Intravenous Caffeine for the Treatment of Acute Migraine: A Pilot Study

Alireza Baratloo, MD,1 Ahmed Negida,2 Gehad El Ashal,3 and Nazanin Behnaz, MD4

Background: Caffeine has a long profile of use as an adjuvant therapy for headache and migraine. This study evaluates the safety and efficacy of intravenous caffeine citrate for patients with acute migraine headache.

Methods: In this single arm study, 61 patients were enrolled who were diagnosed with migraine according to International Headache Society criteria. Patients received 60 mg caffeine citrate intravenously (i.v.) in about 10 min. Visual analog scale (VAS) pain scores were measured on baseline and 1 h and 2 h after caffeine infusion.

Results: The improvement in VAS pain score was >3 point change from baseline to 1 h after i.v. infusion (p < 0.001) and >5 point change from baseline to 2 h after i.v. infusion (p < 0.001). Patients who received other medication before caffeine i.v. infusion did not show better improvement after 1 h (p = 0.304) or 2 h (p = 0.926) compared with other patients.

Conclusions: Infusion of 60 mg caffeine citrate i.v. is safe and well tolerated. It achieved therapeutic success for patients with acute migraine headache after 1 and 2 h. Further controlled studies are recommended.

Introduction

Migraine is defined as recurrent attacks of unilateral severe headache associated with nausea, phonophobia, and photophobia.1 In the United States, 18% of females and 6% of males suffer with migraine.2 In Europe, migraine affects 17% of females and 8% of males.3 Migraine is estimated to count for 2% of years living with disability (YLDS) in females and for 1.4% of YLDS in both sexes.4

Current treatments of migraine

NSAIDs are considered a first-line treatment for acute migraine. However, their use is associated with adverse events such as a tight throat and flushing.5 Triptans are also considered a first-line treatment for severe to moderate acute migraine. There are seven available forms of triptans. However, not all patients respond to the same form.6 Patients taking triptans may develop chest pain and cardiac symptoms.57 Ergotamine can be used in combination with caffeine in acute migraine. It cannot be used alone. Ergotamine has fewer adverse events but inferior efficacy than triptans.910 Intranasal lidocaine has a rapid onset of action, but recurrence of migraine is more common.1112

Caffeine and migraine

Caffeine is an over-the-counter headache medication (Excedrin and Anacin) and is used as adjuvant therapy for headache and migraine.1319 It can cross the blood–brain barrier and reach high concentrations in the central nervous system (CNS).1320 According to neurogenic theory, migraine results from sensitization of trigemiovascular afferents of nociceptive 2nd and 3rd neuron or central sensitization.2127 Therefore, the inhibitory action of caffeine on adenosine receptors (A1 and A2) in the brain and vasculature is the suggested mechanism to relieve migraine pain.202832

To the best of the authors’ knowledge, no previous study has investigated the use of intravenous caffeine for the treatment of acute migraine. The aim of this pilot study is to explore the safety and efficacy of intravenous caffeine citrate for the abortive emergency treatment of acute migraine attacks.
Methods

Study design and setting

A pilot study was designed that is the basic part of a clinical trial entitled “Comparative assessment of caffeine vs. ketorolac intravenous administration efficacy in acute migraine headaches without aura” (registered at www.irct.ir; code: IRCT2013120315640N1). Patients with acute migraine presenting to the emergency department (ED) of Shahid Beheshti University hospital were eligible for this study.

Inclusion criteria

Patients were included if they meet the following criteria: (1) their age ranged from 18 to 60 years old; (b) their complaint of migraine pain fulfilled the criteria of common migraine based on International Headache Society criteria33,34; and (3) Visual analog scale (VAS) pain score indicated severe or moderate pain (VAS pain score > 5).35–38

The International Headache Society criteria for migraine without aura (common migraine) are33,34:

A. At least five attacks fulfilling criteria in B, C, D, and E.
B. Attack lasts 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not attributable to another disorder

Exclusion criteria

Patients with mild VAS pain (< 5 points) were excluded. Patients were also excluded if they had at least one of the following: history of any cardiac dysrhythmia, hypertension, ischemic heart disease, active peptic ulcer disease, inflammatory bowel disease, obsessive compulsive disorder, pregnancy, breast-feeding, coagulopathy, renal failure, hepatic failure, or sleep disorder.

