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A COMPARISON OF MAGNESIUM SULFATE WITH PHENYTOIN FOR THE PREVENTION OF ECLAMPSIA

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Abstract *Background.* Magnesium sulfate is used widely to prevent eclamptic seizures in pregnant women with hypertension, but few studies have compared the efficacy of magnesium sulfate with that of other drugs. Anticonvulsant prophylaxis with phenytoin for eclampsia has been recommended, but there are virtually no data to support its efficacy. Our objective was to compare magnesium sulfate with phenytoin in preventing seizures in hypertensive women during labor.

Methods. We randomly assigned women with hypertension who were admitted for delivery to receive either magnesium sulfate or phenytoin. The magnesium sulfate regimen consisted of a 10-g intramuscular loading dose followed by a maintenance dose of 5 g given intramuscularly every four hours. For women with severe preeclampsia, an additional 4-g loading dose was given intravenous-

ly. The phenytoin regimen included a 1000-mg loading dose infused over a period of 1 hour, followed by a 500-mg oral dose 10 hours later. With either regimen, anticonvulsant therapy was continued for 24 hours post partum.

Results. Ten of 1089 women randomly assigned to the phenytoin regimen had eclamptic convulsions, as compared with none of 1049 women randomly assigned to magnesium sulfate ($P=0.004$). There were no significant differences in any risk factors for eclampsia between the two study groups. Maternal and infant outcomes were also similar in the two study groups.

Conclusions. Magnesium sulfate is superior to phenytoin for the prevention of eclampsia in hypertensive pregnant women. These results validate the long-practiced use of magnesium sulfate in the prevention of eclampsia. (*N Engl J Med* 1995;333:201-5.)

AS early as 1906 magnesium sulfate was injected intrathecally to prevent eclamptic seizures.¹ Because of reports that intramuscular magnesium sulfate controlled convulsions associated with tetanus, a similar regimen was used in 1926 to prevent recurrent seizures in women with eclampsia.² In 1933, the drug was given intravenously to hundreds of women with preeclampsia and eclampsia at the Los Angeles General Hospital.³ In all these studies, the doses of magnesium sulfate were small. Eastman and Steptoe⁴ used larger (pharmacologic) doses given intramuscularly in women with preeclampsia. Later, Pritchard⁵ and Zuspan⁶ formalized intramuscular and intravenous treatment with magnesium sulfate. Although there are a number of clinical studies that attest to the efficacy of magnesium sulfate in preventing recurrent seizures in women with eclampsia,⁷⁻⁹ there are few controlled, comparative studies of its use in the prevention of seizures in women with preeclampsia.

According to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,¹⁰ most authorities in North America recommend the use of magnesium sulfate for women with pregnancy-induced hypertension to prevent eclamptic seizures during labor and the immediate puerperium. By contrast, in the United Kingdom, as well as in a few U.S. centers, conventional antiepileptic drugs

such as diazepam and phenytoin are used.¹¹⁻¹³ Phenytoin was specifically developed as an anticonvulsant and is the most widely prescribed drug for epilepsy in the world.¹⁴ Because of the empirical success of magnesium sulfate in obstetrical practice, phenytoin treatment has been evaluated only in small studies, and reports regarding its efficacy in preventing eclampsia are not conclusive.¹⁵⁻¹⁷ We therefore designed a randomized study to compare intravenous and intramuscular magnesium sulfate with intravenous and oral phenytoin for the prevention of eclamptic convulsions in women with pregnancy-induced hypertension.

METHODS

Following approval of the protocol by the institutional review board of the University of Texas Southwestern Medical Center, women admitted to the Parkland Memorial Hospital Labor and Delivery Unit with systolic blood pressure of at least 140 mm Hg and diastolic blood pressure of at least 90 mm Hg were asked whether they wanted to participate in this study. Women who were about to give birth or who had already given birth were excluded, as were women with epilepsy or those admitted with eclamptic convulsions. Blood pressure was monitored with standard sphygmomanometers, and systolic and diastolic end points were recorded as Korotkoff sounds 1 and 5, respectively. After written consent was obtained, treatment was randomly assigned with the use of numbered opaque envelopes.

