Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial

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ABSTRACT

Background: Magnesium deficiency may play a role in the pathogenesis of migraines and other headaches. Studies in outpatient clinics have found that magnesium administered intravenously (IV) reduces headache pain. We investigated the effectiveness of IV magnesium in patients with acute benign headache who presented to the emergency department (ED).

Methods: This randomized double-blind placebo-controlled trial compared 2 g of IV magnesium versus placebo for the treatment of patients with acute benign headache who presented to the EDs of two teaching hospitals. Pre- and post-treatment pain scores were measured on a 100-mm visual analog pain scale.

Results: Forty-two patients were randomized, 21 in each treatment group. Treatment groups had similar baseline characteristics. After treatment, placebo recipients reported an 8-mm median improvement in pain, and magnesium recipients had a 3-mm improvement ($p = 0.63$). We found no statistically significant difference between groups for any secondary outcomes; however, the patients who received magnesium had significantly ($p = 0.03$) more side effects than did those in the placebo group.

Conclusions: We found no benefit to using IV magnesium to treat patients with acute benign headache who present to the ED.

Key words: headache, migraine; magnesium; randomized controlled trials

RÉSUMÉ

Contexte : Une carence magnésique pourrait jouer un rôle dans la pathogenèse des migraines et autres céphalées. Des études auprès de patients de services de consultation externe ont révélé que le magnésium administré par intraveineuse (IV) soulage la douleur associée au mal de tête. Nous avons étudié l'efficacité du magnésium IV chez des patients reçus à l'urgence pour un mal de tête aigu bénin.

Méthodes : Cet essai randomisé contrôlé en double insu compara l'administration de 2 g de magnésium IV versus un placebo pour le traitement de patients atteints d'un mal de tête aigu bénin ayant visité l'urgence de deux hôpitaux universitaires. Les scores de douleur pré et post thérapeutique furent mesurés à l'aide d'une échelle visuelle analogue.

Résultats : Quarante-deux patients furent répartis au hasard entre deux groupes égaux (21 pa-

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tients dans chacun). Les deux groupes présentaient les mêmes caractéristiques de départ. Après le traitement, les patients ayant reçu le placebo indiquèrent un soulagement moyen de la douleur de 8 mm et les patients ayant reçu le magnésium indiquèrent un soulagement de 3 mm (p = 0,63). Nous n'avons constaté aucune différence statistiquement significative entre les groupes quant à tout autre résultat; cependant, les patients ayant reçu du magnésium ressentirent beaucoup plus d'effets indésirables (p = 0,03) que les patients du groupe placebo.
Conclusions : Nous n'avons constaté aucun avantage à recourir au magnésium IV pour le traitement de patients reçus à l'urgence pour un mal de tête aigu bénin.

Introduction

Magnesium deficiency may play a role in the pathogenesis of migraines and other headaches.[1,2] Serum magnesium levels are lower in migraine sufferers than normal subjects, both during the acute attack and in the headache-free intervals.[3,4] Oral magnesium is an effective prophylactic medication for migraine sufferers.[5,6] One recent publication reported 32 of 40 (80%) patients with various types of headache had complete elimination of pain within 15 minutes after treatment with magnesium administered intravenously (IV).[7] That study was done in a headache clinic, and there was no control group or placebo arm.[7]

Headaches are a common emergency department (ED) presentation, accounting for up to 5% of all visits or more than one million ED visits per year in the US.[8] Greater than 90% of these headaches are described as benign vascular or muscle tension type.[9,10] Despite the frequency of people with acute headaches presenting to the ED, there is currently no consensus on the ideal treatment. Available therapies include phenothiazines,[11,12] narcotics,[13] ergots,[14] serotonin agonists[15] and nonsteroidal anti-inflammatories.[12,13] None of these treatments are completely effective, and many have important side effects, including drowsiness, dystonic reactions or coronary vasospasm. Few studies look at the effect of IV magnesium for acute headache. There have been no randomized placebo-controlled trials of the use of IV magnesium for acute headache in ED patients.

