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Jasna Zidverc-Trajković
Aleksandra M. Pavlović
Zagorka Jovanović
Nadežda Šternić
Vladimir S. Kostić

Efficacy of intravenous magnesium sulfate in severe migraine attacks

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J. Zidverc-Trajković • A.M. Pavlović
Z. Jovanović • N. Šternić • V.S. Kostić (✉)
Institute of Neurology,
Clinical Center of Serbia,
Ul. Dr Subotića 6,
Y-11000 Belgrade, Yugoslavia
e-mail: kostic@imi.bg.ac.yu
Tel.: +381-11-685554
Fax: +381-11-684577

Abstract The aim of this open study was to make a preliminary estimate of the efficacy and tolerability of intravenously administered magnesium sulfate (1 g) in comparison to subcutaneously administered sumatriptan in the treatment of severe migraine attacks. The study comprised 22 consecutive patients whose attacks were treated with magnesium sulfate (5 ml of a 20% solution), and the results were compared with those of another group of 14 consecutive patients whose attacks were treated with sumatriptan (6 mg). Immediately before and 10, 20 and 30 minutes after injections, patients reported pain intensity on a verbal 0–10 scale. Pain disappearance or pain relief >50% were considered significant. Efficacy of sumatriptan was superior that of to magnesium sulfate 20 minutes after the injections ($p<0.05$) and comparable after 30 minutes (magnesium therapy was successful in 68% in comparison to 79% of patients treated with sumatriptan). After only 10 minutes, 3 patients treated with magnesium sulfate were pain free, with the same effect in 5 (22.5%) and 10 (45%) patients after 20 and 30 minutes, respectively. The rate of headache recurrence was low and no major adverse effects were recorded. In conclusion, magnesium sulfate may be a well-tolerated pharmacological alternative for the treatment of severe migraine attacks.

Key words Migraine • Magnesium • Acute treatment

Introduction

A possible link between magnesium deficiency and some types of headache, particularly migraine, has long been suggested. In 1976, Durlach [1] found increased concentration of magnesium in the urine of migraine patients and presumed it to be a result of a transitory serum magnesium decrease in migraine attack. This hypothesis was further corroborated by the observations that in migraine patients intracellular magnesium was reduced during attacks in the brain [2], serum [3, 4] and saliva [4], and between attacks in blood [5], erythrocytes, mononuclear cells [6, 7] and cerebrospinal fluid [8]. However, several studies did not confirm these findings [9, 10]. Therefore, Ferrari and Bach [11] concluded that although "no consistent pattern can be detected with respect to circulating magnesium levels in migraine patients", magnesium in the brain might be involved in migraine pathophysiology.

Several trials of intravenously administered magnesium in the treatment of headache attacks (including migraine) were conducted with a wide spectrum of results, ranging from very enthusiastic [12–14] to highly disappointing [15]. Therefore, the aim of this open study was to estimate the efficacy of intravenous magnesium sulfate (1 g) in the treatment of severe migraine attacks.

Patients and methods

The study comprised 22 consecutive patients with migraine (diagnosed according to criteria of the International Headache Society), whose attacks were treated with magnesium sulfate administered intravenously at the Institute of Neurology CCS, Belgrade. Their results were compared with that of another group of 14 consecutive patients with migraine whose attacks were treated with sumatriptan (6 mg subcutaneously). Demographic and clinical characteristics of both groups are presented on Table 1.

Treatment was applied for a single attack of migraine in each patient. The patients reported pain intensity using the verbal 0–10 scale [9], and only the patients with severe migraine attacks (headache intensity ≥8) were included in the study. The duration of pain before administration of the aforementioned drugs was less than 90 min in all patients.

The migraine attacks in the first group were treated with 5 ml 20% solution of magnesium sulfate, given intravenously for 3–5 min, after obtaining informed and written consent. The pain intensities were recorded before the treatment and in the intervals of 10, 20 and 30 min after the administration of magnesium. The adverse effects and headache recurrence were also recorded. Pain disappearance or pain relief >50% were considered to be significant responses. The number of migraine attacks per month and duration of migraine in years were recorded for each patient.

t Test for independent samples, chi-square and Kruskal-Wallis tests were used to compare clinical characteristics of these two groups.

Results

At 30 min after dosing, intravenous magnesium therapy was effective in 68% of patients with severe migraine attack while sumatriptan was effective in 79% (Table 2). The efficacy of sumatriptan was superior to that of magnesium sulfate 20 min after injection ($p<0.05$), while the 2 drugs were comparable after 30 min. After only 10 min, 3 patients treated with magnesium sulfate were pain free, with the same effect in 5 (22.5%) and 10 (45%) patients after 20 and 30 min, respectively. Interestingly, patients without pain after the treatment with either magnesium or sumatriptan were

Table 1 Demographic and clinical characteristics of patients with migraine

	Magnesium sulfate treatment (n=22)	Sumatriptan treatment (n=14)
Men, n (%)	17 (77)	10 (71)
Age, years [a]	33.7 (10.6)	36.6 (6.4)
Duration of disease, years [a]	13.7 (8.1)	13.4 (3.0)
Migraine aura, n (%)	2 (9)	3 (21)
Attacks per month, n[a]	3.4 (2.5)	4.9 (1.4)
Intensity of pain (0-10)[a]	8.9 (1.4)	8.8 (0.3)

[a] Values are means (SD)
* $p<0.05$ vs. treatment with sumatriptan

Table 2 Treatment efficacy over the course of 60 minutes in migraine patients from two studied groups: (a) those treated intravenously with magnesium sulfate (n=22; magnesium group); and (b) those treated subcutaneously with sumatriptan (n=14; sumatriptan group)