The magnesium sulfate regimen we used was our standardized protocol in use since 1955.¹⁸ This regimen calls for the intramuscular administration of 10 g of a 50 percent solution of magnesium sulfate in divided doses in the upper outer quadrant of each buttock. Thereafter, 5 g of a 50 percent solution is injected intramuscularly every four hours in the upper outer quadrant of alternate buttocks provided that a patellar reflex is present, respirations exceed 12 per minute, and urine output during the preceding four hours exceeds 100 ml. For se-

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vere preeclampsia, an initial loading dose of 4 g of magnesium sulfate is given intravenously as a 20 percent solution before the intramuscular doses. Severe preeclampsia was diagnosed when any of the following was found: diastolic blood pressure of at least 110 mm Hg, systolic blood pressure of at least 160 mm Hg, severe proteinuria ($\geq 3+$ on dipstick), and symptoms including headaches, visual changes, or upper abdominal pain. Antihypertensive therapy with hydralazine at a dose of 5 to 10 mg intravenously every 15 to 20 minutes was given to women whose diastolic blood pressure was 110 mm Hg or higher. Magnesium sulfate was continued for 24 hours after delivery.

For women randomly assigned to the phenytoin regimen, the dosage was based on our prior investigation in which therapeutic serum levels were maintained for approximately 24 hours.¹⁹ With this regimen, 1000 mg of undiluted phenytoin was pumped piggyback with a volumetric pump at a rate of 200 ml per hour over a period of 1 hour into an intravenous catheter delivering normal saline; 10 hours after the loading dose was initiated a maintenance dose of 500 mg of phenytoin was given in a delayed-release capsule (Dilantin, Parke-Davis). Serum phenytoin levels were measured 2 and 10 hours after the initiation of therapy. Maternal cardiac monitoring during the infusion was performed in addition to continuous electronic fetal monitoring. The blood-pressure criteria for treatment with hydralazine were identical to those used in the magnesium sulfate group. Because of the special requirements for phenytoin administration and monitoring, we limited such treatment to women in the labor rooms. If it became necessary to move a woman to a delivery room before the phenytoin loading was completed, the magnesium sulfate regimen was given.

Depending on the regimen used, serum magnesium or phenytoin levels were measured if eclampsia developed. Eclampsia was diagnosed when a generalized tonic-clonic seizure was witnessed, followed by characteristic postictal reduced consciousness and amnesia. Our study protocol stipulated that women in whom eclampsia developed would be treated with intravenous magnesium sulfate regardless of their initial treatment assignment: women originally treated with magnesium sulfate received an additional 2 g intravenously followed in 15 minutes by another 2 g if convulsions persisted; women treated initially with phenytoin received the standard magnesium sulfate loading and maintenance doses described above.

Statistical Analysis

Independent and outcome variables were compared by analysis of variance or regression analysis for continuous variables and by the chi-square test or Fisher's exact test for nonparametric analyses. The analysis was conducted on an intention-to-treat basis. A power analysis was performed before the study was begun, and it was estimated that approximately 4500 participants would be required to detect a 50 percent difference in efficacy with a power of 80 percent. The study was terminated before the projected number of patients was enrolled when an interim analysis showed that phenytoin as administered was comparatively ineffective prophylaxis against eclampsia.

RESULTS

From January 1, 1993, to August 22, 1994, a total of 3534 women with a diagnosis of hypertension in labor gave birth at the study hospital. A total of 2138 women gave their consent for the study; 1089 were randomly assigned to receive phenytoin, and 1049 were assigned to receive magnesium sulfate. As shown in Table 1, the randomized assignment of participants resulted in groups with similar demographic characteristics and severity of intrapartum hypertension. These results indicate that the objective of randomized assignment of women to the two treatment groups was achieved. As summarized in Tables 2 and 3, intrapartum maternal outcomes and infant outcomes were also similar in the two groups. The difference in the number of cesarean deliveries before labor in the magnesium sulfate group rather than to an effect of treatment on labor.

