Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage

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Object. Vasospasm remains a significant source of neurological morbidity and mortality following aneurysmal subarachnoid hemorrhage (SAH), despite advances in current medical, surgical, and endovascular therapies. Magnesium sulfate therapy has been demonstrated to be both safe and effective in preventing neurological complications in obstetrical patients with eclampsia. Evidence obtained using experimental models of brain injury, cerebral ischemia, and SAH indicate that Mg may also have a role as a neuroprotective agent. The authors hypothesize that MgSO4 therapy is safe, feasible, and has a beneficial effect on vasospasm and, ultimately, on neurological outcome following aneurysmal SAH.

Methods. A prospective randomized single-blind clinical trial of high-dose MgSO4 therapy following aneurysmal SAH (Hunt and Hess Grades II–IV) was performed in 40 patients, who were enrolled within 72 hours following SAH and given intravenous MgSO4 or control solution for 10 days. Serum Mg++ levels were maintained in the 4 to 5.5 mg/dl range throughout the treatment period. Clinical management principles were the same between groups (including early use of surgery or endovascular treatment, followed by aggressive vasospasm prophylaxis and treatment). Daily transcranial Doppler (TCD) ultrasonographic recordings were obtained, and clinical outcomes were measured using the Glasgow Outcome Scale (GOS). The patients' GOS scores and the TCD recordings were analyzed using the independent t-test.

Forty patients were enrolled in the study: 20 (15 female and five male patients) received treatment and 20 (11 female and nine male patients) comprised a control group. The mean ages of the patients in these groups were 46 and 51, respectively, and the mean clinical Hunt and Hess grades were 2.6 ± 0.68 in the MgSO4 treatment group and 2.3 ± 0.73 in the control group (mean ± standard deviation [SD], p = 0.87). Fisher grades were similar in both groups. Mean middle cerebral artery velocities were 93 ± 27 cm/second in MgSO4-treated patients and 102 ± 34 cm/second in the control group (mean ± SD, p = 0.41). Symptomatic vasospasm, confirmed by angiography, occurred in six of 20 patients receiving MgSO4 and in five of 16 patients receiving placebo. Mean GOS scores were 3.8 ± 1.6 and 3.6 ± 1.5 (mean ± SD, p = 0.74) in the treatment and control groups, respectively. Significant adverse effects from treatment with MgSO4 did not occur.

Conclusions. Administration of high-dose MgSO4 following aneurysmal SAH is safe, and steady Mg++ levels in the range of 4 to 5.5 mg/dl are easily maintained. This treatment does not interfere with neurological assessment, administration of anesthesia during surgery, or other aspects of clinical care. We observed a trend in which a higher percentage of patients obtained GOS scores of 4 or 5 in the group treated with MgSO4, but the trend did not reach a statistically significant level. A larger study is needed to evaluate this trend further.

Key Words • magnesium sulfate • subarachnoid hemorrhage • vasospasm

SUBARACHNOID hemorrhage caused by rupture of a cerebral aneurysm affects 30,000 persons annually in the United States.6 Delayed cerebral arterial narrowing or vasospasm with subsequent cerebral ischemia affects 25 to 35% of patients after intracranial aneurysm rupture, and is a leading cause of neurological morbidity and mortality.6,7 Treatment of cerebral vasospasm aims to prevent or reverse arterial narrowing and, ultimately, to prevent ischemic neurological deficits. Early surgery for aneurysm clipping or endovascular treatment facilitates the management of vasospasm using triple-H therapy.16 Pharmacological therapies, in which Ca-channel antagonists such as nimodipine are used, have significantly reduced the neurological deficits that result from vasospasm following SAH;1,8 however, despite these current therapies, delayed ischemic effects remain clinically significant and improved treatment strategies are needed.

Intravenous administration of MgSO4 has been clinically used for treatment of obstetrical eclampsia, which has
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been shown to include periods of cerebral vasocostriction as part of its pathophysiological characteristics.\textsuperscript{10,11,13,17} Experimentally, high-dose Mg has been shown to reverse vasospasm induced in the rat SAH model.\textsuperscript{9} Infusions of MgSO\textsubscript{4} have been well tolerated in patients suffering from preeclampsia and eclampsia, acute stroke, and cardiac arrhythmias.\textsuperscript{2,10,12,14,15}

