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Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study

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1. We tested the hypothesis that patients with an acute attack of migraine headache and low serum levels (< 0.54 mmol/l) of ionized magnesium are more likely to respond to an intravenous infusion of magnesium sulphate ($MgSO_4$) than patients with higher serum ionized magnesium levels.
2. Serum ionized magnesium levels were drawn immediately before infusion of 1 g of $MgSO_4$ in 40 consecutive patients with an acute migraine headache.
3. Pain reduction of 50% or more as measured on a headache intensity verbal scale of 1 to 10, occurred within 15 min of infusion in 35 patients. In 21 patients, at least this degree of improvement or complete relief persisted for 24 h or more. Pain relief lasted at least 24 h in 18 of 21 patients (86%) with serum ionized magnesium levels below 0.54 mmol/l, and in 3 of 19 patients (16%) with ionized magnesium levels at or above 0.54 mmol/l ($P<0.001$). Mean ionized magnesium levels in patients with relief lasting for at least 24 h were significantly lower than in patients with no relief or brief relief ($P<0.01$).
4. Measurement of serum ionized magnesium levels may be useful in identifying patients with migraine headaches who may respond to an intravenous infusion of $MgSO_4$.

INTRODUCTION

Magnesium (Mg) deficiency has been implicated in the causation of migraine headaches on theoretical and experimental grounds [1–3]. Anecdotal observations [4, 5] and one double-blind, placebo-controlled trial [6] suggest that oral Mg supplementation is helpful in treating some patients with migraine headaches. One study [7] reported that total serum Mg (TMg) levels in patients with migraine and tension-type headaches were decreased more during an attack than between attacks. Two other studies [6, 8] showed normal TMg levels between migraine attacks. In one of these studies [8], decreased Mg concentration was found in erythrocytes, while in the other [6], Mg concentration in lymphocytes and polymorphonuclear cells was decreased but was normal in erythrocytes. Decreased Mg content in mononuclear cells in migraine patients with and without aura during an interictal period has also been reported [9]. One group [10] found that serum and intracellular Mg levels of patients with migraine with and without aura and familial hemiplegic migraine were not different from those of control subjects.

Mg in cells and blood (including plasma and serum) exists in free or ionized, bound and complex states; the total Mg consists of all three fractions. Recently, it has become possible to rapidly and accurately measure serum-free, ionized Mg (IMg^{2+}) which is the biologically active form of Mg [11, 12]. Using this method we have found significantly lower levels of IMg^{2+} but not TMg in patients with acute migraine headaches than in normal control subjects [13]. In this study we test the hypothesis that an intravenous infusion of magnesium sulphate ($MgSO_4$) will reduce headache pain in patients with an acute migraine headache who have low serum levels of IMg^{2+}.

METHODS

Forty consecutive patients (3 men and 37 women) who presented with an acute migraine but who did not have renal, cardiac or other medical problems were enrolled in this study after informed consent was obtained. The protocol was approved by our hospital's Institutional Review Board. Patients were told that some patients with headaches have been found to have lower Mg levels, and that this study attempts to establish whether giving an injection of Mg relieves headaches in such patients. They were also told that, since we did not want to bias the outcome of the study, we were giving Mg to all volunteers without prior knowledge of their Mg level. The diagnosis of acute migraine headache was established using the International Headache Society's classification [14]. Seven patients had

Key words: migraine, therapy, ionized magnesium, magnesium sulphate.
Abbreviations: ICa^{2+}, ionized calcium, IMg^{2+}, ionized magnesium; TMg, total serum magnesium.
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migraine with aura and 33 migraine without aura. Their mean age was 39.8 years (range 23–58 years).

Immediately before the Mg infusion a blood sample for serum IMg^{2+}, TMg and ionized calcium (ICa^{2+}) was drawn. The laboratory personnel and the physician were blinded to the study. The blood samples were not accompanied by any clinical information, and the clinician who administered the infusion received the laboratory results days after the headache treatment and evaluation were completed. Serum levels of IMg^{2+} and ICa^{2+} were measured using ion-selective electrodes with a NOVA Biomedical Stat Profile 8 Analyzer [11, 12]. TMg was determined with Kodak DT-60 Ektachem Analyzer. Percentage IMg^{2+} and ICa^{2+}/IMg^{2+} ratios were calculated.

