reducing pain-related brain activity in the anterior cingulate cortex, insula, and thalamus.[16-18] However, despite its common use, no prospective studies have been performed evaluating the efficacy of IVF in acute migraine headache exacerbation. Consistent with contemporary uncertainty regarding efficacy, our national survey data indicate that the use of IVF is highly variable across institutions.[12] If IVF is efficacious, then currently it is a highly underutilized opioid-sparing intervention. In contrast, if IVF is not efficacious, then IVF treatment currently adds unnecessary cost, resource utilization, and time to contemporary ED care.

Our study coordinator and network of ED-based research associates currently screen and enroll patients for research studies in the Cooper Hospital ED 14 hours per day, 7 days per week. We will use this research infrastructure to recruit patients (n = 50) presenting to the ED with a chief complaint of headache or migraine who meet International Classification of Headache Disorders-3 (ICHD-3) diagnostic criteria for migraine.[19] As described below, individuals with extensive vomiting or other definitive IVF requirement will be excluded. Patients will be randomized to receive a 1000 ml bolus of normal saline over one hour vs. normal saline at 10 ml/hr for one hour, and pain, functional status, and side effects will be assessed at time zero, one hour, two hours and 48 hours.

Hypothesis 1: The proposed RCT protocol is feasible.
Specific Aims
1a. To determine whether the proposed study protocol can successfully recruit at least 75% of eligible patients.
1b. To assess the ability of the proposed protocol to successfully blind participants to their intervention group, such that fewer than half of participants correctly identify their treatment arm.
1c. To test the ability of the proposed protocol to successfully obtain patient follow-up at one hour, two hours, and 48 hours in at least 85% of participants.

Hypothesis 2: IVF administration will result in reduced pain scores in the ED and at follow-up.
Specific Aims
1a. To test the efficacy of IVF in achieving an improvement in reported pain (0-10 scale) of at least 1.3 (minimally significant pain difference) as compared to controls between time 0 and one hour.

The proposed study constitutes a critical first step in demonstrating the potential feasibility and value of performing a large-scale RCT evaluating the potential efficacy of IVF administration for individuals presenting to the ED with migraine headache. This study will collect the necessary data to advance to initial stage NIH (R03, R21, R34) or PCORI funding.

III. Research strategy

A) Significance

Headache is a substantial global public health problem,[20] and the fourth most common reason that patients visit an emergency department (ED) in the United States (US).[1] Migraine headache accounts for over one million patients encounters in US EDs each year, and many more patients seek care for migraine-like headaches.[5] While multiple drugs are currently used in the management of migraine exacerbations, including non-steroidal anti-inflammatories,[5] phenothiazines,[2] serotonin receptor agonists,[3] and corticosteroids,[4] severe headaches are often refractory to these interventions. As a result, approximately 50% of ED patients with migraine headache receive opioids.[5, 6] Furthermore, ED opioid use for headache has increased over time.[21] This is despite known risks of opioid use in patients with migraine headache, including the development of transformed migraine, in which patients with infrequent migraine symptoms develop increasingly chronic, frequent, and disabling headaches,[7, 11] as well as opioid-related antagonism of other analgesic medications such as COX1/COX2 inhibitors.[9] Additionally, chronic opioid use and abuse is an enormous public health problem in the United States,[22] with opioid-related overdose deaths increasing 200% since 2000.[10] Importantly, initiation of opioid medications for acute pain in the ED among opioid-naïve patients is associated with increased risk of ongoing use one year later.[8] The high rate of opioid utilization for migraine headache despite these known risks indicates the need to development effective, opioid-sparing interventions.

