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Original Research Article

Role of magnesium sulphate as a neuroprotective agent on neonatal outcome in preterm deliveries

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ABSTRACT

Background: Globally, prematurity is a leading cause of death in children under the age of five years and in almost all countries with reliable data, preterm birth rates are increasing. This study was conducted to compare the perinatal outcome of preterm deliveries between women receiving $MgSO_4$ and those who were not received $MgSO_4$.
Methods: This randomization study was conducted in department of obstetrics and gynaecology, GSVM Medical College, Kanpur, Uttar Pradesh, India, over a period of one year. After informed consent and ethical clearance from institutional ethics committee, Kanpur, total 100 pregnant women were recruited for this study and were divided into two group of 50 women each. Women in group I were subjected for $MgSO_4$ therapy. Fetal conditions were monitored. These patients were followed up for the next 6 months for outcome.
Results: Overall maternal age ranged from 21 to 32 years. Majority of cases in both the groups were from rural areas and belonged to lower socio-economic status. Majority of women in both the groups were multigravida (68.75%) and (60%) respectively. In both groups, most common risk factors were severe anemia followed by preeclampsia. APGAR score was better in women who received $MgSO_4$, but the difference was found to be statistically significant only for 5 minutes. Although IVH and periventricular leukomalacia rate was higher in group I as compared to that in group II. Although proportion of alive neonates was higher in group I as compared to that in group II yet there was no significant difference between two groups ($p=0.961$). Incidence of respiratory distress, followed by perinatal asphyxia were most common in both the groups but was not found to be significant statistically ($p>0.05$).
Conclusions: Proportion of those with Apgar score <7 at 1 minute, 5 minutes and 10 minutes was higher in group II as compared to group I but the difference was significant statistically only at 5 minutes evaluation.

Keywords: APGAR score, IVH, $MgSO_4$, Preterm, PROM

INTRODUCTION

Globally, prematurity is a leading cause of death in children under the age of five years and in almost all countries with reliable data, preterm birth rates are increasing.[1] More than three quarters of premature babies can be saved with feasible, cost effective care, such as essential care during child birth and in postnatal period for every mother and baby, provision of antenatal steroid injections, kangaroo mother care and antibiotics to treat newborn infections.[1]

Common causes of preterm labour include multiple pregnancies, infections and chronic conditions such as diabetes and high blood pressure, intrahepatic cholestasis of pregnancy, fetal growth restriction; however, often no cause is identified. There could also be a genetic influence.[1] Better understanding of the causes and

mechanisms will advance the development of solutions to prevent preterm birth.[1]

Impact of preterm birth on growth and development

approximately one third of preterm birth survivors suffer from severe long term neurological disabilities, such as cerebral palsy ,learning disabilities and hearing problem.[2] Two identified patterns of injury appear to underlie the central nervous system are: Intraventricular haemorrhage and white matter injury.

Role of magnesium sulphate as a neuroprotective agent

Kuban et al conducted a study in 1992 designed to test the hypothesis that maternal preeclampsia was associated with reduce risk of intaventricular haemorrhage in the preterm newborn.[3] This was followed by a case control study by Nelson and Gather which suggested that antepartum magnesium treatment may protect early neonates from cerebral palsy.[4]

The most common pathological lesion associated with cerebral palsy in preterm infants is periventricular white matter lesion.[5] N-methyl-D-aspartic acid (NMDA) receptors on oligodendrocytes are thought to be important in the glial injury process. NMDA receptor antagonists are potent neuroprotective agents in several animal models of perinatal brain injury. Magnesium sulphate may reverse the harmful effects of hypoxic/ischemic brain injury by blocking NMDA receptors, acting as a calcium antagonist and reducing calcium influx into the cells.[6,7]

Aim of this study was to compare the perinatal outcome of preterm deliveries between women receiving magnesium sulphate and those who were not received magnesium sulphate and to evaluate the decrease in preterm morbidity.

METHODS

Setting

This randomization study was conducted in department of obstetrics and gynaecology, GSVM Medical College, Kanpur, Uttar Pradesh, India, over a period of one year (September 2017 - October 2018). After informed consent and ethical clearance from institutional ethics committee, Kanpur, total 100 pregnant women were recruited for this study. These 100 patients were divided into two group each having 50 women as a case and control. All the women in both the groups were covered with dexamethasone in order to ensure lung maturity. Women in group I were given magnesium sulphate 4 gm i.v. loading dose slowly over 20 minutes followed by 1 gm/hour infusion for 24 hours or till delivery. Fetal conditions were monitored. Assessment of neonatal wellbeing was with the help of Apgar score at 1 minute, 5 minutes and 10 minutes after delivery and NICU admission. All the neonates underwent cranial USG evaluation. Intraventricular haemorrhage, if any was graded and noted. All the neonates also underwent Moro's reflex, rooting and sucking reflex and neck holding evaluation. These patients were followed up for the next 6 months for outcome.

