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EFFECT OF MAGNESIUM SULPHATE THERAPY IN TERM NEONATES WITH PERINATAL ASPHYXIA: AN OBSERVATIONAL STUDY

Paediatrics

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ABSTRACT

Background- Perinatal asphyxia is a significant health concern globally, affecting Newborns multiple organ systems, with the brain being particularly vulnerable. Severe perinatal asphyxia can lead to hypoxic-ischemic encephalopathy (HIE), resulting in high mortality and long-term neurodevelopmental disabilities. However, there is a lack of consensus regarding the clinical efficacy of magnesium sulphate in perinatal asphyxia, and limited Indian studies exist on this topic. Therefore, this study aimed to investigate the role of intravenous magnesium sulphate therapy in promoting early recovery and favourable neurological outcomes. **Aim and Objective-** To evaluate the role of giving 3 doses of intravenous magnesium sulphate in asphyxiated term neonates on short term favourable neurological outcome at discharge. **Material And Methods-** This study was conducted at the Neonatal Intensive Care Unit (NICU) of tertiary care hospital with a sample size of 280 neonates, consisting of 140 cases and 140 controls. The cases received three doses of magnesium sulphate (MgSO4), 1st dose within the first 6 hours of life and 2 additional doses repeated after 24 hours and later at 48 hours, while Neonates in both the groups were treated according to routine NICU protocol for birth asphyxia. Vital were monitored continuously. Data analysis was conducted using independent t-tests and chi-square tests, with statistical significance set at $p < 0.05$. **Results-** Significant differences were found in post-intervention serum magnesium levels between cases and controls. Cases in which magnesium level is in therapeutic range, demonstrated better neurological outcomes at discharge (cases: 69.6%, controls: 51.5%, $p < 0.001$) and also study group neonates shows early control of seizure (1.76 ± 0.69 days vs. 2.69 ± 0.67 days, $p < 0.001$) and earlier establishment of feeding (1.69 ± 0.71 days vs. 2.56 ± 1.13 days, $p < 0.001$) as compare to comparison group which was also statistically significant. **Conclusion-** The results indicate administration of magnesium sulphate improves short-term neurological outcomes, including early initiation of breast feeding, seizure control, cranial ultrasonography findings and shorter duration of hospitalisation.

KEYWORDS

Perinatal Asphyxia, Magnesium sulphate, Favourable, Neurological

INTRODUCTION-

Perinatal asphyxia is a multisystem disorder caused by impaired gas exchange during labor, resulting in fetal acidosis, hypoxemia, and hypercarbia.[1] The incidence of perinatal asphyxia in the developed world ranges from 1% to 1.5% of live births.[2] However, in developing nations, the incidence is comparatively higher. In India, studies conducted in 16 medical institutes reported an incidence of 5% according to the National Neonatal Perinatal Database.[3] Perinatal asphyxia can adversely affect almost all organs of newborn babies, with the brain and kidneys being the most commonly affected.[1] Severe perinatal asphyxia is associated with hypoxic-ischemic encephalopathy (HIE), which occurs in 50% to 60% of cases.[4] Moderate to severe HIE causes significant morbidity, mortality, and permanent neurodevelopmental disabilities among survivors.[5] Among patients with moderate HIE, 10% to 20% die and 30% to 40% develop neurological deficits. In contrast, 50% of patients with severe HIE die, and almost all survivors develop neurological deficits.[6] Neurologic abnormalities at discharge is a strong predictor of long-term neurodevelopmental delay.[7] Studies, mainly using animal models, have identified two phases of hypoxic-ischemic brain injury characterized by energy depletion.

