Intravenous Fluid for the Treatment of Emergency Department Patients With Migraine Headache: A Randomized Controlled Trial

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Study objective: The objective of this pilot study is to assess the feasibility and necessity of performing a large-scale trial to measure the effect of intravenous fluid therapy on migraine headache pain.

Methods: This was a single-center, pilot randomized controlled trial. We randomized adult emergency department migraine headache patients to receive 1 L of normal saline solution during 1 hour (fluid group) or saline solution at 10 mL/hour for 1 hour (control group). All patients received intravenous prochlorperazine and diphenhydramine at the start of fluid administration. Participants and outcome assessors were blinded; nurses administering the intervention were not. Outcomes were assessed at 60 and 120 minutes, and 48 hours. The primary outcome was the difference in the verbal pain rating (on a scale of 0 to 10) between 0 and 60 minutes. Key secondary outcomes included additional clinical endpoints, the rate of protocol completion, and the effectiveness of blinding.

Results: Fifty patients consented to participate; one withdrew, leaving 25 patients randomized to the fluid group and 24 in the no fluid group. The mean improvement in 0- to 60-minute pain score was 4.5 (95% confidence interval 3.7 to 5.3) in the fluid group and 4.9 (95% confidence interval 3.5 to 6.2) in the control group. Primary outcome data were collected for 49 of 50 enrolled patients, and only one participant correctly identified the group assignment.

Conclusion: This pilot study showed no statistically significant treatment effect from fluid administration, but does not exclude the possibility of a clinically important treatment effect. The study protocol and approach to blinding are both feasible and effective. [Ann Emerg Med. 2019;73:150-156.]

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INTRODUCTION

Background

Headache is the fourth most common reason that patients visit an emergency department (ED) in the United States.[1] Migraine headaches alone account for greater than 1 million patient encounters in US EDs annually.[2] Patients visiting EDs for migraine headache commonly receive intravenous fluids as part of their treatment strategy,[3] though the effect of this intervention on patient-oriented outcome measures is unknown. Studies involving healthy volunteers demonstrate that even mild dehydration decreases pain thresholds and increases central pain-related activity in the anterior cingulate cortex, insula, and thalamus.[4] Consistent with these findings, dehydration has been identified as a trigger for migraine headache.[5] However, intravenous fluid therapy has not been well studied in patients with migraine and the clinical effectiveness of this intervention is unknown.

Importance

Despite a lack of existing clinical evidence, approximately 40% of patients visiting US EDs for headache receive treatment with intravenous fluid.[3] If intravenous fluid is an effective adjunct to migraine symptom control, then expanded intravenous fluid use may benefit additional patients. If, however, intravenous fluid does not improve symptom control, then this intervention may unnecessarily increase costs, occupy staff time, and prolong ED visits.

Goals of This Investigation

The goal of this study was to perform a pilot, randomized trial with ED patients with migraine headache

Editor's Capsule Summary

What is already known on this topic

Dehydration may trigger headaches, yet it is unclear whether intravenous fluids are helpful for migraine.

What question this study addressed

Is a blinded, randomized controlled trial of intravenous fluids for emergency department migraine treatment feasible?

What this study adds to our knowledge

Blinding, enrollment, and intervention delivery were feasible. The reduction in pain from intravenous fluids in this 49-patient study was likely to be smaller than the minimally clinically significant difference established in previous drug trials.

How this is relevant to clinical practice

When added to intravenous prochlorperazine and diphenhydramine, fluids have uncertain benefit, with the magnitude of effect likely to be small.

Research we would like to see

Given the favorable risk-benefit profile of fluids in patients with established vascular access, small reductions in pain from fluids may be important. Larger trials are required to address smaller effect sizes.

to estimate the effect of intravenous fluid administration on pain relief, and to assess the feasibility of the described study protocol.