Intravenous caffeine dose measurement

All current data are related to the dose of caffeine benzoate in cases of hypnic headache and postdural puncture headache. There are no data about intravenous caffeine citrate dose for migraine treatment. Therefore, to resolve this point of study, a meeting of academic neurologist, pharmacologist, and emergency medicine experts was formed, and 60 mg caffeine citrate was considered as the safest dose for this pilot study. This can be the basis for future clinical trials.

Outcome measurement

Patients were asked about their pain score on admission based on VAS, and those with pain score of > 4 received 60 mg caffeine citrate intravenously (i.v.) in about 10 minutes. All patients were monitored for any possible side effects. If any were observed (e.g., tachycardia, hypertension, itching, nausea and/or vomiting, pain on injection site, irritability), the process was stopped. After 1 and 2 h of drug administration, patients were asked about their pain score with VAS. An improvement of more than three points on the pain scale was considered an effective response.38,39

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v22 (IBM Corp., Armonk, NY). To describe continuous variables, means, standard deviations, medians, and interquartile ranges were used. To describe categorical variables, frequencies and percentages were used. The Mann–Whitney U-test and Wilcoxon test were used to analyze differences in VAS pain scores. A p-value of ≤ 0.05 was considered significant.

Ethical considerations

The study was performed in accordance with the ethical considerations of declaration of Helsinki. All eligible patients were informed about the new drug, and all gave signed informed consent. The study was ethically approved by the Shahid Beheshti University hospital, Iran.

Results

Sixty-one patients were enrolled in the study (M ± SD age = 30.75 ± 8.7 years). Of these, 51 (83.6%) patients were female, and 10 patients (16.4%) were male. Twenty-one patients (34.4%) had already taken other medication before arrival to the ED, while 40 (65.6%) patients had not taken any medication. For the group of patients who had already taken other medication, almost all of them had used NSAIDs, and the others had used acetaminophen. No one had used a caffeine-containing drug. The mean (SD) period from taking other medication to i.v. caffeine infusion was 3.4 ± 1.9 h.

The median (IQR) of VAS pain score decreased significantly from 9.0 (2.0) to 5.0 (4.0) after 1 h and to 3.0 (3.0) after 2 h (see Fig. 1).

There was an improvement (> 3 points, > 35%) in VAS pain scale from baseline to 1 h after caffeine infusion (Wilcoxon test Z = –6.5; p < 0.001). After another hour, there was an improvement (> 6 points, > 60%) in VAS pain scale from baseline to 2 h after caffeine...
There was a statistical significant difference in VAS pain score from 1 h to 2 h after caffeine infusion \((Z = –5.89; \ p < 0.001)\). When patients were classified according to taking previous medication before caffeine infusion, the Mann–Whitney test showed no statistical significant difference in VAS pain scores between the two groups of patients (at baseline \(p = 0.845\), 1 h after caffeine infusion \(p = 0.788\), and 2 h after caffeine infusion \(p = 0.696\)). There was no difference between the two groups of patients in terms of change in VAS pain score after 1 h \((p = 0.304)\) or after 2 h \((p = 0.926)\). Figure 2 shows VAS pain scores for the two groups of patients.

**Discussion**

**Effect of treatment**

The results of this study show a significant improvement in VAS pain score from baseline to 1 h and 2 h after caffeine infusion. This improvement was achieved in all except for two patients, whose scores remained at 9 and 10 at 1 h and 2 h after i.v. infusion, respectively. The i.v. caffeine citrate achieved therapeutic success with >3 point improvement in VAS pain score after 1 h and >5 point improvement after 2 h.

