International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2014 Vol. 4 (3) September-December, pp. 19-25/Mhajan and Marwah
Research Article

ARREST OF PRETERM LABOUR: A COMPARATIVE STUDY BETWEEN MAGNESIUM SULPHATE AND ISOXSUPRINE

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ABSTRACT
Prematurity and its prevention continue to be a major challenge for both the obstetrician and neonatologist. Preterm labour is the most common obstetrical complication associated with perinatal deaths. Despite all advances in neonatology, the delivery of a preterm neonate is a clinical crisis that threatens the life and health of an infant. The obstetrician thus faces the challenge of affecting the delivery in such a way as to optimize the status of fetus-infant at birth. It is far more preferable to prevent the intiation of preterm labour than once the cascade of events has already been established. The objective of this study was to compare the efficacy of magnesium sulphate and isoxsuprine as tocolytic agent. A total of 100 pregnant ladies between gestational age 28-37 weeks, regular uterine contraction $\geq$ 2 per 10 minute each lasting for $\geq$ 30 sec, cervical dilatation not more than 3 cm, cervical effacement not more than 50% with intact membranes were randomly assigned group I and group II in equal numbers. All the patients were closely monitored and observed for uterine quiescence and side effects. Both magnesium sulphate and isoxsuprine were effective in attaining successful tocolysis in majority of patients. Magnesium sulphate produces significantly lesser maternal and fetal side effects.

Keywords: *Magnesium Sulphate, Isoxsuprine, Preterm Labour, Tocolytic Agents, Hypotension*

INTRODUCTION
Prematurity and its prevention continue to be a major challenge for both the obstetrician and neonatologist. Prematurity accounts for 75% of perinatal mortality and morbidity (Fuchs, 1976). It accounts for 75% to 80% of perinatal deaths not caused by congenital anomalies (How *et al.,* 1995). Preterm labour is defined as the onset of regular, painful uterine contractions, two or more per 10 minutes each lasting for at least 30 seconds with cervical effacement upto 50% or cervical dilatation upto 3 cm between 28-37 completed weeks of gestation. Although survival of preterm infants exceeds 90% by 30 completed weeks of gestation and 90% of otherwise uncomplicated preterm births occur between 30 and 36 weeks of gestation, neonatal morbidity assumes paramount importance during this latter period of preterm gestation (Creasy, 1993). Preterm infant is subjected to a number of problems like developmental disability (cerebral palsy, mental retardation, hearing deficit, visual loss, learning disability, hyperactivity, attention defects and behavior disorder), chronic lung disease and retinopathy of prematurity. There are a number of demographic, social and medical characteristics of pregnancy with preterm delivery (Meis *et al.,* 1995). Faulty placentation, intrauterine infection, immunological factors, maternal factors, cervical incompetence, uterine factors, trauma and fetal anomalies are various groups of possible causes that lead to preterm labour (Lettieri *et al.,* 1993). The underlying causes are unknown in nearly 50% of the cases (Das, 1969). It is far more preferable to prevent the initiation of preterm labour than once the cascade of events has already been established (Creasy and Merkatz, 1990). The currently used method to arrest preterm labour is by inhibiting uterine contractions with tocolytic agents. These drugs delay the delivery and permit the use of glucocorticoids to facilitate the transfer of patient to a unit where intensive neonatal care facilities are available (Kitchen *et al.,* 1992). Over the years treatment protocols have achieved tocolysis with beta-sympathomimetics like ritodrine, isoxsuprine, salbutamol and terbutaline (Leveno, 1992), magnesium sulphate (Gordon, 1995), calcium channel blockers especially nifedipine (Van, 1993) and nicardipine (Larmon *et al.,* 1999), potassium channel openers (Morrison *et al.,* 1993), oxytocin antagonist-atosiban (Goodwin *et al.,* 1994) and nitric oxide donors (Jones and Poston, 1997). The activity