The principal outcome of interest in this trial — eclamptic convulsion — was significantly more frequent

Table 1. Demographic Characteristics and Severity of Hypertension in Women Randomly Assigned to Receive Phenytoin or Magnesium Sulfate.*

CHARACTERISTIC	PHENYTOIN (N = 1089)	MAGNESIUM SULFATE (N = 1049)
Race or ethnic group — no. (%)		
White	150 (14)	134 (13)
Hispanic	564 (52)	554 (53)
Black	350 (32)	343 (33)
Other	25 (2)	18 (2)
Nulliparous — no. (%)	674 (62)	638 (61)
Maternal age — yr (%)		
≤ 19	347 (32)	322 (31)
20–34	667 (61)	656 (63)
≥ 35	75 (7)	71 (7)
Preterm delivery (≤ 37 wk) — no. (%)	216 (20)	226 (22)
Severity of hypertension		
Proteinuria ($\geq 2+$) — no. (%)	198 (18)	203 (19)
Hydralazine given	44 (4)	47 (4)
Platelet count $< 100,000/\text{mm}^3$ — no. (%)	10 (1)	11 (1)

*There were no significant differences between groups in any of these variables. Because of rounding, not all categories total 100 percent.

in women given phenytoin than in those given magnesium sulfate (10 of 1089 vs. 0 of 1049, $P=0.004$). The characteristics of the 10 phenytoin-treated women in whom eclampsia developed are listed in Table 4. Serum phenytoin levels at the time of seizure exceeded the therapeutic threshold of 10 μg per milliliter¹⁴ in all but one woman.

The distributions of serum phenytoin levels 2 and 10 hours after the initiation of intravenous therapy are shown in Figure 1. There was a significant correlation between the serum phenytoin level and maternal weight (correlation coefficient, -0.68 ; $P=0.001$).

Side effects during and after the administration of phenytoin were minimal and included transient burning at the site of catheterization, dysphoria, nystagmus, occasional dizziness, nausea, and a mild reduction in blood pressure during the intravenous infusion. Only 17 women had symptoms that required discontinuation of the infusion and substitution of magnesium sulfate therapy.

The outcomes of the 1396 hypertensive women who either declined to participate or were ineligible for the study were also analyzed. Twelve were ineligible because they were admitted with eclampsia. There was one eclamptic convulsion in a woman with severe preeclampsia who had declined to participate in the study and was receiving magnesium sulfate. The serum magnesium level at the time of her convulsion was 1.85 mmol per liter (3.7 meq per liter); there were no additional seizures after an additional 2 g of magnesium sulfate was infused.

The results and analysis presented thus far have been reported on an intention-to-treat basis. The phenytoin group included a total of 178 women who were given no phenytoin or only partial loading doses. Twenty-two of these women had protocol violations: they were admitted to labor and delivery more than once and erroneously underwent randomization more than once. One hundred thirty-nine women were randomly assigned to phenytoin treatment but never received this therapy because of logistic problems with drug availability, cardiac-monitor availability, or indicated emergency delivery. As described above, another 17 women were unable to tolerate the phenytoin infusion, and it

Table 2. Selected Intrapartum Factors and the Type of Delivery in Hypertensive Women Randomly Assigned to Phenytoin or Magnesium Sulfate Prophylaxis.

FACTOR	PHENYTOIN (N = 1089)	MAGNESIUM SULFATE (N = 1049)
	no. (%)	
Twin gestation	12 (1)	15 (1)
Breech presentation	17 (2)	24 (2)
Prior cesarean delivery	31 (3)	42 (4)
Post-term delivery (≥42 wk)	103 (9)	121 (12)
Induction of labor	354 (33)	317 (30)
Augmentation of labor	369 (34)	352 (34)
Cesarean delivery	241 (22)	283 (27)*

*P=0.047. There were no significant differences between groups in any of the other variables.

was discontinued. Eclampsia did not develop in any of these 178 women, and in the analysis they were considered to have been successfully treated with phenytoin. In our analysis of the entire cohort of 3534 women according to the actual treatment received, the estimated relative risk associated with phenytoin prophylaxis as compared with magnesium sulfate prophylaxis was 26.

