Magnesium Sulfate in Women With Mild Preeclampsia: A Randomized Controlled Trial

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OBJECTIVE: To determine whether magnesium sulfate prevents disease progression in women with mild preeclampsia.

METHODS: A total of 222 women with mild preeclampsia were randomized to receive intravenous magnesium sulfate (n = 109) or matched placebo (n = 113). Mild preeclampsia was defined as blood pressure of at least 140/90 mm Hg taken on two occasions in the presence of new-onset proteinuria. Patients with chronic hypertension or severe preeclampsia were excluded. Patients were considered to have disease progression if they developed signs or symptoms of severe preeclampsia, eclampsia, or laboratory abnormalities of full or partial HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome.

RESULTS: The groups were similar with respect to maternal age, ethnicity, gestational age, parity, and maternal weight at enrollment. Fourteen women (12.8%) in the magnesium group and 19 (16.8%) in the placebo group developed severe preeclampsia after randomization (relative risk = 0.8, 95% confidence interval 0.4, 1.5, P = .41). None in either group developed eclampsia or thrombocytopenia. Women assigned magnesium had similar rates of cesarean delivery (30% versus 25%), chorioamnionitis (3% versus 2.7%), endometritis (5.3% versus 4.3%), and postpartum hemorrhage (1% versus 0.9%), compared to those assigned placebo. Neonates born to women assigned magnesium had similar mean Apgar scores at 1 and 5 minutes as those born to women assigned placebo (7.7 ± 1.5 versus 7.8 ± 1.6 and 8.7 ± 0.7 versus 8.8 ± 0.6, respectively).

CONCLUSION: Magnesium sulfate does not have a major impact on disease progression in women with mild preeclampsia. Magnesium use does not seem to increase rates of cesarean delivery, infectious morbidity, obstetric hemorrhage, or neonatal depression. (Obstet Gynecol 2003;101: 217–20. © 2003 by The American College of Obstetricians and Gynecologists.)

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In the United States over the last 30 years, the implementation of magnesium sulfate use in women with preeclampsia was based on anecdotal reports and observational studies. Whereas magnesium use is universal in the United States for women with mild preeclampsia, it is often withheld elsewhere. Regarding the use of magnesium sulfate in women with mild disease, the literature contains only a single randomized, placebo-controlled trial. In a study of 135 women enrolled at term, Witlin et al were unable to demonstrate a reduction in the rate of disease progression.[1]

Magnesium sulfate is not a benign drug: It has been associated with significant adverse drug reactions, including overdose (primarily from medication administration errors) and the potential for increased blood loss at delivery. Magnesium is used as a tocolytic and may increase the rates of cesarean delivery, peripartum infection, or hemorrhage. Neonatal depressive effects may also be of concern.[2]

Although the exact mechanism of action of magnesium to prevent eclampsia seizures remains unknown, both central nervous system–specific[3] and systemic mechanisms have been proposed. Systemic effects of magnesium include vasodilation[4] and an increase in endothelium-derived relaxing factor.[5] There are also several mechanisms by which magnesium may prevent disease progression in women with preeclampsia. Although the exact etiology of preeclampsia remains elusive, several theories have been proposed. First, thrombotic lesions of the placenta are more common in women with preeclampsia and may play a role in the pathogenesis of this disease. Plasminogen activator inhibitor type 2 prevents clot degradation by plasminogen. In placental tissue, magnesium cleaves plasminogen activator inhibitor type 2 and therefore may reduce placental thrombosis.[6] Similarly, magnesium may have other anticoagulant effects, because it increases bleeding times in patients with preeclampsia.[7] Second, preeclampsia is a disease of endothelial cell dysfunction. Magnesium has an in vitro protective effect on some endothelial cells.[8] Last, pre-

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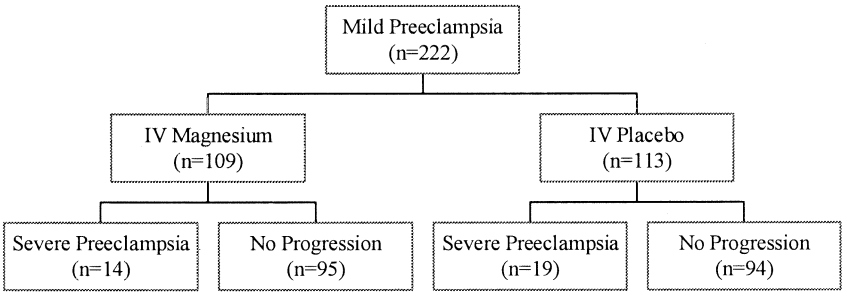

Figure 1. Participant flow to primary end point of progression to severe preeclampsia. IV = intravenous.
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eclampsia is associated with an increase in inflammatory response demonstrated by leukocyte activation. Magnesium may have some anti-inflammatory properties, because it reduces leukocyte activation.[9] We hypothesized that the systemic effects of magnesium may alter progression of mild preeclampsia to severe preeclampsia or eclampsia. The objective of this study was to determine whether magnesium sulfate alters disease progression in women with mild preeclampsia.

