Abbreviated Postpartum Magnesium Sulfate Therapy for Women With Mild Preeclampsia

A Randomized Controlled Trial

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OBJECTIVE: To determine whether women receiving 12-hour and 24-hour postpartum magnesium sulfate ($MgSO_4$) therapy for mild preeclampsia have differing clinical courses.

METHODS: Consenting women with suspected mild preeclampsia were randomly assigned to12 hours or 24 hours of $MgSO_4$ postpartum therapy. Treatment was continued after the assigned time period if there was evidence of severe preeclampsia. The frequency of progression to severe disease and other outcomes were compared between study groups using the Fisher exact, χ^2, and Student *t* tests where appropriate.

RESULTS: Between January 2001 and August 2004, 200 women were enrolled. The 12-hour and 24-hour groups were similar in age, parity, delivered gestational age, anesthesia, and mode of delivery, as well as for proteinuria and blood pressure. In the 12-hour group, $MgSO_4$ treatment was extended in seven women (6.9%) for progression to severe disease versus one (1.1%) in the 24-hour group ($P=.07$). Women who developed severe disease had higher blood pressures at the first prenatal visit (140/78 versus 122/69, $P\leq.02$ for systolic and diastolic pressures), at the time of randomization (152/88 versus 135/78, $P\leq.03$ for systolic and diastolic pressures), and were more likely to have insulin-requiring diabetes (27.3% versus 4.4%, $P=.03$). No 12-hour patients required treatment beyond 24 hours postpartum. There were no seizures, $MgSO_4$ toxicity, or intolerance in either group.

CONCLUSION: Twelve hours of postpartum $MgSO_4$ therapy for mild preeclampsia is associated with infrequent disease progression and a clinical course similar to that with 24-hour therapy. Patients with chronic hypertension and insulin-requiring diabetes are at risk for progression to severe disease postpartum.

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See related editorial on page 824.

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Preeclampsia is a significant source of maternal and neonatal morbidity and mortality, complicating 5–8% of all deliveries, with in excess of 100,000 women treated in the United States each year.[1] Treatment of preeclampsia at term typically includes delivery, administration of parenteral magnesium sulfate for seizure prophylaxis, and management of the attendant severe hypertension and other acute complications. There is currently no consensus regarding the appropriate duration of postpartum seizure prophylaxis.[2] Although practice varies by center, in the absence of such a consensus, magnesium sulfate ($MgSO_4$) is often administered for 24 hours after delivery in the setting of mild preeclampsia.

Recently, shorter duration postpartum $MgSO_4$ therapy has been suggested. Proposed treatment schemes have included shortened courses for selected patients at low risk for eclampsia.[3,4] In these studies, the result was a significantly shorter stay in the acute setting of the labor and delivery unit. The resultant limited duration of magnesium exposure, cost savings, and decreased patient discomfort and inconvenience make this an attractive option for clinicians and patients. Our purpose was to prospectively compare the clinical course of women with mild preeclampsia treated with either 12 or 24 hours of postpartum $MgSO_4$ therapy.

MATERIALS AND METHODS

This randomized prospective trial was performed with approval from the institutional review board at MetroHealth Medical Center. Women with mild preeclampsia, diagnosed antepartum, intrapartum, or postpartum, were eligible for inclusion after delivery. For the purpose of this study, mild preeclampsia was diagnosed based on hypertension and proteinuria. Blood pressure criteria included new-onset systolic (140 mmHg or greater) or diastolic (90 mmHg or greater) hypertension or exacerbation of well-controlled chronic hypertension (defined as outpatient blood pressure elevation requiring initiation or adjustment of oral medications or a diagnosis of exacerbated hypertension during the delivery admission). Proteinuria criteria included a random catheterized urine sample result of 1+ or more or a total urine protein to creatinine ratio of 300 mg or greater.[5,6] Each patient suspected to have the diagnosis of preeclampsia underwent hematological assessment for hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. Patients with symptoms, blood pressures, or laboratory evidence consistent with severe disease at the time of delivery or before randomization were excluded. Blood pressures defining severe preeclampsia were mean arterial blood pressure greater than 120, systolic hypertension greater than 160, or diastolic blood pressure greater than 105 on two or more occasions over 6 hours. Women with suspected mild preeclampsia based on the above criteria and who were at 34 weeks or more of gestation, based on best obstetric estimate, were considered eligible for inclusion. All patients with preeclampsia diagnosed after delivery had the diagnosis made within 2 hours of delivery, before discharge from the labor and delivery unit to the postpartum floor. At the time of randomization, all patients had received intravenous $MgSO_4$, consisting of a 4 g loading dose and a 2 g per hour infusion, initiated either before delivery or within 2 hours postpartum.