The 10 women in whom eclampsia developed despite phenytoin prophylaxis had a seemingly disproportionate number of peripartum complications (Table 4). Five required cesarean section, six had low-birth-weight infants, one had partial abruptio placentae, and two required blood transfusions. Emesis during convulsions put two women at risk for aspiration, although there were no pulmonary sequelae. Three women had two or more seizures, two after receiving a loading dose of magnesium sulfate in addition to the initial phenytoin treatment. In one of these two women, an additional 2 g of intravenous magnesium sulfate arrested the seizures completely. In the other, repeated convulsions post partum were unresponsive to additional magnesium sulfate, phenobarbital, and phenytoin, and general anesthesia with endotracheal intubation was administered to arrest the seizures and provide respiratory support. This woman was one of eight with eclampsia who were examined with either cranial computed tomography or magnetic resonance imaging. Except for low-density areas previously described in association with eclampsia,²¹ no abnormalities were noted.

DISCUSSION

We found that magnesium sulfate was clearly superior to phenytoin when given prophylactically for eclamptic seizures to women with peripartum hypertension. Eclampsia developed in 10 of 1089 women who received phenytoin prophylaxis, whereas none of the 1049 women who were treated with magnesium sulfate had convulsions (P=0.004). Over a period of many years at our hospital, the observed incidence of eclampsia after admission and during magnesium sulfate prophylaxis has been about 1 per 750 women given such treatment.^{18,20} In a manner consistent with this pattern, eclampsia developed in only 1 of the 1384 women with peripartum hypertension who did not participate in

this study and who were given magnesium sulfate according to our standard protocol.

The fact that the phenytoin failure rate was approximately 1 in 100 may be more reflective of the low-risk study population than of the protective effects of the drug. Although the rate of eclampsia in hypertensive women not given anticonvulsant therapy is uncertain, Chua and Redman²¹ reported only one seizure in 78 women with proteinuric hypertension who were purposely given no anticonvulsant therapy. Thus, the observed rate of eclampsia after phenytoin prophylaxis in the women we studied may be slightly lower than the rate in untreated women. Although we cannot assess partial effectiveness without an untreated group for comparison, we can conclude that the observed difference between phenytoin and magnesium sulfate prophylaxis is not an artifact of a chance excess of seizures in the phenytoin-treated group.

We examined our study methods for possible sources of bias. The study protocol allowed women assigned to receive phenytoin to be treated with magnesium sulfate in certain circumstances that create a potential for post-randomization selection bias. If selection for preferential treatment with magnesium sulfate occurred, however, the effect on the results was actually the reverse. Specifically, inclusion of magnesium-treated patients in the phenytoin group augments the apparent effectiveness of phenytoin in the intention-to-treat analysis. A potential criticism of our methods is that we were unable to use a double-blind design. However, since the objective of such a design is to prevent ascertainment bias, we did not consider this to be an important factor in the study, because the end point — eclampsia — is so unambiguous.

The effectiveness of phenytoin as prophylaxis against eclampsia or for treatment of recurrent eclamptic seizures has heretofore been evaluated only in small studies. Slater and colleagues¹⁵ reported no treatment failures in their study of 26 women with preeclampsia or eclampsia who were given intravenous phenytoin to prevent convulsions. Dommissie¹⁶ randomly assigned 22

Table 3. Infant Outcomes According to the Type of Maternal Prophylaxis against Seizures.*

OUTCOME	PHENYTOIN	MAGNESIUM SULFATE
	no. (%)	
Total births	1101	1064
Live birth	1086	1055
Stillbirth	15 (1.4)	9 (0.8)
Neonatal death	1	4
Perinatal mortality (rate per 1000 total births)	14.5	12.2
Apgar score ≤3 at 5 min	16 (1.5)	9 (0.8)
Arterial cord-blood pH ≤7.0	5 (0.5)	3 (0.3)
Birth weight (live-born infants)		
500–1500 g	15 (1)	22 (2)
1501–2500 g	131 (12)	122 (12)
2501–3999 g	869 (80)	823 (78)
≥4000 g	71 (7)	88 (8)
Admission to special-care nursery	35 (3)	34 (3)

