

ORIGINAL ARTICLE

# A Comparison of Magnesium Sulfate and Nimodipine for the Prevention of Eclampsia

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## ABSTRACT

### OBJECTIVE

Magnesium sulfate may prevent eclampsia by reducing cerebral vasoconstriction and ischemia. Nimodipine is a calcium-channel blocker with specific cerebral vasodilator activity. Our objective was to determine whether nimodipine is more effective than magnesium sulfate for seizure prophylaxis in women with severe preeclampsia.

### METHODS

We conducted an unblinded, multicenter trial in which 1650 women with severe preeclampsia were randomly assigned to receive either nimodipine (60 mg orally every 4 hours) or intravenous magnesium sulfate (given according to the institutional protocol) from enrollment until 24 hours post partum. High blood pressure was controlled with intravenous hydralazine as needed. The primary outcome measure was the development of eclampsia, as defined by a witnessed tonic-clonic seizure.

### RESULTS

Demographic and clinical characteristics were similar in the two groups. The women who received nimodipine were more likely to have a seizure than those who received magnesium sulfate (21 of 819 [2.6 percent] vs. 7 of 831 [0.8 percent],  $P=0.01$ ). The adjusted risk ratio for eclampsia associated with nimodipine, as compared with magnesium sulfate, was 3.2 (95 percent confidence interval, 1.1 to 9.1). The antepartum seizure rates did not differ significantly between groups, but the nimodipine group had a higher rate of postpartum seizures (9 of 819 [1.1 percent] vs. 0 of 831,  $P=0.01$ ). There were no significant differences in neonatal outcome between the two groups. More women in the magnesium sulfate group than in the nimodipine group needed hydralazine to control blood pressure (54.3 percent vs. 45.7 percent,  $P<0.001$ ).

### CONCLUSIONS

Magnesium sulfate is more effective than nimodipine for prophylaxis against seizures in women with severe preeclampsia.

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CEREBRAL INFARCTION AND HEMORRHAGE still account for the majority of deaths from eclampsia and preeclampsia.<sup>1,2</sup> Preeclampsia causes regional vasoconstriction, and many believe that eclampsia results from cerebral vasospasm and resultant ischemia.<sup>3-6</sup> Magnesium sulfate is generally accepted as the treatment of choice for eclampsia.<sup>7-9</sup> The use of magnesium sulfate to prevent eclampsia has been common in the United States for decades<sup>10,11</sup> but has not been internationally adopted. The placebo-controlled Magnesium Sulphate for Prevention of Eclampsia (MAGPIE) trial<sup>12</sup> recently confirmed the prophylactic action of magnesium sulfate and is likely to increase the use of this agent in women with preeclampsia worldwide.

Since magnesium sulfate has a cerebral vasodilator effect,<sup>13</sup> one explanation for its antieclamptic action is that it decreases ischemia by reducing cerebral vasospasm. We hypothesized that if eclampsia is caused by cerebral ischemia, nimodipine, a calcium-channel blocker that is a specific cerebral vasodilator,<sup>14,15</sup> would be an ideal alternative drug. Potential advantages of nimodipine also include its oral route of administration, minimal toxicity, and antihypertensive effect. Therefore, we compared the efficacy of nimodipine with that of magnesium sulfate for the prevention of seizures in patients with severe preeclampsia.

#### METHODS

We conducted an unblinded, randomized, controlled trial between 1995 and 2000. We enrolled women with severe preeclampsia at 14 sites in eight countries (see the Appendix). The protocol was approved by the local review board at each site. All patients provided written informed consent. Patients with severe preeclampsia in whom the decision had been made to effect delivery were eligible provided they had not already received magnesium sulfate and did not have a preexisting seizure disorder. The diagnostic criteria<sup>16</sup> are described in detail in the Supplementary Appendix, available with the full text of this article at <http://www.nejm.org>. Severe preeclampsia was defined as elevated blood pressure (at least 140/90 mm Hg) with proteinuria (a dipstick reading of 1+ or more) in association with one or more of the following: headache, clonus, visual disturbances, epigastric pain or pain in the right upper quadrant, oliguria (urinary output of less than 500 ml per 24 hours), pulmonary edema,