The study group was determined after delivery for consenting women. Randomization was achieved using a computer-generated random number table permuted in blocks of 10. Group assignments were kept on labor and delivery in sequentially numbered sealed opaque envelops that were opened after consent was obtained. Patients were assigned to receive either an abbreviated regimen of 12 hours or the traditional 24- hour course of postpartum $MgSO_4$. Intravenous fluids were maintained at a total rate of 125 mL/h for all infused fluids. While on labor and delivery receiving $MgSO_4$, patients were managed with an hourly assessment of vital signs, urine output monitoring via Foley catheter, restriction of oral intake, and complete bed rest. During the initial postpartum period, oral antihypertensive agents were not routinely initiated because patients receiving $MgSO_4$ were allowed nothing by mouth. Patients who developed blood pressure criteria or symptoms consistent with severe preeclampsia remained on labor and delivery for additional $MgSO_4$ therapy and monitoring. Patients deemed clinically stable after the completion of the assigned therapy were transferred to the postpartum ward for continued postpartum care.

Clinical characteristics, laboratory results, maternal morbidities, progression to severe preeclampsia, postpartum labor and delivery, and hospital stay were evaluated. Data were analyzed by intent to treat using Statview 4.0 statistical software (SAS Institute, Cary, NC). Fisher exact, χ^2, and Student t tests were used where appropriate. According to data compiled by Ascarelli et al,[3] we assumed that the mean duration of $MgSO_4$ treatment in the 12-hour group would be 150% of the planned therapy (standard deviation [SD] of 50%, ie, 18 hours $\pm$ 9 hours) and that virtually all patients in the 24-hour group would receive 24 hours $\pm$ 6 hours). A total of 50 patients in each arm would be needed to evaluate the duration of $MgSO_4$ with an adequate power (80%; $\alpha=0.05$). Sixty-eight patients in each arm would be needed evaluate this outcome with a power of 90%. We chose a target enrollment of 100 in each group to ensure sufficient data for analysis. This study was not powered to evaluate the effect of abbreviated $MgSO_4$ prophylaxis on postpartum seizure risk because the number of eclamptic seizures was expected to be extremely low (less than 1%) in this population.

RESULTS

Between January 2001 and August 2004, a pool of 322 women with suspected mild or severe preeclampsia delivered at our center. Of these, 204 were eligible and approached for enrollment in our study. A total of 200 patients were enrolled (12 hours=101; 24 hours=95). Data for four patients in the 24-hour group could not be retrieved, and these patients were considered to be lost to follow-up. Table 1 describes demographic and clinical characteristics of the study population. Twelve-hour and 24-hour patients were similar in age, parity, gestational age, intrapartum analgesia, indication for admission, and mode of delivery. The frequency of concurrent medical conditions, including chronic hypertension and insulin-requiring diabetes, was similar between groups. The two study groups were comparable in severity of

Table 1. Demographic and Clinical Characteristics of Women Assigned to 12- and 24-Hour Postpartum Magnesium Sulfate Therapy