*There was no significant difference between groups in any of these variables.

women with eclampsia to receive either intravenous phenytoin or magnesium sulfate. Four of the 11 women given phenytoin subsequently had recurrent convulsions despite "therapeutic" serum levels (10 to 25 μg per milliliter), whereas no woman given magnesium had another seizure ($P=0.055$). Robson and associates¹⁷ used two dosage regimens to treat 5 women with eclampsia and 67 with severe preeclampsia. Three women — two with preeclampsia and one with eclampsia — had seizures despite serum levels of phenytoin that were considered therapeutic (10.7 to 11.2 μg per milliliter).

There are several possible explanations for the observed superiority of magnesium sulfate. The dose of phenytoin may have been inadequate and may therefore have resulted in subtherapeutic serum levels. Although by definition the dose was subtherapeutic in women who had seizures, 9 of the 10 women in whom eclampsia developed had serum concentrations of at least 10 μg per milliliter, a level considered therapeutic in patients who are not pregnant. This therapeutic threshold has been estimated to be significantly lower for women with preeclampsia, who typically have relatively low serum albumin concentrations and higher free serum phenytoin levels.²² In addition, the mean two-hour phenytoin level in women in whom eclampsia sub-

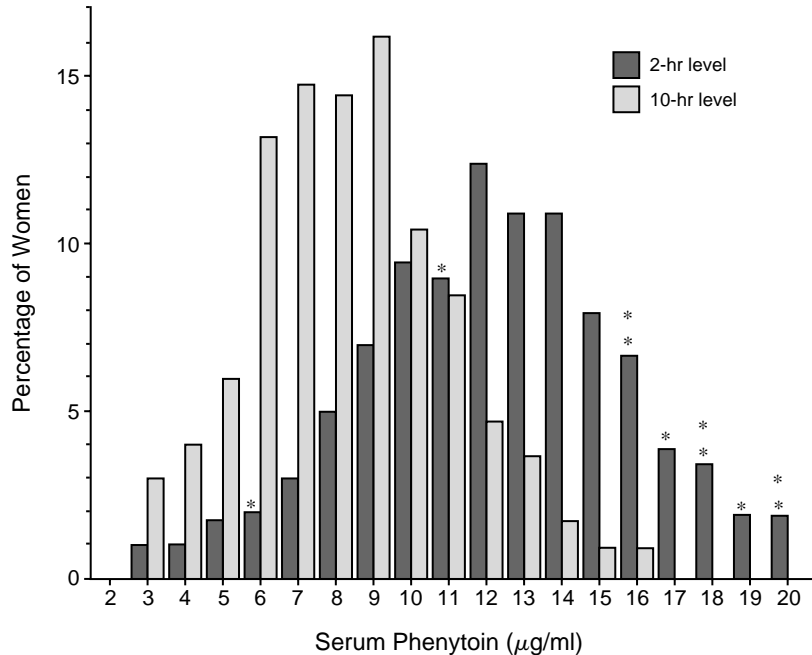


Figure 1. Distribution of Serum Phenytoin Levels 2 and 10 Hours after the Initiation of Phenytoin Therapy.

The mean serum level two hours after the initiation of therapy was significantly higher in the 10 women with subsequent eclampsia (indicated by asterisks) than in the phenytoin-treated population as a whole (17.3 vs. 13.1 μg per milliliter, $P<0.001$).

sequently developed was higher than the mean level for the phenytoin-treated group as a whole. Had the converse been observed, it might have suggested that the dose was inadequate in those who had convulsions.

We suspect that magnesium is superior to phenytoin because mechanisms other than anticonvulsant proper-

Table 4. Characteristics on Admission and Clinical Summaries of 10 Women in Whom Eclampsia Developed Despite Phenytoin Prophylaxis.