The purpose of this study was to evaluate the effectiveness of IV magnesium for ED patients presenting with acute benign headache, in a randomized double-blind placebo-controlled trial. Our hypothesis was that IV magnesium would be superior to placebo in reducing symptoms.

Methods

We enrolled a convenience sample of patients less than 65 years old with acute benign headache who presented to 1 of 2 participating EDs at any time of the day or night. One hospital is a 450-bed academic, tertiary care hospital with 30 000 ED visits a year; the other is a 172-bed military teaching hospital with 80 000 ED visits a year. Patients were eligible for the study if they had a benign headache (migraine, tension-type or mixed) as clinically diagnosed by an attending physician in the ED. Exclusion criteria included meningismus, fever (>38.0°C), pregnancy, altered mental status, history of renal insufficiency, suspicion of intracranial process requiring further work up (i.e., subarachnoid hemorrhage, meningitis or space-occupying lesion), first-time headache or if they were allergic to magnesium. Emergency medicine residents and ED attending physicians at both hospitals enrolled patients. Informed consent was obtained from all participants, and the Institutional Review Boards of both hospitals approved the study protocol.

Eligible patients were asked to grade their pain on an unmarked 100-mm visual analog scale (VAS) with the endpoint descriptors of "no pain" and "worst imaginable pain." They graded their nausea, vomiting and photophobia on similar scales. Each patient then had an IV catheter with saline lock inserted. The pharmacist randomized treatments using a computer-generated random number table. The pharmacy premixed identical, numbered, 50-mL bags of either 2 g of magnesium sulfate or placebo (normal saline). ED staff selected the next consecutive bag to administer. Study drugs were infused over 10 minutes. Patients, nurses and physicians were blinded to the treatment assignment at all times. Vital signs were recorded at 0 and 30 minutes after the beginning of the infusion.

Thirty minutes after infusion, patients were shown their initial VAS ratings and again asked to grade their pain, nausea, vomiting and photophobia. They were also asked to respond to an open-ended question regarding any side effects they experienced. At this time, those still experiencing pain were treated with rescue medications chosen at the discretion of the ED physicians.

For our sample-size calculation, we defined treatment success as a 50% reduction in VAS pain score. Assuming a 30% success rate for patients receiving placebo, 60% for patients receiving magnesium, power of 0.80, and 2-sided alpha of 0.05, we needed 48 patients per group.

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Patient data were entered into an Excel spread sheet (Microsoft Excel X for Mac, Microsoft Corp., Redmond, Wash.). Changes in VAS score were measured from pre-treatment to post-treatment, with high scores indicating more severe symptoms. Thus, positive changes reflected improved symptoms, and negative changes reflected worsening symptoms. Medians and interquartile ranges were used to describe VAS scores; means and standard deviations were also presented. The primary end point was the median difference in VAS pain score (in millimetres) from 0 to 30 minutes. Secondary end points were changes in nausea, vomiting and photophobia, the proportion of patients achieving a 50% reduction in pain, the proportion patients needing rescue medications and the proportion who reported side effects. Results were analyzed by intention-to-treat, with treatment assignments remaining coded. Participants who had only baseline measures recorded due to failure to complete the treatment course were retained in the analysis, using their baseline measures as their outcome measures. The statistical significance of observed differences between groups was analyzed using the Mann–Whitney *U* test for changes in VAS and the chi-squared or Fischer exact test for proportions, defining a 2-sided alpha of 0.05 as significant. All analyses were performed using Stata version 8.0 (Stata Corporation, College Station, Texas).

Results

Because of slow patient accrual, we conducted an interim analysis. Based on this analysis, the study was stopped before the desired sample size was achieved. Forty-two patients were randomized, 21 in each group. This included 30 patients from the academic tertiary care hospital and 12 from the military teaching hospital. Table 1 shows that treatment groups were similar at baseline and that most patients were white females with relatively severe migraine-type headaches. One patient in the magnesium group had only baseline measures recorded but was retained in the analysis using baseline measures as outcome measures.

