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Original Articl

Comparison of efficacy and safety of nifedipine versus magnesium sulfate in treatment of preterm labor

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Abstract

BACKGROUND: Preterm labor with intact membrane is responsible for approximately one-third of preterm births, which account for about 70-80% of all neonatal deaths among normally formed neonates. Premature delivery is the leading cause of perinatal morbidity and mortality. In this study we have compared the safety and efficacy of nifedipine and magnesium sulfate in treatment of preterm labor.

METHODS: In this study, 120 pregnant women experiencing preterm labor at 26-36 weeks gestation were randomly selected to receive either oral nifedipine or intravenous magnesium sulfate. The efficacy and side effects related to nifedipine or magnesium sulfate were recorded and all data was analyzed with SPSS software, using t student, chi-squire and fisher exact tests.

RESULTS: Twenty two of 57 (38.6%) patients in the nifedipine group and 31 of 63 (49.2%) patients in the magnesium sulfate group were delivered before discharge. In 25 (43.8%) patients in the nifedipine group and 24 (38%) patients in the magnesium sulfate group, pregnancy was continued until the 34th-36th week, at which time the patients were delivered. No significant difference has been found concerning any of the following: delivery postponement, drug side effects or neonatal outcomes between nifedipine and magnesium sulfate groups (P>0.05).

CONCLUSIONS: Oral nifedipine may be a suitable alternative to magnesium sulfate, with the same efficacy and side effects.

KEYWORDS: Nifedipine, magnesium sulfate, preterm labor.

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Premature delivery is a leading cause of perinatal morbidity and mortality [1,2]. Preterm labor with intact membrane is responsible for approximately one-third of preterm births, which account for about 70-80% of all neonatal deaths among normally formed neonates [2,3]. Despite the use of tocolytic agents, antibiotics and bed rest, the rate of preterm delivery has continued to increase during the past several decades [4]. Preterm birth still plays a major role in perinatal mortality and morbidity in developed countries [3]. So, preterm labor remains a difficult issue in current obstetrics. Prematurity often results in significant immediate and long-term morbidity and is related to sepsis, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis and retinopathy of prematurity [4]. Most review articles on preterm labor point out that preterm birth rates are not declining but are, in fact, slowly increasing [5]. The rate of preterm delivery in the United State has not decreased, but rather has increased to 12% in 2002 [3]. There is still a perceived need for a safe and effective means of suppressing uterine contractility in those

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selected for treatment [5]. If delivery can be postponed for at least 48 hours, this will enable corticosteroids to be administered to the mother to enhance fetal lung maturation. In addition, this will allow transfer of the mother with her fetus to a neonatal intensive care facility [5]. Tocolysis is the use of medication to prevent preterm delivery. Several classes of medications are used for tocolysis including beta adrenergic agents, calcium channel blockers and prostaglandin synthesize inhibitors such as indomethacin and magnesium sulfate [3]. Studies have compared the efficacy of oral nifedipine with the efficacies of magnesium and β-sympathomimetic agents for the initiation and maintenance of tocolytic therapy [6-8]. Oral nifedipine is as effective as magnesium sulfate and terbutaline in arresting and preventing idiopathic preterm labor [7]. Nifedipine, in comparison with ritodrine in the management of preterm labor, is as effective in suppressing preterm labor, significantly associated with a longer postponement of delivery, as well as fewer maternal side effects, and fewer admissions to the neonatal ICU [6,8].

Methods

This is a randomized clinical trial study conducted in two teaching referral hospitals (Alzahra & Beheshti Hospitals) at Isfahan University of Medical Sciences (IUMS), Isfahan-Iran, between December 2005 and September 2006. The institutional research and ethics committees of IUMS approved this study. The patients had given written, informed consent before enrolling in this study. Eligible women with preterm labor between 26-36 week gestations were selected for the study. Inclusion criteria were women with preterm labor and intact membranes. Preterm Labor was defined as progressive cervical dilation and effacement associated with regular uterine contractions ≥4 per 10 minutes with duration of about 30 seconds [9]. One hundred and twenty preterm women were randomly assigned. We used a table of random numbers to assign each patient independently in sequence to one of the two groups: group 1 received nifedipine and group 2 received magnesium sulfate. The exclusion criteria were taking other tocolytic agents, cervical dilation ≥5 cm or obstetrical contraindication for tocolysis use; i.e. severe preeclampsia, lethal fetal anomalies, chorioamnionitis, significant antepartum hemorrhage, maternal cardiac or liver diseases.

