Intravenous Magnesium Sulfate and Isoxsuprine for Arrest of Preterm Labor: A Comparative Study

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Abstract

Background: Despite advances in obstetrics and neonatal care, the rate of incidence of preterm births continues to increase. Use of tocolytic agents such as magnesium sulfate and isoxsuprine could help in arresting preterm labor. Considering the paucity in studies comparing these two agents, a comparative analysis is obligatory. Objective: The objective of the study was to compare the safety, efficacy, and success rate of magnesium sulfate and isoxsuprine in the arrest of preterm labor. Methodology: Eighty-two antenatal women belonging to 28–37 weeks of gestational age, with regular uterine contractions, cervical dilatation (≤3 cm), and <50% cervical effacement admitted with complaints of preterm labor were randomly allocated into two groups with 41 participants in each group. Group 1 received 40 mg isoxsuprine for 24 h and later, isoxsuprine capsule 40 mg was given orally twice a day for 7 days, and Group 2 received 4 g magnesium sulfate for 12 h if uterine quiescence was achieved by the end of 2 h. Demographic data, medical history, and clinical data were collected. The outcome variables measured included side effects and the success rate (effacement% and cervical dilatation). Statistical analysis was performed using R software (Version 3.6.0). Results: The majority of the patients in both the groups with <25% effacement had successful tocolysis (P > 0.05). In Group 2, patients with <1 cm of cervical dilatation had successful tocolysis compared to Group 1 (P < 0.05). A highly significant association was observed between the percentage of effacement and cervical dilatation, successful tocolysis (P < 0.001). Tachycardia and hypertension were observed more in Group 1, whereas nausea and vomiting were common in Group 2. The overall success rate was better in Group 2 (85.37%) compared to Group 1 (65.85%). Conclusion: Magnesium sulfate was slightly more effective in arresting preterm labor with lesser side effects as compared to isoxsuprine.

Keywords: Gestational age, isoxsuprine, magnesium sulfate, pregnancy, tocolysis

Introduction

The most significant clinical challenge faced by obstetricians globally is preterm labor that threatens the maternal and fetal health and life. Among all types of pregnancy complications, the incidence of preterm labor ranges between 8% and 10% globally, accounting for about 80% of the neonatal morbidity. In developing countries, the incidence of preterm labor is greater in comparison to developed countries. India has a very high incidence (23.3%) of preterm labor and preterm delivery (10%–69%). It is estimated that each year, around 15 million preterm births and over 1 million infant deaths (due to complications of preterm birth) occur.

An essential intervention for arresting preterm labor is tocolytic therapy. Tocolytic agents relax the uterine myometrium and inhibit uterine contractions by various mechanisms causing arrest of preterm labor. Furthermore, they delay preterm delivery, providing time for administration of antenatal corticosteroids, which cause fetal lung maturity.

Different classes of drugs such as nonsteroidal anti-inflammatory drugs (ibuprofen), β-agonists, magnesium sulfate, calcium-channel blockers (nifedipine), oxytocin receptor antagonists, and nitrates are used as tocolytics in the management of preterm labor. However, the choice is limited by their side effects and efficacy and safety. In India, oxytocin receptor antagonists (atosiban), calcium-channel blockers (nifedipine), and corticosteroids, which cause fetal lung maturity, are widely used.

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and β-agonists such as isoxsuprine and magnesium sulfate are the only classes of drugs approved by the Central Drugs Standard Control Organization for preterm labor management.[9] However, some studies have demonstrated that oxytocin receptor antagonists are not associated with increased improvement in neonatal outcomes and cause potential maternal side effects such as chest pain, hypotension, nausea, and vomiting. Furthermore, it was not more effective than placebo in delaying delivery for 48 h and was not found to cause a reduction in the rate of preterm delivery,[9,10] whereas nifedipine has been associated with maternal palpitation, headache, and fetal tachycardia.[11]

Isoxsuprine, a β-adrenergic, is one of the most widely used tocolytic agents in India. It affects vascular smooth muscles directly, causing peripheral vasodilation. It further relaxes the uterine smooth muscles and arrests preterm labor.[14] Previous literature demonstrates that isoxsuprine when administered acutely (IV administration) along with maintenance therapy (oral administration) is effective in pregnancy prolongation in women at risk of preterm delivery.[12] However, there are not sufficient studies available that demonstrate its safety and efficacy,[13] which need to be evaluated.

