

# Nifedipine Versus Magnesium Sulfate for Treatment of Preterm Labor: Comparison of Efficacy and Adverse Effects in a Randomized Controlled Trial

Maryam Khooshideh,<sup>1</sup> Javad Rahmati,<sup>2</sup> and Batool Teimoori<sup>3,\*</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Aesthetic Surgery, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Department of Obstetrics and Gynecology, Zahedan University of Medical Sciences, Zahedan, Iran

\*Corresponding author: Batool Teimoori, Department of Obstetrics and Gynecology, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: TeimooriBatool@gmail.com

Received 2017 February 20; Revised 2017 March 18; Accepted 2017 April 22.

## Abstract

**Objectives:** The study aimed to compare the efficacy and side effects of intravenous magnesium sulfate (MgSO<sub>4</sub>) and oral nifedipine for inhibition of preterm labor.

**Methods:** This randomized controlled trial was performed on 220 women with preterm labor between 32 and 34 weeks of gestation who were randomly assigned to receive either MgSO<sub>4</sub> or nifedipine. The primary outcome was inhibition of preterm labor, defined as prevention of delivery for 48 hours with inhibition of uterine contraction, and the secondary outcome was maternal side effects.

**Results:** From 220 patients, 110 received nifedipine and 110 received MgSO<sub>4</sub>. There were no differences in suppression of labor pain in 24 hours and 48 hours between the two groups. Also, there were not statistically significant differences in one-minute and five-minute Apgar scores, neonatal respiratory distress syndrome, and NICU admission between the two groups. Maternal hypotension was higher in the nifedipine group, but the difference was not significant ( $P = 0.08$ ). Dyspnea ( $P = 0.01$ ) and minor maternal side effects ( $P \leq 0.001$ ) were significantly higher in the MgSO<sub>4</sub> group than the nifedipine group. Serious maternal adverse effects and severe hypotension were not seen in any of the groups.

**Conclusions:** Nifedipine is as effective as MgSO<sub>4</sub> in arresting labor and delaying delivery for 48 hours. However, nifedipine is associated with significantly fewer maternal adverse effects.

**Keywords:** Magnesium sulfate, Nifedipine, Preterm Labor, Maternal Adverse Effects

## 1. Background

The incidence of preterm birth is 9% - 13% of births (1). Tocolytic agents such as beta mimetics, calcium channel blockers, oxytocin receptor antagonists, and magnesium sulfate (MgSO<sub>4</sub>) are used to suppress preterm labor (2, 3). The first-line tocolytic drug in North America is MgSO<sub>4</sub> (4, 5). But in European countries, MgSO<sub>4</sub> is seldom used for tocolysis (6). Crowther in a systematic review in 2014 declared that MgSO<sub>4</sub> administration did not result in a statistical reduction in birth < 48 hours (7). In addition, MgSO<sub>4</sub> may be associated with an increase in maternal and neonatal adverse effects (8, 9). MgSO<sub>4</sub> is recommended as a neuroprotective drug for the neonate < 32 weeks (10-12). Nifedipine as a calcium channel blocker is one of the best drugs for inhibition of preterm labor. Ease of administration, maternal tolerance, low neonatal mortality and respiratory distress syndrome, and low maternal adverse effects are the advantages of nifedipine (13). Flenady in a systematic review in 2014 claimed that calcium channel blockers reduce the risk of delivery within 48 hours without any se-

rious neonatal morbidity and maternal adverse effects (1). Nifedipine is vasodilator and it may cause nausea, flushing, headache, dizziness, palpitations, and transient hypotension (13). An optimal nifedipine dosing regimen for treatment of preterm labor has not been yet established. The American College of Obstetricians and Gynecologists suggests a 30 mg loading dose and then 10 to 20 mg every 4 to 6 hours (14).

## 2. Objectives

A few studies have compared nifedipine versus MgSO<sub>4</sub>. For this reason, in this trial we compared the efficacy and safety of nifedipine and MgSO<sub>4</sub> for inhibition of preterm labor.

## 3. Methods

This single-blind randomized-control trial was performed on pregnant women admitted to Arash Hospital, Tehran, Iran, during 2014 - 2016.

This study was approved by the institutional review board and the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (ethics committee code: 85 - 2592 and IRCT code: IRCT2016120711020N8). An informed written consent was taken from each participant. A total of 220 patients were enrolled. They were low risk singleton pregnant women with gestational age of 32 - 34 weeks and preterm labor as inclusion criteria. Preterm labor was defined as one or more contractions every 10 minutes with cervical change, or  $\geq 2$  cm and  $< 4$  cm dilation and 80% effacement.