Data from both healthy volunteers and from other painful conditions suggest that fluid administration may provide effective analgesia for patients with migraine. Even mild dehydration lowers pain thresholds, and increases central pain-related activity in the anterior cingulate cortex, insula, and thalamus.[16-18] Consistent with this hypothesis, headache is commonly reported by patients undergoing dialysis,[23] and recent research has identified dehydration as a trigger for migraine headache.[13-15]

Despite these theoretical benefits, IVF has not been prospectively studied in patients with migraine and its efficacy is unknown. One recent secondary analysis of data from four ED-based migraine headache trials evaluating the use of metoclopramide demonstrated no association between IVF administration and improved pain outcomes, though the observational nature of these data are subject to substantial confounding. Despite this lack of existing clinical evidence, experts often recommend IVF for patients requiring ED treatment for migraine,[25, 26] and approximately 40% of patients visiting US EDs for headache receive treatment with IVF.[12] If IVF is beneficial, then this represents a substantial opportunity to improve the care of patients with this common, painful condition through increased use of this potentially opioid-sparing intervention. If, however, IVF does not benefit individuals with migraine, then these patients are burdened by unnecessary costs. In addition, while generally safe, risks associated with IV placement and/or fluid administration include pain with insertion,[27] infection,[28] and thrombophlebitis.[29] While these outcomes are rare, the use of IVF in millions of headache patients each year makes them relevant to risk/benefit calculations. If found to be ineffective, IVF may also contribute to ED crowding by unnecessarily prolonging ED length of stay, and by occupying staff time when this time is often critical to ensuring patient safety.

B) Innovation

The proposed study will be the first randomized trial assessing the efficacy of IVF in migraine headache, thereby addressing a significant knowledge gap in the treatment of this common disorder. Additionally, we plan to assess the success of our blinding strategy. Several prior studies assessing the effectiveness of IVF for the treatment of other painful conditions have attempted to achieve blinding by placing opaque covers over the IV bag and IV pump.[30, 31] However, these studies have not assessed the success of this blinding method. Validation of this technique has the potential to inform the design of future studies of IVF across a broad spectrum of clinical conditions.

C. Approach

We intend to perform a small-scale pilot study assessing the effectiveness of IVF therapy for patients presenting to the ED with migraine headache.

1. Study participants

   Participants will be English-speaking patients aged 18 or older, treated in the Cooper Hospital ED with a headache meeting ICHD-3 criteria for migraine.[19] Patients will be excluded if in the opinion of the treating physician IVF administration is definitively indicated (ie. intractable vomiting, severe dehydration) or contraindicated (e.g. exacerbation of congestive heart failure).

   Research assistants who are trained to identify potential clinical study participants and assess their eligibility for study enrollment are available in the ED from 8:30 am until 10:30 pm, 7 days per week to screen patients for inclusion.

2. Interventions

   No previous trials have prospectively studied an IVF bolus for adults with migraine, limiting data on which to make dosing decisions. However, several trials have assessed the impact of IVF on post-operative nausea and vomiting and post-operative opioid requirements. One compared 15 ml/kg (mean total intervention dose of 1215 ml) with 2 ml/kg (mean dose 226 ml) of crystalloid solution before induction of anesthesia for minor surgery, finding a substantial reduction in post-operative nausea and vomiting, along with trends toward lower post-operative opioid requirements.[32] Two additional small trials showed that for patients undergoing gynecologic procedures a 1000 ml crystalloid bolus resulted in improved post-operative nausea and vomiting compared with controls.[33, 34] Finally, another trial comparing a control group of 2 ml/kg crystalloid to 12 ml/kg crystalloid solution or 12 ml/kg colloid solution showed improved post-operative nausea and vomiting among the two experimental arms.[35] In addition to these results showing efficacy with doses of approximately 1000 ml, clinical experience suggests that a dose of 1000 ml is commonly selected by ED physicians when treating patients with migraine, making this dose relevant to current clinical practice. Finally, a dose of 1000 ml limits opportunities for unblinding by avoiding administration of more than one bag of IVF. Based on these considerations, we plan to study the efficacy of a 1000 ml normal saline bolus versus control. In order to maximize the generalizability of our results, we will not restrict the use of additional interventions by ED providers.

Patients will be randomly allocated between two arms:

Patients in the intervention arm ("IVF group") will have a peripheral IV line placed by ED staff, and will receive 1000 ml of 0.9% normal saline bolus over one hour.