MATERIALS AND METHODS

The institutional review board at the University of Tennessee at Memphis approved this study, which followed Consolidated Standards of Reporting Trials (CONSORT) standards for randomized trials.[10] Mild preeclampsia was defined as a systolic blood pressure (BP) of at least 140 mm Hg or a diastolic BP of at least 90 mm Hg recorded on two occasions at least 6 hours apart, in association with new-onset proteinuria. Proteinuria was defined as +1 or greater on dipstick on at least two occasions. Women with chronic hypertension or severe preeclampsia were excluded. We defined severe preeclampsia as a BP of at least 160 mm Hg systolic or at least 110 mm Hg diastolic on at least two occasions or if proteinuria was 5 g or more per 24 hours. Women with symptoms of end-organ involvement (persistent headache, disturbance in vision, protracted nausea and vomiting, or epigastric pain) were considered to have severe disease. Our definition of severe preeclampsia also included those with laboratory abnormalities of full or partial HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome (total bilirubin of 1.2 mg/dL or more, lactate dehydrogenase of 600 U/L or more, aspartate aminotransferase of 72 U/L or more, or platelet count of no more than 100,000/mm^3).

Beginning in July 1996 and ending in July 2001, eligible women (both term and preterm) were admitted for delivery due to spontaneous or induced labor at the Route Center for Women and Newborns, Memphis, Tennessee. Those who developed mild preeclampsia before onset of labor were eligible to participate once admitted for delivery. Women admitted for planned cesarean delivery and women who developed mild preeclampsia only during the postpartum period were also included. Figure 1 shows a study participant flow chart. Computer-generated group assignment was devised by simple randomization sequence. Study group assignment was by sealed, consecutively numbered, opaque envelopes. All medication was mixed in the pharmacy and labeled "study drug" to maintain allocation concealment. Women assigned magnesium ($n = 109$) received a 6-g bolus in 100 mL normal saline over 20 minutes, followed by a maintenance dose of 2 g per hour. Women assigned placebo ($n = 113$) received an identical administration of indistinguishable intravenous saline. Treatment began within 1 hour of randomization and continued until 12 hours postpartum. For those who developed mild preeclampsia only after delivery, study drug was administered for a total of 12 hours. During the treatment period, patients had blood pressure measured every 30 minutes until 1 hour postpartum, then hourly. Patient intake and output as well as deep tendon reflexes were recorded each hour. Study participants had extensive nursing and physician contact and were questioned regarding symptoms of end-organ involvement. Laboratory testing for HELLP syndrome occurred at least once intrapartum and again on the first postpartum day. For those randomized postpartum, testing occurred daily. More frequent testing was at the discretion of the treating physician. For women who developed severe preeclampsia after randomization, group assignment was revealed. If the woman had been assigned to placebo, she subsequently was treated with magnesium by the identical regimen as above.

Data were collected from chart abstraction. Blood loss was determined by clinical estimate of the physician at the time of delivery. Investigators remained blinded during data collection. For the women who developed severe preeclampsia after randomization, data collection was unblinded.

Assuming a 20% rate of progression from mild preeclampsia as well as an α of .05 and β of .2, we estimated that 438 women would need to be enrolled to detect a 50% reduction in disease progression. This study ended

Table 1. Patient Characteristics at Randomization

	Magnesium sulfate* (n = 109)	Placebo* (n = 113)
Age (y)	22 ± 5.9	21.9 ± 5.5
Weight (kg)	95 ± 25	92 ± 23
Parity	0.8 ± 1.5	0.9 ± 1.5
Twins	3 (2.8)	3 (2.7)
Uric acid (mg/dL)	5.2 ± 1.2	5.3 ± 1.4
Mean arterial pressure (mm Hg)	106 ± 12.2	107 ± 13.1
Gestational age (wk)	38.4 ± 2.5	38.5 ± 5.8

Data expressed as mean ± standard deviation or n (%).
* No difference regarding any of the categories studied.

before enrolling the planned sample size, because most of the investigators left the University of Tennessee before study completion. Data were analyzed by intent to treat. Continuous data were analyzed with the unpaired Student t test. Categorical data were analyzed with the χ^2 test (Statview 5, SAS Institute Inc., Cary, NC). Sample size and relative risk (RR) and confidence intervals (CIs) were determined with Epi Info 6 (Centers for Disease Control and Prevention, Atlanta, GA). A P value of .10 was considered significant.

