Magnesium Sulfate Reverses Experimental Delayed Cerebral Vasospasm After Subarachnoid Hemorrhage in Rats

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We induced experimental delayed cerebral vasospasm by the intracisternal injection of > 0.5 ml blood in 30 rats. Seventy-two hours later the basilar artery was exposed via the transclival approach and photographed at high-power magnification through an operating microscope. We then evaluated the effect of topical (n = 30) and intravenous (n = 20) magnesium sulfate on the spastic artery by computerized image analysis. A > 50% reduction in baseline diameter of the basilar artery was observed in the rats subjected to subarachnoid hemorrhage compared with the 10 controls (p < 0.0001). Intravenous magnesium sulfate dilated the spastic artery to approximately 75% of the baseline diameter in control rats (p < 0.0001). Topical magnesium sulfate caused dramatic dilation of the basilar artery in both the control and the subarachnoid hemorrhage groups to near 150% of the baseline diameter in the controls (p < 0.001). All rats receiving intravenous magnesium sulfate reached therapeutic plasma levels of the ion. Hemodynamic effects were mild and immediately reversible upon cessation of magnesium sulfate administration. We suggest that magnesium has a role in the treatment of subarachnoid hemorrhage-induced vasospasm in humans. (Stroke 1991;22:922–927)

Cerebral vasospasm is a major complication of aneurysmal subarachnoid hemorrhage (SAH) that contributes to the high incidence of morbidity and mortality from this disease.1 Different physiological perturbations, such as the activation of lipid peroxidation and the liberation of free radicals, changes in the activity of scavenger enzymes, and the enhancement of arachidonic acid metabolism, have been implicated in the development of SAH-induced vasospasm.2–5 Regardless of the many possible etiologies for SAH-induced vasospasm, it seems that impaired homeostasis of Ca2+ is the final common pathway responsible for this complication.6 Numerous reports investigating the potential of calcium channel blockers and calmodulin inhibitors to prevent or reverse ischemic damage related to vasospasm have been published in recent years with contrasting results.7–13

Recently, cerebral vasospasm has been implicated in the pathogenesis of another disease—
toxemia of pregnancy.14 Computed tomograms of eclamptic women have shown hypodense lesions in the basal ganglia and cortex suggestive of ischemia.15–17 Cerebral angiography performed in such patients reveals widespread diffuse narrowing of all intracranial arteries.18–20

Since 192521 eclampsia has been successfully treated with magnesium sulfate, which is considered to be the drug of choice for preeclampsia-eclampsia in toxemic women.22 It has been suggested that magnesium prevents eclamptic vasospasm via Ca2+ antagonism.23 Accordingly, we evaluated the effect of magnesium on SAH-induced vasospasm.

Materials and Methods

We divided 40 male Sprague-Dawley rats weighing 375–400 g into three groups. Twenty rats were subjected to SAH and were treated with intravenous magnesium followed by topical magnesium, 10 rats were subjected to SAH and were treated only with topical magnesium following the intravenous infusion of saline, and 10 rats were not subjected to surgical procedures for SAH and served as controls for determination of the baseline basilar artery diameter and the effect of topical magnesium.

The 30 experimental rats were anesthetized with 40 mg/kg i.p. pentobarbital sodium and 15 μg/kg i.p. atropine sulfate. Cefazolin (10 mg/kg i.m.) was given
was exposed from the vertebrobasilar junction to just proximal to its bifurcation. A few rats in which a small arachnoidal artery was ruptured during the exposure were excluded from the study due to an extreme spastic response of the artery to the surrounding blood. The basilar artery was washed with warmed (37°C) saline and allowed to recover for 60 minutes from any possible effects of surgical manipulation. Photographs were taken at high (×25) magnification after another blood gas determination was made to document normocarbia and adequate oxygenation (Pao2 of 100–125 mm Hg). Three photographs were taken 5 minutes apart at each phase of the experiment (baseline and following each therapeutic intervention as specified above). An identical procedure was performed on the 10 control rats.

