Chapter 6.

The effect of magnesium sulfate on large cerebral artery blood flow in severe preeclampsia

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ABSTRACT

Objectives

To determine the effect of a 6 gram intravenous bolus of magnesium sulfate on maternal cerebral blood flow in women with preeclampsia.

Study Design

Velocity-encoded phase-contrast magnetic resonance imaging studies were performed on twelve preeclamptic women prior to and immediately after infusion of a 6 gram magnesium sulfate loading dose. Cerebral blood flow was determined at the bilateral proximal middle and posterior cerebral arteries. Study participants returned 6 weeks postpartum for a non-pregnant measurement of cerebral blood flow. The Wilcoxon paired-sample test was used with statistical significance defined as p < 0.05.

Results

There was no significant difference in cerebral vessel diameter nor blood flow for any of the examined arteries between the pre- and post magnesium sulfate therapy states.

Conclusions

The absence of a significant difference in cerebral blood flow of the middle and posterior cerebral arteries before and after infusion of a 6 gram loading dose of magnesium sulfate in women with preeclampsia could suggest the absence of vasoconstriction of the large cerebral arteries in preeclampsia and question the role of magnesium sulfate as a vasodilator of these arteries.
INTRODUCTION

Magnesium sulfate (MgSO$_4$) therapy has been used successfully for many years in the USA for the prevention and treatment of eclamptic seizures $^1$. There remains controversy about this course of treatment since MgSO$_4$ is not a proven anticonvulsant. However, there is sufficient evidence to suggest that MgSO$_4$ is more effective for the prevention of eclampsia than traditional anticonvulsants such as phenytoin and diazepam. In addition, MgSO$_4$ is more effective than placebo or nimodipine, a calcium antagonist believed to have specific cerebral vasodilatory properties $^{2-5}$.

Two major hypotheses have evolved to explain the development of convulsions in eclampsia. In the first, eclampsia is attributed to lesions caused by cerebrovascular “overregulation” with extreme vasospasm that results in ischemia, cytotoxic cerebral edema and infarction $^{6,7}$. The second hypothesis is that eclampsia is caused by a loss of autoregulation leading to hyperperfusion with subsequent interstitial or vasogenic cerebral edema $^{8,9}$.

In this study, velocity-encoded phase-contrast magnetic resonance imaging (MRI) was utilized to measure both velocity and vessel diameter in the intracerebral circulation in women with preeclampsia before and after MgSO$_4$ therapy. Such accurate determination of cerebral blood flow in the large intracranial arteries would confirm the presence, if any, of vasospasm and its resolution after treatment. If eclampsia is due to cerebral vasospasm then MgSO$_4$ may have some vasodilatory properties inducing alterations in blood flow in the large cerebral arteries. If however, eclampsia is associated with hyperperfusion and ensuing focal vasogenic edema, then cerebral blood flow may not be altered after treatment with MgSO$_4$. 

MATERIALS AND METHODS

Twelve patients with preeclampsia were recruited from the labor and delivery suite at Parkland Hospital. Preeclampsia was defined according to the latest criteria of the National High Blood Pressure Education Program Working Group (new onset hypertension with persistent blood pressures ≥ 140/90 mmHg with ≥ 3+ protein on dipstick) \(^{10}\). Women with sustained blood pressures ≥ 160/110 mmHg were excluded from participation secondary to the need for intravenous antihypertensive medication. Those with cerebral symptoms such as headache or scotomata were excluded in order not to delay initiation of MgSO\(_4\) therapy. Women with a history of chronic hypertension or neurologic disorders were excluded as well. None of the women received any drugs or fluid therapy prior to initiation of the study.