**Safety of treatment**

There were no cases of withdrawals or intolerance with the intervention, which indicates the safety of the intravenous caffeine citrate in the studied population. There were no side effects (tachycardia, hypertension, itching, nausea and/or vomiting, pain on injection site, irritability) while the patients were in hospital. However, this should be interpreted cautiously due to the strict inclusion and exclusion criteria for selecting eligible subjects.

**Explanation of results**

Caffeine is already used as an adjuvant for migraine treatment, but according to the changing views about its pathophysiology, its role is becoming more prominent. The present results are supported by the well-established use of caffeine as an adjuvant for the treatment of headache and migraine, the ability of caffeine to cross the blood–brain barrier, and its vasoconstrictor action on cerebral vessels. The intravenous supplementation of caffeine was essential for such high bioavailability and such a rapid action. The possible mechanisms of this therapeutic success are: (1) blocking the pronociceptive action of adenosine; (2) the stimulation of central nor-adrenergic

**FIG. 1.** Box plot shows minimum, maximum, median, and interquartile range at three time points: baseline, 1 h, and 2 h after caffeine infusion.

**FIG. 2.** Box plot shows minimum, maximum, median, and interquartile range of visual analog scale (VAS) pain scores at baseline, 1 h, and 2 h after intervention in the two subgroups of patients (those who took medication and those who did not take medications before caffeine infusion).
pathways that suppress pain; and (3) CNS stimulation modulating the effective component of pain.40-41

**Previous studies**

To the best of the authors’ knowledge, this is the first study to investigate the use of intravenous caffeine citrate in patients with acute migraine headache. PubMed was searched through February 2015 using the following query: (Intravenous AND caffeine AND migraine AND Clinical Trial [ptyp]). This search yielded no results. Oral caffeine has been evaluated as an adjuvant analgesic in previous studies. In the study by Peroutka et al., diclofenac softgel plus caffeine showed statistically significant benefits relative to placebo at 60 min. In addition, there was no statistically significant difference between diclofenac softgel alone versus placebo. In another study, the combination of acetylsalicylic acid, paracetamol, and caffeine was significantly superior to the combination without caffeine \( p = 0.0181 \).43 Results of those two studies highlight the benefit of oral caffeine as an adjuvant analgesic, which supports the possible use of caffeine for the treatment of acute migraine.

**Implications for future research**

The strengths of this study are the careful selection of participants, the diagnosis of acute migraine in strict accordance with the International Headache Society criteria, and the use of a standard outcome measurement (VAS pain score). In addition, excluding participants who may be intolerant to caffeine led to positive results in terms of safety and tolerance of the drug. However, there are some limitations. First, the study is a pilot study and lacks a control group. Other limitations are that the follow-up was limited to the hospitalization period, and the patients’ weight and history of caffeine consumption were not considered in order to estimate the dose for each patient. For future research, the introduction of a control group, using larger sample size, escalating doses, and describing patients who were non-responders to caffeine are recommended.

**Conclusion**

Intravenous caffeine citrate is safe and well tolerated in this population. It seems that intravenous infusion of 60 mg caffeine citrate significantly improves the VAS pain score, and therapeutic success can be achieved for abortive emergency treatment of acute migraine attacks.

**Acknowledgments**

We would like to express our special thanks to the Emergency Department staff of Shohadaye Tajrish Hospital, Tehran, Iran.

**Author Disclosure Statement**

No competing financial interests exist.

**References**

34. IHS—International Headache Society. Migraine without aura[1.1][G43.0. Available at http://ihs-classification.org/en/02_klassifikation/02_teil1/01.01.00_migraine.html (accessed April 6, 2015).
42. Peroutka SJ, Lyon JA, Swarbrick J, Lipton RB, Kolodner K, Goldstein J. Efficacy of diclofenac sodium softgel 100 mg with or without caffeine 100 mg in migraine without aura: a randomized, double-blind, crossover study. Headache 2004;44:136–141.

Address correspondence to:
Ahmed Negida
Faculty of Medicine, Zagazig University
Zagazig
44519 El-Sharkia, Egypt
E-mail: ahmed01251@medicine.zu.edu.eg