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# EFFICACY AND SAFETY OF MAGNESIUM SULFATE AND NIFEDIPINE FOR TOCOLYSIS IN PRETERM LABOR - A COMPARATIVE STUDY

Obstetrics & Gynaecology

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## ABSTRACT

**Background:** Preterm labor is the leading cause of perinatal morbidity & mortality and one of the leading causes of infant mortality. Despite substantial efforts to introduce new therapies for prevention of preterm labor, it continues to contribute significantly to neonatal and infant mortality. **Aim:** To compare the efficacy of magnesium sulfate and nifedipine for tocolysis in preterm labor. **Methods:** This randomized clinical control study was conducted out at the department of Obstetrics & Gynaecology, S.N.M.C., Agra from Dec.2020 to Sept.2022. A total of 100 patients of preterm labor,>18 years of age with singleton pregnancy of gestational age between 28-33 weeks 6days were included in the study and selected on the basis of inclusion & exclusion criteria, and randomly divided into two groups (50 each) i.e. Group 1 (magnesium sulfate) & Group 2 (Nifedipine).Outcome variables like cessation of uterine contractions till 48 hours (efficacy) were noted for successful or unsuccessful outcome. **Results:** The mean gestational age in group1 was 31.66±1.80 weeks and in group2 was 31.72±1.68 weeks (p>0.05).There was cessation of uterine contractions in 44 (88%) and no cessation in 6 (12%) patients in Group 1 while in Group 2, it was seen in 35 (70%) and 15 (30%) patients respectively. So, efficacy was 88% in group 1(MgSO4) and 70% in group 2(oral nifedipine) with p-value of 0.0495. **Conclusion:** Magnesium sulfate has higher efficacy i.e. 88% for acute tocolysis in preterm labor as compared to oral nifedipine and can be used as first line drug to treat preterm labor..

## KEYWORDS

Magnesium sulfate, Nifedipine, preterm labor, acute tocolysis

## INTRODUCTION

Preterm birth is the single largest cause of neonatal deaths. Preterm labor is defined as the occurrence of regular, painful, frequent uterine contractions associated with progressive cervical effacement and dilatation before 259 days or 37 completed weeks of gestation from the first day of last menstrual period (WHO, 1992)[1].American Academy of Pediatrics and American College of Obstetrics and Gynecology considered preterm labor to be established if regular uterine contractions can be documented at least 4 in 20 minutes or 8 in 60 minutes, with cervical dilatation greater than 1 cm and cervical effacement of 80% or greater.Since uterine contractions are the most frequently recognized symptoms and sign of preterm labor, inhibition of uterine contractility with tocolytic agents to prolong pregnancy and reduce neonatal complications continues to be the focus of treatment of preterm labor.

Conventional treatment options for postponing preterm labor include bed rest, fluid therapy and sedation, and tocolytic agents, that each of these has its advantages and disadvantages. However, no convincing evidence has been provided as to the effectiveness of bed rest and hydration.

Several agents have been used for the inhibition of uterine contractility, like beta adrenergic receptor agonists (ritodrine, terbutaline, salbutamol), NSAIDs (Indomethacin, aspirin, ibuprofen, sulindac), oxytocin receptor antagonist (atosiban), nitric oxide donors (glyceryl nitrate), potassium channel opener (diazoxide), Magnesium sulfate, calcium channel blocker (nifedipine) but it remains unclear what the first-line tocolytic agent should be.[2]

## AIMS AND OBJECTIVES

This study was done with the aim to compare the tocolytic efficacy and safety of Magnesium sulfate and Nifedipine and their perinatal outcomes in preterm labor.

## MATERIAL AND METHODS

This was a comparative prospective randomised control study comprising of 100 antenatal cases with 28 weeks to 33 weeks 6 days gestational age with preterm labour were randomly selected from labour room in Department of Obstetrics and Gynecology in S. N. Medical College, Agra. Inclusion criteria were women giving consent to the study, age > 18 years, singleton pregnancies with 28weeks to 33weeks 6 days gestational age as determined by last menstrual period, clinical examination and USG with intact membranes with uterine contractions occurring at least twice in every 10 minutes regularly each lasting for 30 seconds synchronizing with pain with dilatation of cervix less than 4 cms and cervical effacement 50% or less with no evidence of infection.

