Magnesium Sulfate for the Treatment of Eclampsia
A Brief Review

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Background and Purpose—Magnesium sulfate is used extensively for prevention of eclamptic seizures. Empirical and clinical evidence supports the effectiveness of magnesium sulfate; however, questions remain as to its safety and mechanism. This review summarizes current evidence supporting the possible mechanisms of action and several controversies for magnesium sulfate treatment.

Summary of Review—Several mechanisms are presented, including the effects of magnesium sulfate on peripheral and cerebral vasodilation, blood-brain barrier protection, and as an anticonvulsant.

Conclusions—Though the specific mechanisms of action remain unclear, the effect of magnesium sulfate in the prevention of eclampsia is likely multi-factorial. Magnesium sulfate may act as a vasodilator, with actions in the peripheral vasculature or the cerebrovasculature, to decrease peripheral vascular resistance or relieve vasoconstriction. Additionally, magnesium sulfate may also protect the blood-brain barrier and limit cerebral edema formation, or it may act through a central anticonvulsant action. (Stroke. 2009;40:00-00.)

Key Words: eclampsia ■ magnesium sulfate ■ vasodilation ■ blood-brain barrier ■ anticonvulsant

Magnesium sulfate (MgSO₄) has been used throughout the 20th century for prevention of eclamptic seizures,1,2 and it continues to be used extensively.3–5 Empirical evidence supports the effectiveness of MgSO₄ in preventing and treating eclamptic seizures,1,6–8 in addition to recent controlled clinical trials.5,9,10 For eclamptic seizure prophylaxis in preeclamptic women, MgSO₄ is superior to phenytoin,11,12 nimodipine,13 diazepam,14 and placebo.9 In the multinational Collaborative Eclampsia Trial, MgSO₄ reduced the risk of recurrent seizures in eclamptic women by 52% when compared to diazepam and by 67% when compared to phenytoin.15 The publication of these clinical trials significantly increased the use of MgSO₄ versus other anticonvulsants in the United Kingdom and Ireland, where the reported use in preeclampsia increased from 2% to 40%.6,16 In addition, 60% of providers surveyed indicated they would use magnesium as an anticonvulsant for eclampsia in 1998, up from only 2% of eclamptic women who received MgSO₄ in 1992.6,16,17

Although the effectiveness of MgSO₄ in treating and preventing eclampsia has been established, questions still exist as to its safety. There are concerns regarding the possibility of hypermagnesemia toxicity in eclampsia treatment. Normal serum concentrations of Mg²⁺ are 1.5 to 2.5 mEq/L (1.8 to 3.0 mg/dL), with one-third to one-half bound to plasma proteins.18,19 Total magnesium serum concentrations advocated for the treatment of eclamptic convulsions are 3.5 to 7 mEq/L (4.2 to 8.4 mg/dL),2,20,21 which can be obtained by administering it intramuscularly (6 g loading dose followed by 2 g/h), intravenously (2 to 4 g dose up to 1 g/min), or a combination of both.6,18,22 Areflexia, particularly loss of the patellar deep tendon reflex, has been observed at 8 to 10 mEq/L, and respiratory paralysis seen at >13 mEq/L.6,18,22 Progressively higher serum magnesium levels can ultimately lead to cardiac arrest.18,22,23 Some suggest that using standard infusion protocols may not lead to therapeutic serum magnesium levels in all patients, with 36.2% of patients found to have total serum magnesium lower than 4 mEq/L at 30 minutes after treatment initiation in one study,24 though no eclamptic seizures were reported during MgSO₄ treatment. In addition, there are reports that in some patients eclamptic seizures do not cease even with elevated levels of MgSO₄,6,7,25 suggesting that MgSO₄ is not effective in treating all cases of eclampsia.

As technological advances allow for ionized magnesium to be more readily measured, questions have arisen as to whether it is more appropriate to monitor total serum magnesium or the ionized physiologically active form. Studies have shown little correlation between total and ionized magnesium levels, either at baseline before treatment or during MgSO₄ treatment for preeclampsia.19,24 In preeclamptic patients treated with a loading dose of 4 g intravenously followed by 2 g per hour infusion, it was found that both total and ionized Mg²⁺ concentrations increased quickly after

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Magnesium-Induced Vasodilation

Magnesium is a unique calcium antagonist as it can act on most types of calcium channels in vascular smooth muscle and as such would be expected to decrease intracellular calcium. One major effect of decreased intracellular calcium would be inactivation of calmodulin-dependent myosin light chain kinase activity and decreased contraction, causing arterial relaxation that may subsequently lower peripheral and cerebral vascular resistance, relieve vasospasm, and decrease arterial blood pressure. The vasodilatory effect of MgSO₄ has been investigated in a wide variety of vessels. For example, both in vivo and in vitro animal studies have shown that it is a vasodilator of large conduit arteries such as the aorta, as well as smaller resistance vessels including mesenteric, skeletal muscle, uterine, and cerebral arteries. However, the importance of magnesium-induced vasodilation in the treatment and prevention of eclampsia is not completely understood.