MATERIALS AND METHODS

Study Design and Setting

This blinded, single-center, randomized controlled trial was performed in the Cooper University Hospital ED, an urban teaching hospital in Camden, NJ, which serves a socioeconomically diverse patient population. The study was approved by the Cooper University Hospital institutional review board. Study coordinators and volunteer research assistants were trained on the trial protocol before participating in study activities, first in a group didactic session and subsequently in individual training sessions.

Selection of Participants

Patients with a chief complaint of headache were screened for eligibility between 8:30 AM and 10:30 PM, 7 days per week, from January 2017 to September 2017. Patients were eligible for inclusion if they were adults aged 18 years or older, with a headache meeting the third *International Classification of Headache Disorders* definition for migraine headache with or without aura.[6] The third *International Classification of Headache Disorders* defines migraine headache as a headache that lasts 4 to 72 hours without treatment, meets at least 2 of 4 typical migraine characteristics (unilateral, pulsating, moderate or severe pain intensity, and aggravated by routine physical activity), is accompanied by either nausea/vomiting or photo- and phonophobia, and is not better accounted for by another headache syndrome. Additionally, patients must have had a prior history of at least 5 similar headaches. Patients were excluded if they were pregnant, non-English speaking, received more than 500 mL intravenous fluid before enrollment, or if in the opinion of the treating ED attending physician intravenous fluids were either definitively indicated (eg, severe dehydration) or contraindicated (eg, heart failure exacerbation).

Interventions

Consenting participants were randomized to receive either 1 L of 0.9% normal saline solution administered intravenously during 1 hour (intravenous fluid group) or 0.9% normal saline solution at 10 mL/hour for 1 hour (control group). Randomization was performed on a 1:1 basis in randomly permuted blocks of 4 or 6 using sealed, opaque envelopes containing allocation assignments. After enrollment, each participant's nurse opened the envelope and programmed the patient's intravenous pump according to the study instructions. The fluid bag, intravenous pump, and intravenous drip chamber were all hidden with opaque coverings so that participants, outcome assessors, treating physicians, and study investigators were all blinded to the treatment group. The patient's bedside nurse was not blinded. In addition to the intervention and control therapies, all participants received 10 mg intravenous prochlorperazine and 25 mg intravenous diphenhydramine at the start of treatment.

Methods of Measurement

Research assistants assessed pain scores at time 0 (start of the intervention), 60 minutes (end of the intervention), and 120 minutes, using both a categorical pain scale (none, mild, moderate, and severe) and a 0 to 10 verbal pain scale that has been validated for use in the ED setting.[7] We also assessed both nausea and functional disability at 0, 60, and 120 minutes. Patients were asked to describe their functional disability as none, mild (difficulty performing

activities of daily living), moderate (unable to perform some activities of daily living), or severe (unable to perform most activities or requiring bed rest). Research assistants recorded ED visit characteristics, including the need for rescue analgesic or antiemetic mediations administered at any time between study enrollment and ED discharge. ED length of stay was defined as the time between ED arrival and physically leaving the department.

During the 120-minute assessment, we also evaluated the effectiveness of blinding by asking both participants and outcome assessors whether they thought they knew which group the participant was allocated to.

We contacted participants 48 hours after ED discharge by telephone to assess pain, functional status, ability to tolerate oral intake, and adverse effects potentially related to the intravenous fluid administration.

Outcome Measures

The prospectively defined primary outcome was the difference in verbal pain rating (scale of 0 to 10) between the start of the study intervention and the 60-minute time point. The minimum clinically significant difference in verbal pain rating is 1.3.[7] Key secondary clinical outcomes were the difference in 0- and 120-minute pain scores, pain-free status after 120 minutes, functional disability at 60 and 120 minutes, nausea at 60 and 120 minutes, 48-hour pain score, and the global assessment of treatment at 48 hours. We also compared the need for rescue medications and the ED length of stay between the intervention and control groups. We assessed the feasibility of the study protocol by reporting the proportion of participants who were successfully followed at the 60-minute, 120-minute, and 48-hour time points, and by reporting the effectiveness of blinding among participants and outcome assessors.