Patients in the control arm ("control group") will have a peripheral IV line placed by ED staff, and will have a 1000 ml bag of 0.9% normal saline attached to the IV line, but the IV pump will be programmed to infuse 10 ml of fluid over one hour.

3. Allocation and blinding

We will randomize patients in permuted blocks of 4 or 6. Study assignments will be made through the use of sequentially numbered, opaque, sealed envelopes. Following enrollment, the nurse -- who will remain un-blinded -- will open the envelope and initiate the assigned intervention. An opaque cover will be placed over the IV pump, fluid bag, and drip chamber to maintain blinding of the patient, treating physician, and outcome assessor. Following completion of the intervention, in order to evaluate the success of blinding, patients and outcome assessors will be asked which treatment group they think was assigned.

4. Data collection

Research assistants will collect demographic information from patients, including age, sex, race, ethnicity, pre-existing comorbid conditions, and headache history.

We will assess pain at time 0 (start of the intervention), one hour (end of the intervention), and two hours using both a categorical scale (none, mild, moderate, or severe) and an 11 point verbal pain scale ranging from 0 (no pain) to 10 (worst pain imaginable), which has been validated for use in the ED setting.[36]

Functional disability will be assessed before treatment, at one hour, and two hours. As recommended by the International Headache Society,[37] patients will describe their functional disability due to headache as none, mild (able to perform all activities of daily living, but with some difficulty), moderate (unable to perform some activities of daily living), and severe (unable to perform most activities or requiring bed rest).

We will measure adverse effects of treatment, including pain at the IV site by asking participants to rate the pain associated with IV insertion, as well as IV site pain at one and two hours.

Research assistants will record visit characteristics, including the timing of medications administered, need for rescue medication, opioid use, length of stay in the ED, and ED disposition (discharged, observation, admission).

Research assistants will contact participants 48 hours after they leave the ED. It is anticipated that the substantial majority of patients will have been discharged from the hospital, in which case

follow-up will occur over the telephone. During this follow up assessment we will ask participants about their current pain, any recurrence of pain since leaving the hospital, current functional status, ability to tolerate oral intake, and adverse effects potentially related to the study intervention, including pain at the IV site, symptoms of thrombophlebitis, or peripheral edema. Global assessment of treatment is a function of both efficacy and tolerability, and will also be assessed by asking patients "The next time you visit the ED with a headache, would you wish to receive the same IV fluid treatment again?"

5. Outcomes

The primary outcome will be the difference in pain rating (0-10) between the start of the study intervention and one hour later, at completion of the intervention. The minimum clinically significant difference between treatment groups on the 0-10 verbal scale is 1.3.[36, 38, 39]

Secondary outcomes will include:

Percentage of patients in each group who are pain-free two hours after initiation of the study intervention. This outcome is recommended for study by the International Headache Society.[37]

Difference in verbal pain scale between start and two hours.

Global assessment of treatment, as described above.

Functional disability at one and two hours as compared to the start of treatment.

6. Analysis

We performed our sample size calculation with the understanding that the primary goal of this pilot study is to demonstrate the feasibility of the study protocol so as to inform a subsequent larger-scale trial.[40] The sample size calculation assumes a normal distribution. A sample size of 50 patients will provide the ability to detect a protocol adherence rate of 85% (+/- 10%) at a confidence level of 95%. In 2015, the Cooper ED treated over 300 patients who were diagnosed with migraine headache, suggesting that a goal of 50 participants over the 10 month active-enrollment period is attainable.

Using an intention-to-treat analysis, the primary outcome will be analyzed by calculating the mean change in pain scale within each study group, as well as 95% confidence intervals surrounding these point estimates.

IV. Expected outcome

We anticipate that the results from this study will demonstrate the feasibility of identifying and enrolling ED patients with migraine headache, completing the study protocol, and obtaining outcome data including post-discharge follow-up assessments. We will determine the success of blinding both participants and outcome assessors to the study intervention. This study will also provide preliminary

outcome data regarding the use of an IVF bolus for the treatment of migraine headache. These pilot data will be used to support a future grant application for a larger study which will be appropriately powered to determine the efficacy of this intervention.

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