elevated liver aminotransferase levels (an alanine aminotransferase or aspartate aminotransferase level of more than 40 U per liter), elevated creatinine level (at least 1.5 mg per deciliter [133  $\mu$ mol per liter]), hemolysis, thrombocytopenia, intrauterine growth restriction, or oligohydramnios. A blood pressure of 160/110 mm Hg or higher with proteinuria in the absence of any of the other features was also classified as severe preeclampsia. Patients were randomly assigned according to center (Epistat Services) in blocks of six, with the use of sealed opaque envelopes, to receive either nimodipine (60 mg orally every four hours) or magnesium sulfate according to the institutional protocol (a 6-g loading dose followed by an intravenous infusion of 2 g per hour, or a 4-g loading dose followed by an infusion of 1 g per hour). Treatment was continued for up to 24 hours ante partum (after which the protocol called for cesarean section unless delivery was imminent) and for 24 hours post partum. Measurement of blood levels of magnesium sulfate was not required. Blood pressure was measured with the use of automated monitors or manual sphygmomanometry (Korotkoff phase V). Urinary protein was measured with use of a semiquantitative method (dipstick) or, if available, a 24-hour urine collection.

The study was not blinded, because of logistic and economic constraints. The primary outcome measure (eclampsia) was binary, objective, and not subject to observer or measurement bias. Patients were treated according to the usual routine of each hospital, with no interference by the research group. Blood pressure was controlled with intravenous hydralazine for women whose systolic blood pressure was at least 160 mm Hg, whose diastolic blood pressure was at least 110 mm Hg, or whose overall blood pressure was at least 160/110 mm Hg for more than 20 minutes after the initiation of treatment.

The primary outcome measure was eclampsia (defined as a witnessed tonic-clonic convulsion) at any time from the initiation of study-drug administration until 24 hours post partum. Secondary outcome measures included blood-pressure control, complications and adverse drug effects, complications of labor and delivery, and indicators of fetal and neonatal condition. Postpartum hemorrhage (as recorded in the chart) was defined as estimated blood loss in the 24 hours after delivery of more than 500 ml in the case of vaginal delivery and of more than 1000 ml in the case of cesarean delivery.

Women in the nimodipine group who had a sei-

zures received magnesium sulfate. Women who had a seizure while receiving magnesium sulfate continued to receive this drug according to the institutional regimen.

We initially planned to study 1000 patients per group, with interim analyses conducted every six months by an independent trial monitor and adjusted for multiple analyses with use of the Lan-DeMets method. The study was terminated early (August 2000) when a planned interim analysis showed a significantly higher rate of seizure in the nimodipine group.

All statistical analyses were performed with the use of SAS software (version 8, SAS Institute). The Wilk-Shapiro test was used to check the normality of distribution. The two groups were compared with use of analysis of variance, the two-sample t-test, Wilcoxon's rank-sum test, Fisher's exact test, the chi-square test, or logistic regression, as appropriate. Univariate analyses were conducted to identify demographic and clinical variables associated with the occurrence of seizures. Statistically significant variables were identified with the use of Fisher's exact test and univariate logistic regression. Variables that were significantly associated with seizure in the univariate analyses were included as covariates in a multiple logistic-regression analysis, along with other selected variables that were considered to warrant evaluation.

The type of anesthesia was classified as none or local infiltration only, regional (epidural or spinal), and general. The type of anesthesia was excluded from the overall analysis of seizures and was analyzed only in the group of patients who had a postpartum seizure (these patients were all in the nimodipine group). The antepartum effect of anesthesia could not be analyzed, because of uncertainty about the timing of the administration of anesthesia (before or after the seizure).

The odds ratios calculated from logistic regression were considered to provide a reasonable estimate of the risk ratio.<sup>17</sup> In comparisons that contained a zero frequency cell, the logit estimator used for the risk ratio incorporated a correction of 0.5 in every cell and a confidence interval could not be obtained. All significance tests were two-tailed, with an  $\alpha$  level of 0.05.

Bayer provided the nimodipine. This sponsor was not involved with the design of the study, the interpretation of the data, or the writing of this report. The investigators had full access to the data.