Primary Data Analysis

This pilot study was designed to demonstrate the feasibility of the trial protocol and to establish a baseline estimate for the treatment effect of the intervention. A sample size of 50 patients was selected to provide the ability to detect a protocol adherence rate of 85% (+/- 10%) at a confidence level of 95%. Analyses were conducted with an intention-to-treat approach. We report changes in ordinal variables as means with 95% confidence intervals (CIs). Categorical outcomes are reported as proportions with 95% CIs. We excluded participants with missing data from relevant analyses on a pairwise basis but retained these participants within the overall data set.

We used results from this pilot study to estimate the sample sizes necessary for a future larger-scale trial. We also performed a simulation to estimate the probability that these pilot data are consistent with a clinically meaningful difference between the treatment arms with respect to improvement in pain score at 60 minutes. To perform this analysis, we created virtual subjects reflecting random sampling from normal distributions with mean improvements in the pain score of 5.3 in the intervention group and 4.0 in the control group (reflecting the minimally clinically significant difference in pain score of 1.3), with an SD of 2.6 for both groups. Next, we simulated the performance of 1,000 virtual trials by sampling 25 virtual patients from each study arm for each trial. The percentage of these virtual trials showing what we observed in the present trial estimates the probability that our data are consistent with a true clinically meaningful difference across the treatment groups. Data were collected with the Research Electronic Data Capture (REDCap) data management program (Vanderbilt University, Nashville, TN), and analyses were conducted with PASW (version 18.0; IBM Corp, Armonk, NY) and SAS (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

We enrolled and randomized 50 patients, one of whom withdrew before the 60-minute assessment, leaving 25 patients randomized to the intravenous fluid group and 24 in the control (no fluid) group (Figure 1). Most participants were women, including 92% in the control group versus 76% in the intravenous fluid group (between-group difference 16%; 95% CI –5% to 36%). Groups were otherwise relatively well balanced according to their baseline characteristics (Table 1).

Main Results

Participants in both study arms showed a meaningful reduction in pain score by 60 minutes, although the change in pain score was not statistically different between the 2 treatment arms, with improvements of 4.5 (95% CI 3.7 to 5.3) in the intravenous fluid group and 4.9 (95% CI 3.5 to 6.2) in the control group (Table 2). The change in pain score between time 0 and 60 minutes for each participant is shown in Figure 2. At 120 minutes, the mean improvement in pain score compared with baseline was 5.9 (95% CI 4.8 to 7.1) in the intravenous fluid group and 5.5 (95% CI 4.1 to 6.8) in the control group. ED length of stay was also not statistically different between the 2 study groups.

The 48-hour telephone assessments revealed no significant differences in pain between the intravenous fluid and control groups, with a mean score of 2.6 (SD 3.3) and 1.9 (SD 2.5), respectively, on a verbal pain scale of 0 to 10.