The theory of cerebrovascular vasospasm as the etiology of eclampsia seemed to be reinforced by transcranial Doppler (TCD) studies which suggested that MgSO₄ treatment caused dilation in the cerebral circulation as well as in animal studies that used large cerebral arteries. However, a vasodilator such as MgSO₄ would seem to be a paradoxical treatment choice for eclamptic encephalopathy. Eclampsia is thought to be a form of posterior reversible encephalopathy syndrome (PRES) and similar to hypertensive encephalopathy, in which acute elevations in blood pressure cause forced dilatation of the myogenic vasocostriction of cerebral arteries and arterioles, increased BBB permeability and edema formation. Studies from our laboratory have shown that MgSO₄ causes concentration-dependent vasodilatation in both cerebral and mesenteric resistance arteries; however, mesenteric arteries were significantly more sensitive to MgSO₄, particularly during pregnancy. The finding of a modest vasodilatory effect in the cerebral circulation are consistent with other findings that MgSO₄ treatment caused no significant change in cerebral blood flow (CBF), large cerebral artery diameter, or mean middle cerebral artery velocity as determined by MR1 and TCD. Together, these results suggest that the effects of MgSO₄ as an eclamptic seizure prophylaxis may be more closely related to an effect on peripheral vascular resistance and lowering of systemic blood pressure than to a direct effect on CBF (Figure 1).

Reports of the effects of MgSO₄ treatment on arterial blood pressure have been mixed. Hypotensive effects have been noted in various studies particularly with bolus injections, though the duration of decreased blood pressure was varied. In pregnant rats treated with the nitric oxide synthase inhibitor l-NAME to induce hypertension, combination treatment with MgSO₄ resulted in significantly lower blood pressures at term and better neonatal outcomes versus animals treated with l-NAME alone. However, it has been cautioned that MgSO₄ should not be considered primarily an antihypertensive agent, as there are other drugs better suited for that purpose in eclampsia, including hydralazine, labetalol, and nifedipine.

Several reports have suggested that gestation may influence vascular reactivity to MgSO₄ and that sensitivity varies with vascular bed. Human uterine arteries from pregnant patients are 3-fold more reactive to MgSO₄ than uterine arteries from nonpregnant patients. In aorta from pregnant and nonpregnant rats, both increased and decreased sensitivity to MgSO₄-induced vasodilation have been shown based on the preconstriction agent used for in vitro studies. These studies also suggest that pregnancy may differentially affect receptor- versus voltage-operated calcium channels in aortic smooth muscle. In another study of rat aortic rings, the effect of MgSO₄ was dependent on gestation and nitric oxide production such that vasodilation was less at term than during late pregnancy. Our studies found that while mesenteric resistance arteries showed no change in sensitivity with gestation, posterior cerebral resistance arteries from late-pregnant and postpartum animals were significantly less sensitive to MgSO₄-induced vasodilation versus those from nonpregnant animals. This may be attributable to gestation-induced changes in the cerebral endothelial vasodilatory mechanisms that have been demonstrated during pregnancy and the postpartum state. MgSO₄ may have other effects within the vasculature that could also explain its effectiveness in eclampsia (included in Figure 1). Magnesium may act by stimulating production of prostacyclin by endothelial cells causing vasodilation, or by inhibiting platelet aggregation. In patients with pregnancy-induced hypertension, MgSO₄ treatment significantly decreased circulating levels of angiotensin-converting enzyme. These actions may attenuate the endothelial dysfunction associated with (pre) eclampsia.

Effects on the Blood-Brain Barrier and Cerebral Edema Formation

The cerebral endothelium that forms the BBB has unique features compared to the peripheral endothelium including a lack of capillary fenestrations, a low basal rate of pinocytosis, and the presence of high electric resistance tight junctions between adjacent endothelial cells. Disruption of the BBB can result in vasogenic edema formation, an important component in the clinical picture of eclampsia. Decreased BBB permeability with MgSO₄ treatment has been reported in a variety of animal models of BBB disruption.
including traumatic brain injury, septic encephalopathy, hypoglycemia, and mannitol injection. We recently reported MgSO4 treatment decreased BBB permeability in response to acute hypertension in late-pregnant rats. In addition, several studies have shown that MgSO4 decreases cerebral edema formation after brain injury. Together, these studies importantly suggest that one mechanism by which MgSO4 is effective in eclampsia treatment may be through protection of the BBB and decreased cerebral edema formation.