PATIENT No.	AGE	PARITY	WEEK OF GESTATION	ADMISSION VALUES		PHENYTOIN LEVEL			COMPLICATIONS
				BLOOD PRESSURE	URINE PROTEIN	2 HR AFTER START OF TREATMENT	AT TIME OF ORAL DOSE	AT TIME OF SEIZURE	
	yr			mm Hg		$\mu\text{g/ml}$			
1	21	0	34	190/110	Trace	9.3	6.5	5.8	Preterm delivery Cesarean section
2	20	0	39	150/100	Trace	19.0	12.8	11.1	Cesarean section
3	21	0	40	150/90	2+	11.7	9.7	12.2	None
4	20	1	36	174/104	4+	17.5	—*	13.1	Preterm delivery
5	23	2	37	140/100	2+	24.0	—*	24.0	Preterm delivery Partial abruptio placentae Transfusion required
6	19	0	34	160/90	2+	18.0	—*	11.0	Preterm delivery Recurrent seizure Cesarean section
7	23	1	40	120/90	Trace	22.5	—*	11.5	Two seizures before magnesium sulfate given Cesarean section
8	17	0	39	140/90	3+	16.2	10.5	12.1	Fetal growth retardation
9	18	0	38	170/100	2+	16.7	—*	10.4	Cesarean section Fetal growth retardation Transfusion required
10	17	0	37	140/100	Trace	18.2	—*	12.0	Repeated seizures†

*Eclampsia occurred before the oral dose was given.

†Repeated seizures were unresponsive to magnesium sulfate, phenobarbital, and phenytoin, and general anesthesia with endotracheal intubation was administered to arrest the seizures and provide respiratory support.

ties enhance its therapeutic benefits for women with preeclampsia. Although magnesium acts as an anticonvulsant by means of neuronal calcium-channel blockade through *N*-methyl-D-aspartate receptors,²³ Sibai et al.²⁴ found that an infusion of magnesium sulfate did not demonstrably suppress electroencephalographic epileptiform patterns. Conversely, Belfort and Moise²⁵ reported that a 6-g intravenous loading dose of magnesium reversed cerebral arterial vasoconstriction distal to the middle cerebral arteries. This effect is not characteristic of phenytoin.²⁶ Other potentially important actions of the magnesium ion include the release of endothelial prostacyclin and inhibition of platelet aggregation.²⁷ These observations fit well with the more recent recognition that preeclampsia is associated with widespread endothelial injury.²⁸

Criticism of the use of magnesium sulfate has come primarily from nonobstetricians, who have argued that it is not a proved anticonvulsant^{12,29-31} and that eclamptic seizures are "clinically and electroencephalographically indistinguishable from generalized tonic-clonic seizures."³¹ Some critics have alleged that the anticonvulsant properties of magnesium sulfate are due to neuromuscular blockade, even though no paralysis is observed at therapeutic levels. Similarly, coincidental antihypertensive therapy does not account for our results, since both groups were treated with hydralazine. Resolution of the controversy about the anticonvulsant properties — or lack thereof — of magnesium sulfate would require a trial in nonpregnant subjects with seizure disorders. We can conclude, however, on the basis of our results, that a scientifically proved anticonvulsant such as phenytoin is not as effective as magnesium sulfate for the prevention of the generalized tonic-clonic seizures characteristic of eclampsia. These observations also validate the empirically observed success of magnesium sulfate as administered for decades in the United States and abroad.^{8,9,18}

Some have questioned the use of anticonvulsant prophylaxis in such a large number of pregnant women with hypertension — an estimated 5 percent of the 4 million women giving birth annually in the United States — to prevent perhaps as few as 1 seizure per 75 women at risk. Even with modern therapy, morbidity and mortality with eclampsia are substantial. For example, Douglas and Redman³² reported a 1.8 percent mortality rate and a 35 percent rate of complications in 383 women with eclampsia treated in the United Kingdom in 1992. In earlier series, maternal mortality has ranged from 2 to 5 percent.¹⁸ Relevant to this consideration is our observation that recurrent seizures are more difficult to control than is the occurrence of eclampsia and that risks multiply with multiple seizures. For these reasons, and because of its proved safety, we continue to recommend magnesium sulfate for seizure prophylaxis in women with pregnancy-induced hypertension.

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