One gram of $MgSO_4$ in a 10% solution was given intravenously over 5 min. Patients remained in a recumbent position during the infusion and for 5 min after the infusion. Headache intensity was measured on a verbal 1 to 10 scale before and 15 min after the infusion. The recurrence or worsening of a headache within the following 24 h was determined using the verbal 1 to 10 scale in a telephone interview. A greater than 50% reduction of pain intensity lasting at least 24 h was considered a positive response. The clinical response was correlated with the levels of IMg^{2+}, TMg and ICa^{2+}, and with percentage IMg^{2+} and ICa^{2+}/IMg^{2+} ratios. The clinical response was also categorized by levels of IMg^{2+} below and above 0.54 mmol/l, a level selected to maximize the difference between the groups.

Mean values ±SEM of laboratory measures were calculated and compared for statistical significance by analysis of co-variance and Tukey's honest difference contrast test, where appropriate. The difference in frequency of response was evaluated by exact contingency table analysis [15]. A P value <0.05 was considered significant. Correlations were obtained using the Spearman rank correlation coefficient. These data were also compared with identical data previously obtained from 60 normal control subjects [12].

RESULTS

All patients reported a flushed feeling during the infusion and 12 patients felt lightheaded for a few minutes upon sitting up after the infusion. No other side-effects were noted. Patients with positive responses expressed satisfaction with the degree and speed of relief of pain and migraine-associated symptoms.

Of the 40 patients, 35 (87.5%) had a reduction of pain of 50% or more 15 min after the infusion. This included nine patients who had complete relief. In 21 of these 35 patients, at least this degree of improvement or complete relief persisted for 24 h or more (positive response). Of these 21 patients with a

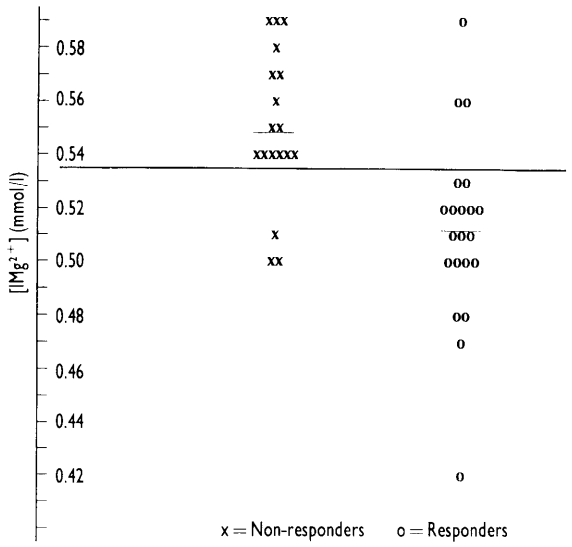

Fig. 1. Individual serum IMg^{2+} levels and means in patients with migraine headaches before magnesium infusions.

positive response, 18 had serum IMg^{2+} levels below 0.54 mmol/l. Of the 19 patients without a positive response, 16 had IMg^{2+} levels of 0.54 mmol/l or above (Fig. 1). Thus, 18 of 21 patients (86%) with a positive response and 3 of 19 patients (16%) without this response had IMg^{2+} levels of 0.54 mmol/l or below. The likelihood of experiencing significant relief among patients with IMg^{2+} levels below 0.54 mmol/l was 28 times greater than for patients with IMg^{2+} levels of 0.54 mmol/l or more (odds ratio = 27.9, $P<0.0001$, 95% confidence interval 5.4–194.4). The sensitivity and specificity of IMg^{2+} (above and below 0.54) in predicting response was 85%, as were the predictive values of a positive and negative test result. Table 1 shows mean laboratory values. Table 2 shows the difference in laboratory values between responders and non-responders adjusting for sex. Responders had significantly lower levels of IMg^{2+}. TMg levels were also lower in responders, but did not reach statistical significance ($P<0.071$) (Table 2). When normal control subjects were included, responders had significantly lower IMg^{2+} and TMg levels than either non-responders or control subjects (Fig. 2). ICa^{2+} levels were not significantly different in responders and non-responders or from values found in normal control subjects. Patients had a significantly higher mean ICa^{2+}/IMg^{2+} and lower percentage IMg^{2+} than normal control subjects. Within the responders and non-responders, correlations of IMg^{2+} with TMg and ICa^{2+} were similar (Table 3).