Intervention protocol

After a random allocation of the two groups of women, the treatments by nifedipine or magnesium sulfate were as the follows: The first step of management was bed rest and hydration by 500 ml IV bolus of ringer solutions. All patients at fewer than 34 weeks of gestation received a course of intramuscular Betamethasone to accelerate fetal lung maturity. Intravenous antibiotics for prophylaxis against group B streptococci (Ampicillin) were given during the acute phase of preterm labor. Group1 received nifedipine (Aboureihan pharmaceutical company: Adalat, Nifedipine) beginning with a 10 mg tablet given orally and repeated every 20 minutes (maximal dose of 40 mg in the first hour). If contractions subsided, then the nifedipine maintenance dose would be 10-20 mg every six hours. Group 2 received magnesium sulfate, consisting of a loading dose of 4 grams IV over 15 minutes, then a maintenance dose of 2-3 grams/h IV infusion. Patients were observed in the labor room for 24-48 hours. Following a successful tocolytic effect from the above treatment, patients were sent to obstetric ward. If contractions did not subside, other tocolytic medication, such as isoxsuprine or indomethacin, was added (treatment failure).

Tocolytic and safety outcomes

The main outcomes of interest in arresting preterm labor were the effectiveness and safety of nifedipine versus magnesium sulfate. Tocolytic effectiveness was assessed in terms of the total number of women in the intent-to-treat population who had not been delivered at 48 hours (primary tocolytic effects) and at more than 48 hours (secondary tocolytic effects) after beginning the treatment. Additional maternal side effects were assessed with particular emphasis

on hypotension, tachycardia, palpitation, flushing, headaches, dizziness, and nausea related to nifedipine side effects [10]; flushing, nausea, headache, drowsiness, blurred vision and respiratory and motor depression of the neonate related to magnesium sulfate side effects [3]. The tocolytic efficacy and tolerability profile was assessed in terms of the proportion of the women who were not delivered and who did not require alternative tocolysis at 48 hours, in addition to an assessment of the progression of labor. For ethical reasons, a composite end point (referred to as tocolytic efficacy and tolerability) was used as a measure of efficacy, because many of investigators are opposed to a protocol that does not allow administration of alternative tocolysis in the event of the progression of labor (treatment failure). Women with previous successful tocolytic treatment, experiencing recurrent preterm labor at any time after the cessation of contractions, were treated again by the same protocol of medication administered previously. In all patients, fetal heart rate, mother's blood pressure, pulse rate, intake and output, and contractions were recorded; also, lung auscultation was performed. The uterine contraction rate was monitored continuously for 2 hours after initiation of the study and then every 15 minutes for 6-12 hours until a contraction rate of 4 contractions/hour was detected, then checked every 30 minutes for 24-48 hours. Safety outcomes were assessed in terms of maternal, fetal, and neonatal adverse events, which were reported on until the patient was discharged from the hospital.

Statistical analysis

A statistical analysis program (SPSS version13, Chicago, IL) was used for data analysis. The comparability of the two groups was checked for all demographic, obstetrical, primary and secondary tocolytic effects. Safety outcomes of all data were evaluated using summary statistics (percentage for categorical data). Differences between groups were analyzed by using the t student test, χ^2 and fisher exact test for determining association between different variables. Because all of the 120 patients took part in tocolytic therapy (by randomized stratification) in the form of nifedipine or magnesium sulfate, the analyzing method was intention to-treat analysis. To perform power calculation, we have depended on 95% confidence interval (CI) and the difference between the two groups was considered significant if $P<0.05$.

Results

0f 120 subjects, 57 patients were randomly assigned to the nifedipine group and 63 were randomly assigned to the magnesium sulfate group.

There were no significant differences between the two groups concerning the demographic characteristics such as maternal age and baseline characteristics including obstetrical history, parity and risk factors of preterm labor (table 1). Enrollment characteristics such as gestational age, fetal heart rate, cervical examination results and days of hospitalization were not significantly different between the groups (table 1).

Patients in the nifedipine group had the following side effects: one case of headache, three cases of fatigue and four cases of flushing. None of the patients had symptomatic hypotension nor chest pain while receiving nifedipine. Patients in the magnesium sulfate group had the following side effects: diaphoresis, flushing and warmth in 5 cases and rapid infusion nausea and vomiting in 2 cases. There were no cases of magnesium toxicity. After random assignment, 31 (49.2%) patients in the magnesium sulfate group and 22 (38.6%) patients in the nifedipine group had progressive preterm labor and subsequently were delivered before discharging from the hospital. Pregnancy terminated between 30-32 weeks of the gestation. In this subgroup there was no significant statistical difference between the first and fifth second apgar scores of neonates (primary tocolytic effect). However, another 24 (38.09%) patients in the magnesium sulfate group and 25 (43.8%) patients in the nifedipine group were discharged and terminated between 34-36 weeks of gestation (secondary to-

colytic effect); and there were no significant differences between the last two groups (P = 0.478). Some of the patients in both groups needed to take other tocolytic medications; e.g. ritodrine or indomethacin (treatment failure). This subset included 10 (17.5%) patients from the nifedipine group and 8 (12.6%) patients from the magnesium sulfate group (table 2).