Magnesium sulfate has been widely used in clinical settings as a tocolytic agent and has an established role in neuroprotection of the fetus and delaying the delivery.[13] However, a few side effects have been noted with magnesium sulfate. Pulmonary edema has been observed in about 1% of patients along with associated comorbidities such as anemia, hypertension, fluid overload, vomiting, nausea, chest heaviness, and muscle weakness.[14]

The available literature does not contain an adequate number of studies comparing the effects of isoxsuprine and magnesium sulfate as tocolytic agents.[15] The better tocolytic agent among the two still needs to be explored. Therefore, the present study focused on comparing the efficacy and success rate of these two agents in arresting preterm labor along with comparing their side effects.

### Materials and Methods

#### Study design

With the institutional ethics committee’s approval (KIMS/DU/IEC/03/2017 Protocol No: 047/2017-18 Dated: 24/11/2017), this single-centered, hospital-based, prospective, comparative study was conducted in the department of obstetrics and gynecology at a private medical college in Karad (Maharashtra) over a period of 19 months (December 2017–June 2019). A written informed consent was obtained from all the patients included in the study. As the CTRI registration was not mandatory during the study initiation, the CTRI number was not provided.

#### Sample size

By assuming moderate effect size of cervical dilation (0.7), 5% level of significance, and 85% power, the sample size is obtained as 38 participants per each group. As a study involves two groups, the minimum sample size required is $38 \times 2 = 76$ participants. Hence, we recruited 82 patients.

#### Selection criteria and grouping

Eighty-two pregnant women at 28–37 weeks of gestation, with regular uterine contractions ($\geq 2/10$ min with each lasting for at least 30 s), cervical dilatation ($\leq 3$ cm), and cervical effacement $\leq 50\%$ with intact membrane, and admitted to the labor room complaining of preterm labor pain were included in the study. The pregnant women were watched to ensure that they were in preterm labor by tracking any cervical change and/or descent of the presenting part. Pregnant women with multiple gestation, antepartum hemorrhage, polyhydramnios, pregnancy with diabetes mellitus, fetal malformation, heart disease, chronic obstructive pulmonary disease, and bronchial asthma were excluded from the study. The preterm labor is defined as the labor which induces delivery before 37 full weeks of gestation.

All the patients were randomly allocated into two groups through computerized randomization. Group 1 ($n = 41$) received 40 mg isoxsuprine in 500 mL of 5% dextrose at 8 drops per min (0.04 mg/min) and Group 2 ($n = 41$) received 4 g magnesium sulfate in 12 mL normal saline as an intravenous loading dose over 20 min.

#### Data collection

Data regarding patient’s age, parity, previous history of abortions and preterm deliveries, last menstrual period, gestational age, and time of onset of preterm labor were collected from all the patients through interviews before the procedure.

Clinical data such as vital signs, general examination, systemic examination, examination of external genitalia, and per vaginal examination were further collected.

#### Study procedure

**Group 1 (isoxsuprine)**

The patients were given 40 mg isoxsuprine in 500 mL of 5% dextrose at 8 drops/min (0.04 mg/min). After every 30 min, the drop rate was increased by 8 drops/min until uterine quiescence was attained or the patient developed adverse effects in the form of maternal tachycardia (>120/min), hypotension (systolic blood pressure <80 mmHg or diastolic blood pressure <40 mmHg), intolerable nausea and vomiting, or fetal tachycardia (fetal heart rate >160/min). The intravenous drip was continued for 24 h and even after attaining uterine quiescence. Six hours before stopping intravenous infusion, injectable isoxsuprine (10 mg) was given intramuscularly every 6 h for the first 24 h and later, isoxsuprine capsule 40 mg was given orally twice a day for 7 days as maintenance therapy as it is effective in prolonging pregnancy in women at risk of preterm delivery.[12]

**Group 2 (magnesium sulfate)**

The patients were given 4 g magnesium sulfate in 12 mL normal saline as an intravenous loading dose for over 20 min, after which an intravenous infusion of magnesium sulfate was started at a rate of 2 g/h (10 ampoules of 50% magnesium sulfate in 5% dextrose at the rate of 25 drops/min). The drop rate was increased to 38 drops if uterine quiescence (<4 contractions/h) was not achieved by the end of 1 h. The intravenous infusion
was continued for 12 h if uterine quiescence was achieved by the end of 2 h and was discontinued if not achieved by the end of 2 h or if the patient developed any adverse effects such as intolerable nausea and vomiting, maternal tachycardia (>130/min), hypotension (systolic blood pressure < 80 mmHg), absent patellar jerk, respiratory depression (<12/min), and decreased urine output (<30 mL/h). No antenatal corticosteroids were administered.

