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A PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL OF HIGH AND LOW DOSES OF MAGNESIUM SULFATE FOR ACUTE TOCOLYSIS

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ABSTRACT

At the present, many drugs are used for inhibition of uterine contractions, but the proportions of preterm labors are increasing. Although magnesium sulfate is the most commonly prescribed parenteral tocolytic agent, but its optimal use has yet to be delineated. In this study a high-dose protocol for magnesium sulfate tocolytic therapy was compared with a low-dose regimen. One-hundred patients admitted to the labor unit of Imam Reza's hospital with preterm labor were enrolled in the trial. The median times to successful tocolysis were 8 hours in the low-dose group and 4 hours in the high-dose group ($p<0.001$). Patients treated with higher doses were also more likely to spend significantly less time in the labor and delivery unit ($p<0.001$). The median gestational age at delivery was 33 weeks in the low-dose group and 36 weeks in the high-dose group ($p=0.001$). There were not any statistically significant differences between the two groups with respect to pre- and post magnesium infusion side effects. These results suggest that in the high-dose group, tocolysis was achieved more rapidly and patients required shorter admissions to the labor and delivery unit without increased maternal or neonatal morbidity.

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INTRODUCTION

Effective methods for treatment of preterm labor have become major goals in modern obstetrics because preterm birth is one of the major leading causes of infant morbidity and mortality. However, treatment has been of limited success, with most efforts concentrated on a few tocolytic medications. Magensium sulfate, perhaps the most commonly prescribed parenteral tocolytic agent,[1] has a long history of safe administration, and numerous investigations support its efficacy.[2-4] However, information describing the preferred manner of administration and the goals of therapy with respect to steady-state serum concentration remains limited.

Two major obstetric texts offer protocols for magnesium sulfate tocolysis ranging from 4 to 6 g for a loading dose and 1 to 4 g/h for a maintenance dose.[5,6] On the basis of these guidelines large variations in standard

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dosage and maintenance infusion rates can be advocated. A serious problem with these protocols is that although many clinicians strive for a serum magnesium concentration of 5 to 8 mg/dL,[7] there appears to be minimal evidence associating serum magnesium concentration with tocolytic success.[8]

Because there are protocols for a myriad of combinations of loading and maintenance doses, we decided to examine whether there was any difference in the length of time required for successful tocolysis with a high- versus a low-dose regimen.

MATERIAL AND METHODS

The study was conducted from October 22, 2000, through May 20, 2001, with approval from the institutional review board of the Mashhad University of Medical Sciences. All patients admitted to the labor unit of Imam Reza's hospital who met the inclusion criteria were offered enrollment. Inclusion criteria were singleton or twin gestation between 24 and 35 weeks estimated gestational age, spontaneous preterm labor, and ability to provide informed consent. We defined preterm labor as: uterine contractions of more than four per 20 minutes along with one of the following observations: cervical dilatation of at least 1 cm but less than 5 cm in diameter, cervical effacement equal or more than 80%, and/or progressive cervical dilatation and effacement. Exclusion criteria included higher-order multiple gestations, rupture of membranes, nonreassuring fetal assessment (abnormalities of the fetal heart rate pattern), evidence of intrauterine infection (a temperature of 38°C or higher, leukocytosis, uterine tenderness, malodorous discharge), vaginal bleeding, patients with history of diabetes mellitus, myasthenia gravis or any other neuromuscular diseases, impaired renal function (serum creatinine $>$ 1.2 mg/dL), hypotension (mean arterial pressure less than 70 mmHg), maternal bradycardia (heart rate of less than 60 per minute), atrioventricular block, and inability or refusal to provide informed consent.

All patients were maintained at bed rest in the labor unit during the initial evaluation. All patients who were eventually treated for preterm labor received dexamethasone to enhance fetal lung maturity. Dexamethasone was administered as four 5mg intramuscular doses given 12 hours apart. Patients did not receive prophylactic antibiotics during tocolysis but did receive ampicillin 2g q 6h for group B streptococcal prophylaxis if delivery appeared imminent.