RESULTS

A total of 222 nonconsecutive women (51% of intended sample size) met inclusion criteria, agreed to participate, and were randomized. Women were similar with respect to maternal age, gestational age, parity, and maternal weight (Table 1). Eighty-one percent of both groups was black. Three women in each group had a twin gestation. Nine women in the magnesium group and three in the placebo group were randomized postpartum. Table 2 illustrates disease progression after randomization. Fourteen women (12.8%) in the magnesium group and 19 (16.8%) in the placebo group developed severe preeclampsia (RR = 0.8, 95% CI 0.4, 1.5, P = .41). No woman in either group developed eclampsia or laboratory abnormalities of full or partial HELLP syndrome.

Table 2. Criteria for Severe Disease After Randomization

	Magnesium sulfate (n = 109)	Placebo (n = 113)
Severe hypertension*	10 (9.2)	14 (12.4)
Persistent headache	6 (5.5)	6 (5.3)
Epigastric pain	3 (2.8)	2 (1.8)
Visual disturbance	2 (1.8)	2 (1.8)
Severe preeclampsia†	14 (12.8)	19 (16.8)

Data expressed as n (%). All P values >.05.
* Systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 110 mm Hg or higher.
† Some women had more than one criteria for severe preeclampsia.

Table 3. Clinical Outcomes

	Magnesium sulfate (n = 109)	Placebo (n = 113)
Cesarean delivery*	30 (30)	27 (25)
Uterine atony*	1 (1)	1 (0.9)
Blood loss* (ml)	500 ± 200	500 ± 200
Chorioamnionitis*	3 (3)	3 (2.7)
Endometritis	6 (5.3)	5 (4.3)
Apgar 1-min score*	7.7 ± 1.5	7.8 ± 1.6
Apgar 5-min score*	8.7 ± 0.67	8.8 ± 0.64
Meconium at delivery*	24 (23)	17 (15)
Maximum systolic BP (mm Hg)	159 ± 14	162 ± 15
Maximum diastolic BP (mm Hg)	101 ± 9	103 ± 9

Data expressed as n (%) or mean ± standard deviation. All P values >.05.
* Women randomized postpartum not included in analysis (magnesium n = 100, placebo n = 110).

There were no differences in any important clinical outcomes (Table 3). When postpartum women were removed from the analysis, there were again no differences in any outcomes (data not shown). No woman assigned placebo developed severe disease before beginning intravenous saline.

DISCUSSION

Witlin and Sibai recently reviewed the literature regarding magnesium sulfate use in women with preeclampsia and eclampsia.[11] There is currently Level I evidence that magnesium is superior to other regimens for preventing eclamptic seizures.[12,13] These comparisons were done primarily in women with severe preeclampsia.[14,15] Coetzee et al conducted a randomized, placebo-controlled trial of intravenous magnesium in South African women with severe preeclampsia.[16] All 699 women were also administered clonazepam. Eclampsia was less likely in the group assigned magnesium (3.2% versus 0.3%, P = .003). One woman in the magnesium group overdosed from medication administration error.

We were unable to demonstrate a beneficial effect of magnesium in preventing disease progression. Our results are comparable to those of Witlin et al, who randomized 135 women with mild preeclampsia into a similar trial of magnesium compared with placebo.[3] No women developed eclampsia. Approximately 10% of women in each arm of that study progressed to severe disease. Consistent with our results, there was no difference in mode of delivery or rate of obstetric hemorrhage. In our study, there was no difference in maternal adverse events theoretically associated with magnesium use, such as higher rates of cesarean delivery, hemorrhage, and infectious morbidity. There were no adverse neonatal effects of magnesium demonstrated by Apgar scores and rate of meconium.

We propose that our study design was responsible for the uniformly good outcomes in both groups. Because our patients were so closely monitored by both nursing and physician contact, early signs of severe preeclampsia were recognized promptly. Once diagnosis of severe disease was made, all the women were then managed with magnesium sulfate and antihypertensive therapy, if needed. We conclude that close observation of women with mild preeclampsia is safe and that there is enough time to subsequently treat those who develop severe disease with intravenous magnesium.

Delivery is the ultimate cure for preeclampsia. Although there may be a difference in the natural course of preeclampsia when developed postpartum, as opposed to ante- or intrapartum, we included postpartum patients to increase the external validity with regard to all women who develop mild preeclampsia. Because this trial was randomized, we expected that if there had been a difference between postpartum and ante- or intrapartum diagnosed patients, an equal number of patients in both groups would have been randomized postpartum. Three women in the placebo and nine in the magnesium group were randomized postpartum. When data were analyzed after removing patients randomized postpartum, there was no difference in outcomes; therefore, ascertainment bias is not likely to influence our results. Although we enrolled 222 women, our power to detect a progression to severe disease is small. In fact, only 51% of the intended sample size was entered into the study. Underpowered studies often result in Type II errors. Based on the rate of disease progression found in this study (from 16.8% to 12.8%), with an α of .05 and a β of .2, 2570 women would need to be enrolled to find a significant reduction in disease progression in women with mild preeclampsia treated with magnesium sulfate.

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