Inclusion criteria

Pregnant women with preterm labour pains at 28-36 weeks of gestation, with no associated complications were included in this study.

Exclusion criteria

Second stage of labour, already received magnesium sulphate during current pregnancy, allergy to drug, renal failure, hypocalcemia, any contraindication to drug: respiratory rate less than 16 per minute, absent patellar reflex, urine output less than 100 ml during previous 4 hours, neuromuscular disorder were excluded from this study.

Groups recruited in this study after a detailed history, thorough physical examination including obstetric and pelvic examination was done. For routine biochemical and specific examination, the blood samples were obtained within first 24 hours of admission from all patients and were done prior to enrolment. Some special investigation like blood culture, high vaginal swab culture sensitivity and urine routine microscopy and culture sensitivity was done.

Simple t-test and chi square test were used for quantitative and qualitative analysis respectively and analysis of variance was used to estimate the improvement in parameter.

RESULTS

Overall maternal age ranged from 21 to 32 years. Mean maternal age in group I was 25.88±2.26 years whereas the same was 25.36±2.23 years in group II. On evaluating the data statistically, the difference between two groups was not found to be significant (p=0.259). Majority of cases in group 1 (81.25%) as well as in group II (74%) were from rural areas. Majority of cases of group I (56.2%) as well as of group II (52%) belonged to lower socio-economic status. On comparing the two groups statistically, the difference was not found to be significant (p=0.893) (Table 1).

Majority of women in group I (68.75%) and group II (60%) were multigravida. But this difference was not significant statistically (p=0.100). Both groups were comparable regarding gestational age. On evaluating the data statistically, the difference between two groups was not found to be significant statistically (p=0.510) (Table 2).

Table 1: Distribution of cases according to their demographic profile.

Age group	Group I (n=48)		Group II (n=50)		Total (N=98)	
Mean Maternal age (range)	25.88±2.26 (22-32)		25.36±2.23 (21-32)		25.61±2.25 (21-32)	
't'=1.136; p 0.259						
Place of residence	**Group I (n=48)**		**Group II (n=50)**		**Total (N=98)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Rural	39	81.25	37	74	76	77.6
Urban	9	18.75	13	26	22	22.4
χ^2=0.739 (df=1); p 0=0.390						
Socioeconomic class	**Group I (n=48)**		**Group II (n=50)**		**Total (N=98)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Upper	3	6.2	4	8	7	7.1
Middle	18	37.5	20	40	38	38.7
Lower	27	56.2	26	52	53	54.1

χ^2=0.226 (df = 2); p 0.893

Table 2: Distribution of patients in two groups according to obstetric profile.

Variables	Group I (n=48)		Group II (n=50)		Total (N=98)	
	No.	**%**	**No.**	**%**	**No.**	**%**
Gravida						
Primigravida	15	31.3	20	40.0	35	35.7
Multigravia	33	68.75	30	60.0	62	63.26
χ^2=7.788 (df=4); p 0.100						
Gestational age						
28-30 weeks	8	16.7	12	24.0	20	20.40
31-33 weeks	22	45.8	24	48.0	46	46.96
34-36 weeks	18	37.5	14	28.0	32	32.65

χ^2=1.35 (df =2); p 0.510

APGAR score was better in women who received, magnesium sulphate as compared to women who have not received magnesium sulphate. But on comparing the data statistically, the difference was found to be significant only for 5 minutes after birth evaluation (Table 3).

Table 3: Comparison between two groups for APGAR score <7 at 1 minute, 5 minutes and 10 minutes after birth.

APGAR score	Group I (n=48)		Group II (n=50)		P valve (Fisher exact test)
	No.	**%**	**No.**	**%**	
At 1 minute	17	35.4	27	54.0	0.072
At 5 minutes	14	29.2	25	50.0	0.041
At 10 minutes	10	20.8	19	38.0	0.078

Cranial USG could be performed in 45 cases each of both groups. Although IVH and periventricular leukomalacia rate was higher in group I as compared to that in group II yet this difference was not significant statistically (p>0.05) (Table 4).