The photographs were analyzed using an image analyzer (Olympus Q2, Galai Corp., Ramat Gavriel, Israel) with a 0.8 magnification ratio. The diameter of the basilar artery was determined as the average for three points (vertebrobasilar junction, middle of the pons, and upper pons just proximal to bifurcation of the basilar artery). For each rat a single value was derived that comprised the average for the three photographs as well as for the three points.

Upon exposure of the basilar artery, baseline photographs were taken and magnesium sulfate was topically applied by placing a piece of Gelfoam soaked with 10 mcg/ml magnesium sulfate solution (37°C) for 10 minutes. After removal of the Gelfoam, the basilar artery was washed with warmed saline (37°C) and photographed. The procedure was repeated with 4,000 mcg/ml magnesium sulfate solution to establish the maximal dilatational effect of magnesium.

In the 10 rats exposed to SAH and topical treatment only, magnesium was applied after the infusion of normal saline at a volume and rate equivalent to that given the 20 rats receiving SAH and systemic intervention as specified above. An identical procedure was performed on the 10 control rats. Photographs were taken 5 minutes apart at each phase of the experiment (baseline and following each therapeutic intervention as specified above). An identical procedure was performed on the 10 control rats.

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In the 10 rats exposed to SAH and topical treatment only, magnesium was applied after the infusion of normal saline at a volume and rate equivalent to that given the 20 rats receiving SAH and topical and intravenous magnesium. In these 20 rats, upon exposure of the basilar artery baseline photographs were taken. Magnesium sulfate (300

mg/kg) dissolved in 10 ml normal saline was infused at a constant rate (0.22 ml/min, Harvard Infusion Pump, Harvard Apparatus) over 45 minutes. Postinfusion photographs of the basilar artery were obtained 15 minutes later. Magnesium was then applied topically as previously described.

At the end of the experiment, arterial blood samples were taken for the evaluation of plasma magnesium levels by atomic absorption spectrophotometry (300S, Perkin-Elmer, Beaconsfield, U.K.). Data were analyzed using analysis of variance and Student's t test for paired samples. Correlations were studied using linear regression analysis. All values are given as mean±standard deviation.

Results

There was no SAH-related mortality. Mean Paco2 and PaO2 remained relatively constant within the range described above for each rat during the experiment, with an average variation of <5%.

All experimental rats showed marked spasm of the basilar artery 72 hours after the induction of SAH compared with the controls (p<0.0001). Mean diameter of the spastic artery in the 30 experimental rats (183±42 μm) was 46% of that in the controls (395±79 μm).

Following the topical application of magnesium, significant dilatation of the basilar artery was observed in the control and both SAH groups (Figure 1). After application of the 10 meq/l solution, the basilar artery in the control rats dilated to 132% (522±81 μm) of baseline values (p<0.001). Application of the 4,000 meq/l solution led to a further increase in diameter, to 145% (574±84 μm) of baseline values. We observed a similar effect in rats subjected to SAH. Following saline infusion, 10 meq/l magnesium dilated the artery from 48% (188±50 μm) of the baseline value in the control rats to 95% (375±132 μm) of baseline in the controls, and 4,000 meq/l magnesium increased the diameter to 148% (585±67 μm) of baseline in the controls (p<0.001). We found similar results when the topical application of both concentrations followed the intravenous infusion of magnesium (Figures 1 and 2), with no significant difference in mean maximum dilatation among the three groups.

The intravenous infusion of magnesium led to significant (p<0.0001) dilation of the spastic basilar artery, from 45% (178±36 μm) of the baseline value in the controls to 74% (293±58 μm) of baseline in the controls (Figure 1). However, the diameter after intravenous magnesium was still significantly lower than baseline in the controls (p<0.05). The intravenous infusion of 10 ml saline to SAH rats later treated with topical magnesium did not change basilar artery diameter (Figure 1).

