Magnesium Sulfate Compared With Nifedipine for Acute Tocolysis of Preterm Labor

A Randomized Controlled Trial

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OBJECTIVE: To compare the efficacy and side effects of intravenous magnesium to oral nifedipine for acute tocolysis of preterm labor.

METHODS: A multicenter randomized trial was performed. Patients in active preterm labor who were at 24 to 33 weeks and 6 days of gestation were randomly assigned to receive magnesium sulfate or nifedipine. The primary outcome was arrest of preterm labor, defined as prevention of delivery for 48 hours with uterine quiescence.

RESULTS: One hundred ninety-two patients were enrolled. More patients assigned to magnesium sulfate achieved the primary outcome (87% compared with 72%, *P*=.01). There were no differences in delivery within 48 hours (7.6% magnesium sulfate compared with 8.0% nifedipine, *P*=.92), gestational age at delivery (35.8 compared with 36.0 weeks, *P*=.61), birth before 37 and 32 weeks (57% compared with 57%, *P*=.97, and 11% compared with 8%, *P*=.39), and episodes of recurrent preterm labor. Mild and severe maternal adverse effects were significantly more frequent with magnesium sulfate. Birth weight, birth weight less than 2,500 g, and neonatal morbidities were similar between groups, but newborns in the magnesium sulfate group spent longer in the neonatal intensive care unit (8.8±17.7 compared with 4.2±8.2 days, *P*=.007).

CONCLUSION: Patients who received magnesium sulfate achieved the primary outcome more frequently. However, delay of delivery, gestational age at delivery, and neonatal outcomes were similar between groups. Nifedipine was associated with fewer maternal adverse effects.

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LEVEL OF EVIDENCE: I

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Although the preterm birth rate continues to increase, complicating 12.3% of births in the United States[1] and contributing substantially to neonatal morbidity and mortality, deliveries due to spontaneous preterm birth and preterm premature rupture of the membranes (PROM) have declined among singletons.[2] Between 1989 and 2000 spontaneous preterm birth and premature delivery after preterm PROM each declined 0.4% among singletons. The increasing rate of preterm birth has resulted in part from an increase in preterm delivery for medical indications[2] and an increase in multiple gestations. Neonatal outcomes have improved at all gestational ages due in part to antenatal steroid administration, which may be enabled by tocolytic agents, and improvements in neonatal care. The cost of preterm birth remains substantial, estimated to be at least

$26.2 billion, $51,600 per preterm infant, in the United States in 2005.[3]

Tocolytic agents are used to inhibit uterine contractions and delay delivery. Ideally, tocolytics should minimize maternal morbidity while delaying delivery during the administration of antenatal steroids. Magnesium sulfate is the most commonly used first-line tocolytic in North America[4,5] although it has not been demonstrated to be superior to saline infusion,[6] and its use has been a source of controversy.[7] Magnesium sulfate requires intravenous administration, has potential for overmedication[8] with serious maternal adverse effects[7,9] and may be associated with adverse neonatal effects.[7,10,11] When compared with betamimetics, magnesium sulfate seems to offer a better maternal safety profile.[12] Nifedipine may be more easily tolerated, is administered orally, and appears to have few adverse effects,[9] although severe dyspnea, hypoxia, and myocardial infarction have been reported among pregnant women,[13] as has fetal death.[14] When compared with betamimetics, nifedipine has been associated with fewer adverse reactions,[15–17] prolonged gestation, and better neonatal outcomes.[15,17] Nifedipine has been compared with magnesium sulfate in two small randomized studies.[18,19] Both studies were underpowered, with 80 and 74 patients, respectively, and suggested no difference in efficacy or maternal adverse effects. Nifedipine may arrest contractions faster than magnesium sulfate.[19] Our objective was to compare the efficacy and adverse effects of magnesium sulfate and nifedipine for the acute tocolysis of preterm labor.

