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A Comparative Study Between Intravenous **Magnesium Sulphate and Intravenous Isoxsuprine** for Arrest of Preterm Labour

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ABSTRACT

Introduction: Wide use of medical management of preterm labour has been obstructed due to low success rate of arrest of labour. This is aggravated by higher incidence of serious side effect of the available tocolytic agents, especially betamimetic tocolytics. With this background, the present study was carried out to compare the efficacy and maternal side effect of magnesium sulphate and Isoxsuprine in the arrest of preterm labour.

Methodology: This was a comparative prospective interventional study conducted among pregnant women coming to department of obstetrics and gynaecology with 28 to 37 weeks of gestation. Patients were divided in to two groups - Group 1 receiving Isoxsuprine and Group 2 receiving Magnesium Sulphate. Base line profile and outcome were compared between the two study groups.

Results: Magnesium sulphate was more effective in arresting labour compared to Isoxsuprine (p<0.05). Tachycardia and hypotension were observed more frequently in group1 (Isoxsuprine) compared to group 2 (MgSO₄). In cases having <1 cm dilatation and or less than 25% effacement MgSO4 was significantly more effective that Isoxsuprine for tocolysis.

Conclusion: Magnesium sulphate is a more effective tocolytic agent than Isoxsuprine. Magnesium sulphate produce lesser maternal and foetal side effects like hypotension, palpitation, tachycardia as compared to Isoxsuprine.

INTRODUCTION

The definition of preterm labour given by American College of Obstetricians and Gynaecologists (ACOG) has been accepted worldwide which defines Preterm labour (PTL) as "regular contractions associated with cervical changes before completion of 37 weeks of gestation".[1] In India, in nearly one out of four pregnancies preterm labour occurs and in 10-69% cases preterm delivery occurs.[2] The occurrence of preterm labour and premature delivery differ among the different subpopulation groups and communities. Prevalence of certain factors in the population affect the incidence of preterm labour and preterm delivery. These factors vary from physical factors of the women, like low weight before pregnancy, uterine abnormalities and interval between two pregnancies, social factors, like poor socioeconomic status, literacy of mother, racial and ethnic factors; occupation of mother, and other factors like tobacco smoking, maternal sexual activity, etc. [3] Preterm delivery is also a risk factor for neonate. It is one of the leading causes of morbidity and mortality during perinatal period. Preterm

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birth is underlying cause for nearly 40-75% of neonatal mortality. [2]

Preterm delivery found associated with certain long-term morbidities like delayed neural development, chronic lung disease and cerebral palsy. Gestational age at the time of delivery is the most important determiner of neonatal outcome, along with another important risk factor i.e. infection. Full term and near full term pregnancy associated with lower morbidity and mortality. In general, lesser the gestational age higher the morbidity and mortality. Thus, identification of high-risk woman and arrest of preterm labour is an important preventive measure to improve neonatal outcome. [4]

However, the major challenge remains the identification high risk women for preterm labour and preterm delivery. Along with identification of risk factors associated with preterm labour, there are certain ways to predict preterm labour. Such method includes Fetal Fibronectin screening and screening for Bacterial Vaginosis. Ultrasonography of the cervical region to assess cervical length, Salivary Estriol and Home Uterine Activity Monitoring (HUAM) are other method to predict preterm labour. Past history of preterm labour is also very important risk factor and predictor for preterm labour in current pregnancy.

After the one preterm delivery, occurrence of preterm labour in subsequent pregnancy increase to 14.3%. The incidence raised to 28% after two previous preterm deliveries. Apart from this twin / multiple pregnancy, uterine abnormalities and cervical incompetence are other importance risk factors. Uterine over-distension (i.e polyhydramnios, fibroids, etc), past history of cervical operation, antenatal bleeding and local infection like bacterial vaginosis are also risk factors for preterm labour. Personnel factors like use of cigarette smoking and use of smokeless tobacco are also associated with preterm labour. Social factors like poor socioeconomic status, low educational status, and young or advanced age of pregnant mother are also associated with preterm labour. Even after knowledge of all these risk factors, successful prediction rate is less, even in pregnant women with presence of established risk factors. [5]