	12 Hours (n=101)	24 Hours (n=95)	*P*
Age (y, mean±SD)	24.4±6.5	25.2±6.5	.39
Black race	48 (47.5)	48 (50.5)	.55
Primiparous	48 (47.5)	45 (47.4)	.98
Pregravid BMI (kg/m^2, mean±SD)	30.3±7.9	28.3±8.8	.09
Insulin-requiring diabetes	11 (11)	9 (9.5)	.82
Chronic hypertension	18 (18)	13 (14)	.44
Gestational age (wk, mean±SD)	38.7±1.7	38.7±1.7	.89
Admission indication			
Preeclampsia	44(43.6)	41 (43.2)	.9
Labor	32 (31.7)	33 (34.7)	.8
PROM	12 (11.9)	6 (6.3)	.2
Preterm PROM	3 (2.9)	1 (1.1)	.6
Postterm	4 (3.9)	5 (5.3)	.7
Diabetes	1 (0.9)	5 (5.3)	.1
Other	4 (3.9)	4 (4.2)	.9
TP:CRE ratio [median (range)]*	588 (110–4,887)	500 (125–4,125)	.2
24-hour urine protein [mg, median (range)]*	466 (27–2,928)	490 (0–5,206)	.5
24-hour urine protein 300 mg or greater (%)	72.2	73.9	.9
Admission blood pressure			
Systolic (mmHg, mean±SD)	143±13	140±13	.1
Diastolic (mmHg, mean±SD)	82±10	82±11	.9
Delivery blood pressure			
Systolic (mmHg, mean±SD)	140±21	138±17	.6
Diastolic (mmHg, mean±SD)	78±15	77±15	.6
Cesarean delivery	22 (21.7)	25 (26.3)	.6

SD, standard deviation; BMI, body mass index; PROM, premature rupture of the membranes; TP:CRE, total urinary protein/creatinine ratio, as measured in a spot urinalysis.
Data are presented as n (%), except where otherwise indicated.
* Median (range), as compared by Mann-Whitney test.

illness as measured by level of proteinuria and blood pressure at the time of admission and delivery, and at 6, 12, 18, 24, 36, and 48 hours postpartum.

The duration of $MgSO_4$ therapy was significantly shorter in the 12-hour group (12.8 versus 24.0 hours, $P<.001$; Table 2). $MgSO_4$ infusion was extended beyond the initially assigned period in seven 12-hour patients and one 24-hour subject (6.9% versus 1.1%, $P=.07$) who developed findings of severe disease: 12 hours: headache (2), visual changes (1), severe hypertension (4); 24-hours: headache (1). Of the seven patients who required extended therapy, three had concomitant diagnoses of chronic hypertension, and three had diabetes, with two of these patients having both. Comparing blood pressures at 6, 12, 18, 24, 36, and 48 hours postpartum between groups found no difference, $P>.05$ for each. There were no seizures, $MgSO_4$ toxicity, or intolerance in either treatment group. Postpartum length of stay was not different between groups. No 12-hour patients required treatment beyond 24 hours postpartum.

When compared with the remainder of the 12-hour group, the seven patients who required prolonged therapy had higher blood pressures at their first prenatal visit (140/78 versus 122/69, $P\leq.02$ for both systolic and diastolic pressures) than those not

Table 2. Outcomes of Women Assigned to 12- and 24-Hour Postpartum Magnesium Sulfate Therapy

	12-Hour $MgSO_4$	24-Hour $MgSO_4$	*P*
Duration of postpartum $MgSO_4$ therapy (h, mean±SD)	12.8±2.8	24.0±2.4	<.001
Progression to severe preeclampsia	7 (6.9)	1 (1.1)	.07
Seizures	0	0	–
Postpartum hospitalization (d, mean±SD)	1.9±0.9	2.1±1.0	.18

$MgSO_4$, magnesium sulfate, SD, standard deviation.
Data are presented as mean±SD or n (%).

requiring prolongation of treatment and were more likely to have had insulin-requiring diabetes (27.3% versus 4.4%, $P=.03$) and blood pressures at delivery were similar between these two subgroups (139/78 versus 146/88, $P=.4$ for both systolic and diastolic pressures; Table 3).