MATERIALS AND METHODS

A randomized clinical trial was performed at Stanford University Medical Center and Santa Clara Valley Medical Center. Patients in active preterm labor who were 24 weeks to 33 weeks and 6 days gestation were randomly assigned to receive magnesium sulfate or nifedipine. Preterm labor was defined by two or more contractions every 10 minutes *with* cervical change, ruptured membranes, or 2-cm or more dilation and 80% effacement. Exclusion criteria included placental abruption, placenta previa, nonreassuring fetal status, intrauterine growth restriction, chorioamnionitis, and maternal medical disease. Randomization was conducted through sequentially numbered opaque envelopes generated from a random numbers table.

All patients received betamethasone, 12 mg intramuscularly twice, 24 hours apart, antibiotic prophylaxis directed against group B *Streptococcus*, and 500 mL hydration with lactated Ringer's solution before tocolysis. Patients with preterm premature rupture of membranes also received erythromycin. Patients randomly assigned to magnesium sulfate received a 4-g bolus followed by 2 g/h infusion. Physicians were allowed to give additional 2-g magnesium sulfate boluses as needed for persistent preterm labor, and to increase the infusion rate up to 4 g/h. Patients assigned to nifedipine received 10 mg sublingually every 20 minutes for three doses total, followed by 20 mg orally every 4 or 6 hours, based on physician judgment. Physicians were instructed to continue treatment with magnesium sulfate or nifedipine until at least 12 hours of uterine quiescence occurred within the first 48 hours. Uterine quiescence was defined as six or fewer contractions per hour. After study treatment was completed, physicians were instructed to manage patients per their usual routine, which may or may not include oral maintenance tocolysis with nifedipine. All patients underwent clinical assessment for magnesium sulfate toxicity, and blood pressure evaluation every 15 minutes for the first 2 hours, and then every 4 hours during the first 24 hours of the study. Adverse effects were assessed by patient interview from a list of adverse effects and chart review.

The primary study outcome was prevention of delivery for 48 hours *with* attainment of uterine quiescence, defined by 12 hours of six or fewer contractions per hour and no further cervical change within 48 hours of tocolytic initiation. Failure of the primary outcome occurred if, in the first 48 hours, patients delivered, ruptured previously intact membranes, experienced recurrent preterm labor, continued to contract or change their cervix throughout, or required the use of supplemental or alternate tocolytics. Secondary outcomes included hours to quiescence, birth weight, gestational age at delivery, maternal adverse effects and neonatal morbidities, and length of stay. A composite of serious maternal adverse effects included chest pain, pulmonary edema, shortness of breath, and hypotension.

All patients who presented to one of the two hospitals in preterm labor and not receiving tocolytic medications were eligible for study enrollment. All patients were enrolled between April 26, 1999, and July 11, 2005. Patients were managed by the attending physicians in conjunction with resident physicians who were working on Labor and Delivery at the time of patient admission and care.

We estimated a 35% incidence of failure of the primary outcome with magnesium sulfate. To have 80% power to detect a 50% reduction in failure, with a two-tailed alpha of 0.05 and a β of 0.2, 192 patients were required. Data were analyzed by intent to treat,

χ^2, Fisher exact test, Student *t* tests, Wilcoxon rank sum, and Kaplan-Meier survival analysis. The study was approved by the human subjects committees at Stanford University Medical Center and Santa Clara Valley Medical Center.

RESULTS

A total of 196 patients were randomly assigned, and 192 patients were enrolled (Fig. 1). Four patients were excluded after randomization and before data analysis for not meeting study entry criteria. One patient's office chart revealed that she was at 35 weeks of gestation; she had not yet received tocolysis. Three patients did not meet criteria for preterm labor: two had cervical dilation but no contractions, and one had frequent uterine contractions but no cervical change.