The safety and effectiveness of MgSO\textsubscript{4} in preventing vasospasm and improving neurological outcome following aneurysmal SAH has only recently been reported.\textsuperscript{4} We present the results of a prospective randomized single-blind (that is, patient-blinded) pilot study of MgSO\textsubscript{4} therapy in patients with SAH. The objectives of our study were threefold: 1) to assess the safety of MgSO\textsubscript{4} infusions in patients with SAH by monitoring hemodynamic indices and the effect on serum electrolytes; 2) to assess the effectiveness of MgSO\textsubscript{4} in preventing vasospasm in aneurysmal SAH, as judged by cerebral blood flow velocities by using TCD ultrasonography, and cerebral angiography in patients with clinical evidence of delayed ischemia; and 3) to assess the effectiveness of MgSO\textsubscript{4} in improving neurological outcomes in patients 3 months following SAH by determination of the patient’s GOS score.\textsuperscript{5}

Clinical Material and Methods

We performed a prospective randomized placebo-controlled patient-blinded pilot study to examine the safety and to compare the effect of MgSO\textsubscript{4} therapy in preventing vasospasm and improving neurological outcome after aneurysmal SAH. The human rights committee at our institution approved the study protocol. Patients were considered eligible for the study if they met the following criteria: presentation less than 72 hours post-SAH (confirmed by computed tomography and angiography studies), a Hunt and Hess score of II to IV on admission, an age older than 18 years, and informed consent. Ineligible patients included those with any of the following conditions, which relate to known adverse clinical effects of hypermagnesemia: pregnancy, congestive heart failure (New York Heart Association Class 3 or 4), renal insufficiency with a calculated creatinine clearance rate of less than 30 ml/minute, known neuromuscular disease (such as myasthenia gravis or myotonic dystrophy), concomitant use of neuromuscular blocking agents, serum K\textsuperscript{+} level greater than 5.5 mg/dl, serum Ca\textsuperscript{2+} level lower than 0.9 mg/dl, or hypotension (systolic pressure < 90 mm Hg or mean arterial blood pressure < 60 mm Hg) unresponsive to intravenous administration of fluid and/or pressors.

Forty patients were enrolled in the study: 20 (15 female and five male patients, with a mean age of 46 years) in the treatment group and 20 (11 female and nine male patients, with a mean age of 51 years) in the control group. Following randomization, patients in the treatment group received MgSO\textsubscript{4} infusion, which was initiated with a bolus of 6 g in a 250-ml solution of 0.9% NaCl over 30 minutes, followed by continuous infusion at 2 g/hour (40 g in a 1000-ml solution of 0.9% NaCl at 50 ml/hour). Subsequent dosage adjustments in the MgSO\textsubscript{4} infusion were made to maintain a target Mg\textsuperscript{2+} level of 4 to 5.5 mg/dl (normal serum Mg\textsuperscript{2+} level 1.5–2 mg/dl). If serum Mg\textsuperscript{2+} was less than 4 mg/dl or between 5.5 and 7.1 mg/dl, the infusion was increased or decreased, respectively, by 0.5 g/hour (12 ml/hour). If the serum level of Mg\textsuperscript{2+} was greater than 7.1 mg/dl, the infusion was suspended until the level decreased below 7 mg/dl, after which the infusion was restarted at 1 g less per hour (25 ml/hour). Patients in the control group received an intravenous placebo consisting of a 250-ml solution of 0.9% NaCl over a 30-minute period, followed by continuous infusion of 0.9% NaCl at 50 ml/hour. Patients received either MgSO\textsubscript{4} or placebo for either 10 days or until discharge from the ICU, whichever was shorter.

Initially, patients in both groups received standard care and management of aneurysmal SAH in our neurosurgical ICU. Standard medical care included administration of nimodipine, phenytoin, triple-H therapy, and mannitol, with or without pentobarbital if needed for ICP control. Early securement of the aneurysm was performed using surgery or endovascular technique.

While in the ICU, patients received daily monitoring for vasospasm with the aid of TCD ultrasonography recordings and neurological and motor examinations. Maximum and mean flow velocities of the right MCA were measured through the temporal bone window. The mean values for maximum and mean daily MCA velocities were calculated for each patient over the entire study period (10 days from the time of admission). Clinical vasospasm was defined as a new focal neurological deficit that could not be accounted for by other causes such as hydrocephalus, hematoma, seizure, or electrolyte abnormality. Motor strength was assessed using the standard five-point scale. Routine ICU monitoring also included compilation of records on hemodynamic parameters, 24-hour input/output measurements, ventilator settings, intracranial pressure monitoring if available, and serum electrolytes. The patient’s serum Mg\textsuperscript{2+} level was checked 6 hours after a dose change and every 12 hours thereafter. Patients in the placebo group received routine infusions of MgSO\textsubscript{4}, if their serum Mg\textsuperscript{2+} levels were lower than 2 mg/dl. All patients received Ca gluconate if serum Ca\textsuperscript{2+} was less than 0.9 mg/dl.