Several mechanisms of action have been proposed to explain the neuroprotective effects of MgSO4 (Figure 2). Magnesium is a calcium antagonist that acts both intracellularly and extracellularly, and may act directly on cerebral endothelial cells. It is possible that by acting as a calcium antagonist at the level of the endothelial cell actin cytoskeleton, MgSO4 opposes paracellular movement of solutes through the tight junctions (Figure 2). This hypothesis is supported by several studies which demonstrated that inhibition of myosin light chain (MLC) phosphorylation decreases agonist-induced permeability by inhibiting actin stress fiber contraction. Alternatively, pinocytosis is induced by acute hypertension and may contribute to increased BBB permeability during elevated intravascular pressure. MgSO4 treatment may therefore decrease pinocytosis caused by acute hypertension and restrict the movement of water and solutes into the brain by transcellular transport, thereby limiting edema formation and improving clinical outcomes in eclampsia.

Anticonvulsant Activity
Although widely used, there is controversy regarding the use of MgSO4 treatment for neurological conditions, such as eclamptic seizures. Concerns have been raised that MgSO4 treatment may mask the outward signs of convulsions through its action at the neuromuscular junction without treating the cause of the seizure in the central nervous system. Dose-related depression of neuromuscular transmission has been shown in preeclamptic women receiving traditional MgSO4 therapy. Studies have also shown that there is little to no change in electroencephalograms obtained during MgSO4 treatment, and minimal signs of central nervous system depression in both normal and eclamptic patients and in animals. However, clinical trials have demonstrated the efficacy of MgSO4 in the treatment and prevention of eclamptic seizures versus more traditional anticonvulsant drugs, including phenytoin and diazepam.

The possible anticonvulsant activity of magnesium may be related to its role as an N-methyl-d-aspartate (NMDA) receptor antagonist, shown in Figure 3. Seizures are thought to be mediated at least in part by stimulation of glutamate receptors, such as the NMDA receptor. In
rats, systemic magnesium treatment results in a resistance to both electrically stimulated and NMDA-induced hippocampal seizures. In addition, systemic treatment with MgSO4 causes a significant reduction in the NMDA receptor binding capacity in the brain. Animal studies have also shown that MgSO4 reduces epileptic seizure activity, though these findings have been challenged because of inadequate controls.

Magnesium ions must cross the BBB to elicit a central anticonvulsant effect. It has been demonstrated in animals that MgSO4 can cross the intact BBB and enter the central nervous system in correlation with the level of serum hypermagnesemia. Interestingly, seizure activity increases the movement of magnesium into the brain. Human studies have also shown small but significant increases in cerebrospinal fluid concentrations of MgSO4 after systemic administration. Conversely, other work has suggested that the BBB prevents changes in brain and cerebrospinal fluid magnesium concentrations. However, this same group later suggested that even a small amount of magnesium in the central nervous system may suppress cortical neuronal activity. The possibility remains that acute hypertension that leads to convulsions and BBB disruption may permit MgSO4 to enter the brain parenchyma and act as an anticonvulsant during eclampsia.

### Future Directions

A better understanding of the mechanisms of action of MgSO4 could allow for more directed use in the treatment of eclampsia and other brain injury disorders. An interesting area for future studies is the relationship between MgSO4 and cerebral edema formation, as it has been proposed that MgSO4 may limit cerebral edema formation through an effect on aquaporin (AQP) expression. Aquaporin-4 (AQP4) is a water channel protein that has been localized to astrocytic endfeet and possibly cerebral endothelium, which is associated with cerebral edema formation (through unknown mechanisms).
models focus on different aspects of the disease including the impact of placental perfusion, preexisting hypertension, and the significance of endothelial dysfunction, oxidative stress, and circulating antiangiogenic factors. The pros and cons of the different models have been reviewed elsewhere, all of which provide opportunities to further study the specific actions of MgSO4 for seizure prophylaxis.

Conclusion
MgSO4 has been shown to be an effective treatment option for the prevention of eclampsia. Its mechanism of action is likely multi-factorial, encompassing both vascular and neurological mechanisms. Being a calcium antagonist, its effect on vascular smooth muscle to promote relaxation and vasodilation may have a role in lowering total peripheral vascular resistance. In addition, MgSO4 may have an effect on the cerebral endothelium to limit vasogenic edema by decreasing stress fiber contraction and paracellular permeability via calcium-dependent second messenger systems such as MLC kinase. Lastly, MgSO4 may also act centrally to inhibit NMDA receptors, providing anticonvulsant activity by increasing the seizure threshold. A more complete understanding of the effects of MgSO4 will likely promote safer and more effective treatments of eclampsia.

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References


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