Ninety-two patients received magnesium sulfate, and 100 patients received nifedipine. Our patient population is described in Table 1. There were no differences between the groups with regard to patient demographics and obstetric characteristics, (Table 1) nor were there differences between the two study centers in type of medication given, total medications given at 24 and 48 hours, failure of the primary outcome, time to failure, and time to uterine quiescence. At 24 and 48 hours patients' mean total medications received were 52.4 g and 79.8 g in the magnesium sulfate group and 84.6 mg and 136.3 mg in the nifedipine group. There were no differences between groups with regard to the number who received maintenance tocolysis with nifedipine.

Significantly more patients assigned to receive magnesium sulfate achieved the primary outcome of prevention of preterm delivery for 48 hours with uterine quiescence (87% compared with 72%, P=.01, Table 2), and this held true when we excluded from analysis patients with twins and preterm PROM. However, among all patients who achieved the primary outcome, time to uterine quiescence was faster with nifedipine. There were no differences between the groups in the proportion of patients who delivered within 48 hours, gestational age at delivery, delivery before 37 and 32 weeks, or episodes of recurrent preterm labor. Kaplan-Meier survival estimates of time to delivery (Fig. 2) revealed no differences between the groups, and the curves are nearly indistinguishable.

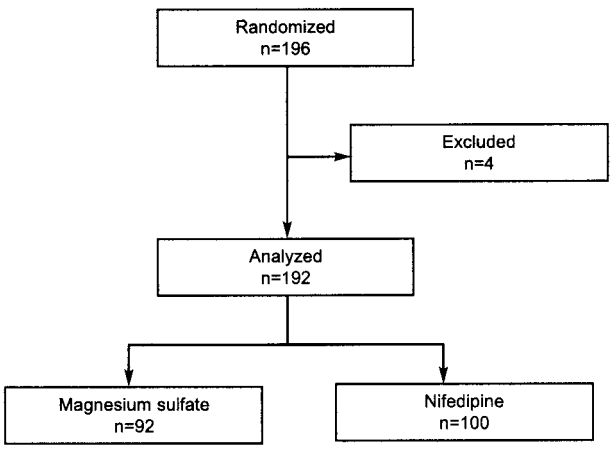

Fig. 1. Flow diagram of randomization.

Lyell. Magnesium Compared With Nifedipine. Obstet Gynecol 2007.

Maternal adverse effects, including serious adverse effects, were significantly more frequent with magnesium sulfate (Table 3), and having no adverse effects at all was significantly more frequent with nifedipine. Three patients experienced pulmonary edema, all of whom had received magnesium sulfate. Of note, there were no differences between the groups in hypotension, defined by a mean arterial pressure of 60 mm Hg or less among women who were initially more than 60 mm Hg.

Neonatal outcomes were not different between the groups (Table 4). There were no differences in average birth weight or low birth weight. There were no differences in individual or composite neonatal morbidities. There was one neonatal death in the magnesium sulfate group, thought to be unrelated to magnesium sulfate. The patient was successfully acutely tocolyzed with magnesium sulfate at 24.5 weeks, then experienced preterm PROM, developed chorioamnionitis, and was delivered at 25 weeks. The newborn died after one day. Data were not available for 13 neonates, seven in the magnesium sulfate group and six in the nifedipine group. Six patients delivered elsewhere and were lost to follow-up, and seven neonatal records could not be located.

Ninety-six neonates were admitted to the neonatal intensive care unit (NICU). Neonates who were exposed to magnesium sulfate in utero spent significantly more days in the NICU, 8.7 compared with 4.2 (P=.007, Table 4) despite a lack of difference in birth weight, gestational age, and individual or composite morbidities. Wilcoxon rank sum analysis confirmed an association between magnesium sulfate exposure in utero with a prolonged NICU stay (magnesium sulfate median 1 day, 25–75% interquartile interval 0–9.5; nifedipine median 0 days, 25–75% interquartile interval 0–4; P=.02). When multivariable analysis was performed to control for birth weight, gestational age at delivery, and twin gestation, newborns exposed to magnesium sulfate were three times more