Patients were randomly assigned by computer-generated random number allocation, with consecutively numbered opaque envelopes used to assign each patient to one of two different schedules of magnesium sulfate therapy. Once entrance criteria were met and written consent was obtained, each patient was randomly assigned to a treatment group by selection of the next numbered envelope.

In the low-dose group, patients received 4g of magnesium sulfate in a 20% solution as an intravenous loading dose over 20 minutes and then a continuous infusion of 2g/h. In the high-dose group, patients received 6g of magnesium sulfate as an intravenous loading dose and then a continuous infusion of 2g/h. In the high-dose group, if after the first hour of therapy the patient continued to have contractions or exhibit further cervical dilatation or effacement, the maintenance dose was increased by 1g/h. This was repeated hourly until the patient had successful tocolysis or treatment failure.

All women enrolled in the study had continuous fetal heart rate monitoring (intermittent auscultation with a fetoscope q 15 minutes), at least hourly assessments of contraction frequency, cervical dilatation and effacement,

Table I. Demographic data.

	Low dose N=50	**High dose N=50**	**Statistical Significance**
Age (y, mean ±SD)	23.8±5.2	24.0±4.4	p=0.805
Primigravid n(%)	22 44%	19 38%	p=0.684
History of preterm delivery n(%)	13 26%	15 30%	p=0.824
Twin gestation n(%)	3 6%	1 2%	p=0.609
Estimated gestational age at admission (week) (median)	31	31	p=0.571
Estimated gestational age at admission $\leq$ 32 wk n(%)	40 80%	34 68%	p=0.254
Initial cervical dilatation (mean ±SD) (cm)	2.1±1	2.5±0.9	p=0.081
Initial effacement (%) (mean ±SD)	45.1±18.0	45.6±16.5	p=0.885
Number of uterine contractions/20min (mean ±SD)	3.7±1.0	3.6±1.0	p=0.923
Time spent for q contraction (seconds) (mean ±SD)	38.6±2.33	35.6±2.2	p=0.073

as well as regular examinations of pulmonary (respiratory rate, pulmonary auscultation), nervous system (deep tendon reflexes, assessing the degree of consciousness), and cardiac status (heart rate, EKG).

Hourly urine output, fluid intake and blood pressure were measured accordingly. Routine laboratory tests for all women included urinalysis, blood urea nitrogen (BUN), serum creatinine, bleeding time, platelet count, and serum magnesium concentrations. Magnesium concentration determinations were repeated serially during (0, 2, 6, 12, 20) hours of magnesium infusion in all patients.

In both groups, successful tocolysis was marked by the occurrence of fewer than four contractions per hour with no further advancement in cervical dilatation or effacement. Patients in whom dilatation progressed to 6cm, and or contractions persisted longer than 30 minutes at the maximum magnesium dose with continued cervical dilatation, were considered to have had treatment failure; tocolytic therapy was discontinued, and the patient was delivered. Once adequate tocolysis was achieved or therapy was judged to have failed according to the criteria described here, magnesium infusion was discontinued. (In the high-dose group, magnesium sulfate therapy was decreased by 1g every 30 minutes and stopped when 2 g/h is reached).

Demographic data were collected including patient age, gravidity, parity, maternal history of preterm delivery, singleton or twin gestation, and gestational age at admission and at delivery. The primary outcome measure was the amount of time required to achieve tocolysis. The secondary outcome measures included the total amount of time spent in the labor and delivery unit and frequencies of tocolytic therapy side effects. To evaluate any effects of the protocols on obstetric outcome, we also collected route of delivery and neonatal data, including birth weight, APGAR scores, number of days of stay in the neonatal intensive care unit and serious neonatal morbidity and death. Additional data encompassing the initial cervical examination, contraction frequency, serum magnesium concentration, and bleeding time was gathered. Categoric variables were analyzed with chi-square tests when sample size was adequate and with the Fisher exact test otherwise. Continuous variables were examined with independent-sample t tests if distributional assumptions were consistent with normality.

Otherwise the data were ranked and nonparametric Mann-Whitney tests were conducted. $p<0.05$ was considered significant.

