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Original article

Nifedipin versus magnesium sulfate for the suppression of preterm labor: a randomized clinical trial

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Abstract

Background: Preterm labor is a leading cause of fetal and neonatal morbidity and mortality. There are various kinds of drugs used to suppress the preterm labor, but they are not thoroughly effective. The aim of this study was to compare the effectiveness of oral nifedipine with intravenous magnesium sulfate in delaying the preterm labor.

Methods: A randomized, clinical trial was conducted in a hospital in Babol, Iran. One hundred twenty singleton pregnant women with preterm labor, 24-37 weeks of gestation, were randomly assigned to receive oral nifedipine or intravenous magnesium sulfate. The main outcome of the study was the inhibition of uterine and the secondary outcome was the side effect related to drugs and neonatal outcome. The data were analyzed with SPSS software, using chi-squared test and independent t test.

Results: According to the results, in 35% of women in the nifedipine group and 23.3% of women in the magnesium sulfate group, the inhibited uterine contraction was less than 48 hours. Also, in 65.0% of women in the nifedipine group and 76.7% of women in the magnesium sulfate group, the inhibited uterine contraction was more than 48 hours. There was no significant difference between the nifedipine and the magnesium sulfate groups in the inhibition of uterine contraction in both less and more than 48 hours. The total side effects of medication were found to be lower in patients receiving oral nifedipine than those who received intravenous magnesium sulfate. (26.6 vs. 45.0) (p= 0.036). There was no significant difference in neonatal outcome between the two groups.

Conclusion: Oral nifedipine should be a suitable alternative to intravenous magnesium sulfate in suppression preterm labor with fewer side effects.

Keywords: Preterm Labor, Nifedipine, Magnesium sulfate.

Introduction

The premature birth term is used for the birth of infants born before the 37th week of gestation (1). The rate of preterm birth in developed countries has been reported as 6-7% (2). This issue is one of the major causes of prenatal morbidity and mortality and includes about 70 to 80% of neonatal deaths.

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Based on obstetric literature, many approaches have already been recommended to inhibit uterine contractions which include: bed rest, fluid therapy, the administration of sedatives, and the use of Tocolytics (3). The Tocolytic agents include beta-agonists, Magnesium sulfate, calcium antagonists, prostaglandin inhibitors, competitive oxytocin antagonists, Nitric oxide donor drugs, progesterone, α-17 hydroxyprogesterone caproate, and antibiotics (4).

Magnesium sulfate is the most commonly used tocolytic drug in both Iran and North America (2,5). The mechanism of action in this drug includes reducing the smooth muscles contraction in myometrium through the reduction of acetylcholine release by magnesium at the junction of nerve and muscle, and decreasing the sensitivity of terminal motor end plate to acetylcholine. Due to the known common maternal and fetal complications and the conflicting reports about its effectiveness and costs, this drug is commonly replaced with other drugs, a calcium blocker called Nifedipine (6). Oral nifedipine can inhibit the contraction of the myometrium through the inhibition of calcium influx into smooth muscle cells via blocking the voltage-dependent calcium channels, and according to some studies, it has been introduced as the preferred tocolytic drug in the treatment of preterm birth (7-8). As some patients might need re-hospitalization due to complications and high recurrence of preterm labor, we strove to investigate and compare the effects and side effects of the oral nifedipine compared with those of intravenous magnesium sulfate, used for the treatment of preterm labor. Our ultimate goal was to find a better alternative for intravenous magnesium sulfate, the one with better effectiveness and fewer side effects, which is used for the better management of preterm labor.

Materials and Methods

This randomized, clinical trial study was conducted in Ayatollah Rohani Hospital in Babol, north of Iran in 2014 and 2015. The protocol of the study was approved by the Ethics Committee of the Babol University of Medical Sciences, and registered in Iranian Clinical Trial Registry (IRCT: 201301281760N20).The gestational age was estimated through the last menstrual period and the ultrasound exam during the first trimester of pregnancy. The inclusion criteria of the study were: preterm labor occurrence, the gestational age between 24-34 weeks, at least four contractions with the duration of 30" in a period of 20 minutes with an increased rate of dilatation and cervical effacement, a previous singleton pregnancy, and a cervical dilatation of more than 5 cm.