Patients with multiple gestation, cervical dilatation of >4cm, maternal contraindication to tocolysis (PIH, cardiac disease, diabetes, myasthenia gravis), Suspected chorioamnionitis, placenta previa or abruptio placent, preterm premature rupture of membranes, prolapsed membranes, human immunodeficiency virus positive, magnesium sulfate or nifedipine tocolysis prior to randomization, maternal renal or liver disease, previous caesarean delivery, disorders of amniotic fluid, fetal death, erythroblastosis fetalis,fetal distress, fetal malformations, lethal congenital or chromosomal abnormalities,fetal growth restriction were excluded from study.

All women were subjected to NST on admission. Only those women with a reassuring trace on NST were considered eligible to participate. In first step all patients were hydrated by 500 ml of Ringer solutions and advised bed rest for 30 minutes during which time, frequency and duration of uterine contractions and fetal heart rates were monitored. Then if contractions continued to persist patients were randomly allotted in 2 groups to receive MAGNESIUM SULFATE or NIFEDIPINE.

GROUP 1-were given 100 mL 5% dextrose 4-6 g $MgSO_4$ as intravenous (IV) loading dose administered over 20 minutes, followed by 2 gr/hour IV as a maintenance dosage, while continuing $MgSO_4$ infusion. During the treatment, patients were monitored at hourly intervals for urine output pattern, deep tendon reflexes, and respiratory rate per minute. Once the uterus is relaxed, the infusion is maintained for 12 hours and then weaned off till 24 hours.

Monitoring: After the initial loading dose, treatment was discontinued if : 1)Patellar reflex is absent ,(2) Respiratory rate $< 16$/min, (3) Urine output $< 100$ml in the preceding 4 hours, (4) Oxygen saturation $\leq 96\%$ on room air Uterine contractions were monitored every 30 minutes for the first 2 hours, then every 4 hours for 24 hours.

Magnesium sulfate treatment was defined as effective if the uterine contractions were reduced more than 30% in frequency and intensity compared to those occurring during the last two hours before magnesium sulfate infusion. Treatment was defined as ineffective if uterine contractions were not reduced by 30% and labor progressed with apparent changes in cervical findings.

GROUP 2- Other group of 50 patients were given nifedipine orally 20mg followed by 10 mg at 6-hour intervals as a maintenance dosage. Maximum dose used in our study was 100-120 mg. Nifedipine dosage regime used in our study: Initial dose of 20 mg.Then repeat dose of 20 mg if no effect and maintenance dose is 10 mg 6 hourly.

Monitoring:-1) Maternal-Pulse Rate, Blood Pressure, Uterine Contractions (2) Fetal- Heart Rate, Rhythm , Tone

All were monitored every 30 minutes for the first 2 hours, then every 4 hours for 48 hours of treatment duration.Treatment was discontinued if: 1)Systolic BP < 100 mmHg, (2) Pulse rate > 100 b/min, (3) Fetal heart rate > 180 b/min

The following parameters were studied

Primary outcomes:
- Arrest of preterm labor and continuation of pregnancy defined as prevention of delivery for 48 hours with uterine quiescence i.e. 12 hours of six or fewer contractions and no further cervical change within 48 hours of tocolytic initiation.
- Perinatal death
- Admission to neonatal intensive care unit (NICU),
- Severe maternal adverse drug reactions for both acute and maintenance tocolysis.

Secondary outcomes:
- Interval between trial entry and delivery, gestational age at delivery,
- Maternal adverse events,
- Discontinuation of treatment because of adverse events,
- Birth weight,
- Apgar score at 1 and 5 minutes,
- Fetal complications like respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, etinopathy of prematurity, neonatal jaundice, neonatal sepsis,
- Length of stay in NIC

**Statistical analysis and interpretation:**
The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 21.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. For continuous variables, students 't' test was applied. When we compared the calculated probability (p) with the level of significance, p value of <0.05 is considered significant and p value of > 0.05 is non-significant.

**RESULT:**
Women belonged to the age group 20-24 years, class V socio-economic status according to revised B.G. Prasad classification and were unbooked cases in both the groups. 60% in Group1 (Magnesium sulfate group) and 54% in group 2 (Nifedipine group) were primigravidas. There was no significant difference in mean age and mean Bishop Score at the time of admission.

