Magnesium infusion for vasospasm prophylaxis after subarachnoid hemorrhage

MARTINA STIPPLER, M.D., ELIZABETH Crago, R.N., M.S.N., ELAD I. LEVY, M.D., MARY E. KERR, R.N., PH.D., HOWARD Yonas, M.D., MICHAEL B. Horrowitz, M.D., AND AMIN KASSAM, M.D.

Departments of Neurological Surgery and Acute and Tertiary Nursing, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Department of Neurosurgery and Toshiba Stroke Research Center, State University of New York at Buffalo, New York; and Division of Surgery, Department of Neurosurgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

Object. Despite the application of current standard therapies, vasospasm continues to result in death or major disability in patients treated for ruptured aneurysms. The authors investigated the effectiveness of continuous MgSO\textsubscript{4} infusion for vasospasm prophylaxis.

Methods. Seventy-six adults (mean age 54.6 years; 71% women; 92% Caucasian) were included in this comparative matched-cohort study of patients with aneurysmal subarachnoid hemorrhage on the basis of computed tomography (CT) findings. Thirty-eight patients who received continuous MgSO\textsubscript{4} infusion were matched for age, race, sex, treatment option, Fisher grade, and Hunt and Hess grade to 38 historical control individuals who did not receive MgSO\textsubscript{4} infusion. Twelve grams of MgSO\textsubscript{4} in 500 ml normal saline was given intravenously daily for 12 days if the patient presented within 48 hours of aneurysm rupture. Vasospasm was diagnosed on the basis of digital subtraction angiography, CT angiography, and transcranial Doppler ultrasonography, and evidence of neurological deterioration.

Symptomatic vasospasm was present at a significantly lower frequency in patients who received MgSO\textsubscript{4} infusion (18%) compared with patients who did not receive MgSO\textsubscript{4} (42%) (p = 0.025). There was no significant difference in mortality rate at discharge (p = 0.328). A trend toward improved outcome as measured by the modified Rankin Scale (p = 0.084), but not the Glasgow Outcome Scale (p = 1.0), was seen in the MgSO\textsubscript{4}-treated group.

Conclusions. Analysis of the results suggests that MgSO\textsubscript{4} infusion may have a role in cerebral vasospasm prophylaxis if therapy is initiated within 48 hours of aneurysm rupture.

KEY WORDS • aneurysm • subarachnoid hemorrhage • vasospasm • prophylaxis

Despite advances in medical and surgical therapy for patients with aneurysmal SAH, cerebral vasospasm remains a major complication and contributes to death and disability. The current standard treatment for SAH is triple-H therapy and administration of a Ca\textsuperscript{2+} channel blocker (for example, nimodipine) in conjunction with early surgical or endovascular intervention. In combination with nimodipine, triple-H therapy has shown results superior to those of triple-H therapy alone.\textsuperscript{13,44} This regimen has reduced mortality rates after aneurysmal SAH to approximately 5 to 15%, compared with almost 20% in the early 1980s.\textsuperscript{17} Despite aggressive therapy, the incidence of cerebral vasospasm (verified by angiography) remains as high as 67%.\textsuperscript{12} A delayed ischemic neurological deficit or symptomatic cerebral vasospasm has been reported in 38% of patients after intracranial aneurysmal rupture.\textsuperscript{12} The significant morbidity and mortality rates associated with vasospasm underscore the importance of prophylactic treatment.

Given the need for improved prevention of vasospasm, we investigated the use of continuous MgSO\textsubscript{4} infusion as a prophylactic treatment for cerebral vasospasm. Magnesium sulfate is thought to be beneficial in preventing cerebral vasospasm or minimizing its severity, not only because it has neuroprotective and vasodilatory effects,\textsuperscript{8} but also because it impedes the formation of reactive O\textsubscript{2} species\textsuperscript{25,32} and inhibits platelet aggregation.\textsuperscript{41,42} The purpose of this study was to evaluate the effect of prophylactic continuous MgSO\textsubscript{4} infusion on symptomatic vasospasm and to assess 3-month outcomes in patients with aneurysmal SAH.