We selected 138 eligible patients based on the inclusion criteria. The women with the diagnosed preterm were screened if they had maternal vaginal bleeding, chorioamnionitis, multiple pregnancy, preeclampsia, placenta previa, placental abruption, intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), fetal distress, fetal major anomaly, heart diseases, liver disease, and maternal hypertension. Finally, 125 women with confirmed preterm labor were provided with a written informed consent. At baseline, intramuscular pethidine 50 mg/ml and 200 cc of lactated ringers were administered by rapid infusion to all patients. If the contractions continued, the injection of betamethasone dipropionate (Diprolene, Diprolene AF, Diprosone, Alphatrex) 12 mg IM was administered in two doses by 24 hours interval. Then, the subjects were randomly assigned to receive oral nifedipine (n= 63) or intravenous magnesium sulfate (n=62) using a means of sealed envelopes. In magnesium sulfate group, 4 g of magnesium sulfate (Alhavi pharmaceutical company, Iran) in 20 minutes, and then, 2 g per hour was intravenously administered with controlled respiration, urine output and deep tendon reflex (DTR), and continued for 12 hours after the cessation of contraction. In the case of the disruption of any of the above or intolerable side effects, sulfate was discontinued temporarily or completely. In the nifedipine group, nifedipine (Alhavi pharmaceutical company, Iran) was administrated initially as oral 10 mg doses, and in case of continued contractions, the doses were continued every 20 minutes to a maximum four doses with controlled blood pressure. Then, 20 mg of nifedipine was prescribed orally every 6 hours in the first 24 hours, and the medication continued as 20 mg every 8 hours in the second 24 hours. Medication was discontinued at any time in the case of blood pressure below 90 50 mm Hg, the heart rate of more than 120 beats per minute, or any intolerable side effects. In both groups, tracing the heart rate was conducted at the beginning, and then simultaneously with fetal heart rate (FHR) monitoring and controlled contractions every 15 minutes during the first hour, and then, every half hour. Of the 125 patients who took nifedpine or magnesium sulfate, three patients in the nifedipine group were excluded due to evidence of no reassuring fetal status and placental abruption (Figure 1). In cases in which the dilation progressed or the contractions were still

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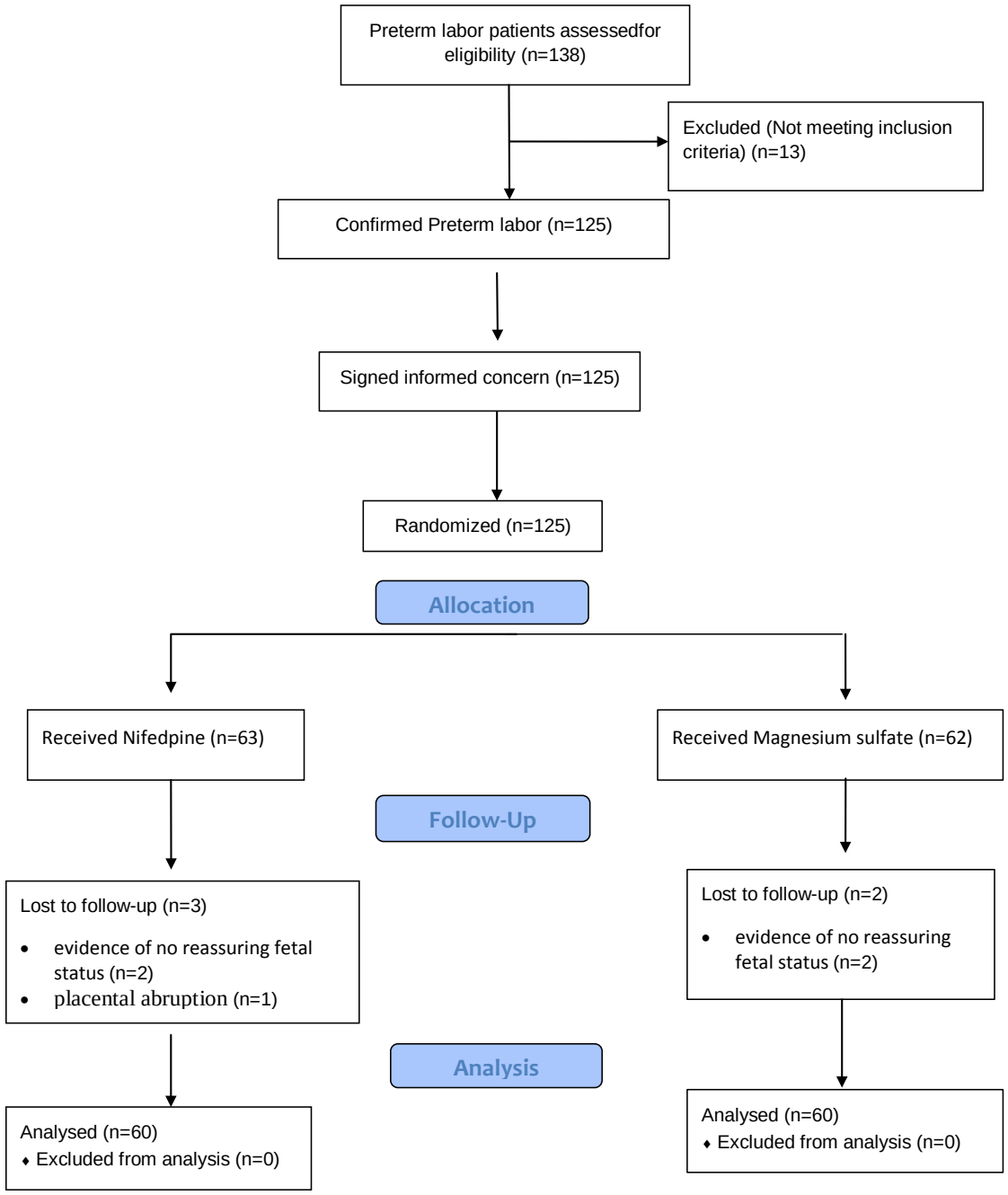