Maximum proportion of babies had incomplete reflex followed by those not showing reflex. On comparing the data statistically, this difference was not found to be significant (p=0.510) (Figure 1).

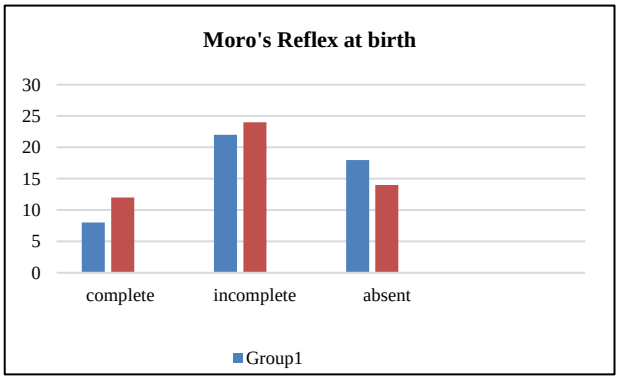

Figure 1: Comparison of Moro's reflex at birth in preterm deliveries between two groups.

Similarly at six months, on comparing the data statistically, this difference was not found to be significant (p=0.684) (Figure 2).

Although proportion was higher in group I as compared to that in group II yet this difference was not significant statistically (p=0.076) (Figure 3).

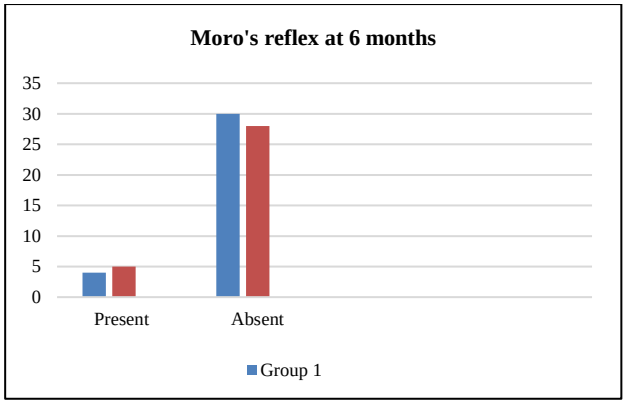

Figure 2 Comparison of Moro's reflex of babies between two groups at 6 months.

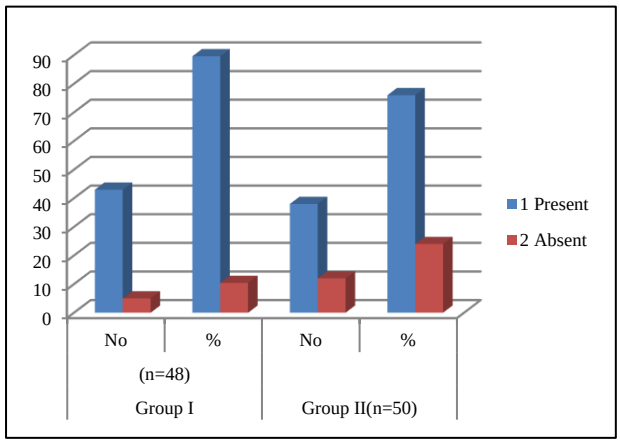

Figure 3: Comparison of rooting and sucking reflexes at birth of preterm deliveries between two groups.
$\chi 2 = 3.15$ (df = 1); p 0.076(NS).

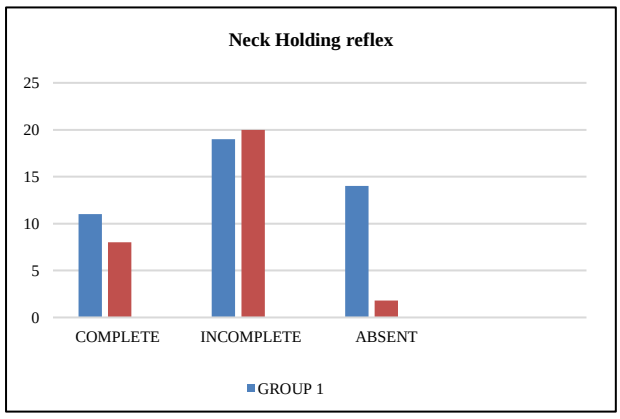

Figure 4: Comparison of neck holding reflex at 4 months in neonates born before term between two groups.

Though the proportion of those with complete response was higher in group I as compared to that in group II and proportion of those with absent or no response was lower in group I as compared to that in group II yet this difference was not significant statistically (p=0.742) (Figure 4).