Time after injection	No response, n (%)	Pain intensity <50%, n (%)	Without pain, n (%)
10 minutes			
Magnesium group	16 (73)	3 (14)	3 (14)
Sumatriptan group	10 (71)	3 (21)	1 (7)
20 minutes			
Magnesium group*	16 (73)	1 (5)	5 (23)
Sumatriptan group	6 (43)	5 (36)	3 (21)
30 minutes			
Magnesium group	7 (32)	5 (23)	10 (45)
Sumatriptan group	4 (29)	3 (21)	7 (50)
60 minutes			
Magnesium group*	9 (41)	6 (27)	7 (32)
Sumatriptan group	3 (21)	3 (21)	8 (57)

* $p<0.05$ vs. sumatriptan group

Table 3 Treatment efficacy in resolving different associated symptoms over the course of 60 minutes in migraine patients from two studied groups: (a) those treated intravenously with magnesium sulfate (n=22; magnesium group); and (b) those treated subcutaneously with sumatriptan (n=14; sumatriptan group)

Time after injection	Nausea	Vomiting	Photo/phonophobia
Patients with a specific associated symptom before treatment, n (%)			
Magnesium group	17 (77)	12 (55)	13 (59)
Sumatriptan group	12 (86)	8 (57)	8 (57)
Patients whose specific symptom resolved after treatment, n (%)			
10 minutes			
Magnesium group	6/17 (35)	3/12 (25)	4/13 (31)
Sumatriptan group	4/12 (33)	3/8 (38)	4/8 (50)
20 minutes			
Magnesium group	6/17 (35)	7/12 (58)	8/13 (62)
Sumatriptan group	7/12 (58)	7/8 (88)	5/8 (63)
30 minutes			
Magnesium group	12/17 (71)	9/12 (75)	8/13 (62)
Sumatriptan group	9/12 (75)	7/8 (88)	5/8 (63)
60 minutes			
Magnesium group	11/17 (65)	10/12 (83)	10/13 (77)
Sumatriptan group	9/12 (75)	7/8 (88)	6/8 (75)

also without accompanying symptoms (e.g. nausea, vomiting, photo- and phonophobia) in the same time pattern (Table 3). Unfortunately, we were unable to accurately address the effect of treatment on functional impairment, since we treated only one attack, but no difference in this dimension was observed between the groups.

Except for a moderate sensation of warmth at the site of the intravenous injection in all patients and palpitations in one patient treated with magnesium sulfate, other adverse effects were not present. In the group treated with sumatriptan, transitory (duration, <45 min) and mild adverse effects were observed in 4 patients (28%): two patients had dizziness; one had global weakness, and one abdominal pain.

Three patients (13.5%) successfully treated with magnesium had headache recurrence in the course of 24 hours from the initial pain relief in comparison to 4 (28%) patients treated with sumatriptan. However, the mean time interval to the development of recurrent headache was shorter in those treated with magnesium (3 hours) than in patients on sumatriptan (11 hours). They were all successfully treated again with the initial drugs. No difference in demographic and clinical characteristics was observed among responders and non-responders to magnesium injections.

Discussion

According to the results obtained in our patients, intravenous treatment with l g magnesium sulfate was successful in 68% of patients with severe migraine attacks and had an efficacy comparable to that of sumatriptan. The rate of headache recurrence was low and no major adverse effects were recorded. However, according to the observation on the limited number of patients, recurrent headaches occurred earlier with magnesium than with sumatriptan treatment. Our results are in accordance with those of Mauskop et al. [12, 13], who reported successful headache relief with the intravenous magnesium treatment in 80% of patients with various types of headache. In the first of two double-blind, randomized studies of intravenous magnesium treatment, comparison of the efficacies of prochlorperazine and magnesium sulfate revealed a moderate magnesium efficacy (56%) in acute headache treatment [14]. However, in the second trial, Corbo et al. [15] found that intravenous administration of magnesium sulfate (2 g) did not appear to be an effective therapeutic adjunct for acute migraine when added to metoclopramide. Moreover, according to their data, magnesium may even attenuate the therapeutic impact of metoclopramide in relieving migraine. In the present open trial, we used magnesium sulfate as a monotherapy in comparison to sumatriptan to obtain the preliminary estimates of its efficacy. Also, we focused on the speed of magnesium action. Major effects appeared 20 min after intravenous administration.

Due to the small number of treated patients, we did not observe any difference in the clinical characteristics of magnesium responders and non-responders, and could not identify those patients who would benefit from magnesium treatment. Mauskop et al. [12] reported a better response to magnesium treatment in patients with low magnesium serum

concentrations. Contrasting results from the study Ginder et al. [14] showed that the response to magnesium sulfate was unrelated to the serum magnesium levels. It is possible that other factors may determine the therapeutic response in a particular patient.

The suggestion that reduced intracellular magnesium during migraine attacks in the brain [2] and serum [3, 4] may be involved in migraine pathophysiology was further strengthened by the finding of reduced magnesium concentration in the cortex during migraine attack, using ^{31}P magnetic resonance spectroscopy [16]. Such a reduction may potentiate the sensitivity of the *N*-methyl-D-aspartate (NMDA) receptors to neuroexcitatory amino acids. These receptors play an essential role in the initiation, propagation, and duration of spreading depression, which is implicated in the mechanisms of migraine [17]. Low magnesium levels potentiate and high levels inhibit the sensitivity of the NMDA receptors to glutamate [18], whose excessive oral intake may induce migraine-like headaches in sensitive subjects [19].

In conclusion, intravenous magnesium sulfate may be one of the possible, well-tolerated pharmacological alternatives for the treatment of severe migraine attacks. However, to establish the rationale for its use in migraine treatment, further controlled clinical trials are needed.

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