Table 1. Maternal and Obstetric Demographics

Characteristics	Magnesium Sulfate (n=92)	Nifedipine (n=100)	*P*
Age	26.6±6.8	26.3±6.3	.38
Age 35 y or older	14 (15)	11 (11)	.39
Public assistance	64 (69)	68 (68)	.82
Multiparous	41 (45)	55 (55)	.15
Prior preterm birth	12 (13)	19 (19)	.26
Gestational age at enrollment (wk)	30.8±2.3	31.2±2.1	.92
Dilation at start of tocolysis (cm)	1.9±0.98	1.8±0.93	.30
Effacement at start (cm)	2.2±1.1	2.2±1.2	.65
Contraction frequency at start (min)	3.6±1.5	3.5±1.2	.24
Twins	20 (22)	17 (17)	.40
Preterm PROM	4 (4)	4 (4)	.90
Maintenance tocolysis	33 (38)	42 (42)	.57

PROM, premature rupture of membranes.
Data are n (%) or mean±standard deviation.

Table 2. Magnesium Sulfate Compared With Nifedipine, Outcomes

	Magnesium Sulfate (n=92)	Nifedipine (n=100)	*P*
Primary outcome	80 (87)	72 (72)	.01
Primary outcome excluding preterm PROM	76 (86)	70 (73)	.02
Primary outcome excluding twins	62 (86)	61 (73)	.05
Time to quiescence (h)	8.4±6.5	6.1±6.3	.02
Delivery in 48 hours	7 (7.6)	8 (8.0)	.92
Gestational age at delivery (wk)	35.8±3.4	36.0±3.1	.61
Gestational age less than 37 wk	50 (57)	52 (57)	.97
Gestational age less than 32 wk	10 (11)	7 (8)	.39
Episodes recurrent preterm labor	0.44±.61	0.40±.61	.32

PROM, premature rupture of membranes.
Data are n (%) or mean±standard deviation.

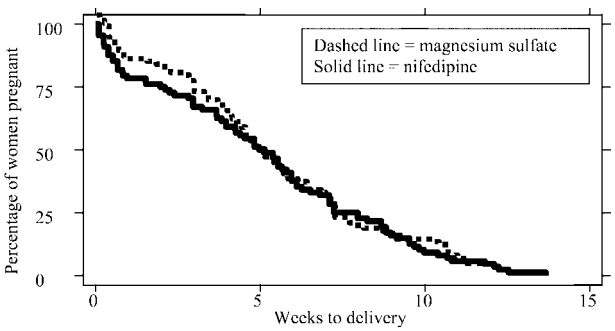

Fig. 2. Kaplan-Meier survival estimates of time to delivery. *Lyell. Magnesium Compared With Nifedipine. Obstet Gynecol 2007.*

likely to be admitted to the NICU (odds ratio 3.0, 95% confidence interval 1.0–9.1).

DISCUSSION

Based on our search of the PubMed, English-language literature from 1980 to 2007, using the key words "magnesium sulfate," "nifedipine," "preterm labor," and "tocolysis," this is the largest randomized study comparing magnesium sulfate and nifedipine.

In our study, magnesium sulfate achieved the primary outcome more frequently than nifedipine. However, no differences were noted between drugs in delay of delivery, gestational age at delivery or major neonatal outcomes. Nifedipine was associated with significantly fewer mild and severe maternal adverse effects.

Magnesium sulfate has been the most frequently used tocolytic at both study sites. Eleven nifedipine patients were changed to magnesium sulfate because of persistent uterine contractions alone, without clearly documented evidence of cervical change, in apparent violation of the study protocol. No women treated with magnesium sulfate were changed to nifedipine. All 11 patients were considered to have failed the primary outcome and were analyzed by intent to treat. Unfortunately, we do not know what would have happened had these contracting patients remained on nifedipine for the full 48-hour window, how many would have achieved the primary out-