The primary neuronal injury occurs during asphyxia and can be mitigated by resuscitative measures. However, the secondary neuronal injury continues for hours to days, even after the asphyxial event has been resolved. Excitotoxicity, particularly excessive release and reduced uptake of glutamate in the newborn brain, plays a significant role in this phase of neuronal death.[8] Glutamate acts on the N-Methyl-D-aspartate (NMDA) receptor, resulting in excessive calcium influx into neurons and inducing irreversible neuronal injury[9]. Magnesium, a naturally occurring NMDA receptor antagonist, has been proposed for clinical use to combat glutamate excitotoxicity and brain damage.[10-12] Many animal experiments have demonstrated the role of magnesium in preventing post-asphyxial injury. They found that magnesium sulphate (MgSO4) attenuates neural membrane dysfunction by preventing hypoxia-induced modification of the NMDA receptors, suggesting its potential neuroprotective effects during hypoxia [13,14]. In view of conflicting results regarding the role of magnesium in perinatal asphyxia and the scarcity of Indian studies, the present study was designed to determine the role of intravenous magnesium sulphate therapy in promoting early recovery and favourable neurological outcomes at discharge for asphyxiated term neonates.

AIM AND OBJECTIVES-

To evaluate the role of giving 3 doses of intravenous magnesium sulphate in asphyxiated term neonates on short term favourable neurological outcome at discharge.

MATERIAL METHODS-

This study was conducted at the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics and Neonatology, Nehru Hospital, BRD Medical College, Gorakhpur, Uttar Pradesh, India. It spanned a year, from October 2020 to September 2021, and focused on birth asphyxia in neonates admitted to the NICU. Ethical approval was obtained from the Institutional Ethical Committee, and written informed consent was obtained from the parents. The sample size for the study was determined using the formula N = 4pq/L^2, where N represents the required sample size, p is the estimated prevalence of birth asphyxia (21% based on prevalence in India in the year 2017 [15]), q is 100-p, and L is the margin error set at 5% (standard value of 0.05). The calculated sample size was initially determined as 315, but due to a decrease in admission rates during the COVID-19 pandemic and completion of the study period, the total sample size was reduced to 280. The case group (140) included neonates born at or beyond 37 weeks of gestation, with perinatal asphyxia as defined by National Neonatal and perinatal database, which is APGAR score of less than 7 at 1 min of age and admission to the NICU within 6 hours of life. The control group (140) had similar characteristics but were admitted after 6 hours of life. Exclusion criteria for the study included preterm, small for gestational age, or large for gestational age Newborns, as well as

those with admission beyond 6 hours of life. Neonates whose mothers received CNS-depressant drugs like pethidine, phenobarbitone etc., had gross congenital malformations or intracranial bleeds, showed evidence of intrauterine infections, had documented bradycardia during MgSO4 infusion, or had serum magnesium levels exceeding the therapeutic range at admission were also excluded.

As soon as the baby is admitted in NICU, consent was obtained from the attendants prior to enrolment, and relevant data, including baseline maternal and neonatal characteristics, were recorded using preformed proforma. Neonates in both the groups were treated according to routine NICU protocol for birth asphyxia. The examination findings including vitals and detailed anthropometry were recorded and a complete neurological examination were done. Cases received intervention involving three doses of magnesium sulphate (MgSO4) within the first 6 hours of life, with subsequent doses given at 24 and 48 hours of 1st dose. The intervention involved the administration of diluted MgSO4 via infusion pump at a rate of 250 mg/kg/dose over one hour, aiming for a target magnesium concentration of 1.2-2.5 mmol/L within the first 72 hours of life. The dosage schedule was in accordance with the recommendations made by M. Levene. The procedure was conducted under the supervision of a neonatologist, following safety guidelines and manufacturer specifications for MgSO4 administration. Clinical assessments included assessments of neurologic status monitored daily, the grade of Hypoxic ischemic encephalopathy, the type of respiratory support, the presence of seizure, the time to control the seizure, the antiepileptic use, the time for establishment of direct breast feeding, and neurologic examination at discharge. Baseline serum magnesium was measured soon after admission and three more serum magnesium levels were measured at 24 hours, 48 hours and at 72 hours in both the groups. Data was collected in Microsoft Excel (version 2016). Quantitative variables were analysed using independent t-tests, and qualitative data was analysed using chi-square tests. Statistical significance was set at $p < 0.05$. Data analysis was conducted using SPSS software (version 2.1).

