

The effects of magnesium prophylaxis in migraine without aura

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Abstract. There are inconsistent findings about the efficacy of magnesium in the prophylaxis of migraine attacks and there is no study of magnesium prophylaxis focused on migraine subtypes without aura. In this double blind, randomized, placebo controlled study; we tried to evaluate the prophylactic effects of oral magnesium in migraine patients without aura. The prophylactic effects of 600 mg/day oral magnesium citrate supplementation were assessed by means of clinical evaluation, visual evoked potential and statistical parametric mapping of brain single photon emission computerized tomography before and after a 3 month treatment period. The results of 30 patients with migraine without aura (20-55 years old with 2-5 migraine attacks per month) on magnesium treatment were compared with those of 10 patients with similar properties on placebo treatment. Migraine attack frequency, severity and P1 amplitude in visual evoked potential examination decreased after magnesium treatment with respect to pretreatment values ($p < 0.001$). In a comparison of the effects of magnesium treatment with those of placebo, post/pretreatment ratios of migraine attack frequency, severity and P1 amplitude in Mg treatment group were found to be significantly lower than those in placebo treatment group (attack frequency $p = 0.005$, attack severity $p < 0.001$, P1 amplitude $p < 0.05$). Cortical blood flow in inferolateral frontal ($p < 0.001$), inferolateral temporal ($p = 0.001$) and insular regions ($p < 0.01$) increased significantly after magnesium treatment with respect to the pretreatment; while such significant changes of cortical blood flow were not observed with placebo treatment. These results have made us think that magnesium is a beneficial agent in prophylaxis of migraine without aura and might work with both vascular and neurogenic mechanisms.

Key words: migraine without aura, magnesium, prophylaxis

Magnesium (Mg) is an essential intracellular cation and is involved in numerous physiological processes [1]. Based on previous studies showing evidence of reduction in Mg levels in patients with migraine, Mg deficiency may play an important role in migraine pathogenesis [2-5]. Low levels of Mg induce cerebral arterial vasoconstriction, increase the aggregation of platelets and thus promote serotonin release, potentiate the vasoactive action of serotonin [6] and reduce the effect of prostacyclin mediated relaxation of vascular smooth muscle [7]. Additionally, reduced Mg levels enhance the sensitiv-

ity of N-methyl-D-aspartate (NMDA) receptors to glutamate, facilitating the development of cortical spreading depression [8].

Besides the studies reporting low Mg levels in migraine patients, at least 4 randomized controlled trials of magnesium as a prophylactic therapy for migraine [9-12] have been conducted. These published trials have yielded mixed results and do not focus on migraine subtypes without aura.

In this study, we tried to evaluate the prophylactic effects of 600 mg/day oral magnesium citrate supplementation in patients with migraine without aura.

For this purpose, before and after the Mg treatment, we performed clinical evaluation and electrophysiological assessments comprising Visual Evoked Potential (VEP) and brain Single Photon Emission Computerized Tomography (SPECT), considering their relation with the neurogenic and vascular theories of migraine pathogenesis. In the analysis of SPECT images, instead of traditional methods like visual inspection and region of interest (ROI) technique, statistical parametric mapping (SPM) was used.