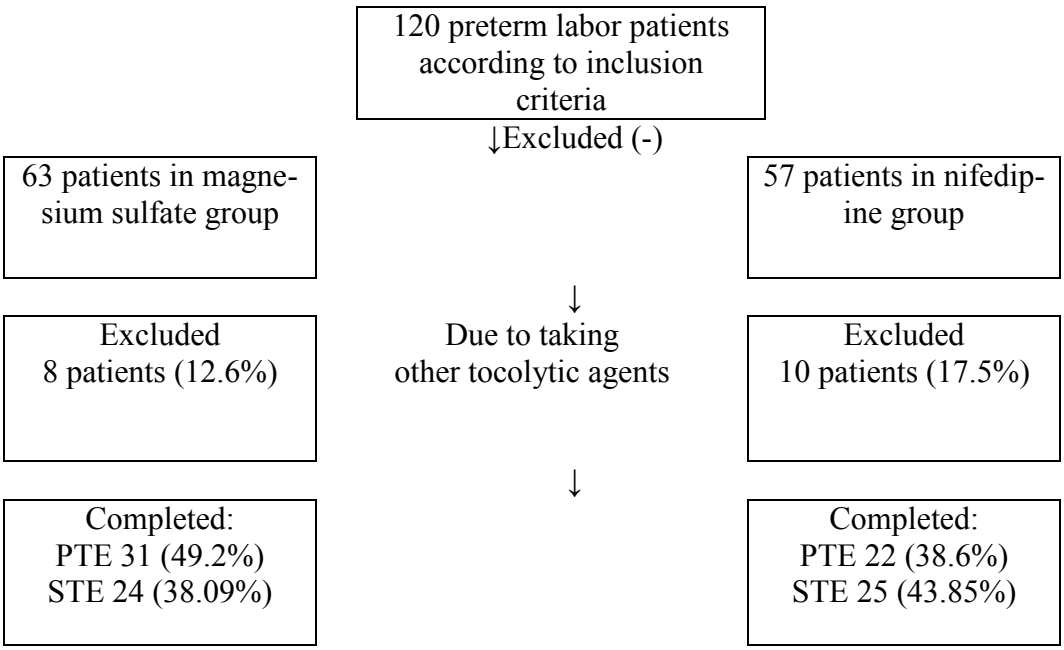

Figure 1. Study design↓
PTE = Primary Tocolytic Effect STE = Secondary Tocolytic Effect

Table 1. Maternal and preterm labor characteristics at enrollment.

	Nifedipine N = 57	Magnesium sulfate N = 63	Difference (95%CI *)
Maternal & obstetrical characteristics			
Age (mean ± SD)	25.98 ± 5.39	25.64 ± 5.12	0.34 (-1.56,2.24)
Primiparous (%)	29 (50.9)	31 (49.2)	1.7 (-16.2,19.6)
Multiparous (%)	28 (49.1)	32 (50.8)	-1.7 (-19.6,16.2)
Previous preterm labor (%)	5 (8.8)	4 (6.4)	2.4 (-7.1,11.9)
Uterine anomaly (%)	1 (1.7)	2 (3.1)	-1.4 (-6.9,4.1)
Preterm labor characteristic			
Gestational age (day)	225.6 ± 28.9 day	224.42 ± 28.1 day	1.18 (-9.1,11.5)
Cervical dilation (cm)	1.52 ± 1.08 cm	1.62 ± 1.12 cm	-0.10 (-2.81,2.61)
Cervical effacement (%)	52.98 ± 25.15%	53.68 ± 22.1%	-0.70 (-18.5,17.1)
31.5±3.7 Height of Fundus (cm)	31.5 ± 3.5 cm	31.5 ± 3.7 cm	0.0 (-1.31,1.31)
1.85±1.14 day Hospital stay (day)	2.45 ± 2.15 day	1.85 ± 1.14 day	0.60 (-0.01,1.21)
133.96±30.72 Fetal heart rate (beats)	141.98 ± 9.2	133.96 ± 30.72	8.02 (-15.4,31.4)

* Confidence Interval

Table 2. Pregnancy Outcomes.