Women with diabetes, hypertension, hypotension, cardiac arrhythmia, myasthenia, or any other medical or surgical complications, uterine malformation, polyhydramnios, vaginal bleeding, ruptured membranes, and history of previous preterm delivery were excluded. Pre-hydration with Ringer solution (500 mL) and betamethasone intramuscularly 12 mg was administered daily for two days to all the patients. The women were randomly assigned equally to either nifedipine or MgSO<sub>4</sub> groups. Randomization was performed through sequentially numbered opaque envelopes using a random numbers table.

Patients in the MgSO<sub>4</sub> group received intravenous 6 g bolus MgSO<sub>4</sub> 20% (obtained from Institut Pasteur, Iran) followed by a 2 g/h infusion. Patients in the nifedipine group received oral nifedipine 10 mg (obtained from Tolidaru, Iran) every 20 minutes for three doses, followed by 10 mg orally every 6 hours (Figure 1). The treatment continued for 48 hours in both groups. All the patients were assessed for pulse rate, blood pressure every 30 minutes for the first 4 hours, and then every 4 hours until 48 hours. Moreover, the patients in MgSO<sub>4</sub> group were examined for MgSO<sub>4</sub> toxicity every 4 hours until 48 hours. Adverse effects were assessed in each patient and recorded. Fetal heart rate was continuously monitored. The primary outcome was inhibition of uterine contraction and prevention of delivery for 48 hours. The secondary outcome was major or minor maternal adverse effects. Serious maternal adverse effects included chest pain, pulmonary edema, and severe hypotension ( $< 60$  mmHg). When an episode of hypotension occurred, nifedipine was withdrawn until the systolic blood pressure returned above 90 mmHg. If a serious complication occurred, the patient would be withdrawn from the study. In mothers that their active delivery process did not stop (neither by nifedipine nor by MgSO<sub>4</sub>) and the delivery occurred, the neonate outcomes would be compared between the two groups.

All data were analyzed using SPSS version 16.0 for windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables were presented as mean  $\pm$  standard deviation (SD) and for categorical variables as numbers (percentages). The baseline characteristics of the two

groups were compared using independent t test for continuous variables and Chi-square test for categorical variables. All the statistical tests were two-sided and  $P < 0.05$  was considered statistically significant. The analysis of the trial obeyed the 2010 CONSORT guidelines.

#### 4. Results

There were no differences between the two groups with regard to the patients' demographic and obstetric characteristics (Table 1). There were no significant differences in birth within 24 hours [80 (72.2%) in the MgSO<sub>4</sub> group vs. 77 (70%) in the nifedipine group;  $P = 0.65$ ] and 48 hours [15 (13.6%) in the MgSO<sub>4</sub> group vs. 16 (14.5%) in the nifedipine group;  $P = 0.84$ ] between the groups (Table 2).

In the MgSO<sub>4</sub> group, 4 (3.6%) women suffered postpartum hemorrhage. 8 women (7.3%) experienced hypotension [ $n = 2$ , (1.8%)], or dyspnea [ $n = 6$ , (5.5%)]. Minor adverse effects were observed in 41 women (45.5%) including flushing [ $n = 32$ , (29%)], nausea or vomiting [ $n = 25$  (22.7%)] and headache [ $n = 3$  (2.7%)]. In the nifedipine group, 1 (0.9%) woman experienced postpartum hemorrhage. 7 (6.4%) women had hypotension, 2 (1.8%) women had nausea or vomiting, 6 of them suffered headache (5.5%), and another 6 women had palpitation (5.5%) (Table 2).

Dyspnea ( $P = 0.01$ ) and minor maternal side effects were significantly higher in the MgSO<sub>4</sub> group than the nifedipine group [41 (37.3%) in the MgSO<sub>4</sub> group vs. 14 (12.7%) in the nifedipine group;  $P \leq 0.001$ ].

Maternal hypotension (defined as a mean arterial pressure of 80 mm Hg or less) was higher in the nifedipine group although the difference was not significant ( $P = 0.08$ ). Fortunately, serious maternal adverse effects and severe hypotension ( $< 6$  mmHg) were not seen in any of the groups.

There were no statistically significant differences in one-minute and five-minute Apgar scores in neonates (Table 2).

Also, there were not any statistically significant difference in neonatal respiratory distress syndrome and NICU admission between the two groups (Table 2).

#### 5. Discussion

In this study, both drugs were equally effective in arresting labor and delaying delivery for 48 hours. Maternal side effects were higher in the MgSO<sub>4</sub> group. Neonatal Apgar scores were not different between the groups.