Following discharge from the ICU, patients underwent daily neurological assessment. A GOS score (5, good recovery; 4, moderate disability but independent; 3, severe disability; 2, persistent vegetative state; or 1, death) was recorded at the 3-month follow-up examination.

To analyze the results of our trial, we focused on the patients’ GOS scores as a measure of the effectiveness of MgSO\textsubscript{4}, for prevention of long-term sequelae of vasospasm from aneurysmal SAH. We considered a GOS score of 4 or 5 as ideal, as this confers functional independence. The GOS data and TCD recordings were analyzed using the independent t-test.

Results

Clinical data are summarized in Table 1 and mean values for groups are given as the means ± SD in both tables and text. Patient characteristics were similar in both groups. Four patients in the control group were withdrawn from the study because study requirements were not met. In one excluded patient, no aneurysm was found at the time of surgery, but instead a slightly dilated anterior communicating artery and A\textsubscript{1} segment were discovered and these were wrapped with cotton fibers during surgery. Another patient

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who had been randomized to the control group was mistakenly given a bolus infusion of MgSO₄. We also excluded a patient whose onset of symptoms was discovered to have been outside the 72-hour enrollment window. Last, one elderly patient was removed from the study when he experienced congestive heart failure and could not tolerate the additional intravenous fluid required for placebo infusion.

Magnesium sulfate did not significantly lower mean arterial blood pressure during bolus or continuous infusion on any day during the treatment period (all \( p > 0.05 \), Student t-test). All patients achieved Mg²⁺ levels within the target range with adjustments in the infusion rate; the mean Mg²⁺ level was 4.6 ± 0.76 (mean ± SD) and the mean infusion rate was 1.5 ± 0.47 g/hour. Mean serum total Ca²⁺ levels were lower in patients in the treatment group (6.8 ± 0.71 compared with 7.9 ± 0.61, \( p = 0.02 \)) and required supplementation. Magnesium and Ca²⁺ levels and supplementation data are shown in Table 2. Clinical Hunt and Hess grades were 2.6 ± 0.68 in the treatment group and 2.3 ± 0.73 in the control group (\( p = 0.87 \)). There was no significant reduction in mean MCA velocity, incidence of symptomatic vasospasm, or clinical outcome in the treatment group. Mean MCA velocity was 93 ± 27 cm/second in the treatment group and 102 ± 34 cm/second in the control group (\( p = 0.41 \)). Mean maximum MCA velocity was 144 ± 48 cm/second in the treatment group and 149 ± 57 cm/second in the placebo group (\( p = 0.77 \)). Subgroup analysis of patients with Hunt and Hess Grade II SAH revealed an average maximum MCA velocity of 162 ± 59 cm/second in treated patients compared with 155 ± 49 cm/second in control patients (\( p = 0.78 \)). Likewise, in the subgroup of patients with Hunt and Hess Grades III and IV hemorrhages, no difference in average maximum MCA velocity was seen (133 ± 53 cm/second compared with 134 ± 46 cm/second, \( p = 0.98 \)).

No significant reduction in the incidence of symptomatic vasospasm was seen; it occurred in six of 20 patients receiving MgSO₄ and in five of 16 patients receiving placebo (\( p > 0.84 \), Student t-test). Angiography confirmed the presence of vasospasm in all cases and was defined as mild, moderate, or severe arterial narrowing. In 80% of patients in the control group who had symptomatic spasm, severe arterial narrowing was revealed by angiography, compared with 77% in the group receiving MgSO₄. Two patients in the MgSO₄ treatment group experienced symptomatic spasm in the absence of elevated MCA velocities measured using TCD ultrasonography (that is, \(< 120 \text{ cm/second} \)), compared with one patient in the control group. Conversely, four patients in the Mg treatment group in whom TCD ultrasonography documented increased MCA velocities failed to experience clinical vasospasm, whereas three patients in the control group remained asymptomatic despite elevated MCA velocities. Significant adverse effects from Mg treatment did not occur. Early in the study two patients experienced transient diplopia and muscle weakness when serum Mg²⁺ levels rose above 6 mg/dl; however, once Mg²⁺ levels were maintained within the 4 to 5.5 mg/dl range, these patients’ symptoms resolved. Deaths among patients in the treatment group were due to brain ischemia or edema in three patients and rupture of the carotid artery during angioplasty in one patient. Deaths in patients in the placebo group were due to massive myocardial infarction 2 weeks postoperatively in one patient and malignant cerebral edema in one patient.