Vitals of the patient (pulse and blood pressure) were monitored every 30 min. The effectiveness (percentage of effacement and cervical dilatation) and safety of magnesium sulfate versus isoxsuprine were the main outcomes of interest in arresting preterm labor. Maternal side effects such as tachycardia, hypotension, palpitation, headaches, flushing, nausea, and dizziness, related to the tocolytic agent, were assessed.

### Outcome variables
The percentage of effacement and cervical dilatation after the intervention was the outcome variables which defined the success of tocolysis. These variables were measured by pelvic examination.

### Statistical analysis
Statistical analysis was performed using R software (Version 3.6.0) (USA). Data were recorded in Microsoft Excel and expressed as mean± standard deviation along with frequency and percentage. Qualitative variables were analyzed using Chi-square test of independence, two-sample proportion test, and paired t-test for continuous variables. Mann–Whitney U test was employed for variables without a normal distribution. Univariate logistic regression was used for predicting the outcome variables. Data were considered statistically significant when \( P \leq 0.05 \).

### RESULTS
The present prospective study was carried out in 82 pregnant women/patients. Table 1 presents data on the distribution of demographic variables.

The patients’ demographic parameters including age, weight, height, and gestational age were comparable in both the groups \( (P > 0.05) \). The mean age and weight were 26 years and 54 kg, respectively, in Groups 1 and 2, which stipulate that the patients were at the right age and had the right weight for pregnancy [Table 1].

In both the groups, no significant association was found with respect to gravida of patients, history of abortion, and percentage of effacement and cervical dilatation \( (P > 0.05) \) [Table 2].

No significant difference \( (P > 0.05) \) was observed between the two groups in terms of successful tocolysis based on the percentage of effacement as the majority of the cases in both the groups with <25% of effacement had successful tocolysis, which stipulates that lesser the percentage of effacement, more the chances of successful tocolysis [Table 3].

In the majority of the women with <1 cm of cervical dilatation, successful tocolysis was observed more in Group 2 than in Group 1. This difference was statistically significant \( (P < 0.01) \), indicating that magnesium sulfate was significantly more effective than isoxsuprine for tocolysis in patients with <1 cm dilatation.

From Chi-square test and Cramer’s V, it is observed that there is moderately significant association between side effects and the groups. Tachycardia and hypertension were observed more frequently in Group 1 than in Group 2, whereas nausea and vomiting were more common in Group 2 than Group 1. Headache, flushing, and lethargy were observed in both the groups with almost same frequency [Table 4]. Apart from the side effects mentioned in the table, the body vitals of the participants were good.

A significant difference \( (P < 0.05) \) was observed between the two groups in terms of overall success rate of tocolytic agents in arresting preterm labor. In Group 2, labor was successfully arrested in a greater number of pregnant women as compared to Group 1 after the 2nd day of administration of magnesium sulfate, indicating that it was slightly more effective in arresting preterm labor as compared to isoxsuprine [Table 4].

Overall success rate was measured by measuring the overall successful arrest of labor among patients in each group.