The mean duration of illness in responders was 210 months (range 6–624 months), while in non-responders it was 165 months (12–336 months). The mean duration of a usual attack in responders was 42 h (4–72 h) and 30 h (4–72 h) in non-responders. Mean attack frequency was 0.9 per week (once a year to three per week) in responders and 1.1 per

Table 1. Laboratory data on patients receiving an infusion of magnesium sulphate for the treatment of an acute migraine. Values are expressed as mean ± SEM. Statistical significance: *$P<0.0001$, **$P<0.001$, ***$P<0.01$ compared with control subjects; †$P<0.01$, compared with non-responders.

	N	IMg^{2+} (mmol/l)	ICa^{2+} (mmol/l)	TMg (mmol/l	IMg^{2+} (%)	ICa^{2+}/IMg^{2+}
Control subjects	66	0.60 ± 0.008	1.22 ± 0.008	0.82 ± 0.009	73.1 ± 0.62	2.03 ± 0.03
Responders	21	0.512 ± 0.008*†	1.23 ± 0.007	0.803 ± 0.019	63.9 ± 0.91*	2.41 ± 0.042†
Non-responders	19	0.549 ± 0.006***	1.23 ± 0.008	0.855 ± 0.015	64.5 ± 0.86*	2.25 ± 0.036**

Table 2. Analysis of co-variance of laboratory data adjusted according to sex

	Response			
	No	Yes	SE	*P*
IMg^{2+} (mmol/l)	0.542	0.505	0.0101	0.001
ICa^{2+} (mmol/l)	1.234	1.284	0.0096	0.986
TMg (mmol/l)	0.832	0.785	0.025	0.071
IMg^{2+} (%)	64.60	65.27	1.304	0.609
ICa^{2+}/IMg^{2+}	2.284	2.450	0.0533	0.004

week (once in 3 months to three per week) in non-responders.

DISCUSSION

Mg deficiency appears to be a common denominator in the leading theories of migraine pathogenesis. Current theories include vascular, 5-hydroxytryptamine and the lesser known theory of neurogenic inflammation [16]. Primary or secondary abnormalities in Mg metabolism could play a causative role in the genesis of migraine headache according to any of these theories, since Mg is involved in control of vascular tone [17, 18], regulation of function of 5-hydroxytryptamine [19] and *N*-methyl-*D*-aspartate receptors [20], nitric oxide production [21], substance *P* release [22] and catecholamine production and activity [23].

IMg^{2+} levels are known to affect entry of Ca^{2+}, intracellular ICa^{2+} levels and release of Ca^{2+} from sarcoplasmic and endoplasmic reticulum membranes in vascular muscle and vascular endothelial cells, which in turn control vascular tone and vascular reactivity to endogenous hormones and neurotransmitters [17, 18]. Cerebral blood vessel muscle cells are particularly sensitive to Mg; Mg deficiency results in contraction and potentiation of vasoconstrictors and excess Mg results in vasodilatation and inhibition of vasoconstrictors [17, 18].

5-Hydroxytryptamine is known to be released from platelets during a migraine attack, and to be a potent cerebral vasoconstrictor and to promote nausea and vomiting. A lowering of IMg^{2+} and an elevation of the ICa^{2+}/IMg^{2+} ratio may increase affinity for 5-hydroxytryptamine cerebral vascular muscle receptor sites, potentiate cerebral vasoconstriction induced by 5-hydroxytryptamine and facilitate 5-hydroxytryptamine release from neuronal storage sites [18, 19].