Mean GOS scores for all patients in the treatment and control groups were 3.8 ± 1.6 and 3.6 ± 1.5 (\( p = 0.74 \)), respectively. Among patients with Hunt and Hess Grade II SAH, a higher percentage of those receiving MgSO₄ had a GOS score of 4 or 5 compared with those receiving placebo, although this did not reach statistical significance (90% compared with 67%, \( p = 0.21 \)). Table 3 summarizes the subgroup analysis data, showing the trend toward improved neurological outcomes.

**TABLE 1**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Placebo-Treated Group</th>
<th>MgSO₄-Treated Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>median patient age (yrs)</td>
<td>51</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>5:11</td>
<td>5:15</td>
<td>NA</td>
</tr>
<tr>
<td>Hunt &amp; Hess score†</td>
<td>2.3 ± 0.73</td>
<td>2.6 ± 0.68</td>
<td>0.87</td>
</tr>
<tr>
<td>MCA velocity (cm/sec)†</td>
<td>102 ± 34</td>
<td>93 ± 27</td>
<td>0.41</td>
</tr>
<tr>
<td>no. of patients w/ clinical vasospasm (%)</td>
<td>5 of 16 (31)</td>
<td>6 of 20</td>
<td>&gt;0.84</td>
</tr>
<tr>
<td>GOS score†</td>
<td>3.6 ± 1.5</td>
<td>3.8 ± 1.6</td>
<td>0.74</td>
</tr>
<tr>
<td>% of patients w/ GOS Score 4 or 5</td>
<td>50</td>
<td>65</td>
<td>0.36</td>
</tr>
</tbody>
</table>

* NA = not applicable.
† Values are expressed as the means ± SDs.

**TABLE 2**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Placebo-Treated Group</th>
<th>MgSO₄-Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgSO₄ infusion rate (g/hr)</td>
<td>NA</td>
<td>1.5 ± 0.47</td>
</tr>
<tr>
<td>serum Mg²⁺ level (mg/dl)</td>
<td>2.0 ± 0.31</td>
<td>4.6 ± 0.76</td>
</tr>
<tr>
<td>serum total Ca²⁺ (mg/dl)</td>
<td>7.9 ± 0.61</td>
<td>6.8 ± 0.71†</td>
</tr>
<tr>
<td>Ca²⁺ supplementation (g)</td>
<td>4.7 ± 1.5</td>
<td>6.4 ± 3.6</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SDs. † \( p = 0.02 \).

**Discussion**

The clinical use of intravenous MgSO₄ in prevention of vasospasm following aneurysmal SAH was investigated in this randomized prospective pilot trial. The use of MgSO₄ was safe and target levels were easily maintained, but no benefit was observed in the proposed end points, which included TCD recordings, incidences of symptomatic vasospasm, and ultimate GOS scores.

Vasospasm remains a significant source of morbidity and mortality following aneurysmal SAH, despite advances in current medical, surgical, and endovascular therapies. Calcium-channel antagonists have significantly reduced the neurological sequelae of symptomatic vasospasm. Despite the use of triple-H therapy with colloids, crystalloids, and pressors to augment cerebral blood flow, 25 to 35% of patients who have suffered an SAH may still experience permanent neurological effects from delayed cerebral isch-
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The use of MgSO₄ has been well established in obstetrical patients with eclampsia and is considered the drug of choice for eclamptic convulsions. The exact mechanism by which MgSO₄ exerts its anticonvulsant effect is unknown; however, researchers have suggested that periods of vasoconstriction result in cerebral pathological findings that may include focal hemorrhages and necrosis. Cerebral angiographic studies in patients suffering from toxemia have demonstrated severe arterial vasospasm. Magnesium sulfate, then, may have a role in the prevention or reversal of vasospasm induced by SAH. In fact, MgSO₄ may prevent vasospasm by acting as a Ca²⁺ antagonist, because Ca²⁺ and Mg²⁺ have opposing effects on vascular tone. Thus, MgSO₄ may have a similar action in blocking the activation of smooth-muscle contraction, as with the dilating effect on cerebral blood vessels exerted by Ca²⁺ channel antagonists. Also, MgSO₄ may produce beneficial effects by antagonizing the damaging actions of increased intracellular Ca²⁺ concentration induced by cerebral ischemia. Magnesium sulfate may compete with Ca²⁺ for intracellular sites or limit the influx of Ca²⁺ from damaged cellular membranes.