Materials and methods

Patient and control groups

This double blind, randomized, placebo controlled study was conducted in Erciyes University, Neurology-Headache Outpatient Clinic and Nuclear Medicine Department. From 40 patients, 20-55 years old, and with at least 2 years of migraine without aura, according to the criteria of International Headache Society [13], 30 patients were allocated as Mg treatment group and 10 patients as placebo treatment group, by using a simple randomization method. Instead of an equal splitting of the patient group into the two treatment groups, we enrolled only 10 patients for the placebo treatment group; for ethical reasons, we wanted fewer patients to be without the active treatment. The Mg treatment group consisted of 30 patients (4 men, 26 women) 20-55 years old age (Mean \pm SD: 36.6 ± 9.3 years) and at least 2 years of disease duration (Mean \pm SD: 5.6 ± 3.9 years) and 2-5 migraine attacks per month (Mean \pm SD: 3.5 ± 8.2) in the previous month. The placebo treatment group consisted of 1 male, 9 female patients (age median: 43.5, min-max: 28-50 years; duration of disease median: 5.0, min-max: 2-14 years; migraine attacks per month median: 3.5, min-max: 2-5). There were no significant differences in the distributions of age, sex, duration of disease, migraine attack frequency between the Mg treatment group and the placebo treatment group ($p > 0.05$). Twenty healthy persons were selected by using a simple randomization method from 500 healthy people with similar ages to the patient group, attending a local primary health center, and were enrolled as a control group for Visual Evoked Potential (VEP) examination. The healthy control group consisted of 3 males and 17 females with mean age of 35.3 years (SD: 10.6 years). The distributions of age and sex in the control group were not different from those of the patients ($p > 0.05$). The study was conducted in accordance with the Declaration of Helsinki. The study design was approved by Investigational

Review Board and Ethics Committee of Erciyes University. All patients and control subjects gave their written informed consent.

Exclusion criteria were contraindication to magnesium therapy (*e.g.* renal failure, nephrolithiasis); pregnancy or planned pregnancy; breast feeding women; menstrual migraine [14]; non migraine headache; dependence or abuse of drugs; psychiatric or chronic systemic illness; foreseeable poor compliance; intake of antidepressants, neuroleptics, minor or major tranquilizers, drugs used for the treatment of affective disorders (*e.g.* lithium, carbamazepine) and for headache prophylaxis (*e.g.* beta receptor blockers, calcium antagonists) within last 3 months. All medicines containing Mg were forbidden in the 4 weeks before baseline and were not permitted throughout the study. Patients on a migraine prophylactic drug treatment underwent a washout period of at least 3 months before admission into the study. During the study, simple analgesics or drugs for treatment of migraine attacks were not allowed to be taken on more than 10 days per month. The patients used the same preparations during the study as they had used before.

Migraine attacks of the patients were investigated before and during Mg or placebo treatment including the relationship to menstruation in female patients. All patients were asked to keep a headache diary during the entire study period, starting 4 weeks before the beginning of the treatment period, and to record the number, intensity and duration of the attacks as well as the dose of the acute medications and any adverse events. All patients were asked to keep a headache diary during the entire study period and to record the number, intensity and duration of the attacks as well as the dose of acute medications and any adverse events. But we evaluated only the number, intensity of the attacks and adverse events, for these parameters were recorded certainly and reliably by the patients, while the others were recorded unreliably.

The average intensity of the attacks were recorded using a 10 cm Visual Analogue Scale (VAS) with the poles 0 (no pain) and 10 (unbearable pain). Mg treatment was performed with magnesium citrate (Magnesium-Diasporal® 300 granules sachet, Protina GmbH, Germany) in the form of a water soluble granulate sachet. The sachet, containing 1 830 mg Mg citrate ($295.7 \text{ mg} = 12.2 \text{ mmol} = 24.4 \text{ mval Mg}$), was given twice a day, every morning and evening. So the patients belonging to Mg treatment group received approximately 600 mg ($24 \text{ mmol} = 48 \text{ mval}$) Mg per day for 3 months.

The patients underwent examinations of VEP and cerebral SPECT imagings before and after the 3 month period of Mg or placebo treatment, at least 7 days after the last migraine attack. Control subjects underwent Visual Evoked Potential (VEP) examination once.

Visual Evoked Potential (VEP) study

VEP recordings were performed by the same technician in standard conditions (in a quiet room with dimmed light, patients seated in an armchair, 1 m in front of a television monitor with 240 cd/m² mean luminance). Stimuli were presented on a 17" monitor viewed at 1 m as a checkerboard pattern of black and white squares subtending 1° of arc (contrast 100%) at a reversal frequency of 2 Hz. With one eye patched, subjects were instructed to fixate on a point in the middle of the screen. The active electrode (Oz) was an silver chloride electrode placed on the scalp in the midline over the occipital region, 5 cm above theinion. The reference electrode (Fz) was in the mid frontal line and the grounding electrode was at the vertex (Cz). The bandwidth was 1 Hz to 100 Hz. During uninterrupted stimulation, 2 blocks of 100 responses were averaged on each eye. Analysis time was 250 msec. The amplitudes (N1-P1) and latencies of P1 were noted.