The analysis demonstrated no significant difference between groups in our primary outcome, with placebo recipients reporting an 8-mm median improvement in pain and magnesium recipients reporting a 3-mm median improvement ($p = 0.63$). Table 2 shows that there were no significant difference between groups in any of the secondary outcomes. Thirty-five patients (83%) required rescue medications, including promethazine or prochlorperazine (with or without diphenhydramine), ketorolac, sumatriptan, morphine, hydromorphone or oxycodone with acetaminophen.

Six patients (29%) in the placebo group and 13 (62%) in the magnesium group reported adverse effects ($p = 0.03$). In the placebo group, 2 had a decrease in blood pressure, 1 had hot flashes, 1 had burning at the IV site and 2 had other symptoms. In the magnesium group, 1 had a decrease in blood pressure, 2 had burning at the IV site, 9 had flushing and 1 had other symptoms.

Discussion

This randomized double-blind placebo-controlled clinical

Table 1. Baseline characteristics for all patients in the study, and by treatment group

		Treatment group	
Characteristic	All patients (*n* = 42)	Placebo (*n* = 21)	Magnesium (*n* = 21)
Age in years, mean (and SD)	33 (9)	29 (8)	36 (8)
Men, %	24	19	29
White, %	86	86	86
Migraine headache, %	93	95	90
VAS score for pain, mm			
Median (and IQR)	80 (71–89)	77 (69–92)	83 (71–88)
Mean (and SD)	79 (15)	78 (16)	80 (13)
VAS score for nausea/vomiting, mm			
Median (and IQR)	43 (20–70)	41 (17–68)	46 (29–76)
Mean (and SD)	44 (28)	41 (26)	47 (29)
VAS score for photophobia, mm			
Median (and IQR)	80 (56–93)	87 (59–98)	77 (54–88)
Mean (and SD)	75 (22)	79 (21)	71 (23)

IQR = interquartile range; SD = standard deviation; VAS = visual analog scale (ranging from 0–100, where 0 = "No pain" and 100 = "Worst imaginable pain."

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trial suggests that IV magnesium does not benefit ED patients with acute benign headache. Previous studies of IV magnesium for patients with acute headache have had mixed results. In an uncontrolled case series based in an outpatient headache clinic, Mauskop and colleagues reported an 80% rate of headache elimination using 1 g of IV magnesium in patients with mixed benign headaches.[7] In another uncontrolled study, Mauskop and colleagues reported that IV magnesium led to significant improvement in patients with cluster headaches.[16] In a similar clinic-based study, Demirkaya and coworkers reported that 14 of 15 patients (86%) who received 1 g of magnesium had complete headache relief, and 1 of 15 (6%) who received placebo had only mild improvement.[17] Unfortunately, the investigators in this study were unblinded and, although the study was described as a randomized trial, the first 15 patients received magnesium and the next 15 received placebo.

Other studies have been less encouraging. In a randomized double-blind placebo-controlled trial conducted in 2 Brazilian public health units, Bigal and associates compared 1 g of IV magnesium to placebo in patients with migraine headaches.[18] These authors concluded that IV magnesium was significantly better than placebo in patients who had "migraine with aura" but not in patients "without aura." In a randomized double-blind placebo-controlled ED migraine trial, 2 g of IV magnesium showed no benefit when given as an adjunct to metoclopromide.[19] In fact, magnesium use actually seemed to attenuate the effectiveness of metoclopramide in relieving migraine. In another randomized double-blind trial, Ginder and coauthors showed that IV prochlorperazine was significantly more effective than 2 g of IV magnesium for acute headaches of various types.[20] In this study, prochlorperazine completely or partially relieved headache pain in 90% of patients and magnesium did so in 56% of patients.

To our knowledge, the current study is the first to compare magnesium to placebo for acute benign headaches in the ED, and our data suggest that IV magnesium does not relieve pain, nausea or photophobia in this patient population. Significantly more patients in the magnesium group experienced side effects, and the vast majority of patients in both groups required rescue medication to treat their headaches.