### Table 1: Comparison of age, weight, and gestational age of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 ( (n=41) )</th>
<th>Group 2 ( (n=41) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.4±4.57</td>
<td>26.9±4.76</td>
<td>0.604 (T)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.4±11.48</td>
<td>53.4±11.48</td>
<td>0.2403 (T)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>33.8±2.48</td>
<td>34.1±2.43</td>
<td>0.5323 (M)</td>
</tr>
</tbody>
</table>

Group 1: Isoxsuprine group, Group 2: Magnesium sulfate group, M: Mann–Whitney U-test, SD: Standard deviation, T: Two-sample t-test

### Table 2: Association of baseline characteristics in study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 ( (n=41), n(%) )</th>
<th>Group 2 ( (n=41), n(%) )</th>
<th>( P ) (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravida</td>
<td>26 (63.41)</td>
<td>25 (60.98)</td>
<td>1</td>
</tr>
<tr>
<td>Multigravida</td>
<td>15 (36.39)</td>
<td>16 (39.02)</td>
<td></td>
</tr>
<tr>
<td>History of abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (9.76)</td>
<td>3 (7.32)</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>37 (90.24)</td>
<td>38 (92.68)</td>
<td></td>
</tr>
<tr>
<td>Percentage of effacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>24 (58.54)</td>
<td>26 (63.41)</td>
<td>0.8209</td>
</tr>
<tr>
<td>25–50%</td>
<td>17 (41.46)</td>
<td>15 (36.59)</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>22 (53.6)</td>
<td>22 (53.6)</td>
<td>0.9464</td>
</tr>
<tr>
<td>&gt;1–&lt;2</td>
<td>11 (26.8)</td>
<td>12 (29.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;2–3</td>
<td>8 (19.6)</td>
<td>7 (17.2)</td>
<td></td>
</tr>
</tbody>
</table>

C: Chi-square test, Group 1: Isoxsuprine group, Group 2: Magnesium sulfate group

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Jeswani, et al.: Magnesium sulfate vs isoxsuprine

Journal of Natural Science, Biology and Medicine | Volume 12 | Issue 2 | July-December 2021
Most of the patients in both the groups were primigravida. This is in contrast with the observation made in a previous published study, in which the majority of the pregnant women in preterm labor were multigravida.[16] This disparity could be due to the much younger age of the pregnant women in their first pregnancy in our study. Most of the patients in both the groups in the present study had no history of abortion, as most of them were primigravida. This was in contradiction to the observation made by Jagapriya et al.[16] which could be due to a greater number of primigravida women in our study.

The percentage of effacement in the majority of the patients was <25% in both the groups. Similar results were obtained by Jagapriya et al., as most of the patients in their study had an effacement of 20%.[16] In young women, cervical effacement during preterm labor is observed due to cervical insufficiency, especially in primigravida.[17] Patients in both the groups had a cervical dilatation of 0–1 cm in our study. This finding is not in agreement with the study findings of Jaju,[11] wherein most of the patients had a cervical dilatation of 1.8–2 cm.[11] This difference could be attributed to the young age and primigravida status of the pregnant women in our study. If cervical dilatation at <34 weeks is noted to be at least 2–3 cm, then the patient is highly likely to deliver preterm.[18]

A decline in the success rate of tocolysis was recorded in both the groups in the present study with an increase in the percentage of effacement. In addition, most of the women with <1 cm cervical dilatation in Group 2 (magnesium sulfate) had successful tocolysis as compared to Group 1 (isoxsuprine). This is in accordance with another study’s results.[16]

This study further showed a highly significant association between the percentage of effacement and cervical dilatation indicating that as the percentage of effacement increased, the chances of increase in cervical dilatation also increased. Furthermore, with a decrease in the percentage of effacement, the success of tocolysis increased. Similar results were obtained by Deepthy et al.[15] These findings suggest that the percentage of effacement is directly proportional to cervical dilatation and inversely proportional to the success of tocolysis.

In this study, tachycardia and hypertension were observed more frequently in Group 1 as compared to Group 2. Furthermore, nausea and vomiting were more common in Group 2 than in

### Table 3: Comparison of successful tocolysis between the two groups based on percentage of effacement and cervical dilatation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=41)</th>
<th>Group 2 (n=41)</th>
<th>P (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of effacement (&lt;25%)</td>
<td>24</td>
<td>23 (95.83)</td>
<td></td>
</tr>
<tr>
<td>25–50%</td>
<td>17</td>
<td>4 (23.53)</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation(cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>14</td>
<td>13 (92.9)</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>19</td>
<td>12 (63.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>8</td>
<td>2 (25.0)</td>
<td></td>
</tr>
</tbody>
</table>

Group 1: Isoxsuprine group, Group 2: Magnesium sulfate group, T: Two-sample proportion tests