**Table 1: Demographical Distribution among Both Groups**

| Variables | Group1 (Magnesium sulfate) | Group2 (Nifedipine) | P-Value |
|---|---|---|---|
| Age in years | 24.82 + 3.821 | 24.66 + 4.168 | 0.8418 |
| Socioeconomic status (class V) | 58% | 62% | 0.5663 |
| Educational status (Illiterate) | 60% | 56% | 0.8394 |
| Unbooked cases | 64% | 60% | 0.8368 |
| Gestational age (weeks) at time of admission | 31.66 + 1.804 | 31.72 + 1.685 | 0.8684 |
| Obstetric code (Primi) | 60% | 54% | 0.3972 |
| Modified BishopScore at admission | 4.38 + 1.38 | 4.46 + 1.57 | 0.7873 |

**Table 2: Maternal Side Effect Profile in Both Groups**

| Side Effects | Group 1 (Magnesium sulfate) | Group 2 (Nifedipine) |
|---|---|---|
| Flushing | 10 (20%) | 0 |
| Headache | 4 (8%) | 7 (14%) |
| Nausea / Vomiting | 3 (6%) | 2 (4%) |
| Drowsiness | 4 (8%) | 0 |
| Reduced Urine output | 1 (2%) | 0 |
| Loss of patellar Reflex | 1 (2%) | 0 |
| Dizziness | 0 | 4 (8%) |
| Palpitations | 0 | 2 (4%) |
| Hypotension | 0 | 1 (2%) |
| Pulmonary Edema | 1 (2%) | 0 |
| Postpartum Hemorrhage | 0 | 0 |
| Total | 24 (48%) | 16 (32%) |

$X^2 = 24.394$ p value = 0.073

**Table 3: Prolongation of pregnancy i.e. on the basis of Treatment Delivery Interval In Both Groups**

| Prolongation Period (Days) | Group 1 (Magnesium sulfate) | Group 2 (Nifedipine) |
|---|---|---|
| < 2 | 6 (12%) | 15 (30%) |
| 2 – 3 | 21 (42%) | 13 (26%) |
| 4 - 7 | 16 (32%) | 12 (24%) |
| >7 | 7 (14%) | 10 (20%) |
| Total | 50 (100%) | 50 (100%) |
| Mean + SD | 5.42 + 6.108 | 5.03 + 4.766 |
| t value | 0.3559 | |
| p value | 0.7227 | |

**Table 4: Time taken for uterine contractions to subside among both groups**

| Time (Min.) | Group 1 (Magnesium sulfate) | Group 2 (Nifedipine) |
|---|---|---|
| < 30 | 2(4.55%) | 1(2.86%) |
| 30 - 60 | 12 (27.27%) | 6 (17.14%) |
| 61 - 120 | 30 (68.18%) | 28 (80%) |
| Total | 44 (100%) | 35 (100%) |
| Mean + SD | 33.52 + 4.256 | 36.71 + 4.528 |
| t value | 3.218 | |
| p value | 0.0019 | |

**Table 5: Comparison of Efficacy between Both Groups**

| Efficacy | Group 1 (Magnesium sulfate) | Group 2 (Nifedipine) | P-Value |
|---|---|---|---|
| Yes | 6 (12%) | 15 (30%) | 0.0495 |
| No | 44 (88%) | 35 (70%) | |
| Total | 50 (100%) | 50 (100%) | |

**DISCUSSION**
Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation[2,3]. Tocolytics are drugs used to prevent or inhibit pre term labor. Acute tocolysis is used to delay preterm birth for 48 hours, the critical period of antenatal steroid administration for fetal lung maturation or to arrest an episode of preterm labor, thus delaying birth and improving neonatal outcomes and, if necessary, to transfer the woman to a facility with a neonatal intensive care unit. The overall goal of tocolytic therapy is to improve neonatal outcome.

Magnesium sulfate (MgSO4) is a widely common agent used for the treatment of preterm labor. It is used as primary tocolytic agent due to similar efficacy to terbutaline[4].

In this study, we have compared the magnesium sulfate with oral nifedipine in acute tocolysis for at least 48 hours or more in preterm labor patients. The mean age of patients in our study was 24.82 ± 3.821 years in group 1 and 24.66 ± 4.168 years in group 2. Majority of the patients (44%)were between 20 to 24 years of age in both groups.