Hypermagnesemia may result in other pronounced effects on respiratory function, cardiac conduction and contractility, neuromuscular transmission, and electrolytes. Magnesium at toxic levels (14–15 mg/dl) can produce respiratory depression, heart block, and cardiac arrest. Lower levels of hypermagnesemia have been associated with arrhythmias and worse outcomes in patients following acute myocardial infarction with heart failure. High levels of Mg²⁺ have been shown to act as a negative inotrope, which may become quite significant in patients with advanced heart failure. In patients with preexisting disorders of neuromuscular transmission, Mg²⁺ may exacerbate weakness. High dosages of Mg²⁺ have also been shown rarely to increase K⁺ and lower Ca²⁺ levels. The effect of Mg on reversing vasospasm in an animal SAH model has been studied. Ram, et al., simulated SAH by intracisternal injection of blood in the rat. Infusion of intravenous MgSO₄ dilated the spastic basilar artery by approximately 75% of the baseline diameter in control rats (p < 0.0001). In that study the plasma Mg²⁺ levels in treated animals reached 2.5 mg/dl compared with 0.9 mg/dl in control rats.

The study of Mg in the prevention of cerebral vasospasm following human SAH has only recently been reported. Boet and Mee studied the clinical course of 10 patients who presented with Fisher Grade 3 hemorrhage in an unblinded noncontrolled pilot study to judge the safety and effectiveness of MgSO₄ infusion. No adverse events were noted during the infusions. Our study documents the first prospective, randomized, single-blind pilot trial. We examined the safety and effectiveness of intravenous administration of MgSO₄ in neurosurgical patients, and measured its efficacy for prevention of vasospasm and improvement in neurological outcome. This treatment had no adverse effects when serum levels ranged between 4 and 5.5 mg/dl. Use of MgSO₄ did not interfere with neurological evaluation, hemodynamic stability, or respiratory function. The serum level of Mg²⁺ could be readily maintained with relatively few adjustments in infusion rate over the 10-day treatment period. Overall outcome measures of MCA velocity determined using TCD ultrasonography, incidence of posthemorrhage vasospasm, and GOS scores demonstrated no significant improvement in patients who received MgSO₄ compared with control patients; however, data obtained in our treated patients did reveal a trend (albeit not a statistically significant one) toward a higher percentage of patients attaining a GOS score of 4 or 5. The 40 patients comprising our pilot trial were an insufficient number to obtain statistical significance. For the percentage of patients in our study who had a GOS score of 4 or 5 to reach significance, we estimate that 170 patients per group (MgSO₄ compared with placebo, Hunt and Hess Grades II–IV) would be needed to achieve the 80% power required for the observed difference. Such numbers would be ideal for further investigations of MgSO₄ in a prospective randomized multicenter trial.

In summary, our clinical trial has shown that high-dose MgSO₄ therapy is safe in neurosurgical patients with SAH and that target therapeutic levels are easily achieved. Although we did not observe any benefit conferred by Mg²⁺ on patients in this pilot trial with respect to MCA velocity, clinical vasospasm, or ultimate GOS score, we did observe a trend in patients with Hunt and Hess Grade II SAH to have improved neurological outcomes at 3 months posthemorrhage. A larger study is warranted to investigate this trend further.

References

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### TABLE 3

<table>
<thead>
<tr>
<th>Hunt &amp; Hess Grade</th>
<th>Placebo Treated Group</th>
<th>MgSO₄ Treated Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>MCA velocity (cm/sec)*</td>
<td>105 ± 33</td>
<td>95 ± 21</td>
</tr>
<tr>
<td></td>
<td>GOS score*</td>
<td>4.2 ± 1.0</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>% of patients w/ GOS Score 4 or 5</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>III or IV</td>
<td>MCA velocity (cm/sec)*</td>
<td>98 ± 38</td>
<td>92 ± 34</td>
</tr>
<tr>
<td></td>
<td>GOS score*</td>
<td>2.9 ± 1.7</td>
<td>2.9 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>% of patients w/ GOS Score 4 or 5</td>
<td>29</td>
<td>40</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SDs.