Unavailability of efficient method to early detection or prediction of preterm labour led to increase thrust on treatment of the cases having preterm labour pain.[6] Treatment targeted toward medical intervention in order to arrest the labour, minimize rate of infection and minimize occurrence of respiratory distress in neonate. To attain this objective, in current practice, the clinical care of preterm labour cases focus basically around the use of tocolytics, corticosteroids, antibiotics and other clinically symptomatic and supportive care.[7] The most frequently used tocolytics agents are Beta-2 agonists (e.g. Isoxsuprine hydrochloride, terbutaline sulfate and ritodrine hydrochloride), calcium channel blockers (e.g. nifedipine), oxytocin receptor antagonists (e.g. atosiban), prostaglandin synthetase inhibitors, magnesium sulfate and nitric oxide donors. [8] Through various biochemical pathway these tocolytic agents reduces bio-availability of ions of calcium intracellularly. This ultimately inhibit interaction of actin- myosin. [5]

Wide use of medical management of preterm labour has been obstructed due to low success rate of arrest of labour. This is aggravated by higher incidence of serious side effect of the available tocolytic agents, especially beta-mimetic tocolytics. Moreover, there is scarcity of data on clinical management of preterm labour in Indian subcontinent population. With this background, the present study was carried out to compare the efficacy and maternal side effect of magnesium sulphate and Isoxsuprine in the arrest of preterm labour.

MATERIAL & METHODS

This was a comparative prospective interventional study conducted in a tertiary care hospital in Madhya Pradesh, India. The study was conducted among pregnant women coming to department of obstetrics and gynaecology with 28 to 37 weeks of gestation.

Eligibility criteria:

Pregnant women with gestational age of 28 to 37 weeks having regular uterine contractions, two or more than two per ten minute each lasting for at least 30 sec with three centimeter or less cervical dilatation, cervical effacement not more than 50% and intact membrane were included in the study.

Any woman with multiple pregnancy, ante- partum hemorrhage, polyhydramnios, pregnancy with diabetes mellitus, foetal malformation, heart disease, COPD or bronchial asthma was excluded from the study.

Methodology

A prospective randomized trial was carried out in obstetrics department of the hospital from June 2019 to June 2021. All the cases coming to department of obstetrics and gynaecology with 28 to 37 weeks of gestation were screened and those who satisfy the inclusion criteria were taken for study. A detailed history was taken, consisting patient's age, parity, previous history of abortions, past-history of preterm deliveries, LMP (last menstrual period), gestational age and time of onset of preterm labour were taken.

After that thoroughly clinical examination was carried out which including recording of vital signs, general examination, systemic examination thoroughly, examination of external genitalia and PV (per vaginal) examination. The investigation included complete blood count, bleeding time, clotting time, urine complete examination, ABO, Rh Grouping, serum electrolyte, random blood sugar levels, vaginal swab, and renal function test.

In the present study 82 pregnant female with complain of preterm labour pain and admitted in labour room were included. The selection of the patient in the groups was done on the computerized randomization method.

Group 1: Patient receiving Isoxsuprine hydrochloride **Group 2:** Patient receiving Magnesium Sulphate

Group 1 patient receiving Isoxsuprine. Patient was given 40 mg Isoxsuprine in 500 ml of 5% dextrose at 8 drops per minutes (0.04mg per minute). Drop rate increased by 8 drop/min after every half hour until uterine quiescence attained or the patient develops adverse effects in the form of maternal tachycardia (>120/minute), hypotension (systolic less than 80 mmHg or diastolic less than 40 mmHg), intolerable nausea and vomiting or fetal tachycardia (FHR>160/min). The intravenous drip continued for 24 hours after uterine quiescence achieved. 6 hours before stopping intravenous infusion. Inj Isoxsuprine 10 mg given intramuscular 6th hourly for 1st 24 hours and capsule Isoxsuprine 40 mg given twice a day orally for 7 days.