Similar to our study, Glock reported in a study that oral nifedipine is as effective as MgSO<sub>4</sub> in arresting and preventing preterm labor (15). Lyell reported in line with our study

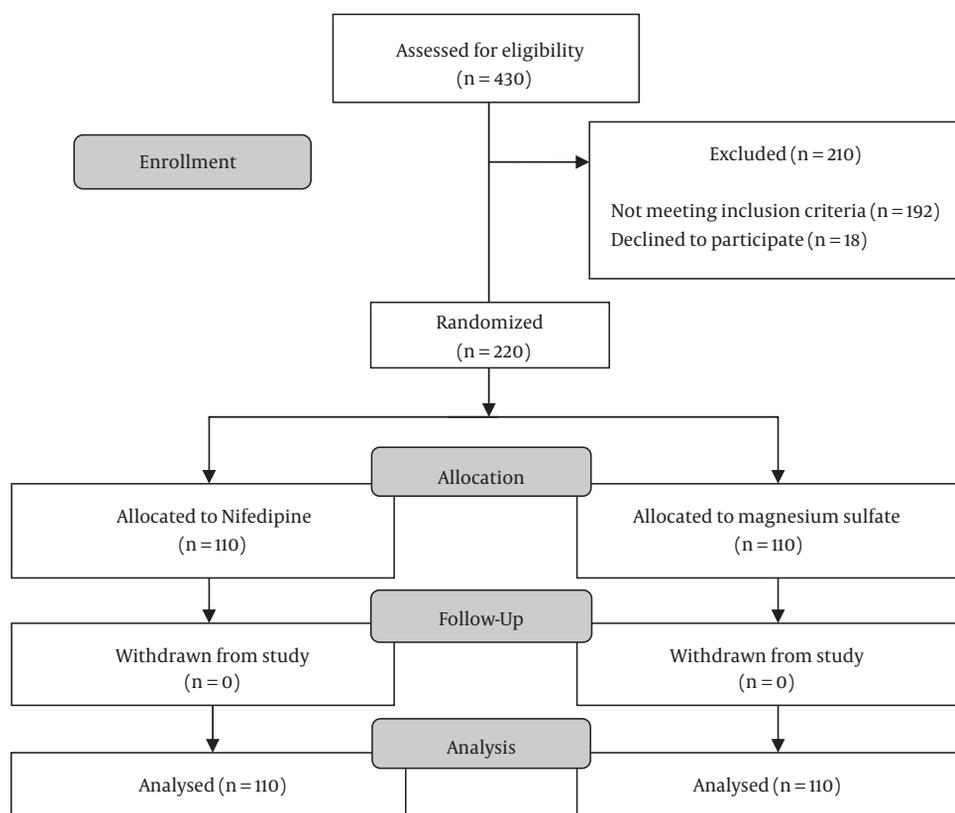


Figure 1. Summary of Patients Flow

Table 1. Baseline and Obstetric Demographics Characteristics

	MgSO <sub>4</sub> Group (n = 110)	Nifedipine Group (n = 110)	P Value
Age (years) <sup>a</sup>	22.32 ± 6.51	22.54 ± 5.58	0.62
BMI (kg/m <sup>2</sup> )	24.38 ± 2.72	24.68 ± 2.74	0.27
Gestational age (Weeks)	33.21 ± 1.10	33.32 ± 1.41	0.31
Pre treatment cervical dilatation (cm)	2.12 ± 0.54	2.21 ± 0.46	0.43
Parity	2.16 ± 1.24	2.2 ± 1.25	0.62
Frequency of contraction/10 min	2.43 ± 1.12	2.52 ± 1.02	0.5
Systolic blood pressure before treatment (mmHg)	113.47 ± 1.89	111.68 ± 1.98	0.3

<sup>a</sup>Values given as mean ± SD.

that maternal adverse effects were significantly more frequent with MgSO<sub>4</sub> than with nifedipine (16).