Table 4: Cranial USG findings at birth.

Findings	Group I		Group II		Statistical significance	
	No.	%	No.	%	χ^2	P
IVH	3	6.66	6	13.3	1.11	0.292
Grade I or II	2	4.44	4	8.88	0.599	0.439
Grade III or IV	1	2.22	2	4.44	1.11	0.292
Periventricular leukomalacia	1	2.22	3	6.66	0.212	0.645

Table 5: Distribution of patients in two groups according to neonatal outcome.

Neonatal outcome	Group I (n=48)		Group II (n=50)	
	No.	%	No.	%
Alive	34	70.8	33	66
Early neonatal death	4	8.3	5	10
Late neonatal death	3	6.2	4	8
Lost to follow up	7	14.7	8	16

Although proportion of alive neonates was higher in group I as compared to that in group II yet there was no significant difference between two groups with respect to neonatal outcome (p=0.961) (Table 5).

At the time of admission in NICU, incidence of respiratory distress, followed by perinatal asphyxia were most common in both the groups. On comparing the data statistically between two groups was not found to be significant statistically (p>0.05) (Table 6).

Table 6: Diagnosis at time of admission in (NICU).

Finding	Group I (n=48)		Group II (n=50)		P value
	No.	%	No.	%	
Respiratory distress	10	20.8	11	22	χ^2=0.020; p=0.888
Perinatal asphyxia	8	16.6	9	18	χ^2=0.030; p=0.862
Neonatal septicemia	7	14.5	8	16	χ^2=0.038; p=0.846
Meconium aspiration Syndrome	4	8.3	5	10	χ^2=0.082; p=0.775

DISCUSSION

Preterm labour resulting into preterm birth is often associated with a number of developmental abnormalities owing to shorter gestational period as well as various perinatal events. Preterm labour is often characterised by a higher risk of neuronal injuries such as intraventricular haemorrhage and paraventricular haemorrhage which

eventually is responsible for different neurological disorders like cerebral palsy or mental retardation.[8]

Mean age of women was 25.61±2.25 years. Similar to our study Rauf et al and Singh et al.[9,10] The present study had most of the women (77.6%) from rural areas and predominantly from lower socioeconomic strata (60.2%) the reason for this could be the fact that the present study was carried out in a state hospital which prioritize the care of lower socioeconomic strata and is a referral centre for all the rural PHCs and CHCs in Kanpur and other adjoining districts. Similar to our study Lipi et al had nearly 60% of women from lower socioeconomic strata.[11] A recent study from Hisar (Haryana) has also showed preterm birth rate to be significantly higher in rural as compared to urban areas.[12] Probably, younger age at marriage, poor nutritional status and lack of proper antenatal care could be the reason for this high prevalence of rural women presenting with preterm labour.

In present study, majority of women were multigravida (64.3%). Similarly, Singh et al and Lipi et al reported majority of their case to be multigravida.[10,11] However, Rauf et al in their study had shown a dominance of primi-para.[9] Thus, in general it suggests that parity cannot be considered as a definite risk factor for preterm labour. In our study, higher prevalence of multigravida women could be attributed to a high prevalence of rural and lower socioeconomic class where the pregnancy rate is higher as compared to urban and higher socioeconomic class where fertility is slowly falling.

In present study, women presenting with preterm labour from 28 to 36 weeks of gestation were enrolled. Maximum number of women presented at gestational age 31-33 weeks (n=46; 46.9%), followed by 34-36 weeks (n=32; 32.7%) and 28-30 weeks (n=20; 20.4%) respectively. Similarly, Lipi et al had maximum number of women with gestational age 31-33 weeks.[11] Thus gestational age variability has shown a considerable variability in different studies and might be responsible for variability in results owing to difference in neurodevelopmental status of the fetus.

In present study, severe anemia (n=38; 38.8%) followed by preeclampsia (n=26; 26.5%), were the major risk factors. Although, there was no statistically significant difference between two groups with respect to risk factors, however, in both the groups with increasing gestational age a decrease in prevalence of risk factors was observed. Statistically, the association between gestational age and risk factors was significant for infections, PROM and APH in group I and for infections and PROM in group II. Singh et al also reported infections and APH among the high risk factors for preterm labour.[10] PROM has often been reported to be strongly associated with presence of infection and a recent Cochrane review that control of infection after antibiotic administration has a limiting role on PROM, thus showing that PROM and infections are somewhat directly associated.[13]

In present study too, we found coexistence of infection and PROM in different cases and thus can conclude that infection initiates PROM which in turn is an imminent reason for preterm labour.