in the uterine muscle is mediated by alpha and beta-adrenergic receptors. Alpha receptors mediate stimulant effect on myometrium and beta-receptor stimulation inhibits uterine contractions (Alquist, 1948). There are two types of beta-receptors in the human's $beta_1$ and $beta_2$. $Beta_2$–receptors predominate in the smooth muscles of the uterus, blood vessels, diaphragm and bronchioles (Higby *et al.*, 1993). Using radioligand binding technique it has been found that there is a comparable concentration of beta-adrenoreceptors in the uterine fundus and lower uterine segment in normal pregnant women (Berg *et al.*, 1985). Of all the group of tocolytic drugs, beta-sympathomimetics have been investigated and used most frequently to arrest preterm labour. Various sympathomimetic agents used are isoxsuprine, fenoterol, ritodrine, salbutamol, terbutaline and orciprenaline. Isoxsuprine hydrochloride was the first beta-agonist used to arrest preterm labour (Bishop and Woutersz, 1961). Isoxsuprine is a drug of beta-phenylethylamine group of epinephrine like compounds (Hendricks *et al.*, 1961). A variety of troublesome side effects like hypotension and tachycardia were reported in patients treated with isoxsuprine (Schenken *et al.*, 1980). This led to research for other drugs like ritodrine, terbutaline & magnesium sulphate. The tocolytic effects of magnesium sulphate were initially reported by (Hall *et al.*, 1959). Ionic magnesium in a sufficiently high concentration alters the myometrial contractility presumably by acting as an antagonist of calcium (Hollander *et al.*, 1987).

MATERIALS AND METHODS

The present study was carried out in the Department of Obstetrics and Gynaecology, Govt Medical College and Rajindra Hospital, Patiala. The study comprised of 100 women with preterm labour admitted in labour room. The cases were divided into two groups:

Group I comprised of 50 patients who were put on magnesium sulphate.

Group II comprised of 50 patients who were put on isoxsuprine hydrochloride.

Selection Criteria

1. Gestational age 28-37 weeks.
2. Regular uterine contractions, 2 or more than 2 per 10 minutes each lasting for at least 30 seconds.
3. Cervical dilatation not more than 3 cm.
4. Cervical effacement not more than 50%.
5. Membranes intact.

Exclusion Criteria

1. Multiple pregnancy
2. Ante-partum haemorrhage
3. Hydramnios
4. Pregnancy with heart disease and diabetes mellitus
5. Fetal malformations.

After selecting the patients, the following details were noted: age of the patient, parity, number of abortions and history of preterm deliveries, exact date of last menstrual period, duration of pregnancy and time of onset of preterm labour. Detailed history and clinical examination of the patients was done which included record of vitals, systemic examination and per-vaginum examination. The investigation which were carried out in all the patients were haemoglobin, bleeding time, clotting time, ABO Rh grouping, urine complete examination, vaginal swab for culture and sensitivity and urine for culture and sensitivity. After selecting the patients the following dosage regime was followed.

Group I (Patients Receiving Magnesium Sulphate)

All the patients were given 4 gm of magnesium sulphate in 20% solution as an intravenous loading dose given over a period of 20 minutes. After the loading dose was given, an intravenous infusion of magnesium sulphate was started at a rate of 2 gm/hour (10 ampoules of 50% magnesium sulphate in 5% dextrose solution at a rate of 25 drops per minute). The drop rate was increased to 37 drops/minute (3 gm/1 hour) if uterine quiescence (<4 contractions/hour with absence of cervical change) was not achieved by the end of one hour. The intravenous infusion was continued for 12 hours after uterine quiescence was achieved. The infusion was discontinued if uterine quiescence was not attained or patient developed

adverse effects like maternal tachycardia (heart rate more than 130/minute), hypotension (systolic blood pressure less than 80 mmHg), absent patellar jerks, signs of respiratory depression (<12/minutes), decreased urine output (<30 ml/hour), intolerable nausea and vomiting or fetal distress. Half hour before discontinuing the infusion the patient was put on 500 mg magnesium sulphate tablet which was given till 37th completed weeks.