RESULTS-

There were no significant differences were found between the cases (N=140) and controls (N=140) in terms of maternal age ($p = 0.755$), parity ($p = 0.497$), mode of delivery ($p = 0.633$), and place of delivery ($p = 0.127$). The mean maternal age was similar between the groups (cases: 25.73 ± 3.83 years, controls: 25.99 ± 4.36 years). The distribution of parity showed comparable percentages of Primigravida (cases: 50.7%, controls: 53.6%), multigravida (cases: 47.9%, controls: 46.4%), and grand multipara (cases: 1.4%, controls: 0.0%). Vaginal deliveries were observed in approximately half of the cases and controls (cases: 51.4%, controls: 48.6%), while the rest underwent caesarean sections (cases: 48.6%, controls: 51.4%). The majority of cases delivered in government hospitals (71.4%), with fewer cases in private hospitals (28.6%), compared to controls (62.9% government hospitals, 37.1% private hospitals). The occurrence of risk factors did not differ significantly between the groups, except for a higher incidence of premature rupture of membranes in cases (3.6%) compared to controls (0%) [Table-1]. Regarding neonatal parameters, no significant differences were observed between the cases and controls. The mean gestational age was similar (cases: 39.19 ± 1.39 weeks, controls: 39.44 ± 1.32 weeks), as was the birth weight (cases: 3.28 ± 0.29 kg, controls: 3.29 ± 0.26 kg). The gender distribution showed similar percentages of males and females in both groups (cases: 54.3% males, 45.7% females; controls: 57.1% males, 42.9% females). The distribution of HIE grades (grade 1, grade 2, and grade 3) was comparable between the cases and controls [Table -2]. Majority of neonates were in hypoxic ischemic encephalopathy (HIE) stage 2 in both groups. Hence, the baseline data in both the groups were comparable with each other. The pre-interventional mean magnesium levels were similar between the groups, with the case group showing a mean of 0.86 ± 0.10 mg/dL and the control group showing a mean of 0.85 ± 0.10 mg/dL ($p = 0.591$). The median magnesium levels were 0.90 (interquartile range: 0.80-1) in the case group and 0.85 (interquartile range: 0.75-0.94) in the control group. The range of magnesium levels in both groups varied from 0.78 to 1.2 mg/dL [Table-3].

Significant differences were observed in post-intervention serum magnesium levels between the cases and controls. The cases had higher mean serum magnesium levels at 24 hours (cases: 1.74 ± 0.30 mg/dL, controls: 0.85 ± 0.10 mg/dL, $p < 0.001$), 48 hours (cases: 2.07 ± 0.29 mg/dL, controls: 0.86 ± 0.14 mg/dL, $p < 0.001$), and 72 hours (cases: 2.36 ± 0.36 mg/dL, controls: 1.00 ± 0.30 mg/dL, $p < 0.001$) which was in the therapeutic and neuroprotective range. No adverse effects related to elevated levels of magnesium were noted in any of the neonates. In terms of post-interventional outcome, the cases had significantly earlier start of feeding (1.69 ± 0.71 days vs. 2.56 ± 1.13 days, $p < 0.001$), control of seizures (1.76 ± 0.69 days vs. 2.69 ± 0.67 days, $p < 0.001$), and direct breastfeeding (2.74 ± 1.28 days vs. 4.45 ± 1.67 days, $p < 0.001$) compared to the controls. Regarding neurological status at discharge and on fallow up one week later, the cases demonstrated better neurological finding compared to the controls. A higher percentage of cases exhibited normal suck and direct breastfeeding (cases: 69.6%, controls: 51.5%, $p < 0.001$). Similarly, a higher percentage of cases had neurologically clinically normal status (cases: 69.6%, controls: 51.5%, $p < 0.001$) and normal neuromotor tone (cases: 68.2%, controls: 53.0%, $p < 0.001$). The duration of hospital stay was also significantly shorter in the cases (6.10 ± 1.28 days vs. 9.69 ± 2.32 days, $p < 0.001$). Additionally, the cases had a higher percentage of normal cranial ultrasonography findings on the 14th day of life (cases: 67.4%, controls: 50.0%, $p < 0.001$). [Table-4, Figure-1]