The incidence of hypotension in this study was higher in the nifedipine group than the MgSO<sub>4</sub> group (6.4% vs. 1.8%). However, severe hypotension (BP < 60 mmHg) was not seen in the nifedipine group. Glock (15) described transient hypotension, lasting less than 10 minutes, among 41% of nifedipine recipient patients. Peripheral vasodilata-

tion can result in the decreased vascular resistance, which is complemented by a compensatory increase in cardiac output (increase in heart rate and stroke volume). These compensatory changes preserve blood pressure in women who have no myocardial dysfunction (1). Prehydration of Ringer solutions also helped the patients in our study maintain an acceptable blood pressure. A blood pressure less than 80 mmHg in our study was considered as hy-

**Table 2.** The Comparison of Outcomes Between the Two Groups

	MgSO <sub>4</sub> Group (n = 110)	Nifedipine Group (n = 110)	P Value
<b>Inhibition of contractions in the first 24 hours<sup>a</sup></b>	80 (72.7%)	77 (70%)	0.65
<b>Inhibition of contractions in the second 24 hours</b>	15 (13.6%)	16 (14.5%)	0.84
<b>No inhibition</b>	15 (13.6%)	17 (15.5%)	0.7
<b>Maternal side effects</b>			
Hypotension ≤ 80 mmHg	2 (1.8%)	7 (6.4%)	0.08
Dyspnea	6 (5.5%)	0 (0%)	0.01
Minor side effects <sup>b</sup>	41 (37.3%)	14 (12.7%)	< 0.001
Postpartum hemorrhage	4 (3.6%)	1 (0.9)	0.17
<b>Fetal outcomes</b>			
Respiratory distress syndrome	9 (8.2%)	5 (4.5%)	0.26
NICU admission	11 (10%)	7 (6.4%)	0.32
Apgar 1 minutes < 7	10 (9%)	11 (10%)	0.81
Apgar 5 minutes < 7	8 (7.3%)	7 (6.4%)	0.7

<sup>a</sup>Values given as number (percentage).

<sup>b</sup>Minor side effects included flushing, nausea, vomiting, and headache.

potension; thus, the incidence of hypotension in our study was higher than the incidence of hypotension in the study of Lyell et al. (16) that considered blood pressure less than 60 mmHg as hypotension.

We included women with preterm labor above 32 weeks in this study, because many studies reported that MgSO<sub>4</sub> would be neuroprotective in preterm newborns < 32 weeks gestation (10-12). However, Lyell et al. included women in preterm labor between 24 and 34 weeks in their study (16).

Many studies reported that nifedipine is a superior drug compared to MgSO<sub>4</sub> in decreasing the rate of respiratory distress syndrome (17, 18) and NICU admission in preterm and very preterm neonates (15). Some authors reported that MgSO<sub>4</sub> may lead to respiratory suppression in neonates (6, 19). In the present study, we have not found any significant difference in the incidence of respiratory distress syndrome and NICU admission between the two groups. We did not also find any respiratory suppression in neonates in our study. The participants in our study comprised a sample that was not large enough in size to allow us to compare the adverse effects between the two groups of neonates.

### 5.1. Conclusion

Oral nifedipine is as effective as magnesium sulfate with regard to inhibition of preterm labor. However, nifedipine was associated with fewer maternal adverse ef-

fects. Future clinical research should focus on large controlled trials powered for perinatal outcomes.

### Acknowledgments

This research was supported by Tehran University of Medical Sciences and health services grant.

### Footnote

**Conflicts of Interest:** There are no conflicts of interest.

### References

- Flenady V, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, Jardine IA, et al. Calcium channel blockers for inhibiting preterm labour and birth. *Cochrane Database Syst Rev.* 2014(6):CD002255. doi: [10.1002/14651858.CD002255.pub2](https://doi.org/10.1002/14651858.CD002255.pub2). [PubMed: 24901312].
- Dombrowski MP, Schatz M, Acog Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: asthma in pregnancy. *Obstet Gynecol.* 2008;111(2 Pt 1):457-64. doi: [10.1097/AOG.0b013e3181665ff4](https://doi.org/10.1097/AOG.0b013e3181665ff4). [PubMed: 18238988].
- Psomiadis N, Goldkrand J. Efficacy of aggressive tocolysis for preterm labor with advanced cervical dilatation. *J Matern Fetal Neonatal Med.* 2005;18(1):47-52. doi: [10.1080/14767050500073142](https://doi.org/10.1080/14767050500073142). [PubMed: 16105791].
- Norwitz ER, Robinson JN, Challis JR. The control of labor. *N Engl J Med.* 1999;341(9):660-6. doi: [10.1056/NEJM199908263410906](https://doi.org/10.1056/NEJM199908263410906). [PubMed: 10460818].
- Lewis DF. Magnesium sulfate: the first-line tocolytic. *Obstet Gynecol Clin North Am.* 2005;32(3):485-500. doi: [10.1016/j.ogc.2005.03.002](https://doi.org/10.1016/j.ogc.2005.03.002). [PubMed: 16125045].