Group II: (Patients Receiving Isoxsuprine)

4 ampoules (40 mg) of isoxsuprine hydrochloride were added to 500 ml of 5% dextrose giving a concentration of 0.8 mg/ml Drop rate was set at 8 drops/minute (0.04 mg/minute). The drop rate was increased by 8 drops/minute after every 15 minutes until uterine quiescence was attained or patient developed adverse effects in the form of maternal tachycardia (heart rate more than 130/minute) or hypotension (systolic blood pressure less than 80 mmHg or diastolic blood pressure less than 40 mmHg), intolerable nausea and vomiting or foetal tachycardia (foetal heart rate greater than 160 beats/minute). The infusion was discontinued then. The intravenous drip was tapered over next 12 hours after uterine quiescence was achieved. After 15 minutes of stoppage of infusion, intramuscular injection of isoxsuprine hydrochloride 10mg 6 hourly was given for 24 hours. 30 minutes before discontinuing the intramuscular therapy, one tablet (10 mg) of isoxsuprine was given 8 hourly and it was continued till 37th completed week or delivery. Treatment was considered successful if the uterine quiescence was maintained for at least 48 hours. Treatment was considered a failure if uterine quiescence could not be achieved or maintained for at least 48 hours inspite of maximum drug dosage or if the patient experienced intolerable side effects requiring discontinuation of the therapy. In all the cases, duration of pregnancy, total duration of delay in labour, mode of delivery, fetal outcome i.e. birth weight of newborn, apgar score at 1 minute and 5 minute were noted. The results in the study were statistically analyzed by means of x^2 test, students t test and statistical significance was defined as a p value of <0.05. A p value of <0.01 indicated highly significant result.

RESULTS AND DISCUSSION

Results

The delivery was delayed successfully for at least 2 days in 82% cases in the patients receiving magnesium sulphate as compared to 66% patients on isoxsuprine. The difference was however statistically not significant. Furthermore, 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) as shown in Table -1.

Table 1: Table comparing 2 day success and 7 day success rate of the two drugs

Parameter	Group I (Magnesium sulphate)		Group II (Isoxsuprine)	
	No. of cases	%age	No. of cases	% age
2 day success	41/50	82	33/50	66
7 day success	37/50	74	25/50	50

Table 2: Table showing relationship between cervical dilatation and success rate

Cervical Dilatation(cms)	Group I (Magnesium sulphate)			Group II (Isoxsuprine)		
	No. of cases	Successful cases	%age	No. of cases	Successful cases	% age
0-1	17	16	94.11	15	12	80.00
1-2	24	21	87.50	26	19	73.08
2-3	9	4	44.44	9	2	22.22

74% cases had vaginal delivery and 26% had a caesarean section in group I. 73.91% patients had vaginal delivery and 26.09% cases had a caesarean section in group II. As the cervical dilatation increased, the

success rate of both the drugs came down. Successful tocolysis was attained in 94.11% cases with cervical dilatation of upto 1 cm in group I as compared to 80% cases in group II. The difference is statistically not significant. In patients with cervical dilatation between 2-3 cm, the success rate was 44.4% in group I as compared to 22.22% in group II. The difference is however, statistically not significant as shown in Table 2.

The successful tocolysis was achieved in 91.68% cases in group I and 76.92% cases in group II with cervical effacement upto 20%. The success rate declined to 83.33% in group I and 54.55% in group II with cervical effacement between 30-40%. A further decline in the success rate to 70.59% and 50.00% was recorded in group I and group II with increase in cervical effacement to 40-50%. The difference in success rate in two groups was statistically not significant ($p>0.05$). The mean time gained was 22.44± 9.36 days in group I and 16.21± 10.45 days in group II. The results was statistically highly significant ($p<0.01$). The commonest adverse effect experienced by patients in group I was lethargy (20%) but fetal tachycardia (18%) and hypotension (18%) were the commonest side effects experienced by patients in group II. Nausea (14%) and dry mouth (8%) were the other common side effects experienced by the patients in group I and palpitation/tachycardia (14%), headache (8%) and nausea (8%) were the other common side effects experienced by patients in group II. Fetal tachycardia necessitated cessation of tocolytic therapy in group II in 2 (4%) patients and hypotension necessitated cessation of treatment in 2 (4%) patients in group II. Fetal tachycardia, hypotension and palpitation/tachycardia were significantly more common side effects seen in group II as compared to group I. Lethargy was significantly more common in group I as compared to group II as shown in Table 3.