Our results differ from those conducted in outpatient headache clinics[7,16,17] but are compatible with more recent studies conducted in the ED. Of note, 2 of the studies that concluded effectiveness[7,16] used no control agent, and the third[17] was unblinded. Although it is conceivable there are fundamental differences between headache patients in EDs and headache clinics, the discrepancy in our findings is more likely explained by differences in study design.

Low serum magnesium levels have been hypothesized to play a role in the pathogenesis of benign headaches.[2] Some studies have shown that magnesium is more likely to be beneficial for headache patients with low serum magnesium levels,[7,16] but other data have not borne this out.[20] We did not evaluate serum magnesium levels in our study patients because the literature is unclear on the role of serum magnesium and because it is not typical ED practice to check serum lab values prior to deciding on a headache treatment.

Limitations

Our study had several limitations. The most serious limita-

Table 2. Outcomes for all patients in the study, and by treatment group

Outcomes	All patients (n = 42)	Treatment group: Placebo (n = 21)	Treatment group: Magnesium (n = 21)	p value
Reduction in pain, mm*				
Median (and IQR)	8 (0–21)	8 (2–30)	3 (0–18)	0.63
Mean (and 95% CI)	16 (8–23)	15 (6–24)	16 (4–29)	0.85
Reduction in nausea/vomiting, mm*				
Median (and IQR)	3 (-5–20)	1 (-15–20)	3 (-1–18)	0.43
Mean (and 95% CI)	6 (-2–14)	4 (-10–17)	8 (-3–19)	0.58
Reduction in photophobia, mm*				
Median (and IQR)	7 (-1–28)	7 (-2–31)	7 (-1–37)	0.90
Mean (and 95% CI)	18 (10–26)	18 (5–30)	18 (6–30)	0.93
Achievement of 50% reduction in pain, %	21	24	19	>0.99
Need for rescue medications, %	83	86	81	>0.99
Side effects, %	45	29	62	0.03

IQR = interquartile range; CI = confidence interval
*According to unmarked 100-mm visual analog scale, where 0 = "No pain" and 100 = "Worst imaginable pain."

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tion is the small number of patients enrolled and the possibility of type II error. Given the very unpromising findings seen at interim analysis, with no significant difference in any outcome, it seemed highly unlikely that further patient accrual would change the study conclusions.[21] A retrospective power analysis showed that our study had 53% power to detect a 15-mm difference in VAS pain scores, which has been previously reported to be the minimum discernible difference ("a little less or a little more") for pain control.[22] More recent work has shown the minimal clinically important VAS change (reflecting "adequate" pain relief) to be between 25 mm and 40 mm.[23,24] Our study had 80% power to detect a 21-mm difference in VAS scores and 98% power to detect a 30-mm difference. Of note, the percentage of patients responding to placebo was somewhat lower in our study than in previous headache studies.[25]

Another possible limitation of our study was the inclusion of patients with all types of benign headache. Clinically, the distinction between headache types frequently blurs. Physicians and patients alike have difficulty distinguishing between types of benign headaches.[10,26,27] Both types of headaches may have similar vascular origins.[26,28,29] Many studies have also demonstrated a similar response to therapy, regardless of diagnosis of headache type.[10,26] Although 93% of our patients were diagnosed with migraines, it is possible that the results may have differed if only patients meeting strict criteria for migraine were included. In addition, our results may not apply to patients treated in settings other than the ED.

Other limitations include not comparing magnesium to other active treatments or studying magnesium as an adjunct. We measured outcomes at 30 minutes because a previous study showed effectiveness within 15 minutes.[7] It is possible that magnesium might have shown greater effectiveness at 1 or 2 hours after administration, but we were reluctant to expose patients to prolonged pain, and if magnesium's onset of analgesia is delayed to this extent, then it is inappropriate for emergency symptom relief.

Conclusion

Intravenous magnesium performed no better than placebo and is unlikely to be of benefit in the management of patients presenting to the ED with acute headache symptoms. Given the existence of effective alternate therapies, a larger placebo-controlled trial of IV magnesium is not justified.

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