There were no significant differences in the incidence of other complications between the cases and controls, including hypoxic-ischemic encephalopathy (87.9% vs. 82.9%, $p = 0.624$), disseminated intravascular coagulation (7.9% vs. 9.3%), acute kidney injury (2.9% vs. 5.7%), and the combination of acute kidney injury and disseminated intravascular coagulation (1.4% vs. 2.1%) [Table-6].

DISCUSSION-

The presented study aimed to investigate the effects of postnatal magnesium sulfate administration and short term neurological outcomes in neonates with perinatal asphyxia. The results indicate that there were no significant differences between the cases (treatment group) and controls (placebo group) in terms of maternal characteristics, neonatal parameters, and pre-interventional serum magnesium levels. However, significant differences were observed in post-interventional serum magnesium levels, with the cases showing higher magnesium levels at 24, 48, and 72 hours after the intervention. Based on the pharmacokinetics and estimates of plasma half-life of magnesium sulphate as reported by Levene M et al, this dosage regimen will ensure plasma concentration of magnesium in the neuroprotective range for 72 hours. In the present study all the physiologic variables like heart rate, respiratory rate, BP and oxygen saturation remained unchanged before and after intervention between two groups. Hence, no adverse effects of Magnesium were noted in this study. The study findings also highlight the positive impact of magnesium sulfate administration on neurological outcomes. Neonates in the cases group exhibited better neurological outcomes at discharge compared to the controls. This was evident from a higher percentage of cases demonstrating normal suck and direct breastfeeding, normal neuromotor tone on discharge and on fallow up one week after discharge with normal cranial ultrasonography findings on the 14th day of life. Additionally, the cases group had significantly earlier start of feeding, control of seizures, and direct breastfeeding, leading to a shorter duration of hospital stay.

These results are consistent with previous research studies that have explored the neuroprotective effects of magnesium sulfate in neonates with hypoxic-ischemic encephalopathy (HIE) or perinatal asphyxia. For instance, **Mami AG et al.,**[16] demonstrated that magnesium sulfate administration to newborn piglets subjected to severe hypoxia prevents hypoxia-induced modification of neuronal nuclear membrane function, leading to intranuclear calcium-dependent transcription of apoptotic proteins and hypoxic neuronal programmed cell death. Other studies, such as **Cetinkaya M et al.,**[17] and Geetha **Gathwala et al.,**[10] showed that magnesium sulfate administration in neonatal rat and term neonate models with hypoxic-ischemic insult significantly reduced brain infarct volume and limited neuronal injury. However, some studies, like **Greenwood K et al.,**[18] and **Penrice J et al.,**[19] did not find beneficial effects following magnesium sulfate administration in newborn piglets subjected to hypoxic-ischemic insult. Several randomized controlled trials have also supported the neuroprotective effects of magnesium sulfate in neonates with HIE. **Ichiba et al.,**[20] found that intravenous magnesium sulfate in term neonates with moderate to severe asphyxial encephalopathy resulted in short-term neurological benefit, improved survival with normal cranial computed tomography and electroencephalography results, and establishment of oral feeding by 14 days of age. **Bhat MA et al.,**[4] conducted a double-

blind randomized controlled trial and showed that postnatal magnesium sulfate infusion within six hours of life in term neonates with severe perinatal asphyxia improved short-term neurological outcomes, including reduced neurologic abnormalities at discharge. While some studies, like **Savitha M.R. et al.,**[21] **Nadeem Iqbal et al.,**[22] **and Prakash R et al.,**[23] found beneficial effects of magnesium sulfate treatment on seizure control, early initiation of feeding, and improved short-term outcomes, others, such as **IR Okonkwo et al.,**[24] and **B Sreenivasa et al.,**[25] reported significant reductions in mortality and improved survival rates but did not find significant differences in other outcomes. In our study significantly less number of neonates had neurological abnormalities at discharge in study group and majority of babies in intervention group could establish normal suck and feeding at discharge, it may be because of we had more number of neonates in HIE stage 1 and HIE stage 2 in both the groups.