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## RESULTS

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We enrolled 1750 patients from July 1995 until November 2000. The Appendix shows the number of patients enrolled and the number who received study drug at each site. Data were available for 1650 of 1750 patients (94.3 percent): 819 of the 1650 were given nimodipine, and 831 were given magnesium sulfate. A total of 99 patients were enrolled, were assigned a study number, and underwent randomization but did not receive either drug. In most cases this was because they gave birth before the drug could be administered or because of logistic issues that prevented timely administration of the study drug. Hence, data sheets were not completed on these patients. One patient in the magnesium sulfate group was withdrawn from the study because the induction of labor was stopped and conservative management instituted. The median antepartum duration of treatment was 8.8 hours in the magnesium sulfate group and 8.1 hours in the nimodipine group.

Base-line demographic and clinical characteristics were generally similar in the two groups (Table 1); the only exception was that base-line systolic blood pressure was slightly higher in the magnesium sulfate group ( $P=0.04$ ). No significant differences between groups were found in any of the recorded laboratory variables: hematocrit, platelet count, alanine aminotransferase level, aspartate aminotransferase level, uric acid level, creatinine level, blood urea nitrogen level, sodium level, or potassium level (data not shown).

Patients given nimodipine were significantly more likely to have a seizure than those who received magnesium sulfate (2.6 percent vs. 0.8 percent,  $P=0.01$ ) (Table 2); the crude relative risk of seizure associated with nimodipine use, as compared with magnesium sulfate use, was 3.0 (95 percent confidence interval, 1.3 to 7.1). Twelve of the 21 patients in the nimodipine group who had a seizure did so in the antepartum period; 9 had a postpartum seizure. All seven of the women who had a seizure while receiving magnesium sulfate did so in the antepartum period. Although the nimodipine group had a higher rate of antepartum seizure than the magnesium sulfate group (1.5 percent vs. 0.8 percent), the difference was not significant ( $P=0.26$ ). In the postpartum period, however, patients given nimodipine had a significantly higher rate of seizure than those who received

**Table 1. Base-Line Characteristics of the Study Population.\***

Characteristic	Nimodipine Group (N=819)	Magnesium Sulfate Group (N=831)	P Value
Age — yr	25±6	25±6	0.65
Gravidity			0.71
Median	1	1	
Interquartile range†	2	2	
Racial or ethnic group — %			0.64
Hispanic	18	20	
Black	43	41	
Asian	4	3	
White	11	13	
Mixed race	24	23	
Gestational age — wk	36±4	36±4	0.93
Systolic blood pressure — mm Hg	167±20	169±21	0.04
Diastolic blood pressure — mm Hg	111±15	111±14	0.61
Mean arterial pressure — mm Hg	127±16	127±16	0.67
Heart rate — beats/min	86±12	87±13	0.27
Urinary dipstick result — +	3±1	3±1	0.54
Weight — lb	146±49	146±47	0.87
Gestational diabetes — no. (%)	22 (2.7)	17 (2.0)	0.42
Preeclampsia in a prior pregnancy — no. (%)	86 (10.5)	102 (12.3)	0.28
Chronic renal disease — no. (%)	6 (0.7)	6 (0.7)	1.00
Chronic hypertension — no. (%)	48 (5.9)	46 (5.5)	1.00
Headache — no. (%)	429 (52.4)	419 (50.4)	0.43
Facial edema — no. (%)	245 (29.9)	252 (30.3)	0.87
Visual-field loss — no. (%)	27 (3.3)	24 (2.9)	0.67
Scintillation — no. (%)	150 (18.3)	141 (17.0)	0.48
Epigastric pain — no. (%)	165 (20.1)	195 (23.5)	0.11
Pulmonary edema — no. (%)	15 (1.8)	10 (1.2)	0.32
Oliguria — no. (%)	47 (5.7)	55 (6.6)	0.47
Features of HELLP syndrome — no. (%)	65 (7.9)	52 (6.3)	0.21
Severe thrombocytopenia — no. (%)	10 (1.2)	4 (0.5)	0.11