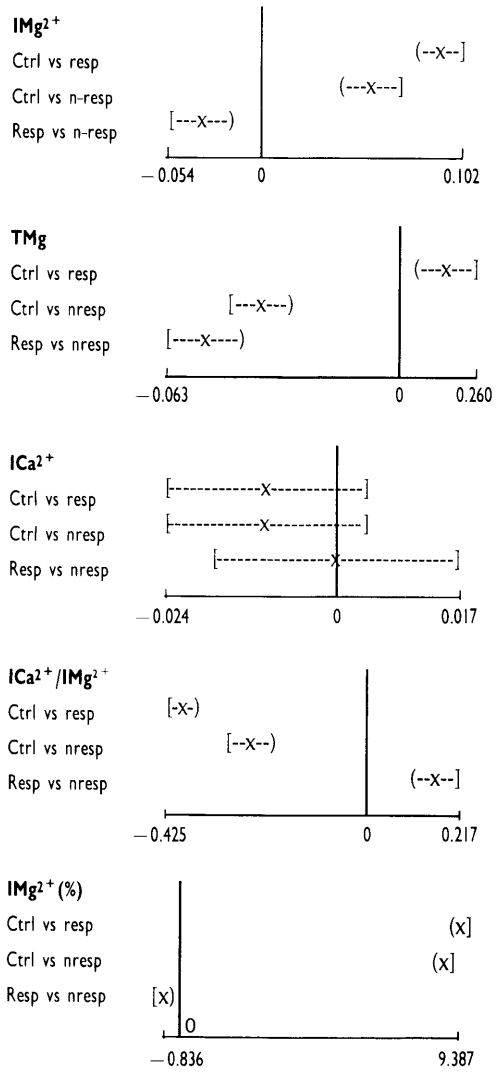

Fig. 2. Multiple comparisons of the difference in laboratory measures among control subjects, responders and non-responders using 95% confidence intervals. Abbreviations: Ctrl, control subjects; Resp, responders; Nresp, non-responders; ( ], width of interval.

A Mg-deficiency-induced state has recently been shown experimentally to result in significant generation and release of substance *P* into the bloodstream [22] and according to the neurogenic inflammation theory of migraine, pain in headache results from the action of substance *P* on sensory fibres [16].

There are several limitations in the present study. It was not a randomized double-blind study, there-

Table 3. Spearman rank correlations of laboratory measures in patients with and without a positive response. Statistical significance: $^*P<0.01$.

	Responders		Non-responders	
	IMg^{2+}	TMg	IMg^{2+}	TMg
IMg^{2+}	—	—	—	—
TMg	0.63*	—	0.64*	—
ICa^{2+}	-0.28	-0.20	-0.37	-0.12

fore there were no concurrent controls for comparison. However, the focus of our hypothesis was on the differential response to IMg^{2+} levels. Furthermore, laboratory personnel were blinded to all of the clinical data, and the clinician received laboratory results only after the completion of all treatments and evaluations. Thus, any placebo effect should have played an equal role in all patients.

There was a very strong relationship between headache reduction and low IMg^{2+}. Patients with low IMg^{2+} were 28 times more likely to respond than those with high IMg^{2+} ($P<0.01$). However, this number probably overstates the magnitude of the association since the breakpoint of 0.54 mmol/l was selected to maximize the difference. We justified this *post-hoc* selection by the fact that this was the first study of its kind. Furthermore, there does appear to be a natural break in the distribution of the IMg^{2+} levels and we do know, on the basis of evaluation of several hundred patients with other diseases [12] that IMg^{2+} levels below 0.54 mmol/l are most probably abnormal.

The sustained relief in 3 of 19 patients with high IMg^{2+} levels may reflect the placebo effect, which has been described in up to 45% of patients with migraine headaches. Lack of significant headache reduction in 3 of 21 patients with lower IMg^{2+} levels might be attributed to the probable multiple mechanisms involved in migraine headache causation. The predominance of women in our study exceeds what would be expected of the known distribution of migraine sufferers by sex. However, this reflects our patient population. It is an established fact that a higher proportion of women than men seek medical attention.

In conclusion, our findings suggest that Mg metabolism is disturbed in at least some patients with migraine headaches, and that infusion of 1 g of $MgSO_4$ relieves acute migraine attacks in patients with serum IMg^{2+} levels below 0.54 mmol/l. Since an IMg^{2+} level below or above 0.54 mmol/l correctly predicted 85% of the subjects who did and did not benefit from intervention, this may be a clinically useful screening approach. Randomized, double-blind, placebo-controlled trials of Mg infusions for migraine headaches need to be performed.

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