Original Article

Magnesium Sulfate in Acute Stroke: A Randomized Double-Blind Clinical Trial

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Abstract

Background: Administration of magnesium sulfate has neuroprotective effects and reduces infarct volume in animal models of stroke. Previous small clinical trials have reported beneficial effect of magnesium on the outcome in patients with stroke. This study was a randomized, placebo-controlled, double-blind study , investigated the benefit of magnesium sulfate the administration given intravenously as a neuroprotective.

Methods: Patients who had cortical infarction in the middle cerebral artery territory (superior or inferior division) with moderate neurologic deficits (Orgogozo scale score greater than 30 and less than 70) and onset less than 24 hours were included. The patients were treated with magnesium sulfate (4gr stat and 1gr/hr) or placebo for 4 days and examined by a blind investigator. NIH Stroke Scale was obtained on admission and fifth day after stroke.

Results: Eighteen patients were given treatment and nineteen patients were given placebo who demonstrated significant beneficial effects on the difference between NIH Stroke Scales on the day of admission and day 5 (3.16 ± 0.98 vs. 1.84 ± 1.06; p = 0.000 respectively).

Conclusion: Intravenous magnesium sulfate had significant beneficial effect on acute phase of stroke patients and, as a result, may reduce duration of admission.

Key words: Stroke, Magnesium sulfate, Neuroprotective.

Magnesium ion has two possible role in protecting neurons and glia from ischemic damage, effect on cerebral blood flow and neuronal action. Vascular effects of magnesium consist of antagonistic role to wards vasoconstrictive mediators (for example endotheli-1)[1-3], enhancing cerebral blood vessels[4] , and increasing cardiac output[5, 6].

Also the magnesium effect on neuronal action is antiexitotoxic through inhibition of ischemic-induced glutamate release[7] and through antagonistic properties of the NMDA receptor ion channel[8-10] and calcium channel antagonism through voltage gated channels of all types and enhancing mitochondrial buffering of excessive calcium[11]. In animals, many studies have shown decreasing the infarct volume after magnesium administration[12-14].

Trials on humanbeing also have shown reduction in death and dependency, but some findings lacke statistical

Significance[15-19]. Lampl et al[20] reported good prognosis in acute stage and over 30 days after stroke in the magnesium group.

This study tested the primary hypothesis that in acute ischemic stroke in the midlle cerebral artery (MCA) territory, magnesium sulfate improves neurologic status at 5 days compared with placebo, and showed effect of magnesium on early recovery.

Materials and Methods

The study was performed as a placebo-controlled, randomized double-blind trial during the years of

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2000–2002 in Al-Zahra Hospital of Isfahan University of Medical Sciences. Local ethics committee approved the trial. Each of the patients signed a consent form. Both genders and adults older than 45 years of age were included. Patients had to be in the acute stage of stroke (having deficit lasted more than 6 hours and less than 24 hours) and the stroke deficits had to be of moderate degree (Orgogozo21 scale greater than 30 and less than 70). Simple randomization was performed according to a random number table.

Patients with intracerebral, subdural, epidural or, subarachnoid hemorrhage; cerebrodege- nerative, demyelinating diseases; brain tumor; previous stroke; metabolic disorders abnormal magnesium or calcium values; and muscular or neuromuscular junction diseases were excluded.

The study was limited to middle cerebral artery territory infarction (determined by brain computed tomography scan on the admission and 3rd day after stroke) to have a homogeneous study group. The final diagnosis was performed based on the second brain CT scan results (after the 3rd day). Each patient was examined and scored using the National Institute of Health Stroke Scale (NIHSS) on the admission day by the physician in emergency room and fifth days later with another neurologist in the ward (investigators were blind to the type of intervention).

The Barthel activities of daily living index22 and Rankin score23 were checked after 3 months. The study end point was the completion of the 90-days follow-up period. The first stage of study was planned with magnesium loading of 4 gr in 100 mL saline over a 20-minute period and 48 gr in 1000 ml over a 24-hours period in a continuousinfusion form. but after performing this protocol in three patients we observed magnesium intoxication, thus the infusion was completed and new protocol was planned in which magnesium was given intravenously with a loading dose of 4 g in 100 ml saline over a 20-minutes period and 24 g in 1000 ml over a 24-hours period in a continuous infusion form for 5 days.

The placebo was normal saline with the same volume that was used for magnesium group. The magnesium sulfate or placebo was administered during 24 hours after onset of the acute event. Out of the total of 40 patients, 18 received magnesium sulfate, 19 received placebo, and 3 dropped out (2 from the active treatment group and 1 from the placebo group). The levels of magnesium were measured routinely at 3rd day. In addition, each patient was treated by the same antiplatelet therapy, consisting of acetylsalicylic acid (microcoated) 500 mg orally per day.

During the first 2 days the patients were monitored continuously with vital signs. After this, vital signs were taken every 6 hours, and electrocardiography was performed on admission and 3rd day. Also if seizure occurred in acute phase, it was entered to data.