\* Plus-minus values are means ±SD. Data on age were available for 791 women in the nimodipine group and 807 women in the magnesium sulfate group; data on gravidity for 801 and 816, respectively; data on gestational age for 795 and 817; data on systolic blood pressure for 801 and 813; data on diastolic blood pressure for 800 and 814; data on mean arterial pressure for 805 and 826; data on heart rate for 763 and 771; data on urinary dipstick results for 652 and 653; and data on weight for 744 and 746. Gestational diabetes was defined as diet- or insulin-controlled diabetes during the current pregnancy. The diagnosis of chronic renal disease was a clinical diagnosis. Chronic hypertension was defined by a history of hypertension treated with medication. Visual-field loss was defined as the new onset of partial loss of clear vision (including blurred vision) in a defined visual field. Scintillation was defined by the occurrence of flashes of light behind closed eyes. The diagnosis of pulmonary edema was based on clinical findings, which included shortness of breath, consolidation on percussion, and crackles on auscultation, with or without radiologic evidence of pulmonary edema. Oliguria was defined as an average hourly urinary output of 30 ml or less for three or more hours. HELLP denotes hemolysis, elevated liver enzymes, and low platelet levels (<150,000 platelets per cubic millimeter). Severe thrombocytopenia was defined as fewer than 50,000 platelets per cubic millimeter. To convert values for weight to kilograms, divide by 2.2.

† The interquartile range is the difference between the 25th and 75th percentiles.

**Table 2. Maternal Complications.\***

Complication	Nimodipine Group (N=819)	Magnesium Sulfate Group (N=831)	P Value
	no. of women (%)		
Eclampsia	21 (2.6)	7 (0.8)	0.01
New-onset headache	47 (5.7)	45 (5.4)	0.83
Need for hydralazine	374 (45.7)	451 (54.3)	<0.001
Hypotension with syncope	5 (0.6)	7 (0.8)	0.77
Hypotension without syncope	15 (1.8)	10 (1.2)	0.32
Flushing	13 (1.6)	59 (7.1)	<0.001
Vomiting	19 (2.3)	23 (2.8)	0.64
Nausea	30 (3.7)	35 (4.2)	0.61
Abruption	6 (0.7)	8 (1.0)	0.79
Oliguria	47 (5.7)	55 (6.6)	0.48
Diplopia	7 (0.9)	9 (1.1)	0.80
Cardiac failure	0	2 (0.2)	0.50
Cerebral hemorrhage	0	0	—
Coagulopathy	5 (0.6)	3 (0.4)	0.50
Respiratory difficulty	3 (0.4)	11 (1.3)	0.06
Postpartum hemorrhage	8 (1.0)	20 (2.4)	0.03

\* Eclampsia was defined as a witnessed tonic-clonic seizure; new-onset headache as a nonmigraine type of headache of recent (within hours) onset; the need for hydralazine by a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 110 mm Hg after the administration of nimodipine or magnesium sulfate; hypotension by a systolic blood pressure of less than 70 mm Hg; abruption as a clinical diagnosis of antepartum separation of the placenta from the uterine wall, with or without vaginal bleeding; oliguria by an average hourly urinary output of 30 ml or less for three or more hours; cardiac failure as a clinical diagnosis in the medical record; cerebral hemorrhage on the basis of the results of computed tomography or magnetic resonance imaging; coagulopathy as clinically abnormal bleeding or a laboratory diagnosis of a coagulation abnormality; respiratory difficulty as new onset of difficulty breathing, as evidenced by any of the following: tachypnea (rate of more than 22 per minute), dyspnea, or low peripheral oxygen saturation (less than 90%); and postpartum hemorrhage as blood loss of more than 500 ml after vaginal delivery and of more than 1000 ml after cesarean section (clinical estimate as recorded in the delivery notes).

magnesium sulfate (9 of 819 vs. 0 of 831; 1.1 percent vs. 0 percent;  $P=0.01$ ). Three patients who initially received nimodipine had further seizures despite subsequent treatment with magnesium sulfate in the postpartum period.

Women who received magnesium sulfate were more likely than women who received nimodipine to require hydralazine for blood-pressure control and to have flushing after drug administration (Table 2). There was also a higher incidence of postpartum hemorrhage in the magnesium sulfate group.

There was a tendency toward more respiratory difficulty in the magnesium sulfate group, although this difference was not significant ( $P=0.06$ ). Other maternal and neonatal outcomes did not differ significantly between groups (Tables 2 and 3).