All women were studied on a 1.5T magnet (Signa Horizon LX NVI, GE, Milwaukee, WI) after signing an informed consent document approved by the University of Texas Southwestern Medical Center Institutional Review Board. A single shot fast spin echo T\(_2\) weighted sequence in the axial plane was obtained first to document edema or other findings as later interpreted by a radiologist. A rapid three dimensional time of flight magnetic resonance angiogram sequence of the circle of Willis (TR=22, TE=4, flip angle = 20°, NSA=1) using magnetization transfer contrast enhancement was performed with the resulting magnetic resonance angiogram maximum intensity projection reconstructed from a data matrix of 64 slices (1.6 mm thickness, 18 cm FOV, 256 x 224 matrix). Velocity images were then obtained of the proximal right and left middle cerebral arteries and right and left posterior cerebral arteries. In order to ensure that the velocity images were obtained in a straight section of the artery under investigation, a scout image (TR=34, TE=17, flip angle = 20°, 20 cm FOV, 512 x 256 matrix) along the long axis of the vessel in the circle of Willis visualized in the maximum intensity projection was recorded for each artery. A peripherally gated phase contrast sequence (TR=34, TE=7, flip angle = 40°, 3 mm slice thickness, 20 cm FOV, 256 x 256 matrix) was applied perpendicular to the course of the artery as seen on the scout image to obtain velocity information. Velocity encoding was in the slice select direction with a set value of 120 cm/s (Figure 1 - 4). This range of encoded velocities has been found to be effective for measuring normal cerebral arterial flow velocities \(^{11}\) and should allow for the
unambiguous measurement of higher velocities which are predicted in the event that significant vasospasm was found.

After this first magnetic resonance imaging study set which lasted a total of 20 minutes was completed, the women were given 6 grams of MgSO₄ intravenously over a 20-minute period, directly after which an identical 20 minute imaging sequence as the pre-treatment one was repeated. Upon completion of the study the patient was transported back to the labor and delivery suite for delivery. Magnesium sulfate infusion was continued per protocol at 2 grams/hour until 24 hours postpartum. Study participants returned 6-8 weeks postpartum for a non-pregnant cerebral blood flow determination. One patient elected not to return due to claustrophobia and one was lost to follow-up.

Cerebral blood flow measurements \[ \text{Flow (mL/min)} = \text{vessel area (cm}^2\text{)} \times \text{velocity (cm/min)} \] were analyzed with a Wilcoxon paired-sample signed-ranks test which tested for differences between the pre-MgSO₄, post-MgSO₄ and follow-up studies in each artery for each patient. Statistical significance was defined as \( p < 0.05 \).

RESULTS

Some clinical characteristics of the twelve women with preeclampsia are shown in Table 4. Eight were nulliparous. The mean gestational age at delivery was 36.8 ± 2.6 weeks.

Flow data was not obtained in the posterior cerebral arteries of one patient due to excessive motion. Using a Wilcoxon paired-sample signed-ranks analysis, there was no significant difference in blood flow between the pre- and post-MgSO₄ studies (Table 5). In addition, there was no significant difference in flow in any of the arteries when the pre-MgSO₄ and postpartum studies were compared (p-values 0.38, 0.28, 0.11, and 0.77 for the right and left MCA, and the right and left PCA, respectively).

The same holds true for vessel diameter. There was no significant difference in vessel diameter between the pre- and post-MgSO₄ studies (Table 6, Figure 14). In addition, there was no significant difference in diameter in any of the arteries when
the pre-MgSO₄ and postpartum studies were compared (p-values 0.16, 0.56, 0.63, and 0.99 for the right and left MCA, and the right and left PCA, respectively).

No evidence of edema was seen on the T₂ weighted image; edema would be seen as increased signal intensity on these images. There was no change in the diameter of the large vessels of the Circle of Willis to suggest vasospasm or vasodilation. Based on the MRI velocity image resolution, the minimum detectable change in vessel diameter was calculated to be 20%. Thus, probability testing at the 0.05 level of significance to detect a 20% difference in flow compared with the postpartum study revealed a power of 93-99% for the right and left middle cerebral arteries and right posterior cerebral artery, but 60% for the left posterior cerebral artery.