Fig 1. Flowchart of the clinical trial.

going on two hours after the fourth dose of nifedipine or 24 hours after the onset of magnesium sulfate, despite the continued treatment, the situation was considered as not responding to the treatment, and the medication was discontinued. Finally, 120 patients were assessed for the primary and secondary tocolytic effect and side effect of drugs. The primary tocolytic effects were defined as a postponement at 48 hours after the outset the treatment. In addition, the patients who delivered more than 48 hours after the start of the treatment were defined as secondary tocolytic effects. Besides, the side effects of both drugs during the therapy and pregnancy outcomes (Apgar score 1minute, Apgar score 5 minutes, hospitalized in the NICU) were assessed.

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Statistical analysis:

Having collected the data, the statistical analyses were performed by SPSS version 18.0 (SPSS Inc., Chicago, II., USA). Chi-square and Fisher-exact tests were used to determine the association between categorical variables, while the quantitative variables were evaluated using T-Test. All the statistical tests were two-sided and the P-value of less than 0.05 was considered insignificant.

Results

There were no significant differences between the mean age, the gestational age, and the gravity of the participants (Table 1).

Regarding the inhibition of contractions, the difference between the two groups was not significant. The results were as follows: less than 48 hours in 21 patients (35%) in the nifedipine group and 14 patients (23.3%) in the sulfate group; more than 48 hours in 39 patients (65.0%) in the nifedipine group and 46 patients (76.7%) in the sulfate group. (Table 2).

The total side effects of medication were seen in 17 patients (28.3%) in the nifedipine group and in 27 patients (45%) in the magnesium sulfate group. This means that the difference was statistically significant. The nifedipine-receiving patients experienced the side effects less than those receiving sulfate (p= 0.036) (Table 2). Hot flashes were significantly higher in the magnesium sulfate group [22(36.7%) vs. 5 (8.3%) in the nifedipine group; p= 0.0008]. There were no statistically significant differences between the two groups in terms of experiencing hypotension, headaches, nausea, and vomiting.