After adjustment for the covariates listed in Table 4, the adjusted risk ratio associated with the use of nimodipine, as compared with that of magnesium sulfate was similar to the unadjusted risk ratio (3.1; 95 percent confidence interval, 1.3 to 7.3). Table 4 shows the statistically significant risk factors that were found to be associated with eclampsia.

There were no significant differences between groups in the type of anesthesia they received ( $P=0.24$ ). Only in the nimodipine group was the risk of postpartum seizure related to the type of anesthesia ( $P<0.01$ ). None of the 250 women who received either no anesthesia or local anesthesia for delivery had a seizure, whereas seizure occurred in 3 of 392 patients who had regional anesthesia (0.8 percent) and in 6 of 86 who had general anesthesia (7.0 percent).

There was no significant difference between the two groups in the mean arterial pressure recorded before an antepartum seizure (mean [ $\pm$ SD],  $124\pm 17$  mm Hg among 12 patients in the nimodipine group and  $115\pm 11$  mm Hg among 7 patients in the magnesium sulfate group;  $P=0.22$ ). In addition, the 19 women who had an antepartum seizure did not have a significantly higher mean arterial pressure at admission than those who did not have an antepartum seizure ( $131\pm 20$  mm Hg vs.  $125\pm 16$  mm Hg,  $P=0.35$ ). Base-line blood pressures and overall blood-pressure readings were similar in the two groups (data not shown), although the magnesium sulfate group more often required hydralazine. Among the patients whose initial mean arterial pressure exceeded 126 mm Hg, fewer in the nimodipine group than in the magnesium sulfate group required hydralazine for blood-pressure control (57.8 percent vs. 66.7 percent,  $P=0.04$ ). Patients in the nimodipine group who required hydralazine were more likely to have eclampsia than patients in the magnesium sulfate group who required hydralazine (4.0 percent vs. 1.1 percent,  $P=0.01$ ). Among patients who did not receive hydralazine, the rate of eclampsia was 1.4 percent in the nimodipine group and 0.5 percent in the magnesium sulfate group ( $P=0.30$ ). Patients who required hydralazine had significantly higher blood-pressure values on admission than those who did not require hydrala-

zine (data not shown). The increased risk of seizure associated with nimodipine persisted after adjustment for hydralazine use and systolic blood pressure at admission (Table 4).

The mean arterial pressure in the nimodipine group was reduced by a mean of 8.2 percent in the first hour after drug administration, and this reduction was maintained at three hours (8.3 percent). There was a 4.2 percent decrease in mean arterial pressure during the first hour in the magnesium sulfate group, and a 7.2 percent decrease within three hours.

## DISCUSSION

This study showed that parenterally administered magnesium sulfate is significantly better than oral nimodipine at preventing eclamptic seizures in women with severe preeclampsia. This difference was especially apparent in the postpartum period.

Although we compared magnesium sulfate with nimodipine, the recent MAGPIE trial<sup>12</sup> compared magnesium sulfate with placebo in women with mild or severe preeclampsia and also demonstrated a beneficial effect of magnesium sulfate. In that study, there was also a lower maternal mortality rate in the magnesium sulfate group, although the difference was not significant. On the basis of these findings, there is now a considerable effort to promote the prophylactic use of magnesium sulfate in countries where its use was previously not the norm. Despite this, neither the cause of eclampsia nor the mechanism of action of magnesium sulfate as a seizure prophylactic is known.

It has been hypothesized that cerebral vasospasm and resultant ischemia are the predominant cause of eclampsia. If this were true then a specific cerebral vasodilator would be more effective at relieving vasospasm (and thus a better drug to prevent eclampsia) than magnesium sulfate. Our findings do not support this hypothesis.