<table>
<thead>
<tr>
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<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>23.5 ± 6.2</td>
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<tr>
<td>Gestational age (wks)</td>
<td>36.8 ± 2.6</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>2666 ± 673</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>156 ± 9.7</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>100.5 ± 8.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>33.4 ± 4.2</td>
</tr>
<tr>
<td>Platelets (x10³/mm³)</td>
<td>224 ± 49</td>
</tr>
<tr>
<td>AST (Aspartate Aminotransferase) (IU/L)</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>29.0 ± 27.2</td>
</tr>
</tbody>
</table>

Table 4. Clinical characteristics of 12 women with severe preeclampsia
<table>
<thead>
<tr>
<th></th>
<th>Right MCA</th>
<th>Left MCA</th>
<th>Right PCA</th>
<th>Left PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-MgSO$_4$</strong></td>
<td>154.0 (17.2)</td>
<td>147.0 (21.0)</td>
<td>58.2 (9.2)</td>
<td>61.7 (15.6)</td>
</tr>
<tr>
<td><strong>Post-MgSO$_4$</strong></td>
<td>154.2 (28.8)</td>
<td>147.6 (22.7)</td>
<td>60.1 (9.1)</td>
<td>62.2 (20.3)</td>
</tr>
<tr>
<td><strong>6 w postpartum</strong></td>
<td>158.7 (16.3)</td>
<td>153.4 (29.5)</td>
<td>63.3 (13.0)</td>
<td>64.0 (19.4)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.79</td>
<td>0.99</td>
<td>0.83</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* p-value comparing pre- and post MgSO$_4$ values

**Table 5.** Mean calculated flow (mL/min) and standard deviations for all examined arteries.

<table>
<thead>
<tr>
<th></th>
<th>Right MCA</th>
<th>Left MCA</th>
<th>Right PCA</th>
<th>Left PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-MgSO$_4$</strong></td>
<td>2.42 (0.08)</td>
<td>2.42 (0.09)</td>
<td>1.85 (0.10)</td>
<td>1.89 (0.12)</td>
</tr>
<tr>
<td><strong>Post-MgSO$_4$</strong></td>
<td>2.42 (0.13)</td>
<td>2.39 (0.05)</td>
<td>1.86 (0.16)</td>
<td>1.85 (0.15)</td>
</tr>
<tr>
<td><strong>6 w Postpartum</strong></td>
<td>2.45 (0.06)</td>
<td>2.46 (0.07)</td>
<td>1.88 (0.12)</td>
<td>1.90 (0.08)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.97</td>
<td>0.21</td>
<td>0.85</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* p-value comparing pre- and post MgSO$_4$ values

**Table 6.**

Mean vessel diameter (mm) and standard deviations for all examined arteries.
DISCUSSION

In this study we used a velocity-encoded phase-contrast magnetic resonance imaging technique to measure cerebral blood flow in women with preeclampsia before and after administration of MgSO₄ as well as postpartum. The middle cerebral and posterior cerebral arteries were the ones studied because of the high velocity of the middle cerebral artery and the clinical findings in eclampsia suggesting symptoms related to the posterior circulation. We found that cerebral blood flow and the caliber of these arteries did not change with administration of MgSO₄.

To better understand the cerebrovascular mechanism(s) involved in the pathophysiology of eclamptic convulsions, a number of neuroimaging techniques have been used that include cerebral angiography⁶,⁷, computed tomography⁶,¹²,¹³, MRI¹¹ and Doppler velocimetry⁸. Of the techniques listed, only phase-contrast MRI is an established method of accurately measuring both velocity and arterial cross-sectional area, the two quantities required for the accurate determination of blood flow¹¹,¹⁴. A prior phase-contrast MRI study from our institution¹¹ showed no significant difference in either the middle or posterior cerebral artery blood flow in women with eclampsia and severe preeclampsia between their acute postpartum and delayed baseline follow up studies, as well as compared to their normal cohorts. The blood flow was unchanged despite the presence of remarkable brain lesions in all 8 women with eclampsia. However, all the subjects in that study were examined after receiving MgSO₄. Thus, in spite of the findings of varying levels of severity of edema on MRI, it is possible that any vasospasm could have resolved by the treatment and therefore, before blood flow was measured. In the current study, women with preeclampsia were examined before and immediately after receiving a therapeutic bolus of MgSO₄ so that any acute vasodilatory effects of magnesium could be assessed.