Table 3. Adverse Effects

	Magnesium Sulfate (n=92)	Nifedipine (n=100)	*P*
Any adverse effects	60 (65)	34 (34)	<.001
Serious adverse effects*	20 (22)	10 (10)	.03
Shortness of breath	13 (14)	5 (5)	.03
Pulmonary edema	3 (3)	0 (0)	.07
Hypotension	2 (3)	3 (5)	.72
Chest pain	7 (8)	4 (4)	.28
Lethargy	27 (29)	3 (3)	<.001
Nausea	29 (32)	6 (6)	<.001
Vomiting	24 (26)	5 (5)	<.001
Flushing	20 (22)	1 (1)	<.001
Blurry vision	12 (13)	0 (0)	<.001
Dizziness	16 (17)	3 (3)	<.001
Double vision	3 (3.3)	0 (0)	.07
Headache	11 (12)	22 (24)	.07
Palpitations	1 (1)	0 (0)	.30
Heartburn	6 (7)	6 (6)	.87

Data are n (%).
* A composite of shortness of breath, pulmonary edema, hypotension, and chest pain.

Table 4. Neonatal Outcomes*

	Magnesium Sulfate (n=106)	Nifedipine (n=110)	*P*
Birth weight (g)	2,550±802	2,650±698	.38
Birth weight less than 2,500 g	52 (49)	46 (42)	.48
RDS	24 (23)	21 (19)	.48
IVH	3 (3)	2 (2)	.61
NEC	0	0	
Sepsis	5 (5)	3 (3)	.43
Death	1 (1)	0	.31
Composite morbidity†	27 (25)	22 (20)	.32
NICU admission	55 (52)	41 (37)	.04
GA at NICU admission (wk)	33.1±2.3	33.8±2.2	.28
BW at NICU admission (g)	1,973±494	2,095±570	.38
Days in NICU	8.8±17.7	4.2±8.2	.007

RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; GA, gestational age; BW, birth weight.
Data are n (%) or mean±standard deviation.
* Data include twins, so the group totals are greater than seen in the maternal data. Data were not available for 13 neonates, seven in the magnesium sulfate group and six in the nifedipine group.
† Composite morbidity included respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and fetal or neonatal death.

come, and whether nifedipine would indeed have achieved uterine quiescence faster than magnesium sulfate.

Because of the practice paradigms at both our institutions where magnesium sulfate has traditionally been the first-line tocolytic of choice, we anticipated and attempted to reduce this study bias by using uterine quiescence as part of the primary outcome; patients who received magnesium sulfate but continued to contract throughout the 48-hour window could not also be viewed as successful. Importantly, regardless of which tocolytic the patient received, gestational age at delivery, birth weight, and major neonatal morbidities were not different between groups. Our study suggests that one can safely start nifedipine, and change the patient to another tocolytic if needed.

Some have raised safety concerns with oral and sublingual nifedipine in nonpregnant[20] and pregnant[14,20] patients. Nifedipine antagonizes voltage-dependent L-type calcium channels, causing vascular and smooth muscle relaxation, vasodilatation, reflexive cardioacceleration, and increased sympathetic tone. When used during hypertensive crisis, nifedipine can lead to acute severe hypotension resulting in

cerebrovascular ischemia, stroke, myocardial infarction, fetal distress, conduction disturbances, and death.[20] The immediate release formulation can decrease blood pressure within 5 to 10 minutes.[20] When used for tocolysis, diastolic blood pressure has been reported to decrease by 8% after the first sublingual dose, heart rate also increases, and the effect lasts for 3 hours.[21] Twenty minutes after oral, as opposed to sublingual, dosing, diastolic blood pressure decreased by a mean of 11%, and heart rate increased. Nifedipine's half-life was 1.35 hours.[22] Clinically significant hypotension did not occur in this study or in our own, but has been reported (Johnson KA, Mason GC. Severe hypotension and fetal death due to tocolysis with nifedipine [letter-reply]. BJOG 2005;112:1583). Because of the potential for hypotension we prehydrated all patients with 500 mL of lactated Ringer's solution, monitored blood pressure frequently, and excluded women with hypertension or cardiac disease.