Natural vaginal delivery was significantly higher in the Nifedipine group [25(41.7%) vs. 12 (20.0%) in the sulfate group; p= 0.010)]. The need for hospitalization in the NICU arose in 14 (23.3%) infants born in the nifedipine group and 18 cases (30%) born in the sulfate group (P = 0.536). The mean Apgar score in one and five minutes in both groups was equal, neither of which was significant (Table 2). There were no significant differences in neonatal outcomes between the two groups.

Discussion

The results of this study proved that both Nifedipine and Magnesium sulfate were effective in the suppression of pretem labor for more than 48 hours. However, the women receiving magnesium sulfate experienced more side effects than those receiving nifedipine.

The main findings of our study were consistent with the previous clinical trial studies in which there was no significant difference between nifedipine and magnesium sulfate in delaying the preterm labor (9-15). However, in Faraji et al.'s (16) study conducted on 100 pregnant women in north of Iran, the mean delayed time in delivery was significantly higher in nifedipine receivers compared with the group receiving magnesium sulfate. This discrepancy could be due to the lower sample size and higher mean of the gestational age, specifically in the group receiving nifedipine (31.5 ± 2.5 weeks in the present study versus 32.6 ± 2.8 weeks in Faraji's study), and the higher dose used in Faraji's study compared with that used in the present study (10 mg every 20 minutes in the present study compared with 10 mg every 15 minutes in the Faraji's study) can be mentioned.

In our study, the administration of magnesium sulfate was associated with more complications when compared with the administration of nifedipine. The observed complications of magnesium sulfate compared with the complications of nifedipine were higher in Lotfalizadeh et al.'s (2) study, which is similar to the results of this study. Compared with the side effects of Nifedipine, which were more similar to the results of this study, the frequency of complications in the group receiving magnesium sulfate was more than that of the nifedipine group in Behnamfar et al.'s study (9). Niroomanesh et al. (11) revealed that the incidence rate of complications in the group receiving sulfate was higher in the group receiving Nifedipine, which was consistent with the findings of Keikhahi et al. (12). But Glock et al. indicated that there was no difference in the incidence of side effects between the group receiving magnesium sulfate and the one receiving Nifedipine (13). Several investigators demonstrated that nifedipine treatment did not

Table 1. Demographic characteristics of the participants.

Variables	**Magnesium sulfate**	**Nifedipine**	**P-value**
Age (Years)	25.5±4.1	24.9±4.3	0.824
Gestational age (Weeks)	31.8±2.8	31.5±2.5	0.464
Parity	1.6±0.9	1.7±0.7	0.597

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Table 2. The comparison of outcomes between the two groups of the study.

	Magnesium sulfate (N=60)	Nifedipine (N=60)	P value
Inhibition of contractions for less than 48 hours	14 (23.3)	21 (35.0)	0.160
Inhibition of contractions for more than 48 hours	46 (76.7)	39 (65.0)	0.160
Natural vaginal delivery	12 (20.0)	25 (41.7)	0.010
Side effects			
Dyspnea	2 (3.3)	2 (3.3)	1.000
Hypotension ≤ 80 mm Hg	1 (1.7)	5 (8.3)	0.094
Hot flashes	22 (36.7)	5 (8.3)	0.0008
Nausea/vomiting	1 (1.7)	3 (5.0)	0.094
Headache	1 (1.7)	1 (1.7)	1.000
Total side effects	27 (45.0)	16 (26.6)	0.036
Neonatal outcome			
NICU admission*	18 (30.0)	14 (23.3)	0.408
Apgar score at minute 1 Mean (SD)	8.3 (1.2)	8.5 (1.0)	0.353
Apgar score at minute 5 Mean (SD)	9.6 (0.8)	9.4 (1.0)	0.452

* NICU: Neonatal Intensive Care Unit

influence either fetal or uteroplacental circulation, and that the major maternal adverse effects were due to the vasodilatation effect by nifedipine, which would disappear within short time (14).

Also, the neonatal outcomes, considered in our study, were not different between the two groups, which was consistent with the results of the previous studies (15-16).

Conclusions

According to our findings, oral nifedipine had the same efficacy in delaying the preterm labor compared with magnesium sulfate with lower side effects. It could also be an alternative choice for magnesium sulfate. However, the clinical application of this drug should be accompanied by systematic reviews and meta-analysis based on present evidence.

Conflict of interest

The authors declared no conflict of interest.

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