6. Wolf HT, Huusom L, Weber T, Piedvache A, Schmidt S, Norman M, et al. Use of magnesium sulfate before 32 weeks of gestation: a European population-based cohort study. *BMJ Open*. 2017;7(1):013952. doi: [10.1136/bmjopen-2016-013952](https://doi.org/10.1136/bmjopen-2016-013952). [PubMed: [28132012](https://pubmed.ncbi.nlm.nih.gov/28132012/)].
7. Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2014(8):CD001060. doi: [10.1002/14651858.CD001060.pub2](https://doi.org/10.1002/14651858.CD001060.pub2). [PubMed: [25126773](https://pubmed.ncbi.nlm.nih.gov/25126773/)].
8. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol*. 2006;108(4):986-9. doi: [10.1097/01.AOG.0000236445.18265.93](https://doi.org/10.1097/01.AOG.0000236445.18265.93). [PubMed: [17012463](https://pubmed.ncbi.nlm.nih.gov/17012463/)].
9. Malaeb SN, Rassi AI, Haddad MC, Seoud MA, Yunis KA. Bone mineralization in newborns whose mothers received magnesium sulphate for tocolysis of premature labour. *Pediatr Radiol*. 2004;34(5):384-6. doi: [10.1007/s00247-004-1148-1](https://doi.org/10.1007/s00247-004-1148-1). [PubMed: [14985884](https://pubmed.ncbi.nlm.nih.gov/14985884/)].
10. Gano D, Ho ML, Partridge JC, Glass HC, Xu D, Barkovich AJ, et al. Antenatal Exposure to Magnesium Sulfate Is Associated with Reduced Cerebellar Hemorrhage in Preterm Newborns. *J Pediatr*. 2016;178:68-74. doi: [10.1016/j.jpeds.2016.06.053](https://doi.org/10.1016/j.jpeds.2016.06.053). [PubMed: [27453378](https://pubmed.ncbi.nlm.nih.gov/27453378/)].
11. Binette A, Blouin S, Ardilouze A, Pasquier JC. Neuroprotective effects of antenatal magnesium sulfate under inflammatory conditions in a Sprague-Dawley pregnant rat model. *J Matern Fetal Neonatal Med*. 2016;1-6. doi: [10.1080/14767058.2016.1223031](https://doi.org/10.1080/14767058.2016.1223031). [PubMed: [27578415](https://pubmed.ncbi.nlm.nih.gov/27578415/)].
12. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection: A Meta-analysis Based on PRISMA Guidelines. *Medicine (Baltimore)*. 2016;95(1):2451. doi: [10.1097/MD.0000000000002451](https://doi.org/10.1097/MD.0000000000002451). [PubMed: [26735551](https://pubmed.ncbi.nlm.nih.gov/26735551/)].
13. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ*. 2012;345:6226. doi: [10.1136/bmj.e6226](https://doi.org/10.1136/bmj.e6226). [PubMed: [23048010](https://pubmed.ncbi.nlm.nih.gov/23048010/)].
14. Practice Bulletin No. 159: Management of Preterm Labor. *Obstet Gynecol*. 2016;127(1):29-38. doi: [10.1097/AOG.0000000000001265](https://doi.org/10.1097/AOG.0000000000001265). [PubMed: [26695585](https://pubmed.ncbi.nlm.nih.gov/26695585/)].
15. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulfate in the management of preterm labor: a randomized study. *Am J Obstet Gynecol*. 1993;169(4):960-4. [PubMed: [8238157](https://pubmed.ncbi.nlm.nih.gov/8238157/)].
16. Lyell DJ, Pullen K, Campbell L, Ching S, Druzin ML, Chitkara U, et al. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial. *Obstet Gynecol*. 2007;110(1):61-7. doi: [10.1097/01.AOG.0000269048.06634.35](https://doi.org/10.1097/01.AOG.0000269048.06634.35). [PubMed: [17601897](https://pubmed.ncbi.nlm.nih.gov/17601897/)].
17. Papatsonis DN, Van Geijn HP, Ader HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol*. 1997;90(2):230-4. doi: [10.1016/S0029-7844\(97\)00182-8](https://doi.org/10.1016/S0029-7844(97)00182-8). [PubMed: [9241299](https://pubmed.ncbi.nlm.nih.gov/9241299/)].
18. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med*. 1992;327(2):76-81. doi: [10.1056/NEJM199207093270203](https://doi.org/10.1056/NEJM199207093270203). [PubMed: [1603139](https://pubmed.ncbi.nlm.nih.gov/1603139/)].
19. Cox SM, Sherman ML, Leveno KJ. Randomized investigation of magnesium sulfate for prevention of preterm birth. *American J Obstetrics Gynecol*. 1990;163(3):767-72.