### Table 4: Side effects and overall success rate of the groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=41), n (%)</th>
<th>Group 2 (n=41), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side-effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>5 (12.20)</td>
<td>5 (12.20)</td>
<td>0.01199</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (12.20)</td>
<td>4 (9.76)</td>
<td>MC* (0.4431)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (21.95)</td>
<td>2 (4.88)</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>6 (14.63)</td>
<td>5 (12.20)</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (4.88)</td>
<td>7 (17.07)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>7 (17.07)</td>
<td>1 (2.44)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7 (17.07)</td>
<td>17 (41.46)</td>
<td></td>
</tr>
<tr>
<td>Overall success rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>27 (65.85)</td>
<td>35 (85.37)</td>
<td>0.039 (C)</td>
</tr>
<tr>
<td>Failure</td>
<td>14 (34.15)</td>
<td>6 (14.63)</td>
<td></td>
</tr>
</tbody>
</table>

C: Chi-square test, Group 1: Isoxsuprine group, Group 2: Magnesium sulfate group, MC: Chi-square test with Monte Carlo simulation

Multivariate logistic regression was used for predicting the outcome variable (P<0.05). It indicated that the model fit the data well. Only age and percentage of effacement were better predictors as they had the least Akaike information criterion (AIC) (lesser the AIC, better the model) [Table 5].

Labor was successfully arrested till the end of 2 days in 65.85% of pregnant women in Group 1 (isoxsuprine) and in 85.37% women in Group 2 (magnesium sulfate). This difference in the overall success rate was statistically significant (P<0.05), indicating that magnesium sulfate was slightly more effective in arresting preterm labor as compared to isoxsuprine.

### DISCUSSION

The present prospective study was carried out to compare the efficacy, success rate, and maternal side effects of isoxsuprine (Group 1) and magnesium sulfate (Group 2) in the arrest of preterm labor. Data regarding percentage of effacement, cervical dilatation, and successful tocolysis in both the groups formed the basis of the study.

The majority of the patients in both the groups were in the age group of ≥26 years with weight ≥53 kg and gestational age of ≥33 weeks in the present study. This is in accordance with a study conducted by Deepthy et al.,[15] in which the mean age, weight, and gestational age of most pregnant women were 25–30 years, 54 ± 4 kg, and 35 weeks, respectively.[15]
Group 1. Headache, flushing, and lethargy were observed in both the groups in our study. Similar results were obtained in previous studies where the maternal side effects such as those related to the heart were significantly higher in the isoxsuprine group.[14,19] Labor was successfully arrested till the end of the 2nd day in 65.85% of pregnant women in Group 1 (isoxsuprine) and in 85.37% women in Group 2 (MgSO4). This indicated that magnesium sulfate was slightly more effective in arresting labor as compared to isoxsuprine. In a study by Mahajan and Marvah,[20] the delivery was delayed successfully for at least 2 days in 82% of the patients receiving magnesium sulfate as compared to 66% of patients on isoxsuprine, which is in accordance with our results. Similar findings were also noted in another study.[11,13]

The multivariate regression model for prediction of the clinical outcome will be the key in determining the patients who are in the risky zone. In addition, the $P$ value indicated the reliability of model in making predictions.

The overall success rate was more in Group 2 (85.37%) as labor was successfully arrested in a greater number of pregnant women as compared to in Group 1 (65.85%) after 2nd day of administration. This indicated that magnesium sulfate was slightly more effective in arresting labor as compared to isoxsuprine. Similar observations were noted in previous investigations.[15,20]

The present study has its own limitation as it did not include twin pregnancies. Furthermore, only the standard doses of the drugs were employed in the study, and the effect at higher doses should be evaluated as well. Large-scale, randomized, controlled studies are warranted to substantiate the results.

**CONCLUSION**

Magnesium sulfate was successful in the prevention of delivery for 48 h with uterine quiescence more frequently than isoxsuprine with an overall success rate of 85.37%. In addition, it was slightly more effective than isoxsuprine about tocolysis in patients having $< 1$ cm dilatation. It showed lesser maternal side effects such as hypotension, palpitation, and tachycardia as compared to isoxsuprine due to which, it was better tolerated. Hence, magnesium sulfate is recommended for use as a tocolytic agent in preterm labor.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**