Group 2 patient received Magnesium Sulphate. Patients were given 4 gm Magnesium sulphate in 12 ml normal saline as an intravenous loading dose over 20 minutes, after which intravenous infusion of magnesium sulphate would be started at a rate of 2 gm per hour (10 ampoules of 50 % magnesium sulphate in 5% dextrose at the rate of 25 drops per minute). And drop rate increased to 38 drops if uterine guiescence (<4 contraction per hour with absence cervical change) was not achieved by end of one hour. The intravenous infusion was continued for 12 hours if uterine guiescence achieved by the end of 2 hours. Vitals of the patient (Pulse and Blood pressure) were monitored half hourly. Deep Tendon Reflexes, urine output and respiratory rate were monitored every four hourlies. The infusion was discontinued if uterine guiescence was not achieved by the end of 2 hours or if the patient developed any adverse effects such as Intolerable nausea and vomiting, maternal tachycardia (>130/min.), hypotension (systolic <80mmHg) absent patellar jerk, respiratory depression (<12/min) and decreased urine output (<30ml/hour)

Analysis

All collected information was entered in to excel sheet and analysed using software Epi Info[™] For Windows version 7.2. All qualitative data were presented by frequency and percentage. All quantitative data were presented by mean and standard deviation. Initially baseline profile were compared between study group and control group. This was followed by comparison of outcome variable between two study groups. Statistical difference between two groups were assessed using chi square for study variable was qualitative. P value below 0.05 indicate statistically significant difference in two groups.

Ethical Consideration

Study was conducted only after approval of institutional ethical committee. All the subjects were explained about the study in the vernacular language. Participation in the study was purely voluntary and all women were informed about their right to withdraw at any stage of the study. Informed written voluntary consent was taken from all study participants before the study. Data were analysis and presented without direct identifier.

RESULTS

The study was conducted among 82 women having preterm labour and fulfilling the eligibility criteria.

As shown in the table 1, there no significant difference in mean age of women, mean weight, gestational age at the time of reporting, gravidity and history of abortion between the cases of both the study groups (p > 0.05).

| Table 1: Comparison of | baseline | profile | among | the two |
|------------------------|----------|---------|-------|---------|
| study groups | | | | |

| Variables | Group 1 Isoxsuprine | Group 2 MgSO4 | P value | |
|---------------------|------------------------|------------------|------------|--|
| | (n=41) | (n=41) | | |
| Age of women | | | | |
| <20 yr | 3 (7.32) | 3 (7.32) | 0.9565 | |
| 20-25 yr | 13 (31.71) | 12 (29.27) | | |
| 25-30 yr | 18 (43.9) | 17 (41.46) | | |
| >30 yr | 7 (17.07) | 9 (21.95) | | |
| Weight of women | 63.17 ± 8.84 | 59.51 ± 10.1 | 0.084 | |
| (mean ± SD kg) | | | | |
| Gestational Age | | | | |
| <32 week | 8 (19.51) | 7 (17.07) | 0.6476 | |
| 33-35 week | 21 (51.22) | 18 (43.9) | | |
| 35-37 week | 12 (29.27) | 16 (39.02) | | |
| Gravidity | | | | |
| Primigravida | 26 (63.41) | 25 (60.98) | 0.8198 | |
| Multi gravida | 15 (36.59) | 16 (39.02) | | |
| History of Abortion | | | | |
| Yes | 4 (9.76) | 3 (7.32) | 0.999* | |
| No | 37 (90.24) | 38 (92.68) | | |

Table 2: Comparison of clinical variables and outcome between the two study groups