Mild hemodynamic changes were observed during the intravenous infusion of magnesium (Figure 3). By the end of the infusion, heart rate had decreased from a mean of 240/min to 180/min. By 60 minutes after the infusion, heart rate had increased to a plateau slightly lower than the baseline value (230/min). Mean arterial blood pressure also decreased, from a mean of 105 mm Hg at the start of the infusion to 79 mm Hg at the end, with a return to near-baseline values (100 mm Hg) 30 minutes later.

Plasma magnesium levels reached 10.5±2.5 mg%/ in arterial blood samples drawn from 12 rats 120 minutes after completion of the magnesium infusion. This level was significantly higher than that of control
rats (3.0±0.9 mg%) and rats subjected to topical magnesium application only (3.2±1.1 mg%, p<0.0001). No correlation was found between basilar artery diameter following magnesium infusion and plasma magnesium levels.

Discussion

Our results clearly demonstrate the ability of magnesium to dilate normal cerebral arteries as well as arteries with delayed spasm secondary to SAH in rats. In this model, significant delayed vasospasm of the basilar artery was evident 72 hours following massive SAH. The highly reproducible delayed arterial spasm found in our study is related, in our opinion, to the massive amount of blood introduced into the subarachnoid space. A similar correlation between the severity of arterial spasm and the amount of blood in the subarachnoid cisterns is well documented in humans.24

The role of calcium in mediating arterial vasospasm is well established.6 Calcium is involved in smooth muscle contraction by forming a complex with the intracellular protein calmodulin and activating the enzyme myosin light chain kinase. This enzyme catalyzes the covalent phosphorylation of myosin light chains. The interaction between actin and myosin that follows leads to arterial constriction.25,26

The mechanism by which magnesium reverses vasospasm has not been settled yet. However, magnesium has been shown to antagonize the calcium activity on vascular tone and in the neuromuscular junction.23,27,28 An increased calcium concentration induced vasospasm in isolated cerebral arteries; this effect was amplified by lowering and alleviated by increasing the magnesium concentration.27,28 In addition, hypermagnesemia has been shown in vitro to reverse the vasospasm induced by various agents.27

As a bivalent ion resembling Ca2+, Mg2+ is a competitive antagonist of calcium.23 High levels of magnesium have been shown to block the neuromuscular junction and lead to skeletal muscle paralysis by competing with Ca2+ at the presynaptic membrane and inhibiting Ca2+-dependent acetylcholine secretion. The injection of calcium gluconate, which is used as an antidote to magnesium intoxication, corrects the synaptic blockade by increasing the Ca2+ concentration at the synapse.14 Magnesium may antagonize Ca2+ at the N-methyl-D-aspartate subtype of glutamate receptor site and decrease calcium influx into smooth muscle cells.29 Magnesium may also block Ca2+ activity by a calmodulin-inhibiting effect.

Clinical studies combined with wide experience in the treatment of toxemia of pregnancy have shown that the antieclamptic effect is attained at serum magnesium levels below those depressing neuromuscular transmission.22 Our results demonstrate that arterial dilation was achieved at plasma magnesium levels similar to those considered “therapeutic” in eclamptic patients. Indirect clinical evidence for the possible role of magnesium in vasospasm due to SAH was supplied recently. Patients with SAH were divided according to the presence or absence of cerebral vasospasm. The CSF of patients with vasospasm demonstrated a slight but significant decrease in the Mg2+ concentration 6–8 days following SAH, with no change in the plasma Mg2+ level. The Mg2+ concentration was unchanged in the CSF of patients without vasospasm.26

The fact that magnesium is a well-known drug approved for the treatment of many clinical conditions coupled with our results suggest that magnesium has a role in the treatment of SAH-induced vasospasm in humans.

References


**KEY WORDS** • cerebral vasospasm • magnesium sulfate • subarachnoid hemorrhage • rats
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