A recent report<sup>18</sup> on the cerebral hemodynamic changes in patients with preeclampsia may explain our findings, since it suggests that elevated cerebral perfusion pressure, rather than decreased cerebral blood flow, is the primary cause of injury. Increased cerebral perfusion pressure is believed to result in "cerebral barotrauma" and vasogenic (and, rarely, cytotoxic) edema. Nimodipine has been shown to increase cerebral perfusion pressure in patients with preeclampsia, whereas magnesium sulfate decreases it.<sup>19</sup> Our finding that nimodipine is less effective

**Table 3. Type of Delivery and Neonatal Complications.\***

Variable	Nimodipine Group (N=819)	Magnesium Sulfate Group (N=831)	P Value
Vaginal delivery — no. (%)			0.55
Normal	292 (35.7)	300 (36.1)	
Forceps or vacuum assisted	42 (5.1)	33 (4.0)	
Unspecified type	48 (5.9)	41 (4.9)	
Cesarean section — no. (%)	437 (53.4)	457 (55.0)	
Primary indication for cesarean section — no. (%)			0.11
Fetal distress	32 (7.3)	39 (8.5)	
Cephalopelvic disproportion	142 (32.5)	126 (27.6)	
Severe hypertension	140 (32.0)	174 (38.1)	
Other	122 (27.9)	108 (23.6)	
Unspecified	1 (0.2)	10 (2.2)	
Estimated blood loss — ml	505±306	512±335	0.38
Gestational age at delivery — wk	36±4	36±4	0.93
Infants' characteristics			
Birth weight — g	2509±818	2447±798	0.14
Apgar score at 1 minute			0.23
Median	8	8	
Interquartile range	3	3	
Apgar score at 5 minutes			0.73
Median	9	9	
Interquartile range	1	1	
Apgar score <7 at 5 minutes — no./total no. (%)	59/729 (8.1)	76/770 (9.9)	0.24
Respiratory distress syndrome — no./total no. (%)	43/767 (5.6)	55/797 (6.9)	0.30
Dysrhythmia — no./total no. (%)	2/767 (0.3)	0/797	0.24
Hypotonia — no./total no. (%)	13/767 (1.7)	24/797 (3.0)	0.10
Intubation — no./total no. (%)	38/767 (5.0)	54/797 (6.8)	0.13
Hypotension — no./total no. (%)	6/767 (0.8)	2/797 (0.3)	0.17

\* Plus-minus values are means ±SD. Fetal distress was defined as a fetal condition requiring immediate delivery in the opinion of the clinician. Cephalopelvic disproportion was defined as the inability to deliver vaginally owing to mechanical disproportion in the opinion of the clinician. Other reasons for cesarean section included prior cesarean section, breech presentation, placenta previa, suspected abruptio placentae, vaginal bleeding, failed induction of labor, and unspecified reasons. The diagnosis of respiratory distress syndrome, dysrhythmia, hypotonia, and hypotension was obtained from the patients' medical records. The interquartile range is the difference between the 25th and 75th percentiles.

than magnesium sulfate in preventing seizures suggests that seizures in patients with eclampsia that are not the result of obvious hemorrhage are more likely to be due to overperfusion (hypertensive encephalopathy)<sup>18,20-24</sup> than ischemia. The higher rate of seizure in the nimodipine group may be explained on the basis of the nimodipine-induced reduction in protective vasoconstriction, which initiated or worsened overperfusion. This effect may be amplified in the postpartum period when the levels of constrictor substances released by the placenta<sup>25</sup> are reduced. We observed a higher rate of seizure

**Table 4. Risk Factors for Seizure.\***

Risk Factor	Adjusted Risk Ratio (95% CI)†	P Value
Nimodipine (vs. magnesium sulfate)	3.2 (1.1–9.1)	0.03
Need for hydralazine (vs. no need)	2.8 (1.0–7.7)	0.05
Systolic blood pressure >180 mm Hg at admission (vs. ≤180 mm Hg)	2.9 (1.0–8.3)	0.04
History of hypertension treated with medication (vs. no such history)	4.3 (1.3–14.8)	<0.02
Serum sodium <136 mmol/liter (vs. ≥136 mmol/liter)	3.5 (1.4–8.9)	0.01
Maternal age <18 yr (vs. ≥18 yr)	4.2 (1.4–13.0)	0.01

\* The need for hydralazine was defined by a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 110 mm Hg after the administration of nimodipine or magnesium sulfate. CI denotes confidence interval.

† The adjusted risk ratio was obtained by logistic regression.

post partum, but not ante partum, in the nimodipine group than in the magnesium sulfate group.