| Variables | Group 1 | Group 2 | Ρ | |
|------------------------|---------------|------------|--------|--|
| | Isoxsuprine | MgSO4 | value | |
| | (n=41) | (n=41) | | |
| Cervical dilatation | | | | |
| 0-1cms | 14 (34.15) | 15 (36.59) | 0.9507 | |
| 1-2cms | 19 (46.34) | 19 (46.34) | | |
| >2cms | 8 (19.51) | 7 (17.07) | | |
| Percentage of Effacer | nent | | | |
| <25% | 24 (58.54) | 26 (63.41) | 0.5226 | |
| 25-50% | 17 (41.46) | 15 (36.59) | | |
| Success of tocolysis a | after 2nd day | | | |
| Successful | 27 (65.85) | 35 (85.37) | 0.039 | |
| Failure | 14 (34.15) | 6 (14.63) | | |
| Side effects | | | | |
| Tachycardia | 7 (17.07) | 1 (2.44) | | |
| Hypotension | 9 (21.95) | 2 (4.88) | | |
| Headache | 5 (12.2) | 4 (9.76) | | |
| Flushing | 5 (12.2) | 5 (12.2) | | |
| Lethargy | 6 (14.63) | 5 (12.2) | | |
| Nausea Vomiting | 2 (4.88) | 7 (17.07) | | |

| Variables G | | Group 1 - Isoxsuprine (n=41) | | Group 2 - MgSO4 (n=41) | |
|--------------------------|--------------------------|------------------------------|--------------------------|------------------------|---------|
| Cases | Successful Tocolysis (%) | cases | Successful Tocolysis (%) | - | |
| Cervical dilatation | | | | | |
| 0-1 cm | 14 | 13 (92.9) | 15 | 15 (100.0) | <0.0001 |
| 1-2 cm | 19 | 12 (63.2) | 19 | 16 (84.2) | 0.1415 |
| >2 cm | 8 | 2 (25.0) | 7 | 4 (57.1) | 0.2055 |
| Percentage of Effacement | | . , | | . , | |
| <25% | 24 | 23 (95.8) | 26 | 26 (100.0) | <0.0001 |
| 25-50% | 17 | 4 (23.5) | 15 | 9 (60.0) | 0.0359 |

*Z test of proportion

Out of 41 in group1 (Isoxsuprine), 8 (19.51%) women were having gestational age less than 32 week while in group 2 (MgSO₄) 7 (17.07%) were having gestational age less than 32 weeks. Women with 33 to 35 weeks of gestational age were 21 (51.22%) and 18 (43.9%) in group1 (Isoxsuprine) and group 2 (MgSO₄) respectively. Women with 35 to 37 weeks of gestational age were 12 (29.27%) and 16 (39.02%) in group1 (Isoxsuprine) and group 2 (MgSO₄) respectively. Distribution of cases according to their gestational age between two groups was statistically non-significant (p > 0.05).

As shown in the table 2, there no significant difference cervical dilatation and effacement at the time of reporting between the two study groups (p > 0.05).

Out of 41 in group1 (Isoxsuprine), 14 (34.15%) women were having cervical dilatation less than 1 cm while in group 2 (MgSO₄) 15 (36.59%) were having cervical dilatation less than 1cm. Women with 1-2 cm of cervical dilatation were 19 (46.34%) in each of group1 (Isoxsuprine) and group 2 (MgSO₄). Women with more than 2 cm of cervical dilatation were 8 (19.51%) and 7 (17.07%) in group1 (Isoxsuprine) and group 2 (MgSO₄) respectively. Out of 41 in group1 (Isoxsuprine), 24 (58.54%) women were having percentage of effacement less than 25% while in group 2 (MgSO₄) 26 (63.41%) were having percentage of effacement were 17 (41.46%) and 15 (36.59%) in group1 (Isoxsuprine) and group 2 (MgSO₄) respectively.

Tachycardia and hypotension were observed more frequently (17.0% and 21.95% respectively) in group1 (Isoxsuprine) compared to group 2 (MgSO₄) were these side effects were observed in 2.44% and 4.88% cases respectively.

In group1 (Isoxsuprine), out of 41, in 27 (65.85%) women labour was successfully arrested till the end of 2 days while in group 2 (MgSO₄), out of 41, in 35 (85.37%) women labour was successfully arrested till the end of 2 days. The difference in success rate was statistically significant (p<0.05) indicating that magnesium sulphate was more effective in arresting labour compared to Isoxsuprine.