Brain SPECT imaging

SPECT imagings of the patients were performed using a maximal dose of 500 MBq ^{99m}Tc-HMPAO (Ceretek; Amersham, International plc, UK) in supine resting position with closed eyes. The radiotracer was prepared according to the manufacturer's instructions and injected within 10 min after labeling. Image acquisition began approximately 20 min after the injection. A 360° rotating single head camera system (Toshiba GCA 602 A/SA, Japan) equipped with a low energy all purpose collimator interfaced to a Toshiba computer system was used to acquire the projection data. Each subject's head was held in a plastic holder during scanning to prevent movements. Data were obtained in 64 x 64 pixel matrices at 6° intervals, for 30 s per arc interval. The corresponding pixel size was 5.5 mm. Reconstruction was performed by filtered back-projection by using a Butterworth filter (cut off frequency 0.25, power factor 8). The images were reoriented to obtain transaxial slices parallel to the orbitomeatal line.

In the analysis of SPECT images, instead of traditional methods like visual inspection and ROI technique, SPM was used. It offered objective, quantitative voxel by voxel analysis; avoiding the

preselection of samples depending on the observer's *a priori* hypothesis [15]. Recently, it has evolved and become accepted in activation and structural studies of the brain [16].

The raw image files were read into an automated 3D image analysis software package (MEDX, Sensor) and subsequently saved in the format of ANALYZE files. These files were then imported into the SPM 2 (2005 version). In SPM, the data was transformed into a standard stereotactic three dimensional space defined by Talairach and Tournoux [17]. The scans were then smoothed using a Gaussian filter with a kernel of 12 mm full width half maximum (FWHM) to improve the signal-to-noise ratio and to reduce errors attributed to interindividual variation in gyral and sulcal anatomy. The gray matter threshold was set to 0.5. Voxel size was 2 x 2 x 2 mm.

Evaluation and statistics

Statistical Products Solution Service (SPSS) software, version 10.0 was used for statistical analysis. The study groups were compared with each other with respect to the properties like age, gender, duration of disease and frequency of attacks by using the t test for independent groups, Mann Whitney U test or χ^2 test (for gender) as appropriate. In the Mg treatment group and placebo treatment group, to compare the pre and post treatment values of clinical and VEP parameters; the t test for dependent groups or Wilcoxon test was used according to the presence of parametric or nonparametric conditions respectively. To compare the pretreatment values of VEP parameters in the patient groups under Mg treatment and placebo treatment with the values of the control group, the t test for independent groups or the Mann Whitney U test was used, as suitable to the presence of parametric or nonparametric conditions respectively. For the comparisons of post to pretreatment ratios of clinical and VEP parameters between the Mg treatment group and placebo treatment group, the Mann Whitney U test was used. In these statistical evaluations, $p < 0.05$ values were considered as significant.

As a method of SPM analysis, a general linear model was used to compare each voxel within each image data set and then the theory of Gaussian field was used to make statistical inferences about the regional effects. To eliminate the effects of age and gender, they were taken as cofactors. SPECT images were compared by means of voxel by voxel contrasts using t statistics for dependent groups to compare pre and post treatment images of the patients under

treatment of Mg or placebo. The extent threshold was taken as 50 voxels.

The resulting sets of t values for each contrast constituted a statistical parametric map $SPM(t)$. The $SPM(t)$ map was transformed into units of normal distribution ($SPM(z)$), where the significance of each region was estimated with a threshold of uncorrected $p < 0.01$.

Results

When frequencies and severities of migraine attacks in the last one month period just prior to the beginning and ending of the treatment were evaluated; both parameters were found to be decreased ($p < 0.001$) after the Mg treatment, while only the frequency of attacks decreased significantly ($p < 0.05$) after the treatment with placebo (*table 1*). Four patients (10%) reported either diarrhea or soft stools within the first 4 weeks of Mg treatment, lasting 5-7 days. Two patients (5%) complained of gastric irritation. None of the side effects caused discontinuation of the treatment.