The increased risk of seizure associated with elevated cerebral perfusion pressure may be compounded by the use of anesthetic agents or potent vasodilator drugs that interfere with cerebral autoregulation<sup>26</sup> or by clinically significant volume expansion (such as through iatrogenic infusion of fluid or autologous uterine transfusion at the time of uterine contraction post partum). We found that women who required hydralazine for blood-pressure control were more likely to have a convulsion when they were given nimodipine than when they were given magnesium sulfate. Although the number of patients studied was small and the implications of this finding are not clear, in these patients the combination of a potent specific cerebral vasodilator (nimodipine) and a drug that prevents functional cerebral autoregulation (hydralazine)<sup>26</sup> may have caused hypertensive encephalopathy.

Magnesium sulfate has been traditionally thought to have a transient hypotensive effect.<sup>27</sup> In a third of women whose mean arterial pressure exceeded 126 mm Hg at admission, no drug other than magnesium sulfate was required for blood-pressure control. Although this difference may simply represent the effect of bed rest, a change in position, or the use of anesthesia, this observation

warrants further study. The fact that no patient in this study died, had an intracranial hemorrhage, or had permanent renal or liver failure suggests that the degree of blood-pressure reduction associated with the administration of magnesium sulfate can be regarded as safe.

Although our analysis suggested that magnesium sulfate was associated with an increased risk of postpartum hemorrhage and respiratory difficulty, we do not believe that these are major risks of this therapy. These findings came to light as the result of post hoc analyses and were not anticipated a priori. The average estimated blood loss was similar in the two groups at the time of delivery, and we did not collect data on the need for blood transfusion. Respiratory difficulty was not objectively measured, and we relied on the subjective assessment of the delivery team. Neither of these two complications was reported as being associated with magnesium sulfate in the MAGPIE trial.<sup>12</sup>

We also found that chronic hypertension, a systolic blood pressure of more than 180 mm Hg at admission, the need for additional hydralazine, low blood sodium levels, and a young age were independent risk factors for eclampsia in women with severe preeclampsia. Although underlying hypertension, extremely elevated blood pressure, and young age have been previously reported as risk factors for eclampsia,<sup>28</sup> the association of eclampsia with low sodium levels is less well known. The findings that regional and general anesthesia were associated with a higher risk of seizure than either no anesthesia or local anesthesia among patients taking nimodipine raise the possibility that these medications have an additive cerebral excitatory interrelation that magnesium sulfate does not. Given that these secondary findings were not the result of a priori hypotheses and may be the result of confounding factors, they should be regarded as hypothesis-generating observations.

Our study demonstrates that magnesium sulfate is more effective than nimodipine in preventing eclampsia in women with severe preeclampsia and reinforces the use of magnesium sulfate as the standard of care against which potential alternatives should be measured. Finally, the lack of effectiveness of nimodipine, a cerebral vasodilator, supports the hypothesis that eclampsia may be caused by cerebral overperfusion rather than decreased cerebral blood flow.

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## APPENDIX

The members of the Nimodipine Study Group were as follows (the numbers in parentheses are the numbers of patients who received at least one dose of study drug and the total numbers enrolled): John Anthony, University of Cape Town, Cape Town, South Africa (806/882); Maria Nobrega de Oliveira, Maternidade Escola J. Cicco, Natal, Brazil (282/303); Michael A. Belfort, Baylor College of Medicine, Houston (158/159); Omur Taskin, Inonu University School of Medicine, Malatya, Turkey (79/79); Jack Moodley, Nelson Mandela Medical School, Durban, South Africa (56/56); Jorge Carillo, Hospital Padre Hurtado, Santiago, Chile (51/52); Mario Festin, University of the Philippines, Manila (53/53); Liliana Voto, Fundacion Miguel Marguiles, Buenos Aires, Argentina (39/39); David Adair, Louisiana State University Medical Center, Shreveport (34/34); Baha Sibai, University of Tennessee, Memphis (33/34); Bjorn Uys, Frere Hospital, East London, South Africa (22/22); Jose Garrido Calderon, Esquina J.J. Perez, Santo Domingo, Dominican Republic (15/15); James W. Van Hook, University of Texas Medical Branch, Galveston (12/12); and Claudia Maria Vilas Freire, Maternidade Odete Valadares, Bello Horizonte, Brazil (10/10).

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