As shown in table 3, women having less than 1 cm of cervical dilatation successful tocolysis observed in 92.9% cases of group1 (Isoxsuprine) while it was 100%

in group 2 (MgSO₄). This difference was statistically significant (P<0.01) indicating that in cases having <1 cm dilatation MgSO4 is significantly more effective that Isoxsuprine for tocolysis. In women having less than 25 percentage of effacement, successful tocolysis observed in 95.8% cases of group1 (Isoxsuprine) while it was 100% in group 2 (MgSO₄). This difference was statistically significant (P<0.01) indicating that in cases having less than 25% effacement, MgSO4 is significantly more effective that Isoxsuprine for tocolysis.

DISCUSSION

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and guality of life. [9] Pre-term labour is causing about one-third of pre-term births and its prevention has been a major challenge for the obstetrician as well as the neonatologist. Prematurity contributes to 75% of perinatal deaths and illnesses.[10] It accounts for 75% to 80% of perinatal mortality not caused by congenital deformities.[11] Pre-term labour is responsible for about one-third of pre-term births and is an important cause of prenatal mortality and morbidity. In humans, preterm birth refers to a birth of less than 37 weeks of gestation. The cause for preterm birth is in many situations elusive and unknown; many factors appear to be associated with the development of preterm birth, making the reduction of preterm birth a challenging proposition.

Cervical Dilatation in the cases

In the present study distribution of cases according to cervical dilatation between two groups was statistically non-significant (p > 0.05). In the present study in cases having <1 cm dilatation MgSO4 is significantly more effective that Isoxsuprine for tocolysis (p<0.05).

A study by Mahajan A et al [12] concluded that as the cervical dilatation increased, the success rate of both the drugs MgSO4 and Isoxsuprine came down. Successful tocolysis was attained in 94.11% cases with cervical dilatation of upto 1 cm in magnesium sulphate group as compared to 80% cases in Isoxsuprine group. The difference is statistically not significant. In a study by Jagapriya JS et al [13], Successful tocolysis was attained in 91.67% cases with cervical dilatation of up to 1

cm in Isoxsuprine group as compared to 81.81 % cases in magnesium sulphate group. In patients with cervical dilatation between 1-2 cm, the success rate was 88.24 % in Isoxsuprine group as compared to 72.2 % in magnesium sulphate group. The difference was however statistically not significant.

Effacement in the cases

In the present study in women having less than 25 percentage of effacement, successful tocolysis observed in 95.8% cases of group1 (Isoxsuprine) while it was 100% in group 2 (MgSO₄). This difference was statistically significant (P<0.01) indicating that in cases having less than 25% effacement, MgSO4 is significantly more effective that Isoxsuprine for tocolysis. In group 2 (MgSO4) successful tocolysis rate was higher (60%) in cases having 25-50 percentage of effacement compared to group 1 (Isoxsuprine) (23.5%) and this difference was also statistically significant (P <0.05).

A study by Mahajan A et al [12] the successful tocolysis was achieved in 91.68% cases in magnesium sulphate group and 76.92% cases in Isoxsuprine group with cervical effacement up to 20%. The success rate declined to 83.33% in magnesium sulphate group and 54.55% in Isoxsuprine group with cervical effacement between 30-40%. In a study by Jagapriya JS et al [13], a decline in the success rate was recorded in Isoxsuprine group and magnesium sulphate group with increase in cervical effacement. The difference in success rate in two groups was statistically not significant (p > 0.74). The slight disparity in the success rate in either group could be due to different criteria used for success, varied dosage regime, difference in the number of patients who entered the study with different initial cervical dilatation or cervical effacement, frequency and duration of uterine contractions.

Arrest of Labour in the study cases

Isoxsuprine is a beta-adrenergic agonist and also a potent vasodilator. It was actually the first drug to be published as a tocolytic agent to arrest uterine contractions. [14,15] Isoxsuprine is also approved by CDSCO for the medical treatment of Preterm labour. [16] A very effective therapeutic outcome of Isoxsuprine is reported by good number of RCTs in women at risk of preterm labour and risk of abortion. [15] In the previous fifty year, Magnesium sulfate has been commonly used in a wide range of doses, both as a tocolytic agent and also as seizure prophylaxis in pregnant female with preeclampsia. [17]

In the present study, Magnesium Sulphate was able to arrest labour successfully in 85.37% women till the end of 2 days. In a study by Jagapriya JS et al [13], Magnesium sulphate was successful in attaining tocolysis in 60% cases. These results are comparable to other studies (Saha, 2002 [18]; Vaja and Goyal, 2014 [8]; Amit Mahajan et al 2014 [12]).