We first compared VEP latencies and amplitudes between the right and left eyes in each patient prior to

the treatment and in each healthy control subject. Because t -test revealed non significant differences between the two eyes, we subsequently calculated mean values from both eyes for each subject. We found that amplitudes were higher ($p < 0.001$) and latencies were longer ($p < 0.05$) in migraine patient group prior to the treatment (P1 amplitude, Mean \pm SD = 5.98 ± 0.98 μ volt; P1 latency, Mean \pm SD = 100.55 ± 3.91 msec) than those in healthy control group (P1 amplitude, Mean \pm SD = 4.58 ± 1.01 μ volt; P1 latency, Mean \pm SD = 98.19 ± 3.68 msec). After the treatment with Mg, the amplitudes were observed to be significantly lower ($p < 0.001$) in comparison to the pretreatment levels (*table 2*). However, the latencies did not show any significant change between pre and post treatment evaluations. In the placebo treatment group, none of VEP parameters changed significantly with treatment (*table 2*).

When the effects of Mg treatment in comparison to placebo were evaluated by means of post/pretreatment ratios of clinical and VEP parameters, all of the ratios were found to be significantly lower (ratio for attack frequency $p = 0.005$, ratio for attack severity $p < 0.001$, ratio for P1 amplitude $p < 0.05$) in the Mg treatment group as compared to the placebo

Table 1. The effect of the treatment (Mg and placebo) on attack frequency, and attack severity in Visual Analogue Scale (VAS) score.

	Before treatment	After treatment	p
Mg treatment group attack frequency Median (min-max)	3.0 (2-5)	2.0 (0-3)	< 0.001
Mg treatment group VAS score Mean \pm SD	7.57 \pm 0.86	4.00 \pm 1.53	< 0.001
Placebo treatment group attack frequency Median (min-max)	3.5 (2-5)	3.0 (2-5)	< 0.05
Placebo treatment group VAS score Median (min-max)	7.0 (6-8)	7.0 (5-8)	> 0.05

Mg treatment group n = 30 Placebo treatment group n = 10.

The average intensity of the attacks were recorded using a 10 cm Visual Analogue Scale (VAS).

Table 2. Visual Evoked Potential parameters of the patients before and after the treatment.

	Before treatment	After treatment	p
Mg treatment group P1 amplitude (μ volt) Mean \pm SD	5.98 \pm 0.98	5.62 \pm 0.87	< 0.005
Mg treatment group P1 latency (msec) Mean \pm SD	100.55 \pm 3.91	100.17 \pm 1.89	> 0.05
Placebo treatment group P1amplitude (μ volt) Median (min-max)	5.85 (4.0-7.2)	5.65 (4.2-6.8)	> 0.05
Placebo treatment group P1 latency (msec) Median (min-max)	102.00 (91-105)	101.70 (93-105)	> 0.05

Mg treatment group n = 30, Placebo treatment group n = 10.

Table 3. Post/pretreatment ratios of attack frequency, attack severity, P1 amplitude and P1 latency in patients under treatments of Mg and placebo.

	Mg treatment group Median (min-max)	Placebo treatment group Median (min-max)	p
Attack frequency 2/1	0.55 (0.00-1.00)	1.00 (0.67-1.00)	= 0.005
Attack severity 2/1	0.57 (0.00-0.71)	1.00 (0.83-1.17)	< 0.001
P1 amplitude 2/1	0.95 (0.73-1.11)	1.02 (0.92-1.11)	< 0.05
P1 latency 2/1	0.98 (0.97-1.09)	0.99 (0.96-1.03)	> 0.05

2/1: the ratio of post to pretreatment value.

treatment group, showing more beneficial effects of the treatment with Mg (table 3).