Some limitations in the present study were – Umbilical cord pH and base deficit were not used to either diagnose or quantitate severity of asphyxia, special investigations such as magnetic resonance spectroscopy (MRS) and amplitude integrated electroencephalography were not done. Therapeutic induced hypothermia which is major therapeutic intervention of asphyxiated neonates, also not available at our institute. Also long term follow up to assess future neurologic sequelae is another limitation.

CONCLUSION

The present study provides additional evidence supporting the use of postnatal magnesium sulphate infusion in term neonates with perinatal asphyxia. The findings demonstrate that magnesium sulphate administration significantly increases serum magnesium levels and improves short-term neurologic outcomes, including early initiation of feeding, early seizure control, favourable neurologic examination and normal cranial ultrasonography findings. These results are consistent with previous studies, highlighting the potential neuroprotective effects of magnesium sulphate in this population. Further research is warranted to clarify the long-term effects and optimal administration protocols of magnesium sulphate in neonates with perinatal asphyxia.

Conflict Of Interest: None

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Table -1- Baseline Distribution Of Maternal Characteristics In Cases And Controls

Parameters	Cases (N=140)	Controls (N=140)	P-value
Maternal Age (Years)*	25.73 ± 3.83	25.99 ± 4.36	0.755
Parity#			
Primigravida	71 (50.7%)	75 (53.6%)	0.497
Multigravida	67 (47.9%)	65 (46.4%)	
Grand Multipara	2 (1.4%)	0 (0.0%)	
Mode of Delivery#			
NVD	72 (51.4%)	68 (48.6%)	0.633
LSCS	68 (48.6%)	72 (51.4%)	
Place Of Delivery#			
Government Hospital	100 (71.4%)	88 (62.9%)	0.127
Private Hospital	40 (28.6%)	52 (37.1%)	
Risk Factors			
Prolonged Labour	21 (15.0%)	26 (18.6%)	
APH	9 (6.4%)	13 (9.3%)	
Meconium-Stained Liquor	9 (6.4%)	6 (4.3%)	
Cord Around Neck	6 (4.3%)	8 (5.7%)	
CPD	9 (6.4%)	1 (0.7%)	
Premature Rupture of Membrane	5 (3.6%)	0 (0.0%)	

* Data expressed as mean ± SD (Wilcoxon-Mann-Whitney U Test)
# Data expressed as number (percentage) (Chi-Square Test)

Table 2 - Baseline Distribution Of Neonatal Characteristics In Cases And Controls

Parameters	Cases (N=140)	Controls (N=140)	P-value
Gestational Age (Weeks)*	39.19 ± 1.39	39.44 ± 1.32	0.129
Birth Weight (kg)*	3.28 ± 0.29	3.29 ± 0.26	0.926
Gender#			
Male	76 (54.3%)	80 (57.1%)	0.630
Female	64 (45.7%)	60 (42.9%)	
APGAR (1 Minute)*	2.25 ± 0.62	2.28 ± 0.65	0.330
HIE Grade#			
Grade 1	42 (30.0%)	38 (27.1%)	0.509
Grade 2	85 (60.7%)	83 (59.3%)	
Grade 3	13 (9.3%)	19 (13.6%)	

* Data expressed as mean ± SD (Wilcoxon-Mann-Whitney U Test)
# Data expressed as number (percentage) (Chi-Square Test)

Table 3- Comparison Of The S. Magnesium (mg/dL) (Preintervention level) Between Case And Control Group