Clinical Material and Methods

Patient Population

This cohort of patients was prospectively recruited as part
of an ongoing SAH database for a National Institutes of Health–funded study (R01NR04339). The sample included adult patients (age range 18–75 years) in whom a diagnosis of SAH from a ruptured cerebral aneurysm had been verified by DS angiography or CT angiography and in whom the Hunt and Hess grade was greater than or equal to II and/or the Fisher grade was less than 1. Patients were admitted to the neurovascular intensive care unit at the University of Pittsburgh Medical Center between July 6, 1999, and June 30, 2004. Informed consent was obtained on the basis of an institutional review board–accepted protocol. All patients received standard nursing and medical care, including triple-H therapy, nimodipine, and early (within 24 hours) surgical or endovascular intervention. Patients were excluded from the parent study if they had a preexisting neurological disorder, if their SAH resulted from a mycotic aneurysm or trauma, or if they presented more than 48 hours after the initial aneurysmal SAH. Cardiomyopathy and electrocardiography changes on admission also constituted exclusion criteria because of the negative cardiac side effects of high serum Mg levels.

**Magnesium Sulfate Infusion**

Magnesium sulfate infusions were initiated as the standard of care after verification of the presence of SAH from a ruptured aneurysm. Each day, 12 g of MgSO\(_4\) in 500 ml of 0.9% NaCl was given intravenously at a rate of 21 ml/hour. The target infusion duration was 12 days. All medications administered during the hospital course were reviewed using electronic medical records. Nursing and pharmacy notes were analyzed for verification of MgSO\(_4\) infusion and detection of any adverse events. In patients receiving continuous MgSO\(_4\) infusion, measurement of Mg\(^{++}\) levels was part of the daily standard serological studies. In the historical control patients, serum Mg\(^{++}\) levels were obtained less frequently, but at least one serum Mg\(^{++}\) level was available.

**Cerebral Vasospasm**

Cerebral vasospasm was diagnosed by the documentation of narrowed cerebral vessels on cerebral angiography (DS angiography [Fig. 1] or CT angiography) or TCD ultrasonography–measured elevations when accompanied by a blood flow study such as CT perfusion.\(^{33,42}\)

Cerebral angiography or CT angiography was conducted as the standard of care on admission, at follow up, or in the event of any neurological deterioration. The angiographic studies were interpreted and graded by neuroradiologists and neurosurgeons at the University of Pittsburgh Medical Center for evidence and degree of vasospasm. The degree of vasospasm was defined as the percentage of cerebral vessel narrowing, as follows: none to minimal, 0 to 25%; moderate, 26 to 75%; and severe, 76 to 99%. In cases involving either moderate or severe vasospasm, findings were classified as positive for cerebral vasospasm.

Each patient underwent TCD ultrasonography daily, from the time of consent in the parent study through the 14th day after onset of hemorrhage, unless he or she was discharged early from the acute inpatient setting. An MCA systolic velocity greater than 200 cm/second, a mean velocity greater than 120 cm/second, or a Lindegaard ratio (ratio of the mean MCA velocity to mean internal carotid artery velocity) greater than 2.5 was coded as indicating a high risk of vasospasm.\(^{28}\)

Patients were monitored for signs of neurological deterioration every 2 to 4 hours for up to 14 days after the aneurysmal rupture. Criteria for determining neurological deterioration included a decline of more than two points on the Glasgow Coma Scale or the National Institutes of Health Stroke Scale and/or documented focal or global neurological change.

Symptomatic vasospasm was defined as neurological deterioration accompanied by CT angiography– or DS angiography–documented vasospasm, or neurological deterioration accompanied by elevated TCD velocities and low-flow CT perfusion scans.