On the comparison between SPECT SPM results of the patients before and after the treatment, we found that blood flow in insula and inferolateral frontal cortex on right hemisphere and in inferolateral temporal cortex on left hemisphere increased significantly after the treatment with Mg (table 4, figure 1). In the placebo treatment group, no significant difference in blood flow was observed as a result of the treatment.

Discussion

This is a study trying to evaluate the potential beneficial effects of Mg in the prophylaxis of migraine without aura. In this evaluation, in addition to the clinical assessment, possible vascular and neurogenic mechanisms of action are assessed with brain SPECT and VEP respectively. As a result, Mg prophylaxis in patients with migraine without aura is found to be clinically beneficial; and might work with both vascular and neurogenic mechanisms.

Intravenous Mg was reported to be useful in acute treatment of migraine, especially of migraine with aura [18-20]. The first randomised controlled trial of Mg for migraine prevention involved only 20 menstrual migraine patients and was positive; the active therapy was 360 mg Mg pyrrolidone carboxylic acid divided TID [9]. The second randomised controlled

trial by Peikert *et al.* involved 81 adult women and 600 mg (24 mmol) Mg (trimagnesium dicitrate) daily demonstrated a 41.6% reduction in attack frequency with verum versus 15.8% for placebo ($p < 0.05$) [10]. Duration and intensity of the attacks also tended to decrease as compared to placebo but failed to be significant. The third randomised controlled trial for migraine prophylaxis, published by Pfafferath *et al.* [11] involved 69 patients taking 486 mg (20 mmol) Mg; no benefit for Mg as compared to placebo was found; at the end of the 3-month treatment phase, the responder rate was 28.6% in the Mg group and 29.4% in placebo subjects, according to the primary efficacy end point (at least 50% reduction of migraine duration in hours or intensity of migraine). Diarrhea was reported in significant numbers of both patients receiving placebo (23.5%) and patients receiving Mg (45.7%); the high rate in the active arms suggests that a poorly absorbed Mg preparation lent to the negative outcome [10, 21]. In the last trial; Wang *et al.* gave 9 mg/kg Mg oxide divided TID to subjects aged 3 to 17 years [12]. Approximately three-quarters of eligible subjects completed the study, with a significant downward trend in headache days in the active treatment group versus placebo. The lack of any difference in the slope of treatment trends, however, was such that no significant superiority of Mg over placebo could be documented. Due to inconsistent findings from multiple trials, the evidence level for Mg in prevention of

Table 4. Localization of significant increase in regional cerebral blood flow after Mg treatment as compared to pretreatment.

Structure	Brodman's area	Voxel p (uncorrected)	Voxel p (FDR corrected)	Voxel t	Talairach coordinates x,y,z (mm)
Right inferolateral frontal cortex	47	< 0.001	0.767	4.26	26, 12, -22
Left inferolateral temporal cortex	37	0.001	0.767	3.66	-48, -58, -20
Right insula	13	< 0.01	0.767	3.14	42, -16, -4

FDR: false discovery rate.