Maternal adverse effects occurred in nearly two thirds of women exposed to magnesium sulfate and one third of women exposed to nifedipine, a significant and important difference. Of concern, serious adverse effects, including shortness of breath and pulmonary edema, were also more frequent with magnesium sulfate. Significant hypotension was not seen among our nifedipine patients, although Glock and Morales[18] describe transient hypotension, lasting less than 10 minutes and not requiring drug discontinuation, among 41% of nifedipine patients. Excluding blood pressure changes, they reported more adverse effects among magnesium sulfate patients, 10% of whom required drug discontinuation.

No difference in any of the major neonatal outcomes was noted between groups. We did find that newborns exposed to magnesium sulfate spent more time in the NICU despite a similar incidence of major morbidities and similar birth weights and gestational ages at delivery and at NICU admission. Our data do not offer a clear explanation for this finding. Our study did not address the frequently multiple and complex array of reasons for NICU admission and ongoing hospitalization. Whether there is a causal link between magnesium sulfate and NICU length of stay is unproven and merits future investigation. Some investigators have speculated that magnesium sulfate may slow gastrointestinal function, leading to feeding issues, and may lead to significant respiratory suppression.[23] In the two prior studies comparing magnesium sulfate with nifedipine, NICU length of stay was not assessed in one[18] and was reported as not different in the other,[19] but the number of patients included was not given. Neonatal intensive care unit stay was not prolonged when magnesium sulfate was compared with saline infusion.[6] Some have expressed concerns about fetal exposure to tocolytic doses of magnesium sulfate (Mittendorf R, Covert R, Boman J, Khoshnood B, Lee KS, Siegler M. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? [letter-reply] Lancet 1997;350:1517–8).[7] An excess of fetal and neonatal death among magnesium sulfate–exposed newborns has been shown by some,[6,7] with the possible explanation that there were more cases of severe fetal anomalies or twin–twin transfusion syndrome in the magnesium sulfate groups. A Cochrane meta-analysis suggested increased fetal and pediatric death related to magnesium sulfate exposure (relative risk 2.82, 95% confidence interval 1.2–6.62), although all deaths were from only one of the seven trials under review.[24] Others have reported that magnesium sulfate exposure does not increase neonatal mortality or morbidity[25] and actually may protect against gross motor dysfunction.[26] In Glock and Morales'[18] trial of magnesium sulfate compared with nifedipine, there were two neonatal deaths, both attributed to extreme prematurity, and both from the nifedipine group.

Our study was limited by several factors. Neither magnesium sulfate nor nifedipine has been shown to be an effective tocolytic in a double-blind, placebo-controlled trial. However, tocolytic agents have been shown to delay delivery for 48 hours, with the purported benefit of allowing steroid administration or maternal transport. To perform a placebo-controlled, study of tocolysis during the window of steroid administration is outside the standard of care for our community. A double-blind study comparing magnesium sulfate and nifedipine could have overcome potential physician management bias in this study, although maternal adverse effects may make blinding difficult. Fetal fibronectin was not a requirement for study entry because it was not initially available at both study sites. Ideally a study of preterm labor would exclude patients with a negative fetal fibronectin. We enrolled patients, however, who were clinically in active preterm labor. Although the optimal doses of magnesium sulfate and nifedipine have not been established, we used the standard doses used in our institutions. However, higher doses may be needed for clinical efficacy. Our nifedipine protocol has been evaluated among patients in our institution, with evidence of safety and efficacy.[21]

In conclusion, magnesium sulfate achieved the primary outcome (prevention of delivery for 48 hours *with* uterine quiescence) more frequently than nifed-

ipine. However, no differences were noted between drugs in delay of delivery, gestational age at delivery or major neonatal outcomes. Nifedipine was associated with significantly fewer mild and severe maternal adverse effects.

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