**Treatment Outcomes**

Outcomes were evaluated by means of telephone conversations or face-to-face meetings, using a battery composed of the GOS, mRS, BI, and the Physical Function subscale of the SF-36. Patients participated in the telephone interview if able; otherwise, a family member or caregiver responded to the questions.

**Statistical Analysis**

Descriptive statistics, analysis of variance, and chi-square analysis were conducted using SPSS software (version 11.0.1; SPSS, Inc., Chicago, IL), with alpha levels set at 0.05. The chi-square test was used to determine the association between GOS scores, mRS scores, and the presence/absence of MgSO\(_4\) infusion. Analysis of variance was used to determine differences in BI and SF-36 scores between the groups. Outcome was dichotomized into poor (mRS Score 2–6; GOS Score 1–4) and good (mRS Score 0 or 1; GOS Score 5). The association between poor outcome and MgSO\(_4\) infusion was examined using the chi-square test. Mean values are presented ± standard deviations.

**Results**

Table 1 summarizes the characteristics of the 76 patients included in this study. Thirty-eight patients who received continuous MgSO\(_4\) infusion were identically matched for age, race, and sex with 38 patients in the control group who did not receive this therapy, and closely matched on severity of hemorrhage and treatment intervention (endovascular coil embolization or craniotomy with clip placement). There was no significant difference between the groups with regard to medical history, including smoking. The average time from onset of hemorrhage to admission was 15 ± 23.6 hours (range 1–148.5 hours). The mean patient age was 54.6 years, and the majority (71%) were female. The most common aneurysm sites were the anterior communicating artery (31 cases [41%]), posterior communicating artery (12 cases [16%]), MCA (10 cases [13%]), and basilar artery (10 cases [13%]). Thirty-three patients (43%) underwent craniotomy and insertion of an aneurysm clip, and 43 (57%) underwent coil embolization.

**Results of MgSO\(_4\), Infusion**

The total infusion duration ranged from 6 to 21 days. In-
fusions were standardized regardless of the initial serum Mg$^{++}$ levels. Baseline serum Mg$^{++}$ levels were higher in the MgSO$_4$ infusion group; however, in some cases Mg$^{++}$ levels may have been measured after the initiation of MgSO$_4$ infusion (Table 2). The patients who received infusions for fewer than 10 days either were discharged early from the inpatient setting or suffered terminal events such as withdrawal of medical therapy or brain death. One patient underwent MgSO$_4$ therapy for 21 days. Because this patient experienced persistent problems with vasospasm, the MgSO$_4$ therapy was continued beyond Day 12. No adverse events that would have led to discontinuation of MgSO$_4$ therapy were detected. Serological studies were performed to monitor MgSO$_4$ levels. Serum Mg$^{++}$ levels ranged from 0.9 to 5.2 mmol/L (mean 2.16 ± 0.38 mmol/L) in the MgSO$_4$-treated group, compared with 1.1 to 3.8 mmol/L (mean 1.17 mmol/L) in the control group, a difference that was statistically significant ($p < 0.0001$; Table 2).

**Magnesium Sulfate and Symptomatic Cerebral Vasospasm**

There was a significant difference in the incidence of symptomatic cerebral vasospasm in patients who received the MgSO$_4$ infusions compared with control patients (Fig. 2). Symptomatic cerebral vasospasm was present in 23 (30%) of the 76 patients with cerebral vasospasm. Based on DS angiography findings and evidence of neurological deterioration, we found that symptomatic cerebral vasospasm was present in seven (18.4%) of 38 patients who received MgSO$_4$ infusion. In contrast, symptoms were present in 16 (42%) of 38 control patients ($\chi^2 = 5.05, p = 0.025; OR 1.99, 95\% CI 0.99–3.7$). In two control patients who did not undergo angiography or CT angiography, the presence of cerebral vasospasm was indicated by TCD ultrasonography–measured elevated velocities, neurological changes, and low-flow CT perfusion scans.