DISCUSSION

In this prospective trial, we have found that a 12-hour course of postpartum $MgSO_4$ in the setting of mild preeclampsia is associated with a clinical course similar to that of the traditional 24-hours of planned treatment, significantly reducing the duration of $MgSO_4$ exposure and the need for intensive nursing care.

Previous studies have attempted to limit $MgSO_4$ infusion time after delivery. Ascarelli et al,[3] in a study of 168 women with mild or severe preeclampsia, used clinical characteristics as a guide for duration of treatment of preeclampsia after delivery. Once diuresis signaled entry into a recovery phase of the disease, blood pressures and maternal symptoms such as headaches and visual changes were used to guide discontinuation of therapy. $MgSO_4$ treatment time was reduced by 50% with this approach. This study was not restricted to women with mild preeclampsia, and the initial severity of disease was associated with the duration of therapy administered. Women with mild preeclampsia were treated for an average of 9.5 ± 4.2 hours, and those with severe disease received treatment for an average of 16 ± 5.9 hours. We did not use urine output as a criterion for duration of treatment because inclusion was limited to women with mild preeclampsia in whom urine output was expected to remain relatively unchanged. Waiting for significant diuresis in such women might well have prolonged therapy in the 12-hour group.

Our findings are consistent with those of Ascarelli et al,[3] albeit in a more focused patient population. Although we found a small group of women at risk for more frequent disease progression ($P=.07$, relative risk 0.15, 95% confidence interval 0.01–1.22), this finding was not statistically significant, and the sample size needed to address this with 80% power ($\alpha=0.05$) would have been 211 patients in each group. Our study also indicates an association between the need for extension of therapy beyond the initial 12-hour period and preexisting conditions including chronic hypertension or insulin-requiring diabetes.

In recent work, Isler et al also used clinical symptoms to guide postpartum therapy among 503 women with mild or severe preeclampsia. This study included women with HELLP syndrome and also eclampsia. In the subgroup with mild preeclampsia, the duration of $MgSO_4$ therapy was reduced to a mean of 3.5 hours. Among those with mild preeclampsia, 6.3% required reinitiation of $MgSO_4$ because of exacerbated hypertension or headaches after the cessation of therapy. Patients with rebound disease were more likely to have chronic hypertension or insulin-requiring diabetes or both.[4] This finding concurs with our own results and raises the possibility that there are certain patients in whom abbreviated postpartum $MgSO_4$ therapy may not be appropriate.[7] It is worth noting that in our study the blood pressure at randomization for those women assigned to 12 hours of treatment, who did not require prolongation of treatment, appears to be lower than the required entry criteria. However, these women were in fact preeclamptic, with blood pressure values above the required diagnostic thresholds at the time of diagnosis. As reflected by their lower blood pressures after delivery, they may have had more mild preeclampsia.

Length of postpartum hospital stay was not influenced by treatment group. This is consistent with our

Table 3. Characteristics of Women Initially Assigned to 12-Hour Treatment According to the Need for Prolongation of Therapy for Postpartum Severe Preeclampsia

	12 Hours (n=94)	Extended $MgSO_4$ (n=7)	*P*
Time in Labor & Delivery (h)	12.3±1.6	19.6±5.7	<.001
Blood pressure (mmHg)			
1st prenatal visit systolic	122±16	140±37	.01
1st prenatal visit diastolic	69±9	78±16	.02
Delivery systolic	139±21	146±22	.4
Delivery diastolic	78±15	88±13	.4
Randomization systolic	135	152	.03
Randomization diastolic	78	88	.03
Insulin requiring diabetes (%)	4.4	27.3	.03

$MgSO_4$, magnesium sulfate; SD, standard deviation.
Data are presented as mean±SD, except where otherwise indicated.

primary finding that the course of recovery from mild preeclampsia is not influenced by the duration of magnesium sulfate therapy. It may also be possible that, because all patients enrolled had mild disease with typically normal hospital stays, no difference would have been able to be detected in this sample size.