	Nifedipine N = 57	Sulfate magnesium N = 63	Difference (95%CI)
PTE*: labor in the first 48 hours	22 (38.6 %)	31 (49.2%)	-10.6 (-28.3,7.1)
STE** A: labor in 2-10 days	5 (8.7%)	7 (11.1%)	-2.3 (-13.0,8.4)
STE** B: labor in >10 days	20 (35.08%)	17 (26.9%)	8.1 (-8.4,24.6)
GA*** of Delivery PTE* (mean ± SD)	30.22 ± 1.26wk	30.01 ± 1.38wk	0.21 (-0.27,0.69)
Delivery GA of STE	34.30 ± 1.33wk	34.10 ± 1.52wk	0.20 (-0.32,0.72)
Neonatal birth weight	2002 ± 213g.	2014 ± 164g.	-12.0 (-80.0,56.4)
Apgar score 1minute	7.8 ± 2.3	7.5 ± 2.4	0.30 (-0.55,1.15)
Apgar score 5 minutes	6.9 ± 2.5	6.7 ± 2.7	0.20 (-0.74,1.14)
Treatment failure	10 (17.5%)	8 (12.6%)	4.9 (-8.0,17.7)
Side effect	7 (12.28%)	8 (12.6%)	-0.4 (-12.3,11.4)

*Primary tocolytic effect
**Secondary tocolytic effect
***Gestational Age

Discussion

Preterm birth is a major contributor to perinatal mortality and morbidity and affects approximately 6-7 percent of birth in developed countries [10,11]. No progress had been made over the last two decades in reducing the incidence of preterm birth in the developed countries but some benefits have been identified from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturation, and the ability to transfer the pregnant woman to a center with neonatal intensive care unit facilities [10]. A range of tocolytic agents has been used to inhibit preterm labor in order to have the time for such co-intervention. In Iran, the tocolytic agent which has been most widely used is magnesium sulfate, but the update Cochran review on magnesium sulfate has found no effect favoring magnesium sulfate over controls (other tocolytics or placebos) in a short or long term delay in delivery. However, there is a higher risk of death (fetal and infant) when magnesium sulfate is used as a tocolytic agent [12,13]. This drug has unexplained side effects for both mother and the neonate. Nifedipine has been used in the majority of studies. A 2002 Meta analysis reviewed 12 randomized controlled studies involving 1029 women and found that nifedipine is more effective than ritodrine and is clearly safer [3].

In this randomized clinical trial we evaluated and compared the efficacy of oral nifedipine vs. that of magnesium sulfate in preterm labor. 38.6.8% patients in nifedipine group and 49.2% patients in magnesium sulfate group delivered before discharge in the first 48 hours (primary tocolytic effect). Twenty five (43.7%) patients in the nifedipine group and twenty four (38%) patients in the magnesium sulfate group postponed delivery for more than 48 hours (secondary tocolytic effect). From the view point of effectiveness and side effects there was no significant difference between the two groups. Nifedipine must be taken by the oral route, in comparison with magnesium which must be used by only the infusion route and requires special monitoring and close observation. Patients taking magnesium sulfate should be monitored for toxic side effects such as respiratory depression or even cardiac arrest, which can occur at super-therapeutic levels. Common maternal side effects include flushing, nausea, headache, drowsiness, and blurred vision. Magnesium crosses the placenta and can cause respiratory and motor de-

pression of the neonate [3]. On the other hand, calcium channel blockers have minimal side effects and may be more effective than magnesium and beta sympathomimetics and should be considered as the first line tocolytic agent [2,14,15]. Calcium channel blockers reduce calcium influx into cells and thereby decrease muscle contractility.

In our study there was no significant difference between nifedipine and magnesium sulfate groups concerning the maternal side effects (chest pain, nausea and vomiting, headache and transient hypotension). Then, oral nifedipine with the same efficacy, side effects and faster action could be a suitable and more convenient alternative to intravenous magnesium sulfate in arresting preterm labor. Several studies have shown the efficacy and safety of nifedipine in preterm labor, but limited data is shown concerning the safety and efficacy of nifedipine vs. that of magnesium sulfate [16]. Maternal side effects reported in the nifedipine group were similar to and not greater than those reported by both pregnant and non-pregnant patients taking a similar dose of nifedipine [4]. The nifedipine–treated neonates also had decreased risk of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhages [3]. Approximately half of the patients in both groups had progressive preterm labor. This may be due to the lack of information about preterm delivery signs, symptoms and complications in our society, and therefore delayed admission to the hospital. This problem shows the need for better educated mothers. Because the pathologic mechanisms involved in preterm labor are complex and probably differ among patients and it may not involve uterine contractions as primary events leading to preterm labor, we have yet to find an effective agent for suppression of preterm labor. Consequently, a tocolytic drug such as nifedipine may not be effective for all patients and requires more study.

Conclusions

In this study we have compared the safety and efficacy of nifedipine versus magnesium sulfate in treatment of preterm labor. Our data in this study showed that oral nifedipine is a suitable alternative for magnesium sulfate with the same efficacy and side effects. Similar results have been shown by other studies too [7,16].

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