**Magnesium Sulfate and 3-Month Outcomes**

There was no significant difference in mortality rate between the MgSO$_4$-treated group and the control group. By 3 months, four patients (10.5%) in the MgSO$_4$-treated group had died, whereas seven (18%) in the control group had died ($\chi^2 = 0.957, p = 0.328; OR 1.7, 95\% CI 0.56–5.5$).

**TABLE 1**

*Summary of demographic, presenting, and treatment data*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cases</th>
<th>Sex Distribution</th>
<th>Mean Age (yrs)</th>
<th>Race</th>
<th>Hunt &amp; Hess*</th>
<th>Fisher</th>
<th>Treatment</th>
<th>Smoking History</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>38</td>
<td>27 F, 11 M</td>
<td>54.4</td>
<td>35 Caucasian, 3 African-American</td>
<td>2.92, 2.89</td>
<td></td>
<td>clip 18, coil 20</td>
<td>24 smokers, 3 quitters, 11 non-smokers</td>
</tr>
<tr>
<td>MgSO$_4$ infusion</td>
<td>38</td>
<td>27 F, 11 M</td>
<td>54.9</td>
<td>35 Caucasian, 3 African-American</td>
<td>2.74, 2.84</td>
<td></td>
<td>clip 15, coil 23</td>
<td>28 smokers, 2 quitters, 8 non-smokers</td>
</tr>
<tr>
<td>total</td>
<td>76</td>
<td>71% F</td>
<td>54.6</td>
<td>Caucasian 92%</td>
<td>2.83, 2.87</td>
<td></td>
<td>clip 33, coil 43</td>
<td></td>
</tr>
</tbody>
</table>

* Hunt and Hess grades are written in Arabic numbers to accommodate fractions.
The mean mRS score was $2.22 \pm 1.943$ for the entire group—2 for the MgSO$_4$ group and 2.45 for the control group. When the data were dichotomized into good (mRS Score 1) and poor (mRS Score > 1) outcomes, the OR was $2.1\ (\chi^2 = 0.168, \ p = 0.084; \ 95\% \ CI 0.84–5.27)$. The mean GOS score was $3.84 \pm 1.35$ for the entire group—3.89 for the MgSO$_4$ group and 3.79 for the control group. There was no significant intergroup difference in outcomes when the data were dichotomized into good (GOS Score 5) and poor (GOS Score 1–4) outcomes ($\chi^2 = 0.00, \ p = 1.0; \ OR \ 1, \ 95\% \ CI 0.4–2.49)$.

There was no significant difference in BI scores between groups ($p = 0.84$). The mean BI score was $17.3 \pm 5.5$ in the MgSO$_4$-infused group and $17.5 \pm 5.3$ in the control group. At the 3-month follow-up, the mean SF-36 Physical Function score in the overall sample was $19.4 \pm 6$ (range 9–27). The mean SF-36 Physical Function score in the MgSO$_4$ group was $24.3 \pm 17.7$, whereas that in the control group was $28.4 \pm 19.8$. This difference was not significant ($p = 0.34$).

**Discussion**

In this study, we have demonstrated that prophylactic continuous MgSO$_4$ infusion after SAH is beneficial and safe. Infusion of MgSO$_4$ decreased the incidence of cerebral vasospasm and resulted in a trend toward improved clinical outcome. Magnesium is thought to ameliorate cerebral vasospasm by many mechanisms: vasodilation, inhibition of free radical formation, impedance of vasoconstrictive substances, and inhibition of platelet aggregation. It may also be beneficial to patients with cerebral vasospasm because of its neuroprotective properties.