Sample size based on Lampl study[20] was calculated. The two groups were tested by Student t test for continuous scores and Chi-square test for categorical variables.

Results

Forty patients (20 treated with magnesium and 20 receiving placebo) entered the study. Three control subjects (two male and one female patient) dropped out of the study. In two patients of the placebo group, the treatment were discontinued after development of severe arrhythmias and fever with dyspnea. One patient of the magnesium-treated group developed pulmonary edema and was also taken out of the study. No patient needed to be excluded on account of a misinterpretation of the stroke location. Preliminary analysis ensured that the two treatment arms were equal at baseline (Table 1).

Table 1. Baseline characteristics of the treatment arms.Data are means or percentage. No significant differences are between groups

	Mg (n=18)	Placebo (n=19)
Age (y)	62.5	63.4
Sex (M: F)	12:8	11:9
NIHS scale	12.27	12.17
Hypertension	55%	50%
Smoking	10%	15%
Diabetic	30%	20%
Ischemic Heart Diseases	45%	30%

The onset of treatment were 10.3 ± 2.3 hours (range from 8 to 22 hours) for the treated group and 11.4

± 2.9 hours (range from 9 to 21 hours) for the untreated group.

On the baseline, the Orgogozo scores were similar for the two groups (44.5 ± 13.5 vs. 46.2 ± 13.1; P = 0.242). The two groups' NIHSS scores also were similar at baseline (12.27 ± 2.8 vs. 12.17 ± 1.8, P = 0.075) and then showed a steady divergence during the 5-days follow-up period. At the end of this time, there was a 1.32 point difference, on average, between treated and placebo groups and difference scale of day 1 and day 5 in two groups was statistically significant (3.16 ± 0.98 vs. 1.84 ± 1.06, P < 0.05).

At the end of the follow-up, only 13 and 15 patients from treated and placebo groups, respectively, referred to clinic. An average Rankin disability score had a trend toward higher values (2.17 ± 1.17 vs. 2.85 ± 1.36, P = 0.15) and the Barthel activities of daily living index score was nonsignificantly higher (81.3 ± 22.3 vs. 68.5 ± 19.9, P = 0.08).

Average level of magnesium at 3rd day was 4.2±0.7.

Discussion

The results of this study demonstrated a signifi- cant trend of neurologic deficit improvement in the treated, compared to the control group. Rankin disability score was lower in the treated group than in the control subjects showing a trend toward improvement and the Barthel activities of daily living index was higher in the treated group, but in both score swere not significant. The reasons for the nonsignificant results can be attrition or selection bias after 3 months. In larger study with longer follow up (6 months) a more reliable result may be achieved.

Magnesium sulfate was chosen for this study, because of its assumed neuroprotective and vasodilatory trait, its safety from frequent serious adverse effects[16] , and its effect on control of seizure and headache.

Because of the majority of stroke patients arrive at the hospital several hours after appearance of symptoms, the therapeutic window to 24 hours, was designed, but the usually accepted therapeutic window for neuroprotective medications is up to 6 hours and it seems that if the therapeutic window will be lesser, the result will be better. Indeed, studies on animal models showed that the evaluation of inclusive changes to infarction is not limited to the first 24 hours[24].

In developing country, the stroke patients usually arrive to hospital after 6 hour sand then, thrombolytic therapy would not be used and if patients arrive sooner, this drugs are expensive and inaccessible. But neuroprotective agents such as magnesium are accessible, chipper and more beneficial. Also in the study design, in spite of Lampl et al20, the days of using magnesium were limited to 4 days because many patients needed to be admitted only for 5 or < 5 days. In other studies, which have compared the efficacy of neuroprotective agents with placebo, the functional assessment scores showed a trend toward delayed recovery and lead to the hypothesis that neuroprotective medications may have an additional role in the reorganization phase of the brain tissue in a late stage after the onset of infarct, but in this study, because of attrition of patients in long time follow up, the result can not be conclusive.

The mechanism of improvement in stroke by using magnesium as was demonstrated in this study, can be assumed to be neuroprotective based on antiexitoxic[7-11] and vascular effects[1-6]. This effect was shown on the penumbra by the action of a competitive blockage of the glutamate receptor[25, 26], the glutamate release inhibition[27], mitochondrial calcium buffering[7], and cellular energy metabolism recovery[11]. As a result, magnesium can be probably more beneficial for ischemic stroke with larger penumbra area.

This study used magnesium with dose of 1 gr/hr that was lesser than Lampl et al[20] study but almost the same effect was seen and the serum level of magnesium was proper. This study was performed with a small number of patients so larger study needs for the results to be conclusive. However, it seems that in acute phase of stroke magnesium can recover neurological deficit and the future study with magnesium and other additive neuroprotective agents and evaluation of stroke complications such as seizure and headache is recommended.

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