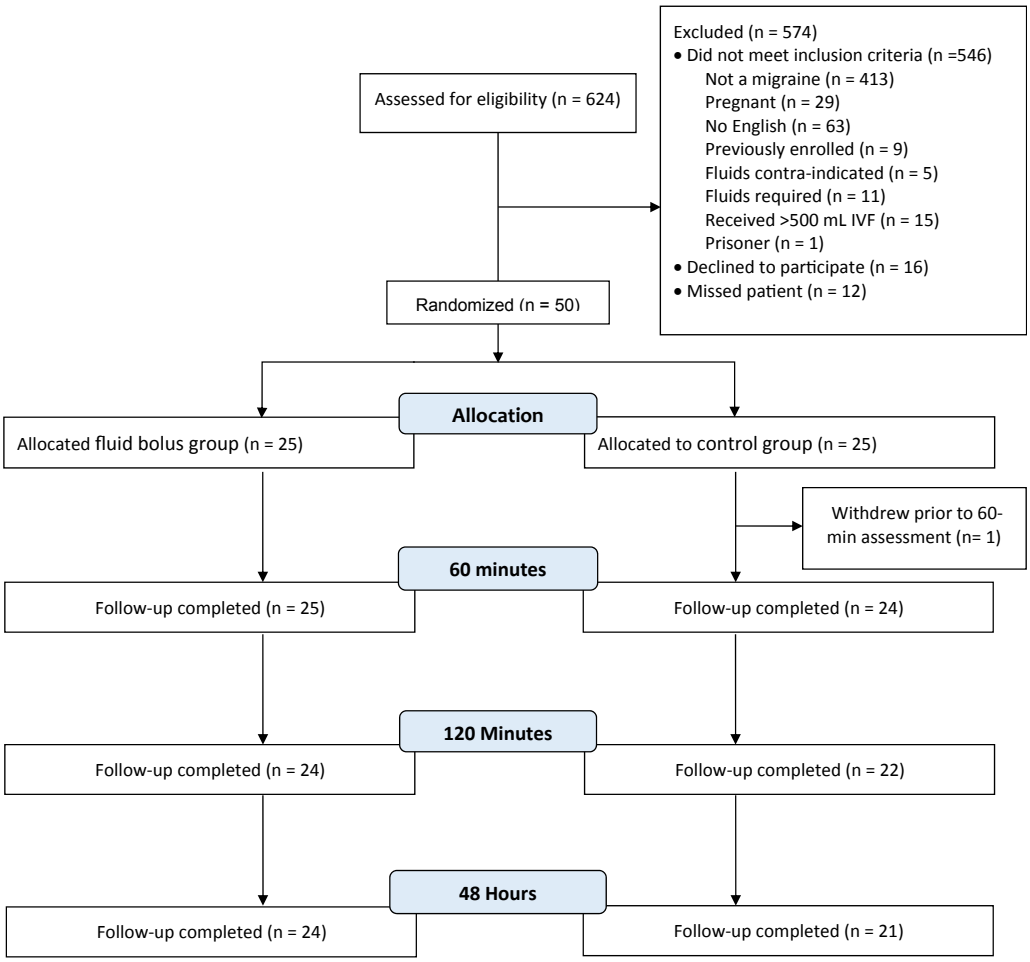

Figure 1. Flowchart of potentially eligible study participants.

Two of 24 patients (8%) contacted for 48-hour follow-up in the intravenous fluid group and none of the 21 contacted in the control group reported moderate or severe nausea at 48 hours. When asked whether they would wish to receive the same treatment in the future, 19 of 24 patients (79%) in the intravenous fluid group wished to receive the same treatment in the future compared with 14 of 21 (67%) in the control group (difference 12.5%; 95% CI –13% to 38%). One patient in the intravenous fluid group reported leg swelling.

Outcome data were available for 49 of 50 enrolled participants at the 60-minute point, for 46 participants at 120 minutes, and for 45 participants at 48 hours. Blinding was generally effective. Two participants thought they knew their group assignment; one correctly identified the treatment arm and one did not. A research assistant correctly identified the group assignment for one participant.

Using the outcome data from this pilot study to inform a power calculation for a more definitive trial reveals that to detect a "clinically meaningful" treatment effect of at least 1.3 (ie, 4.5 to 3.2 on a 0 to 10 scale) in 1-hour pain scores between the 2 treatment groups, a minimum of 65 persons per group would be necessary according to an SD of 2.6, a P value of .05 (2-tailed), and 80% power. For 90% power to detect a difference of 1.3, a minimum of 85 persons per group (total 170) would be necessary.

Based on our simulation in which a clinically important treatment difference was assumed, 75 of 1,000 virtual trials showed a between-group difference of less than 0.4 point on a 0 to 10 pain scale favoring intravenous fluid (ie, the result observed in our pilot trial). Therefore, the probability that our observed data are consistent with a true, clinically meaningful difference between treatment arms is approximately 7.5%. According to these estimates, a large-scale trial is unlikely to show a clinically important treatment effect caused by the intervention.

LIMITATIONS

This study has several important limitations. First, this was a small-scale pilot study. The wide confidence intervals

Table 1. Baseline characteristics of study participants.