In present study, in both the groups, proportion of babies with Apgar score <7 at 1, 5 and 10 minutes after birth was higher in lower gestational age (28-30 weeks and 31-33 weeks) as compared to higher gestational age (34-36 weeks), however, the association was significant statistically only in group I at 1- and 5-minutes observations. However, at all the time interval (at 1 minute, 5 minutes and 10 minutes) after birth, proportion of those with Agar score <7 was higher in group II as compared to that in group I but the difference was significant statistically only at 5 min evaluation. This finding suggested that magnesium sulphate provided protection against fetal respiratory distress. Similar finding was observed in study of Floyd et al who also observed that proportion of patients with Apgar <7 was lesser in magnesium sulphate as compared to group not receiving magnesium sulphate but receiving nifedipine.[14] Nguyen et al also observed the relative risk of Apgar score <7 at five minutes to be just half (RR=0.51) in magnesium sulphate group as compared to placebo.[8]

Contrary to these findings, Zeng et al in their meta analysis reported the risk of Apgar score <7 at 5 minutes to be higher (RR=1.12) in magnesium sulphate exposed neonates as compared to those who were not exposed to magnesium sulphate.[15] These findings are thus contradictory and warrant further validation in larger studies.

In present study, cranial USG evaluation could be done in 45 cases, proportion of those with IVH and periventricular leukomalacia was higher in controls (13.3% and 6.66%) as compared to that in cases (6.66% and 2.22%) but this was not significant statistically.

In present study, with increasing gestational age, there was a significant increase in proportion of babies showing Moro's reflex at birth in both the groups. These findings in turn indicate that addition of magnesium sulphate did not alter the gestational age-related risk of reflex loss. In fact, Moro's reflex is an imminent measure of neuromotor assessment of neonate and hardly depicts the neurodevelopmental impairment as perceived in preterm labour. At birth evaluation hardly had an impact of magnesium sulphate.

In present study, we found that at birth rooting and sucking reflex was present in significantly higher proportion of cases with gestational age as compared to those with lower gestational age in both the groups. These findings in fact depict that lower gestational age has an impact on the neuromotor coordination as a result of lesser in utero neuronal development of the fetus.

With respect to more contextual outcomes depicting neurodevelopment outcome the present study did not find a significant association between gestational age at birth and outcome of neck holding test at 4 months was observed in either of two groups. There was no significant difference in outcome of neck holding test at 4-month, magnesium sulphate failed to provide a significant impact. A similar result was also obtained for Moro's reflex evaluation at 6 months follow up too.

On evaluating the final outcome no significant difference in final outcome of two groups was observed. However, survival rate slightly higher in cases (70.8%) as compared to that in controls (66%). On evaluating the literature, we did not come across any study reporting a higher survival rate in magnesium sulphate group as compared to placebo group. However, Zeng et al similar to our study found the survival rate to be higher in magnesium sulphate exposed group as compared to unexposed group.[15]

Most of the previous studies conducted to study the neuroprotective role of magnesium sulphate in preterm labour had a longer duration of follow-up at least upto two years and evaluating the outcome in terms of cerebral palsy 23-25.[15] However in present study we had a limitation of six month of follow-up, hence no subsequent assessment was possible to evaluate neuroprotective role of magnesium sulphate in a more cognitive and objective manner.

Despite these limitations, the findings of present study showed a protective impact of magnesium sulphate against respiratory depression as depicted by lower incidence of Apgar <7 at 5 minutes in exposed group as compared to unexposed group. Moreover, cranial USG outcome and other neuromotor outcomes were slightly better in magnesium sulphate exposed group as compared to unexposed group, thus showing a possible neuroprotective effect.

The study also showed a better survival rate in magnesium sulphate exposed group as compared to unexposed group.

CONCLUSION

Proportion of those with Apgar score <7 at all the time intervals (1 minute, 5 minutes and 10 minutes) was higher in group II as compared to group I but the difference was significant statistically only at 5 minutes evaluation.

Cranial USG evaluation was for IVH and periventricular leukomalacia was higher in group II than group I but was not statistically significant.

Survival rate was slightly higher in group I as compared to group II but was not statistically significant.

Study showed that in both the groups, Apgar score at 1 minute and 5 minutes, in cases in which magnesium sulphate given was more than the control group which was statistically significant which reflects the neuroprotective effect of magnesium sulphate treatment in preterm labour.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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