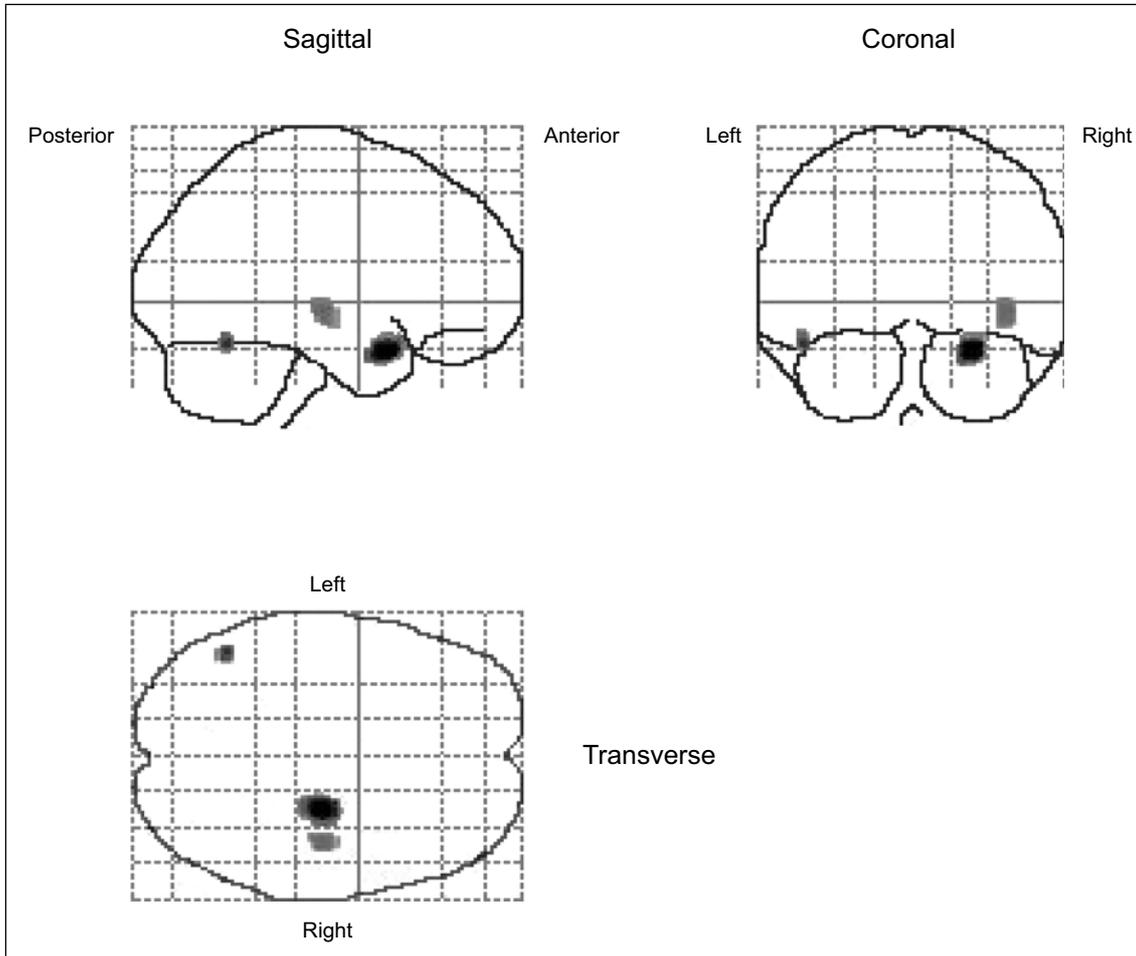


Figure 1. Statistical parametric brain mapping showing regions with significantly increased blood flow after Mg treatment as compared to pretreatment (uncorrected $p < 0.01$).

migraine is accepted as Grade B [22]. In these studies, the evaluations were performed in all migraine patients regardless of the types of migraine.

In our study, we used the same Mg formulation and the same dosage as in the study of Peikert *et al.* [10]; which we mentioned in the previous paragraph. In our study, we found approximately 33 and 47% reduction in attack frequency and intensity respectively. The difference between our results and those of Peikert *et al.* might come from the differences in the study populations of the studies. Their study involved migraine patients with and without aura, while our study involved only patients without aura. When we compared the post/pretreatment ratios of the Mg treatment group with those of the placebo treatment group,

we found the ratios related to attack frequency and severity in the Mg treatment group significantly lower (attack frequency $p = 0.005$, attack severity $p < 0.001$) as compared to the placebo treatment group, showing the beneficial effect of Mg.

Spreatico *et al.* in their study [23] with 53 migraine patients (21 on prophylactic migraine treatment and 32 not on any prophylactic treatment of migraine) and 20 healthy control subjects found that migraine patients who were not on any prophylactic treatment presented lower P1 latencies in VEP study as compared to healthy control subjects, and the P1 latencies of migraine patients on prophylactic migraine treatment showed the same trend as seen in the control group. They did not mention P1 amplitudes

in their results. The drugs used in prophylaxis were beta blockers, antiepileptic drugs, 5 HT receptor antagonists, calcium channel blockers and antidepressants.