RESULTS

One hundred patients were enrolled in the trial. There were 50 patients in the low-dose group and 50 patients in the high-dose group. The two groups were similar with respect to demographic variables (Table I). The maximum dose of magnesium sulfate in the high-dose group was 4g/h. Mean serum magnesium concentration was 3.45±0.44 mEq/L in the low-dose group and 5.48±0.29 mEq/L in the high-dose group.

This value reflects the mean of at least three measurements at the maximum magnesium sulfate infusion rates. There were a total of 32 patients (32%) who did not have adequate tocolysis and were subsequently delivered. We compared multiple variables between the 68 patients who had successful tocolysis and the 32 patients who had failure of tocolysis (Table II). The only differences that we were able to establish were that the women with treatment failure were more likely to have cervical

Table II. Comparison of successful tocolysis with failed treatment.

	Successful N=68	**Failed N=32**	**Statistical Significance**
Age (y, mean ± SD)	23.8±4.6	24.2±5.1	p=0.694
Estimated gestational age at admission ≤32 weeks n (%)	46 67.6%	28 87.5%	p=0.062
Estimated gestational age at Delivery ≤32 weeks n (%)	4 5.9%	27 84.4%	p< 0.001
Primigravid n(%)	28 41.2%	13 40.6%	p=0.958
History of preterm delivery n(%)	18 26.5%	10 31.3%	p=0.797
Initial cervical dilatation <3cm n(%)	16 23.5%	25 78.1%	p<0.001
Initial effacement >80% n(%)	17 25%	27 84.4%	p<0.001

Table III: Comparison of efficacy and tolerability of high dose and low dose magnesium sulfate therapy.

	Low dose N= 50	High dose N= 50	Statistical Significance
Failure rate n(%)	22 44%	10 20%	p=0.009
Time to tocolysis (hr) (median)	8	4	p<0.001
Time in labor and delivery unit (hr) (mean±SD)	22.55±2.5	12.86±2.0	p<0.001
Cesarean delivery rate n(%)	21 42%	16 32%	p=0.401
Estimated gestational age at delivery (weeks) (median)	33	36	p=0.001
Side effects: n(%)			
Flushing	13 26%	15 30%	p=0.412
Headache	4 8%	5 10%	p=0.5
Nausea-Vomiting	15 30%	19 38%	p=0.263
No side effects	21 42%	18 36%	p=0.341

Table IV: Comparison of bleeding time, platelet count, and mean arterial pressure in low & high dose group.

	Baseline		Statistical Significance	Post-infusion		Statistical Significance
	Low-dose N=50	High-dose N=50		Low-dose N=50	High-dose N=50	
Bleeding time (min) (mean±SD)	3.2 ±0.3	3.3±0.3	p=0.272	4.3 ±0.6	4.54± 0.5	p=0.053
Platelet count ($\times 10^3$/mm^3) (mean±SD)	282.7±45.2 45.2	288.7±30.2 30.2	p=0.443	284.6±45.0 45.0	288.7±30.3 30.3	p=0.60
MAP (mmHg) (mean±SD)	83.4(7.1	80.0±8.1	p=0.087	83.2±6.7	78.9±8.3	p=0.005

M A P:Mean arterial pressure.

dilatation of >2cm and cervical effacement of>80% initially.

Among those who received low-dose therapy 22 of 50 (44%) had treatment failure, whereas 10 of 50 (20%) in the high-dose group had treatment failure. This represents a statistically significant difference between the two groups in failure rate (p= 0.009). The median time to successful tocolysis was 8 hours in the low-dose group and 4 hours in the high-dose group (Table III). The difference in proportions was statistically significant (p<0.001). Patients treated with higher maintenance doses were also more likely to spend significantly less time in the labor and delivery unit (p<0.001). The median gestational age at delivery was 33 weeks in the low-dose group and 36 weeks in the high-dose group (Table III). This represents a statistically significant difference between the two groups (p= 0.001). Patients who received the high-dose protocol were more likely to report side effects, such as headache, flushing, nausea and vomiting. But there was not any statistically significant difference between the two groups (Table III). No patients had treatment discontinued because of side effects such as severe hypotension, pulmonary edema or respiratory depression.

All the patients included in the study group had a normal initial mean bleeding time of 3 minutes. Magnesium sulfate infusion was found to prolong the bleeding time whereas the platelet count remained unchanged (Table IV).