In a study by Mahajan A et al [12] magnesium sulphate was successful in delaying the delivery for 7 days or

more in 37 (74%) cases as compared to Isoxsuprine which was successful in 25 (50%) cases. This is statistically highly significant (p value <0.01). In a study by Jagapriya JS et al [13], the delivery was delayed successfully for at least 2 days in 74.3% cases in the patients receiving Isoxsuprine as compared to 60% patients on magnesium sulphate. (p<0.20). A study by Jaju PB et al[19] found that delivery was successfully delayed for at least 2 days in 57.76% cases in the patients receiving Isoxsuprine as compared to 50% patients on magnesium sulphate. The difference was however statistically not significant (p<0.20).

Side Effect of the drugs

In a number of randomised control trials, therapeutic effectiveness of Isoxsuprine, have been proven. These trials include trial in cases at risk of preterm labour and at risk of abortion. Isoxsuprine has shown good tolerability when used orally, intramuscularly or for intravenous therapy. [14,15]

Though better tolerated, a vigilant monitoring of serious side effect is required for Magnesium sulphate. Monitoring for respiratory depression and cardiac arrest is very essential. Common side effects of Magnesium sulphate include flushing, nausea, headache, drowsiness, and blurred vision. In addition to the above side effect Magnesium also crosses the placental barrier and causes respiratory and motor depression in the newborn. [20]

In the present study tachycardia and hypotension were observed more frequently (17.0% and 21.95% respectively) in group1 (Isoxsuprine) compared to group 2 (MgSO₄) where these side effects were observed in 2.44% and 4.88% cases respectively. Nausea and vomiting were observed more frequency in group 2 (MgSO₄) (17.07%) compared to group1 (Isoxsuprine) (4.88%). Headache, flushing and lethargy were observed in 12.2%, 12.2% and 14.63% respectively in group 1 (Isoxsuprine) while these were observed in 9.76%, 12.2% and 12.2% in group 2 (MgSO₄).

In a study by Mahajan A et al [12] the commonest adverse effect experienced by patients in Magnesium sulphate group was lethargy (20%) but fetal tachycardia (18%) and hypotension (18%) were the commonest side effects experienced by patients in Isoxsuprine group. Nausea (14%) and dry mouth (8%) were the other common side effects experienced by the patients in Magnesium sulphate group and palpitation/tachycardia (14%), headache (8%) and nausea (8%) were the other common side effects experienced by patients in Isoxsuprine group.

In a study by Jagapriya JS et al [13], the commonest adverse effect experienced by patients in Isoxsuprine group was hypotension (30.78 %) and tachycardia (23.08 %) but the commonest side effects experienced by patients in Magnesium sulphate group was lethargy (26.09%) and nausea (26.09%). Nausea (4%) and headache (4 %) were the other common side effects experienced by the patients in Isoxsuprine group and flushing (21.73 %), headache (13.04 %) and hypotension (8.7%) were the other common side effects experienced by patients in Magnesium sulphate group.

In a study by Nemani S et al [21], hot flushes was the common complaint from most of the patients studied 23 (46%), followed by Nausea and Vomiting 14 (28%). All the patients in the study experienced side effects which were minor

CONCLUSION

From this study, we conclude that magnesium sulphate is a more effective tocolytic agent than Isoxsuprine. Magnesium sulphate produce lesser maternal and fetal side effects like hypotension, palpitation, tachycardia as compared to Isoxsuprine

Magnesium sulphate is better tolerated than Isoxsuprine, its other advantages include neuroprotective property and ability to use in patients with cardiac diseases. Hence recommended to use as the tocolytic agent in preterm labour.

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