**Effect of MgSO$_4$ on Cerebral Vasospasm**

First, Mg$^{++}$ antagonizes Ca$^{++}$-initiated vascular constriction by inhibiting the binding of Ca$^{++}$ to voltage-dependent Ca$^{++}$ ion channels. By hampering the binding of Ca$^{++}$ to the myosin-binding protein in the smooth-muscle cells of the cerebral vessel wall, Mg$^{++}$ impedes vascular constriction. The results in animal models have shown that Mg$^{++}$ ameliorates cerebral vasospasm$^{40}$ and augments cerebral blood flow.$^9$ In addition, by blocking postsynaptic voltage-gated Ca$^{++}$ ion channels, Mg$^{++}$ could potentiate the effect of nimodipine also functioning as a Ca$^{++}$ antagonist.$^{20}$ Experimental pharmacological treatments intended to prevent or modulate cerebral vasospasm include nitric oxide donors (such as nitroglycerine and nitroprusside);$^{19,49}$ endothelin antagonists;$^{11}$ potassium channel activators (cromakalim);$^{27,50}$ and most recently, recombinant human erythropoietin.$^{11}$ Whereas these treatments work on one specific pathophysiological mechanism involved in the genesis of cerebral vasospasm, MgSO$_4$ counteracts various pathways and spasmogenic substances, such as endothelin-1,$^{23}$ norepinephrine, angiotensin II,$^2$ and serotonin.$^{45}$ This could contribute further to the vasodilatory effect.

**TABLE 2**

* Summary of infusion duration and serum Mg$^{++}$ levels*

<table>
<thead>
<tr>
<th>Group</th>
<th>Days of Infusion</th>
<th>Serum Mg$^{++}$ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Min</td>
</tr>
<tr>
<td>MgSO$_4$ infusion</td>
<td>11.8</td>
<td>1.53</td>
</tr>
<tr>
<td>(6–21)</td>
<td>(0.9–4.0)</td>
<td>(1.3–5.2)</td>
</tr>
<tr>
<td>control</td>
<td>1.632</td>
<td>1.39</td>
</tr>
<tr>
<td>(1.1–3.8)</td>
<td>(1.1–2.0)</td>
<td>(1.3–3.8)</td>
</tr>
</tbody>
</table>

* Values in parentheses represent the range.

![Fig. 2. Bar graph showing a decreased incidence of cerebral vasospasm in patients who underwent MgSO$_4$ infusion compared with control patients (No MgSO$_4$). The marble bars represent the incidence of symptomatic cerebral vasospasm, whereas the gray bars represent its absence in the controls. Vasospasm was present in seven (18.4%) of 38 patients in the MgSO$_4$ group and in 19 patients (50%) in the control group.](image-url)
Magnesium for cerebral vasospasm prophylaxis

Magnesium is not only a vasodilator; it also has shown an antiplatelet effect in clinical studies. Thromboxane and serotonin released from platelets during platelet aggregation in the subarachnoid clot are suspected to contribute to vasospasm. This process is reflected in the correlation of Fisher grade with vasospasm severity and the reduced risk of cerebral vasospasm brought about by the removal of blood products from the subarachnoid space via cisternal drainage. In a rabbit model of cerebrovascular injury, as well as in healthy human volunteers, high serum concentrations of Mg++ were associated with inhibited platelet aggregation and prolonged bleeding time. No hemorrhage-related complications were reported in several large clinical trials of Mg++ in patients with myocardial infarction, even in combination with antiplatelet agents and thrombolytic drugs. Increased blood loss was reported, however, in women who received MgSO4 for the treatment of pre-eclampsia. In contrast, the authors of a study of patients with SAH who received similarly high Mg++ doses did not report any bleeding-related complications. In the present study, we did not observe any hemorrhage-related complications or other adverse effects as a result of MgSO4 administration.