There was a significant lowering of the mean arterial pressure after magnesium infusion in the high-dose group (p= 0.005) (Table IV).

Selected neonatal outcomes according to maternal treatment group are summarized in Table V. Results in

Table V: Selected neonatal outcomes in pregnancies randomized to low-dose and high-dose groups.

Neonatal outcomes	Low dose N=53	High dose N=51	Statistical Significance
Birth weight (g)(mean ±SD)	2529.2±634	2807.8±420	p=0.01
1-min Apgar score <8 n(%)	25 47.2%	23 45.1%	p=0.988
5-min Apgar score<8 n(%)	17 32.1%	7 13.7%	p=0.047
Neonatal stay at NICU			
n(%)	14 26.4%	6 11.8%	p=0.01
Mean ±SD (days)	13.6±7.7	10.5±3.8	p=0.013
Complications: n(%)			
Respiratory distress	14 26.4%	4 7.6%	
Hypoglycemia	1 1.9%	1 2%	
Bradycardia	4 7.9%	1 2%	p=0.017
Hypocalcemia	1 1.9%	0 0%	
Neonatal death	6 11.3%	2 3.9%	

NICU: Neonatal intensive care unit

pregnancies randomized to receive high-dose magnesium sulfate differed significantly from the low-dose group with respect to birth weight (p= 0.01), 5-minute APGAR scores (p= 0.047), percent of neonatal need for NICU[1] (p=0.01), number of days of stay at the NICU (p= 0.013), and serious neonatal morbidity such as respiratory distress syndrome (p= 0.017). There were a total of eight neonatal deaths, of which 6 occurred in the low-dose group.

DISCUSSION

The treatment of preterm birth and the consequent morbidity associated with it is an enigma that has confounded physicians for centuries. Improvements in neonatal outcome are primarily the result of improved neonatal care and corticosteroid therapy. As the pathogenesis of preterm labor has become better understood, headway has been made in discerning which patients are at risk.[9-11] Unfortunately, discrimination of the patients at the highest risk for preterm delivery is useful only if there is an effective intervention. Tocolytic agents are the primary tools used to prevent preterm delivery once the process of preterm labor has been initiated. Considering the frequency with which tocolytic agents are used, it is a matter for concern that specific dosing schedules have not been compared.[12]

In this study, we carefully selected patients with documented preterm labor. Tocolytics were found to be less effective in patients with the cervix dilated more than 2cm and/or effacement equal to or more than 80%. We found that tocolysis was achieved more rapidly among patients treated with high-dose therapy, and as a result these patients required less time in the labor and delivery unit.

Between the two groups was a significant difference in failure rate. Because patients in the high-dose group had more successful tocolysis and delivered at higher gestational age, the weight of their neonates were more than that of neonates in the low-dose group. More patients in the high-dose group received a total dose of dexamethasone (4 doses) and neonatal respiratory distress syndrome was lower than low-dose group.

Neonates with suitable weight had less morbidity and mortality and their APGAR scores were more than 7. We therefore conclude that neonatal outcome in the high-dose group was better than the low-dose group.

We were unable to demonstrate a significant difference in incidence of side effects between the two groups. Our data suggest that cautious evaluation of the blood pressure is required in patients receiving high-dose magnesium sulfate. Although the prolonged bleeding time in each group was not out of the normal range, the results of our study suggest that measurement of the bleeding time is also required in patients receiving magnesium sulfate. Magnesium sulfate concentration in the high-dose group compares favorably with the results of Hollander (6.6 mg/dL, equivalent to 5.3 mEq/L) and Elliott (4 to 6 mEq/L).[4,7]

Higher doses of magnesium sulfate appear to offer a

rapid method to achieve tocolysis. If appropriate safeguards are implemented, a high-concentration of safety can be expected. By decreasing the time required to achieve uterine quiescence, overall drug exposure and the expense of prolonged therapy could be ameliorated. Higher doses can be used safely, which may allow the clinician to have more confidence in maximizing therapy with magnesium sulfate and avoid the considerably increased risks associated with multiple tocolytic agents.

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