On the basis of two recent randomized prospective studies of $MgSO_4$ therapy for women with mild preeclampsia,[8,9] it has been suggested that further study regarding the need for magnesium sulfate prophylaxis is needed or appropriate in this setting.[10] In fact, it has been suggested that magnesium sulfate therapy is not needed at all for asymptomatic women with mild preeclampsia.[11] As suggested, approximately 20,000 women would be needed to fully address the efficacy of magnesium sulfate for seizure prophylaxis in this setting, The recent American College of Obstetricians and Gynecologists (ACOG) practice bulletin[1] regarding the management of preeclampsia suggested that there is "no unanimity of opinion regarding the prophylactic use of magnesium sulfate for the prevention of seizures in women with mild preeclampsia" and did not make a specific recommendation for its administration in this clinical setting. Regardless, many practitioners continue to administer ante- and postpartum $MgSO_4$ to women with mild preeclampsia. We have not addressed the influence of antepartum $MgSO_4$ therapy. Patients enrolled in our study were already receiving $MgSO_4$ at the time of randomization and had already delivered. Our data, combined with those for mild preeclamptics participating in the studies of Ascarelli et al[3] and Isler et al,[4,7] offer information regarding 483 women with mild preeclampsia who were randomized to conventional therapy or an alternative abbreviated regimen. The inherent differences in approach to abbreviated therapy between our trial and the two previously published trials preclude combination of the studies for meta-analysis. However, the consistent findings among these three studies provide support for the concept that the conventional duration of postpartum $MgSO_4$ therapy may not be required in all cases and offer the basis for further evaluation of the $MgSO_4$ therapy for appropriately selected women with mild preeclampsia.

The management of mild preeclampsia at term includes delivery, treatment of severely elevated blood pressure, and $MgSO_4$ seizure prophylaxis. The risk of seizures occurring postpartum in this setting is low, and this study was not designed with adequate power to address the effectiveness of abbreviated postpartum treatment on the risk of seizures. However, without reaching statistical significance (P=.07), we did identify a population at risk of progression to severe disease among women treated with $MgSO_4$ for 12 hours postpartum. We suspect this to be a result of a heightened suspicion for progression to severe disease in the patient being assigned to the 12-hour group. Although these patients might have been more closely scrutinized by physicians than patients assigned to 24-hour therapy, this caution is clinically appropriate. Abbreviated therapy should not result in lowered suspicion for severe disease. The continued evaluation of women recently delivered with mild preeclampsia should be considered integral to any abbreviated treatment protocol. This group of women with underlying vascular disease such as diabetes or chronic hypertension warrants further study with regard to abbreviated postpartum $MgSO_4$ therapy in the setting of preeclampsia.

We have been able to identify characteristics in patients who "failed" abbreviated therapy, and this may be helpful to physicians considering shortened courses of postpartum $MgSO_4$ infusion and may be important to future studies. These women were more likely to be insulin-requiring diabetics and have higher mean blood pressures at their initial care visit and delivery. This finding agrees with that of Isler et al[4,7] and may help identify women in whom abbreviation of therapy is not feasible.

Magnesium sulfate therapy carries risk of fluid overload, pulmonary edema, inadvertent overdose with cardiopulmonary depression, and nausea and vomiting with attendant risks of aspiration in the obtunded patient. In light of these risks, postpartum women being treated with $MgSO_4$ require more intensive nursing care, often at the expense of appropriate bonding with and breastfeeding of the newborn due to staffing limitations in the labor and delivery suite. The close monitoring of urine output requires the use of a Foley catheter, which women may find unpleasant and invasive after delivery. Abbreviated therapy in this period of low risk for seizure can potentially reduce the risks and discomforts of $MgSO_4$ therapy without significantly altering the clinical course. Our findings, in combination with those of Ascarelli et al[3] and Isler et al[4,7] suggest that a 12-hour postpartum infusion of $MgSO_4$ is appropriate for selected women with mild preeclampsia in the absence of pre-existing disease such as chronic hypertension or insulin-requiring diabetes.

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