Magnesium for Prevention of Cerebral Vasospasm

Several studies have been performed to establish the efficacy of MgSO4 in cerebral vasospasm prevention. In these studies, MgSO4 was administered in accordance with different protocols, which could account for the variety of results. Whereas the authors of one study in which mean serum Mg++ levels were in the 1 to 1.5–mmol/L range found significant reduction of radiographically documented vasospasm, the authors of another study in which serum Mg++ levels were maintained in the 2–2.5–mmol/L range did not observe any benefit. Additionally, high-dose MgSO4 infusion, resulting in a serum Mg++ level as high as 4 to 4.5 mg/dl (3.3–3.7 mmol/L), did not alter vasospasm or improve outcome significantly. Administration of a single bolus of MgSO4 produced similar results. It seems that the MgSO4 bolus has a predominantly vasodilatory effect on systemic vasculature but no detectable effect on intracranial circulation. An intravenous MgSO4 bolus immediately elevates serum Mg++ levels but may take hours to affect CSF levels. In the present study, a continuous infusion of Mg++ was started prophylactically within 48 hours after aneurysm rupture was verified. Consequently, there was sufficient time for tissue loading before the onset of cerebral vasospasm. This emphasizes the importance of administration of MgSO4 continuously and as early as possible after aneurysm rupture to prevent cerebral vasospasm. In addition, if MgSO4 therapy is not initiated before the onset of vasospasm, vasoparalysis may abolish the vasodilatory effect of magnesium in cerebral arteries.

Although the neuroprotective properties of a serum Mg++ concentration of 1.49 mmol/L have been established in patients with stroke, the proper concentration needed to achieve a vasodilatory response in the intracranial circulation is unclear. Analysis of data obtained in primates shows that the concentration of MgSO4 in CSF increases simultaneously with the concentration of Mg++ in serum, but to a lesser extent. The goal of future studies should be to establish in vivo vasoactive concentrations in both serum and CSF.

Neuroprotective Effects of MgSO4

In addition to its vasodilatory effect, MgSO4 is thought to exert a neuroprotective effect. This neuroprotective effect was first established in animal models of traumatic brain injury. In the most recent clinical trials involving patients with acute stroke, a neuroprotective effect could be seen only in a small subgroup. For example, in the Intravenous Magnesium Efficacy for Stroke study, a much smaller dose (16 mmol or 2 g) of MgSO4 was used. In addition, because MgSO4 cannot be given prophylactically to treat acute stroke, its neuroprotective property might be diminished in that clinical setting. Magnesium is able to impede neuronal death via multiple pathways. It disrupts the excitotoxic cascade by competitive antagonism at the N-methyl-D-aspartate receptor. Moreover, MgSO4 inhibits glutamate release by enhancing the effect of adenosine on the magnesium-dependent presynaptic adenosine–1 receptors, further diminishing excitatory glutamate neurotoxicity. Magnesium affects O2 radical formation, one of the major pathways contributing to vasospasm.

Magnesium also alters postanoxic depolarization. Depolarization induces an ion shift that contributes to energy failure, cerebral ischemia, and cell death in the ischemic brain. Van den Bergh, et al., recorded ischemic depolarization potentials for as long as 90 minutes after SAH. They used diffusion-weighted magnetic resonance imaging to measure the volume of ischemic tissue. Significantly less ischemic brain tissue was found in rats pretreated with intravenous Mg++. This finding has led researchers to suggest that Mg++ provides a measure of neuroprotection, even in the presence of cerebral vasospasm, and could explain the trend toward better neurological outcomes in patients treated with magnesium.

Conclusions

The findings of this study lead us to suggest that continuous MgSO4 infusion is safe and may play a role in the prophylaxis of cerebral vasospasm. We found a significant reduction in vasospasm and a trend toward improved outcome when continuous MgSO4 therapy was initiated within 48 hours after aneurysm rupture. This study did not have sufficient power to show a statistically significant difference in outcome, but the evidence derived herein provides support for a large-scale randomized clinical trial in which the Mg++ dose is titrated to gain the maximum vasodilatory and neuroprotective effects. It may also be essential to administer MgSO4 prophylactically and continuously, so that tissue binding and transport across the blood–brain barrier occur before the onset of cerebral vasospasm.

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Reprint reprint requests to: Martina Stippler, M.D., Department of Neurological Surgery, University of Pittsburgh Medical Center–Presbyterian Hospital, 200 Lothrop Street, Suite 400B, Pittsburgh, Pennsylvania 15213. email: stipplerm@upmc.edu.