Previous studies evaluating the effects of MgSO₄ on the cerebral circulation in preeclampsia have mainly used transcranial Doppler ultrasound. One group reported no significant differences in antepartum (before MgSO₄ administration) and postpartum (after MgSO₄ discontinuation) mean middle cerebral artery flow velocity in a group of 46 women with preeclampsia⁰¹⁵. Another study evaluated the antepartum middle cerebral artery before and after MgSO₄ administration and found no changes in flow velocity, but a significant decrease in pulsatility index was noted.
which led the investigators to speculate that MgSO$_4$ acted to vasodilate more distal vessels \textsuperscript{16}. In another study, the blood velocity of the middle cerebral artery in 12 preeclamptic patients was observed to increase in response to MgSO$_4$ therapy \textsuperscript{17}, whereas a later study suggests that middle cerebral artery velocity decreases in the 13 eclamptic women who received a loading dose of 4 grams MgSO$_4$ \textsuperscript{18}. Major limitations of transcranial Doppler ultrasound are its inability to measure vessel cross sectional area and therefore true blood flow \textsuperscript{19,20}. Typically, blood flow is inferred from velocity and other mathematically derived indices.

The lack of any statistically significant change in either the diameter or flow after the administration of MgSO$_4$ in this study suggests it may not act as an arterial vasodilator of large vessels in preeclampsia. Current MRI technology does not permit the accurate evaluation of flow in smaller, downstream arterioles. Even though the mean change in blood flow was not significant, it is possible that some of the smaller arterioles responded with vasodilation while others did not. Indeed, the occurrence of ischemia may be secondary hyperperfusion rather than hypoperfusion. Vasogenic edema secondary to hyperperfusion is seen in hypertensive encephalopathy and seems to play an important role when eclampsia develops \textsuperscript{8,9}. The neuroimaging findings of women with eclampsia are remarkably similar to those described in non-pregnant patients with hypertensive encephalopathy \textsuperscript{13,21}. In addition, neuropathological findings reported in non-pregnant individuals with fatal hypertensive encephalopathy resemble those described for eclampsia \textsuperscript{22}.

Some limitations to our study should be addressed. First, while phase-contrast MRI is suitable for evaluating blood flow in the large cerebral arteries, it does not measure blood flow in the more downstream resistance arterioles where changes in diameter may occur in response to the instituted therapy. Due to the limitations in resolution imposed by the MR sequence parameters, if such changes did occur in the diameters of the more distal vessels, it is very likely that our technique missed any resulting changes in blood flow in the proximal large cerebral arteries of less than 20 \%. In comparison, other studies, which did detect a change in MCA flow in preeclamptic women pre- and post MgSO$_4$ infusion, have reported increases of 32 \% in blood velocity. Second, this study excluded the most severe of the preeclamptic patients such as those with headache and/or scotoma. Also, women with blood pressures exceeding 160/110 mmHg required immediate initiation of antihypertensive therapy, which would confound cerebral blood flow studies. Since
the process of obtaining informed consent, transporting and imaging the patients took close to 2 hours, it was felt that their therapy could not be delayed for that long and thus they were excluded from the study. Third, it is known that the effects of MgSO$_4$ peak almost immediately after administration$^{23}$. We particularly chose to repeat the study at the end of the bolus infusion because serum concentrations of Mg$^{2+}$ are maximal at that time$^{24}$. In addition, our patients showed the typical side effects of a bolus infusion such as flushing. The MRI determination of flow for each artery was performed at one moment in time and any effects of MgSO$_4$ that did not coincide with that time-window were probably missed. Last, we report this study having only 12 study participants. Power analysis after the 12$^{th}$ woman had enrolled revealed sufficient power to conclude that there is no change in cerebral blood flow after administration of MgSO$_4$ in the right and left MCA and the right PCA. There was insufficient power to conclude the same for the left PCA. Our explanation for the differential behavior of this vessel is that during the study protocol this was always the last of the 4 blood vessels to be examined. Patient fatigue and motion likely played a role in obtaining reliable measurements.

In summary, our findings suggest that MgSO$_4$ does not act by means of direct vasodilation of the large cerebral arteries, challenging the vasoconstriction model for symptoms of preeclampsia and eclampsia. Until further studies of the mechanism of preeclampsia and eclampsia are performed, MgSO$_4$ remains the therapy of choice for the control and prevention of eclamptic convulsions, based on its clinical effectiveness in several trials$^{2-5}$.
REFERENCES


23. Pritchard JA. The use of the magnesium ion in the management of eclamptogenic toxemias. Surgery, Gynecology & Obstetrics 1955; 100(2):131-140