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A RANDOMIZED CONTROLLED STUDY OF MAGNESIUM SULFATE VERSUS DIHYDROERGOTAMINE IN THE MANAGEMENT OF ACUTE MIGRAINE ATTACKS

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ABSTRACT

Introduction: There is a hypothesis that magnesium sulphate can provide relief from headaches caused by migraine. In this study, we have compared the effects of magnesium sulfate and dihydroergotamine (DHE) in the management of severe migraine headaches. **Methods:** The study includes 120 patients who presented to our hospital's emergency room with headache due to migraine. They randomly received either 100 ml normal saline solution with 1g of magnesium sulfate or dihydroergotamine mesylate, which is standard acute migraine treatment. Patients evaluated their pain on the visual analogue scale (VAS) at 30, 60 and 90 minutes after the intervention. **Results:** Thirty minutes after intervention, mean VAS was 6 ± 1.29 in the magnesium sulfate group and 5.85 ± 1.02 in the DHE group. Sixty minutes after intervention, it was 4.08 ± 1.67 (magnesium sulfate) and 4.62 ± 1.21 (DHE). While at 90 minutes it was 2.48 ± 1.61 (magnesium sulfate) and 3.48 ± 1.26 (DHE). Pain score comparisons were statistically significant at 60 and 90 minutes, although not at 30 minutes. The two groups were similar in terms of gender distribution and migraine subtype. **Conclusion:** Treatment with 1g of magnesium sulfate in 100 ml normal saline solution provides significant pain relief in migraine without any serious side effects.

Headache attacks are one of the most common complaints presenting to the emergency room,[1] with women twice as likely to present with migraine headaches as compared to men.[2] Dihydroergotamine (DHE) is commonly used for pain relief during acute migraine, but this drug has limiting side effects, such as nausea and vomiting.[3] Research for drugs or components that relieve pain during a severe attack without side effects is ongoing. Magnesium deficiency has been postulated to play a role in migraine pathophysiology,[4] and it is hypothesized that magnesium sulfate can provide relief from headaches caused by migraine. In this study, the therapeutic effects of magnesium sulfate in acute migraine were compared with the beneficial effects of DHE.

METHODS

The study was conducted in the emergency department of Shahid Sadoughi Hospital (Yazd, Iran) between March and November 2006. A sample of 120 patients (60 in each group) presenting with headache due to migraine were included. The study protocol was reviewed and approved by the University's Ethics Committee and informed consent was obtained from all patients. Age of less than 15 years, allergic reaction to magnesium sulfate, abnormal findings in physical examination, blood calcium level less than 8.3 mg/dl, and presence of cardiac or renal problems were the exclusion criteria for the study. Patients randomly received either 1g magnesium sulfate in 100 ml normal saline solution or DHE (standard treatment of acute migraine). Patients and the treating physician were blinded to the treatment type used for each patient, with the identification code assigned to each case kept confidential until after the primary analysis. Patients evaluated their pain on the visual analogue scale (VAS) with endpoints of none and greatest pain.0-10 The patients were requested to evaluate their pain on the VAS again at 30, 60 and 90 minutes after receiving the intervention. Statistical analysis employed t-test and chi-square test, with the level of significance set at 95%.

RESULTS

Of 120 patients enrolled in the study, 80 (66.7%) were female and 40 (33.3%) male. Classic migraine was present in 47 patients (39.2%), while 73 patients

(60.8%) had common pattern migraine. Mean serum magnesium level before intervention was 1.99 ± 0.81 mg/dl, while mean serum calcium level before intervention was 9.10 ± 0.83 mg/dl.

Table 1: Comparison between mean and standard deviation of VAS at 0.5, 1 and 1.5 hours after intervention in both study groups

Group of study	VAS	0.5 hours after intervention	1 hour after intervention	1.5 hour after intervention
Magnesium Sulfate	Number	60	60	60
	Mean	6	4.08	2.48
	S.D	1.29	1.67	1.61
Dihydroer-gotamine	Number	60	60	60
	Mean	5.85	4.62	3.48
	S.D	1.02	1.21	1.26
Total	Number	120	120	120
	Mean	5.93	4.35	2.98
	S.D	1.16	1.47	1.52

(P-value = 0.48 for 0.5 hour, P-value = 0.047 for 1 hour, P-value = 00.0 for 1.5 hours after trial)

Tables 1 and 2 summarize the VAS results. At 30 minutes after intervention, mean VAS was 6 ± 1.29 in the magnesium group and 5.85 ± 1.02 in the DHE group, which changed to 4.08 ± 1.67 (magnesium group) and 4.62 ± 1.21 (DHE group) at 60 minutes, and 2.48 ± 1.61 (magnesium group) versus 3.48 ± 1.26 (DHE group) at 90 minutes ($p < 0.01$) . A significant reduction in pain intensity at 60 and 90 minutes after treatment, compared with baseline, was seen in both groups (at 60 min, $p = 0.047$; at 90 min, $p < 0.01$). Mean VAS of patients in the magnesium group was significantly lower than the ergotamine group. This reduction in pain intensity was not different between the groups at 30 minutes after intervention ($p = 0.48$; figures 1 and 2)

Table 2: Comparison between mean and standard deviation of VAS at 0.5, 1 and 1.5 hours after intervention in both sex groups

Group of study	VAS	0.5 hours after intervention	1 hour after intervention	1.5 hour after intervention
Male	Number	40	40	40
	Mean	5.97	4.55	3.10
	S.D	1.33	1.57	1.52
Female	Number	80	80	80
	Mean	5.90	4.25	2.93
	S.D	1.07	1.43	1.53
Total	Number	120	120	120
	Mean	5.92	4.35	2.98
	S.D	1.16	1.48	1.52