Table 3: Table showing adverse effects of the two drugs

Side effects	Group I (Magnesium sulphate)		Group II (Isoxsuprine)	
	No. of cases	%age	No. of cases	% age
Fetal tachycardia	2	4	9	18
Lethargy	10	20	1	2
Hypotension	1	2	9	18
Palpitation/Tachycardia	1	2	7	14
Nausea	7	14	4	8
Dry mouth	4	8	1	2
Headache	2	4	4	8
Dizziness	2	4	1	2
Nystagmus	1	2	-	-

The 1 minute apgar score was in the range of 0-4 in 4% cases in group I and in 4.35% cases in group II. 1 minute apgar score was in the range of 8-10 in 70% and 65.22% cases in group I and group II respectively. The results were statistically not significant. None of the newborn had 5 minute apgar score in the range of 0-4 in any of the two groups.

Discussion

In the present study magnesium sulphate was successful in attaining tocolysis in 82% cases. These results are comparable to other studies (Saha, 2002; Larmon *et al.,* 1999; Hollander *et al.,* 1987). Isoxsuprine was able to attain tocolysis in 66% cases. The results of this study are consistent with other study (Yogol *et al.,* 2009; Sirohiwal *et al.,* 2001; Kalita *et al.,* 1998; Bhide *et al.,* 1995). 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. In the present study magnesium sulphate was able to maintain tocolysis for 7 days or more in 74% cases. These observations are similar to observation made by other studies (Saha, 2002; Hollander *et al.,* 1987). In the present study delivery was successfully delayed for 7 days or more in the patients receiving isoxsuprine in 50% cases. These results are similar to results of other studies (Vaja and Goyal, 2014; Singh *et al.,* 1987). In the present study successful

tocolysis was obtained in 94.11% cases with cervical dilatation up to 1 cm in patient of group I as compared to 80% in patients of group II. As the cervical dilatation increased the success rate of both the drugs came down. In patient with cervical dilatation between 2-3 cms, the success rate was 44.4% in group I as compared to 22.22% in group II. The difference is however statistically not significant. These results are comparable to results of other studies (Steer and Petrie, 1977; Singh *et al.*, 1990). In the present study the mean time gained was 22.24± 9.36 days in group I and 16.21 ± 10.45 days in group II. These results are similar to the results of other studies (Larmon *et al.*, 1999; Hollander *et al.*, 1987; Sirohiwal *et al.*, 2001; Kalita *et al.*, 1998; Patki *et al.*, 1993; Gulati and Rai, 1993). The mean prolongation of pregnancy is more with magnesium sulphate as compared to isoxsuprine and the difference is statistically significant. In the present study lethargy and nausea were the most frequent adverse effects which occured in 20% and 14% patients respectively in group I. Dry mouth was reported in 8% patient, dizziness and headache were reported by 4% patients each while 2% patient experienced nystagmus or hypotension each. Fetal tachycardia was recorded in 4% patient. These results are similar to several other studies (Hollander *et al.*, 1987; Larmon *et al.*, 1999; Saha, 2002). In the present study fetal tachycardia and hypotension was observed in 18% patients each. Isoxsuprine had to be discontinued in 4% patients due to severe fetal tachycardia and in another 4% patients due to maternal hypotension. Tachycardia and palpitations were observed in 14% patients each while headache and nausea/vomiting were observed in 8% patients each. These results are similar to results of other studies (Singh *et al.*, 1987; Kalita *et al.*, 1998; Sirohiwal *et al.*, 2001). 70% newborns delivered to mother receiving magnesium sulphate as a tocolytic agent had 1 minute apgar score of 8-10 as compared to 65.22% in mothers receiving isoxsuprine. 84% neonates in group I had apgar score of 8 or more as compared to 80.43% patients in group II. This reflects that both magnesium sulphate or isoxsuprine given to mothers had no adverse effects on neonatal outcome. A Cochrane review of five randomized trials done to assess the neuroprotective effects of magnesium sulphate revealed that magnesium sulphate exposure significantly decreases the risk of cerebral palsy (Doyle *et al.*, 2009; Marret *et al.*, 2008).

Conclusion

Our study showed that both magnesium sulphate and isoxsuprine are effective tocolytic agents. Magnesium sulphate produces lesser maternal and fetal side effects like hypotension, palpitation/tachycardia and fetal tachycardia as compared to isoxsuprine.

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