Aloisi *et al.* in their study [24] in juvenile migraine patients found an inverse correlation between increased P1 amplitude and lowered serum Mg levels in headache free period. They observed a statistically larger amplitude and shorter latency of P1 in migraine patients as compared to healthy control subjects at the basal evaluation. After a 20 day treatment with oral Mg pidolate, P1 latency did not change significantly, but amplitude was significantly reduced as compared to the pretreatment level.

Diener *et al.* [25] observed that VEP amplitudes were larger and latencies were higher in patients with migraine at interictal periods as compared to healthy control subjects, as in our findings. They found a significant decrease in VEP amplitude in migraine patients after the treatment with beta blocking agents. But this effect was not related to the effectiveness of the drug in migraine prophylaxis, because nonresponders also showed a significant decrease in VEP amplitude during treatment. The VEP amplitudes of nonresponders returned to initial levels in the follow up period without prophylactic treatment, whereas those of responders remained reduced. In a similar way, we found a significant decrease of VEP amplitude in migraine after the treatment with Mg. Additionally, we found that the post/pretreatment ratio of VEP amplitude was significantly lower in the Mg treatment group as compared with that of the placebo treatment group.

The treatment effect on VEP latencies and amplitudes of migraine patients was found to be mostly an amplitude decrease, as mentioned above. Our study ended up with a similar result. We found that the VEP amplitudes of the patients approximated to the values of normal persons after the treatment with Mg. We thought that the decrease of amplitude with the treatment might be related to a lowering of the cortical or visual system hyperexcitability or a decrease of possibly potentiated amplitudes in our patients, who had had frequent attacks prior to the prophylactic treatment.

Migraine represents the classic primary headache that has been considered to have vascular problems [26]. The pathophysiological concept of vascular headaches is based on the idea that changes in vessel diameter or gross changes in cerebral blood flow trigger pain and can, in part, explain the mechanism of action of vasoconstrictor drugs. From a physiological viewpoint, the concept of a vascular headache as a pathophysiological entity implies abnor-

malities in vessel behaviour. Regional cerebral blood flow studies have emphasised a dysfunction of cerebrovascular regulation in headache [26].

Many studies using SPECT with ^{99m}Tc-HMPAO have demonstrated cerebral blood flow abnormalities in pain free intervals as well as during pain intervals in migraine patients [27-29], while some others showed no changes [30, 31]. In the literature, the vascular effects of asetazolamide and sumatriptan in migraine patients were investigated by means of SPECT studies. As a result of these studies, it was found that asetazolamide enhanced low flow regions of the cortex (temporobasal, temporoparietal and frontal regions in migraine patients without aura; temporobasal, temporoparietal, temporal, parietal and occipital regions in migraine patients with aura) [30], while sumatriptan had no effect on cerebral blood flow [32]. In our study, we found that Mg treatment caused an increase of blood flow in the frontal, temporal and insular cortex. This result has showed that Mg has a vascular effect, probably resulting in a beneficial effect in the prophylactic treatment of migraine.

Mg is an ion effective on many biomechanisms, mostly likely migraine is a disease with many different biomechanisms. As one considers the vascular and neurogenic theory of migraine pathogenesis, it seems reasonable that Mg must have prophylactic effects as a vasoconstrictor and as a NMDA receptor antagonist. This study, additional to the evaluation of clinical effectiveness of Mg prophylaxis in migraine without aura, tries to display the possible vascular and neurogenic effects of Mg. Our study limitations were, we could not study the relations between clinical effect, VEP and cortical blood flow changes because of the limitations of the study population and the methods of the investigation.

In conclusion, our results have made us think that Mg is effective clinically as a prophylactic agent in migraine, and it might work with both vascular and neurogenic mechanisms. The evidence level of Mg usage in migraine prophylaxis has been regarded as Grade B [22]. We think that Mg is a drug which should be evaluated in a more detailed way for its promising wider and more accepted usage. It will be more informative to do some studies with larger and different groups of migraine patients, and with different Mg formulations and dosages.

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