S. Magnesium (mg/dL) (Preintervention)	Group		Wilcoxon-Mann-Whitney U Test	
	Case (140)	Control (140)	W	p value
Mean (SD)	0.86 ± 0.10	0.85 ± 0.10	15076.500	0.591
Median (IQR)	0.90 (0.80-1)	0.85 (0.75-0.94)		
Range	0.78 - 1.2	0.7 - 1.2		

Table 4- Comparison Of Post-interventional Neonatal Outcome

Parameters (Post-Intervention)	Cases (N=140)	Controls (N=140)	P-value
S. Magnesium (mg/dL) (24 Hours)*	1.74 ± 0.30	0.85 ± 0.10	<0.001
S. Magnesium (mg/dL) (48 Hours)*	2.07 ± 0.29	0.86 ± 0.14	<0.001
S. Magnesium (mg/dL) (72 Hours)*	2.36 ± 0.36	1.00 ± 0.30	<0.001
Mean duration of recovery (days) ± SD, from neurological normalities	3.16 ± 1.36	4.68 ± 1.30	<0.001
Feeding pattern and Neurological Status at Discharge#			
Normal suck and on direct breast feeding	92 (69.6%)	68 (51.5%)	<0.001
Neurologically clinically normal	92 (69.6%)	68 (51.5%)	
Normal neuromotor tone (Amiel Tison criteria)	90 (68.2%)	70 (53.0%)	
USG Cranium (on 14th day of life) #			
Normal	89 (67.4%)	66 (50.0%)	<0.001
Neonatal Mortality	9 (6.4%)	8 (5.71%)	0.185

* Data expressed as mean ± SD
# Data expressed as number (percentage)
Highly Significant – p<0.001

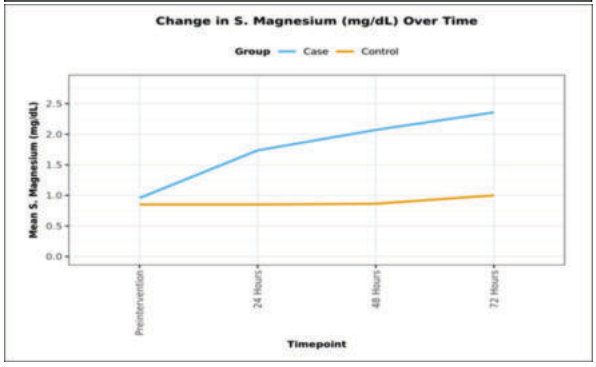

Figure 1- Line diagram depicting the change in S. Magnesium over 72 hours

Table 5- Comparison Of The Case And Control In Terms Of Change In S. Magnesium (mg/dL) Over Time

S. Magnesium (mg/dL)	Group		P value (Wilcoxon-Mann-Whitney Test)
	Case (140)	Control (140)	
	Mean (SD)	Mean (SD)	
Pre-Intervention	0.86 ± 0.10	0.85 ± 0.10	0.591
Post-Intervention			
24 Hours	1.74 ± 0.30	0.85 ± 0.10	<0.001
48 Hours	2.07 ± 0.29	0.86 ± 0.14	<0.001
72 Hours	2.36 ± 0.36	1.00 ± 0.30	<0.001

Table 6- Comparison Of The Case And Control In Terms Of Post-interventional Outcome

Parameters (Post-Intervention)	Cases (N=140)	Controls (N=140)	P-value
Start of Feed (Day)	1.69 ± 0.71	2.56 ± 1.13	<0.001
Control of seizure (Days)	1.76±0.69	2.69±0.67	<0.001
Direct BF (Day)	2.74 ± 1.28	4.45 ± 1.67	<0.001
Duration of Hospital Stay (Days)	6.10 ± 1.28	9.69 ± 2.32	<0.001
Other Complications			
HIE	123 (87.9%)	116 (82.9%)	0.624
DIC	11 (7.9%)	13 (9.3%)	
AKI	4 (2.9%)	8 (5.7%)	
AKI+DIC	2 (1.4%)	3 (2.1%)	

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