Characteristic	No. (%)		
	All Participants, n=49	**Received Fluid Bolus, n=25**	**Control, n=24**
Sex			
Men	8 (16)	6 (24)	2 (8)
Women	41 (84)	19 (76)	22 (92)
Age, median (IQR), y	35 (28–49)	34 (25–40)	37 (30–50)
Ethnicity			
Hispanic or Latino	17 (35)	10 (40)	7 (29)
Not Hispanic or Latino	30 (61)	13 (52)	17 (71)
Unknown	2 (4)	2 (8)	
Race			
Black	18 (37)	10 (40)	8 (33)
White	20 (41)	10 (40)	10 (42)
Other	11 (22)	5 (20)	6 (25)
Median baseline pain score (IQR)	9 (7.5–10)	8 (7–10)	9 (8–10)
Baseline nausea			
None/mild	29 (59)	14 (56)	15 (63)
Moderate	17 (35)	10 (40)	7 (30)
Severe	3 (6)	1 (4)	2 (8)
Baseline disability caused by pain*			
None/mild	10 (21)	6 (24)	4 (17)
Moderate	16 (33)	10 (40)	6 (26)
Severe	22 (46)	9 (36)	13 (57)

IQR, Interquartile range.
*One patient did not report pretreatment disability.

we report do not exclude the possibility of a clinically relevant treatment effect. Although both treatment arms were relatively similar with respect to the baseline characteristics we measured, the study is also small enough that there may be important between-group differences in unmeasured confounders because of chance. Furthermore, intravenous fluid may be more likely to benefit patients with nausea, vomiting, and clinical dehydration as prominent manifestations of their migraine syndrome as compared to those without prominent fluid losses.

We studied a 1-L saline solution bolus because in our experience this dose is commonly used in clinical practice for treating migraine patients. Other crystalloid solutions or fluid doses may produce different results. Also, all participants in our study, including those in the control arm, had to have an intravenous line placed, and all received intravenous prochlorperazine. Consequently, our observations in regard to length of stay should not be generalized to a strategy in which intravenous access was avoided altogether. The length-of-stay data are further limited by our use of fixed times for the main study outcomes. Finally, this was a single-center study conducted during daytime and evening hours on adult patients; results may differ among other patient populations.

DISCUSSION

This randomized, blinded study of ED patients with migraine headache treated with prochlorperazine and diphenhydramine compared outcomes between patients receiving a 1-L bolus of normal saline solution with those receiving no fluid bolus. We observed no significant between-group outcome differences, though the small sample size means that we have not ruled out either a clinically important treatment benefit or harm from intravenous fluids. The method of blinding and approach to data collection were both successful, suggesting that a larger-scale study using these methods would be feasible.

An important consideration when interpreting these results is that both the control and treatment arms received prochlorperazine, which has been shown to produce short-term symptomatic improvements similar to those observed

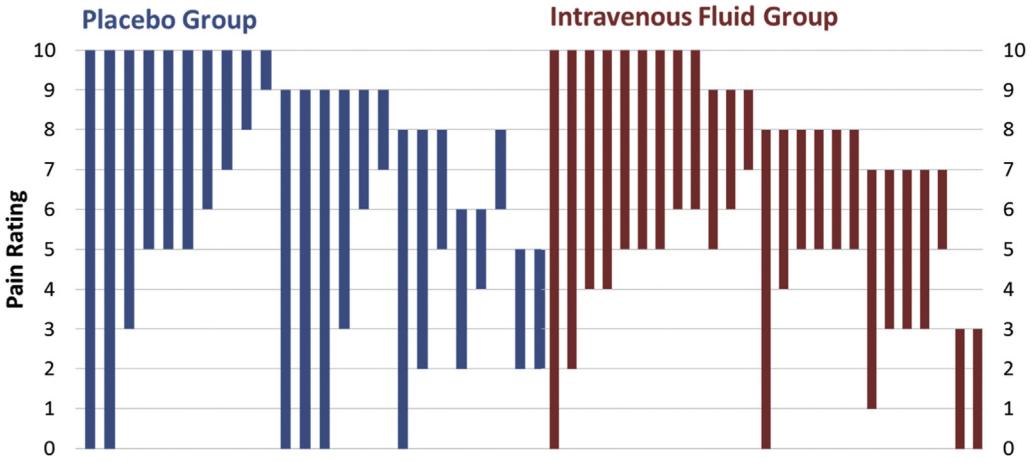

Figure 2. Waterfall plot showing baseline and 1-hour pain scores for participants in each treatment group.

