Magnesium Sulfate for the Treatment of Eclampsia
A Brief Review

Anna G. Euser, PhD; Marilyn J. Cipolla, PhD

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;40:1169-1175.)

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

Magnesium sulfate (MgSO_4) has been used throughout the 20th century for prevention of eclamptic seizures, and it continues to be used extensively. Empirical evidence supports the effectiveness of MgSO_4 in preventing and treating eclamptic seizures, in addition to recent controlled clinical trials. For eclamptic seizure prophylaxis in preeclamptic women, MgSO_4 is superior to phenytoin, and nimodipine, diazepam, and placebo. In the multinational Collaborative Eclampsia Trial, MgSO_4 reduced the risk of recurrent seizures in eclamptic women by 52% when compared to diazepam and by 67% when compared to phenytoin. The publication of these clinical trials significantly increased the use of MgSO_4 versus other anticonvulsants in the United Kingdom and Ireland, where the reported use in preeclampsia increased from 2% to 40%. 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 MgSO_4 in 1992.

Although the effectiveness of MgSO_4 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 Mg^{2+} 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. 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), 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. 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. Progressively higher serum magnesium levels can ultimately lead to cardiac arrest. Though no eclamptic seizures were reported during MgSO_4 treatment, 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, though no eclamptic seizures were reported during MgSO_4 treatment. In addition, there are reports that in some patients eclamptic seizures do not cease even with elevated levels of MgSO_4, suggesting that MgSO_4 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 MgSO_4 treatment for preeclampsia. 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 Mg^{2+} concentrations increased quickly after
infusion, but steady-state concentrations for total magnesium were 4.84±0.24 mg/dL, whereas for ionized magnesium it was 2.04±0.14 mg/dL.24 Similar results have been found by other groups using the same infusion protocol.24 Interestingly, as MgSO4 infusion caused significant increases in ionized Mg2+ levels, serum ionized calcium (Ca2+) concentrations were unchanged,26 suggesting that the effect of MgSO4 is not exerted through modulations of ionized calcium levels.

Though the use of MgSO4 is widespread and effective, its mechanism of action remains unclear. Several possible mechanisms of action have been proposed, including acting as a vasodilator, with actions either peripherally or in the cerebral circulation to relieve vasoconstriction, protecting the blood-brain barrier (BBB) to decrease cerebral edema formation, and acting as a central anticonvulsant. Each of these possible mechanisms of action are discussed below.

**Magnesium-Induced Vasodilation**

Magnesium is a unique calcium antagonist as it can act on most types of calcium channels in vascular smooth muscle27 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,27 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,28,29 as well as smaller resistance vessels including mesenteric,27,30–32 skeletal muscle,27 uterine,33 and cerebral arteries.27,30,34 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 seems to be reinforced by transcranial Doppler (TCD) studies which suggested that MgSO4 treatment caused dilatation in the cerebral circulation35–37 as well as in animal studies that used large cerebral arteries.34 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 vasoconstriction of cerebral arteries and arterioles, increased BBB permeability and edema formation.38–40 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.30 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 MRI41 and TCD.42-43 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,2,36,44 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.45 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.20,22

Several reports have suggested that gestation may influence vascular reactivity to MgSO4 and that sensitivity varies with vascular bed.28–30,33 Human uterine arteries from pregnant patients are 3-fold more reactive to MgSO4 than uterine arteries from nonpregnant patients.31 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.28 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.29 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.30 This may be attributable to gestation-induced changes in the cerebral endothelial vasodilatory mechanisms that have been demonstrated during pregnancy and the postpartum state.46

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,47 or by inhibiting platelet aggregation.47,48 In patients with pregnancy-induced hypertension, MgSO4 treatment significantly decreased circulating levels of angiotensin-converting enzyme.49 These actions may attenuate the endothelial dysfuction associated with (pre)eclampsia.50–52

**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,51 a low basal rate of pinocytosis,52–55 and the presence of high electric resistance tight junctions between adjacent endothelial cells.54,56 Disruption of the BBB can result in vasogenic edema formation, an important component in the clinical picture of eclampsia.57,58 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\textsuperscript{81} and NMDA-induced hippocampal seizures.\textsuperscript{82} In addition, systemic treatment with MgSO\textsubscript{4} causes a significant reduction in the NMDA receptor binding capacity in the brain.\textsuperscript{78} Animal studies have also shown that MgSO\textsubscript{4} reduces epileptic seizure activity,\textsuperscript{83} though these findings have been challenged because of inadequate controls.\textsuperscript{76}

Magnesium ions must cross the BBB to elicit a central anticonvulsant effect. It has been demonstrated in animals that MgSO\textsubscript{4} can cross the intact BBB and enter the central nervous system in correlation with the level of serum hypermagnesemia.\textsuperscript{81} Interestingly, seizure activity increases the movement of magnesium into the brain.\textsuperscript{81} Human studies have also shown that MgSO\textsubscript{4} reduces epileptic seizure activity,\textsuperscript{83} though these findings have been challenged because of inadequate controls.\textsuperscript{76}

Future Directions
A better understanding of the mechanisms of action of MgSO\textsubscript{4} 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 MgSO\textsubscript{4} and cerebral edema formation, as it has been proposed that MgSO\textsubscript{4} 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).

![Figure 2. Effect of magnesium sulfate on cerebral edema and the blood-brain barrier. The calcium antagonistic effects of magnesium can also affect the cerebral endothelium that forms the blood-brain barrier. Decreased cell calcium inhibits endothelial contraction and opening of tight junctions that are linked to the actin cytoskeleton. Decreased tight junction permeability limits paracellular transport of vascular contents, ions, and proteins that can promote vasogenic edema and seizures. It is also possible that magnesium sulfate diminishes transcellular transport by limiting pinocytosis, which is known to occur rapidly during acute hypertension. Magnesium may also downregulate aquaporin 4 (AQP4), a water channel protein localized to astrocytic endfeet, and possibly cerebral endothelium.](http://stroke.ahajournals.org/)

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One of the difficulties in studying preeclampsia and eclampsia is the lack of appropriate animal models, particularly as (pre)eclampsia is a disease specific to bipedal species.\textsuperscript{93} In our laboratory, we have used a rat model of hypertensive encephalopathy during pregnancy to study the neurological outcomes of eclampsia, specifically how acute elevations in blood pressure lead to forced dilatation of myogenic vasoconstriction, causing increased blood-brain barrier permeability and subsequent edema formation.\textsuperscript{63,94} Other animal models of preeclampsia and eclampsia exist, including reduced uterine placental perfusion (RUPP), Dahl Salt-Sensitive rats, nitric oxide synthase inhibition, and exogenous soluble fms-like tyrosine receptor kinase-1 (sFlt-1). These...
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,93,95 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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Disclosures

None.

References


Anticonvulsant Activity of Magnesium Sulfate.

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Figure 3. Anticonvulsant activity of magnesium sulfate. Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate. Excessive glutamate can activate the NMDA receptor, leading to massive depolarization of neuronal networks and bursts of action potentials. Magnesium may act to increase the seizure threshold by inhibiting NMDA receptors, thereby limiting the effect of glutamate.


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