These results were very much comparable with **Taherian et al**[15], **Abasalizadeh S et al**[13] and **Shirazi et al**[14] studies. In our study, majority of patients were primigravida i.e. 58%. **Taherian et al**[15]has also shown 50.05% primigravida in his study which was also comparable to **Shirazi et al**[14] and **Kawagoe et al**[6] study. So, the results of our study had shown the increase risk of preterm labor in younger primigravida females. Study conducted by **Lyell et al**[8] and **Glock et al**[5] have also reported that preterm labor usually develops in younger females & this may be associated with primiparity. Mean gestational age at delivery in group 1 was 32.36 ± 2.37 weeks and in group 2 was 32.30 ± 1.96 weeks, in this study while **Taherian et al**[15] had found mean gestational age for magnesium sulfate group as 32.06 weeks and for oral nifedipine group as 32.23 weeks.

In this study, there was cessation of uterine contractions in 88% after magnesium sulfate therapy while oral nifedipine has shown this in 70% patients. In a study by **Naz et al**[10] showed that the efficacy of oral nifedipine as a tocolytic agents in stopping uterine contractions at 48 hours was 74.1% while **Kawagoe et al**[6] showed that after magnesium sulfate infusion, 90% patients prolonged their pregnancy for >48 hours. In addition, one trial[22] reported that severe maternal adverse effects were significantly less frequent among women receiving nifedipine than among women receiving magnesium sulfate (10.0% vs 21.7%). There were no significant differences between the groups in the risk of major adverse neonatal outcomes, although a significant reduction was seen in the risk of admission to NICU and NICU length of stay in the nifedipine group compared with the magnesium sulfate group. Both study groups had a similar incidence of side effects, although 3(6%) of magnesium sulfate-treated and 1 (2%) of nifedipine treated patients required drug discontinuation because of severe symptoms. However, there was no significant difference between nifedipine and magnesium sulfate groups concerning the maternal side effects (flushing, chest pain, nausea and vomiting, head- ache and transient hypotension).

In our study, prolongation of pregnancy in relation to parity did not show any statistical significant difference between the two groups which is comparable to studies like **Nikbakht et al**[12], **Shirazi et al**[14]. And prolongation of pregnancy as per gestational age was found to be in Group 1 and 2, 83.3% and 68.69% respectively in G.A between 28-32.6 weeks which was significant but it showed that prolongation of pregnancy is directly proportional to gestational age, the results were comparable to study conducted by **Nemani S *et al***[11] The success rate of prolongation of pregnancy for >48 hrs in relation to Bishop's Score in our study in $MgSO_4$ group was 92.6% with Bishop's Score of <3 as compared to 89.2% and 61.0% with score of 4-6 and >7 respectively. In Nifedipine group was 70% with Bishop's Score of <3 as compared to 76.19% and 55.55% with score of 4-6 and >7 respectively Thus success rate declined with increasing Bishop's score which was statistically significant (p value 0.0006) and this was consistent with **Mahajan A and Marwah P et al**[9]

The mean time taken by uterine contractions to subside was 33.52 ± 4.256 min. in $MgSO_4$ group and 36.71 ± 4.528 min. in Nifedipine group in our study, the results were comparable to study conducted by **Nemani S *et al*.,**[11]

**Lyell et al**[8] in his randomized trial has shown opposite results as compared to this study i.e. 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). 48% patients in the nifedipine group and 38% patients in the magnesium sulfate group postponed delivery for more than 48 hours (secondary tocolytic effect). **Larmon et al**[7]in his comparative trial had found that both these drugs were equally effective in arresting labor and delaying delivery > 48 hours, 92% versus 93%.

## CONCLUSIONS

The success of such therapy depends on proper selection of cases, judicious administration of therapy and strict monitoring. This study concluded that magnesium sulfate is associated with higher efficacy i.e. 88% for acute tocolysis of preterm labor as compared to oral nifedipine. Moreover, magnesium sulfate have also shown better efficacy for younger primigravida females. However in our study there was no significant difference between nifedipine and magnesium sulfate groups concerning the maternal side effects (flushing, chest pain, nausea and vomiting, head- ache and transient hypotension). We recommend that magnesium sulfate should be used as a first line tocolytic agent in cessation of preterm labor, so that some benefit could be achieved from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturation which would help to reduce perinatal mortality and morbidity of both mother and fetusBecause 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.

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