in the present study.[8] ED-based migraine studies using placebo have generally shown that placebo administration results in smaller magnitude but still clinically relevant short-term improvements of up to 3 points on a 0 to 10 pain scale.[8] The meaningful improvement in pain score observed in our control group may therefore be due to the use of prochlorperazine in both study arms, a placebo effect, or both.

Table 2. Outcome comparisons between migraine patients randomized to receive a 1-L fluid bolus and controls.

Outcome Variable*	Received Fluid Bolus, n=25	Control, n=24	Difference Between Fluid Bolus and Control, % (95% CI)
Change in pain score at 60 min, mean (95% CI)	4.5 (3.7 to 5.3)	4.9 (3.5 to 6.2)	−0.4 (−1.9 to 1.1)
Change in pain score at 120 min, mean (95% CI)	5.9 (4.8 to 7.1)	5.5 (4.1 to 6.8)	0.5 (−1.3 to 2.2)
Pain free at 120 min, No. (%)			
Yes	9 (38)	7 (32)	6 (−22 to 33)
No	15 (63)	15 (68)	
Unknown			
Functional disability because of headache at 60 min, No. (%)			
None/mild	18 (72)	18 (75)	−3 (−28 to 22)
Moderate/severe	7 (28)	6 (25)	
Functional disability because of headache at 120 min, No. (%)			
None/mild	21 (88)	18 (86)	2 (−18 to 22)
Moderate/severe	3 (13)	3 (14)	
Nausea at 60 min, No. (%)			
None/mild	22 (88)	22 (96)	−8 (−23 to 8)
Moderate/severe	3 (12)	1 (4)	
Nausea at 120 min, No. (%)			
None/mild	23 (100)	21 (95)	5 (−4 to 13)
Moderate/severe	0	1 (5)	
Rescue medication within 120 min, No. (%)			
Yes	5 (20)	7 (29)	−9 (−33 to 15)
No	20 (80)	17 (71)	
ED length of stay, mean (SD), min	309 (68)	316 (93)	−7 (−54 to 40)

*Cases with missing data were removed on a pairwise basis.

The results of the present study are consistent with those from a recent secondary analysis of data from 4 ED-based migraine headache trials that evaluated the use of metoclopramide for patients with migraine headache.[9] This secondary analysis also failed to demonstrate a clinically important association between intravenous fluid administration and improved pain outcomes. Similarly, a prospective study of pediatric patients with migraine headache showed that initial treatment with intravenous fluid alone in the absence of other analgesic medications was associated with very limited improvement in baseline pain scores after fluid administration.[10] However, these studies are also limited by small sample sizes and the use of secondary or exploratory analyses. While our study was also small, it represents an important step forward as, to our knowledge, the first clinical trial to prospectively randomize participants to either receive fluids or not, and the first study in this population to demonstrate the feasibility of effectively blinding participants and outcomes assessors to intravenous fluid administration. Future studies aimed at identifying patients most likely to benefit from adjunctive treatment with intravenous fluid are warranted. Dose-finding studies may also be helpful to determine the fluid dose most likely to provide a clinically important treatment effect.

In conclusion, this small randomized controlled trial of ED patients with migraine headache showed no evidence of clinically important outcome differences between patients treated with or without intravenous fluids, though an important treatment effect due to fluid use has not been entirely excluded. Patients and outcome assessors were successfully blinded to the assigned treatment arm, and high rates of data collection suggest that the present study protocol was feasible.

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