(P-value = 0.74 for 0.5 hour, P-value = 0.29 for 1 hour, P-value = 0.56 for 1.5 hours after trial)

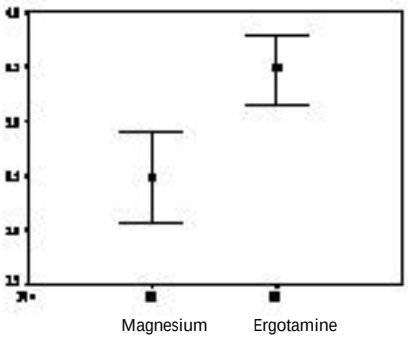

Figure 2: Mean and confidence interval of VAS in both group of study at 90 min after intervention

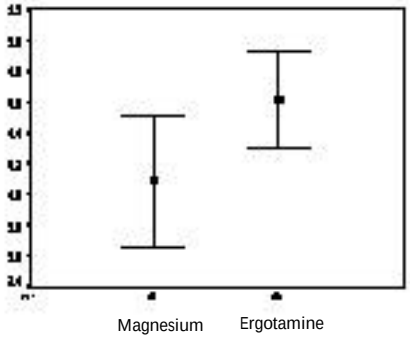

Figure 1: Mean and confidence interval of VAS in both group of study at 60 min after intervention

Patients were also divided into two groups according to their baseline magnesium level (above or below 1.5). There were significant differences between mean VAS score at 60 and 90 minutes after intervention among the two groups ($p = 0.004$ for 60 min; $p < 0.01$ for 90 min). At 30 minutes, however, the scores in both groups were similar (Table 3). VAS scores also did not differ according to gender (Table 2) or migraine type.

DISCUSSION

Increasing evidence supports a role for both systemic and brain magnesium deficiency in patients with migraine, especially migraine localized to the occipital lobes. Magnesium normally maintains a strongly coupled state of mitochondrial oxidative phosphorylation. It also plays a role in gating the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Magnesium deficiency causes

Table 2: Comparison between mean and standard deviation of VAS at 0.5, 1 and 1.5 hours after intervention according to magnesium level of patients before intervention

Group of study	VAS	0.5 hours after intervention	1 hour after intervention	1.5 hour after intervention
Magnesium less than 1.5 mg/dl	Number Mean S.D	21 5.71 1.15	21 3.52 1.40	21 1.57 1.08
Magnesium more than 1.5 mg/dl	Number Mean S.D	99 5.70 1.16	99 4.53 1.44	99 3.28 1.44
Total	Number Mean S.D	120 5.93 1.16	120 4.35 1.48	120 2.98 1.52

(P-value = 0.36 for 0.5 hour, P-value = 0.004 for 1 hour, P-value = 0.00 for 1.5 hours after trial)

instability of neuronal polarization because of a loss of ionic homeostasis, leading to neuronal hyperexciitability and a lower threshold for spontaneous depolarization.[5]

Migraine pathophysiology remains incompletely understood. Evidence suggests that vascular components play a basic role in the pathophysiology of migraine. Our study has shown magnesium administration as a treatment strategy for migraine. The results of our study show that 100 ml normal saline solution with 1 g of magnesium sulfate provided significant pain relief in migraine headache attacks presenting to the ER. It is important to note that these effects were most noticeable at 60 and 90 minutes and were not appreciated at 30 minutes after intervention. Mauskop and Altura have reported that around 50% of migraineurs had low levels of magnesium during migraine attacks. Magnesium infusion causes rapid and continuous relief during migraine attacks.[4,6]

Other studies have compared the efficacy of magnesium sulfate with other drugs or placebo in migraine. Mauskop et al note that magnesium therapy in patients with low baseline levels of serum magnesium had decreasing pain effects.[6,7] On the other hand, Ginder and co-workers have reported in their study that serum levels of magnesium sulfate had no relationship with the response of migraine patients to magnesium infusion.[8] Barkley and colleagues confirmed the sensitivity of spontaneous neural discharges to magnesium in migraine patients who had low levels of intracellular magnesium.[9]

Thompson has outlined that therapeutic effects of drugs come from three components: a direct drug effect, reflecting the natural course of the disease with or without a placebo effect; the reputation of the treating physician or the establishment he represents; and the culture and expectation of patients.[10] In chronic diseases such as migraine, prior treatment history may influence patients' expectation of the pain relief properties of drugs. The route of administration of a drug can also influence the relief response, possibly as an augmentation of the placebo effect.

Bigal and colleagues have reported that magnesium sulfate can reduce all symptoms in migraine with or without aura.[11] Other investigators have reported that a disturbance in magnesium ion homeostasis in the brain underlies the pathogenesis of migraine disease.[12] Literature reports indicate that 1 g intravenous magnesium sulfate is an efficient, safe, and well tolerated drug for the treatment of migraine attacks. It is possible that magnesium sulfate may be used in a broader spectrum of patients other than those in the acute attack phase.[13]

Our results are subject to certain limitations. We enrolled all patients presenting with migraine headache regardless of a prior history of migraine or any co-morbid conditions. We also did not ask about symptoms associated with migraine (such as photophobia or nausea) and relied exclusively on pain relief as the sole outcome measure. The study did not conduct follow-up assessments beyond 90 minutes, and the long-term beneficial of magnesium beyond this duration, if any, are unknown. For confirmation of our results, the effect of magnesium sulfate in acute migraine should be examined in large-scale studies.

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