ORIGINAL RESEARCH

Intravenous Magnesium Sulphate In Perinatal Asphyxia: An Open Labelled Trial

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ABSTRACT

Background: Perinatal asphyxia is one of the causes of early neonatal deaths. The objective of the study was to determine the effectiveness of intravenous magnesium sulphate infusionfor achieving a good neurological outcome and reducing the mortality and morbidity in term neonates with moderate to severe perinatal asphyxia.

Methods: 108 term neonates with birth asphyxia were assigned randomly in equal numbers to either magnesium sulphate infusion (study group) and control group. Neonates in both the groups were treated according to routine NICU protocol for birth asphyxia. Study group in addition had received magnesium sulphate intravenous infusion at 250 mg/kg/dose (1 ml/kg/dose in 20 ml of 5% dextrose solution) over 1 hour within 6 hours of birth followed by 2 additional doses at 24 hours and 48 hours. Vitals were monitored continuously. Clinical and neurological assessments were done in both the groups till discharge and further assessment were done during the follow-up at 1 month and 3 months of age.

Results: Each group included 54 neonates. More number of neonates in the study group had their seizures controlled by a single anticonvulsant as against the control group. In the study group 89% neonates had seizure control within 2 days as compared to 72% in the control group. There was early initiation of feed among the study group as against comparison group which was statistically significant. In study group, 43 neonates (88%) recovered from abnormal neurological examination as compared to 28 (69%) in control group (p=0.001). Infants on follow-up showed a good neurological outcome with fewer neurological impairment.

Conclusions: Intravenous magnesium sulphate given within 6 hours of life to term neonates with birth asphyxia helps in early control of seizure, early establishment of full enteral feed and fewer chances of neurological abnormalities at discharge and promoting good neurological outcome on follow-up at 3 months of age.

Keywords: Perinatal asphyxia, Magnesium sulphate, Hypoxic Ischaemic Encephalopathy, seizures, neurological outcome

INTRODUCTION

Perinatal asphyxia refers to the medical condition cause by impaired blood flow or gaseous exchange in the fetus leading to fetal acidosis, hypoxemia, and hypercarbia.[1]It is decided by interaction of various maternal, placental, uterine and fetal factorsfrom pregnancy to delivery. Despite the advancements in obstetrical and perinatal care, perinatal asphyxia still has remained as one of the leading causes of neonatal mortality and morbidity. The incidence in developed countries is nearly 1- 8 per 1000 live births while in developing countries, rate of birth asphyxia is several folds higher as estimated nearly 26 per 1000 live births.[2] World Health Organisation has recorded birth asphyxia at an incidence of nearly 900,000 deaths in each year.[3]Perinatal asphyxia affects all major organs like kidneys, heart, lungs and adrenals which is often reversible but the injury to the brain is irreversible leading to the neurological consequence defined by Hypoxic Ischaemic Encephalopathy (HIE). Studies on pathophysiology of HIE has concluded it as a cascade of oxidative stress mediated reaction. There

occurs an immediate primary neuronal injury mediated by necrosis during the hypoxia-ischaemic event which ceases with resuscitation followed by reoxygenation-reperfusion leading to delayed cell death(apoptosis) of neurons. This secondary cell death occurs through different mechanisms from which glutamate mediated excitotoxicity is a predominant mechanism. Glutamate released abundantly from the damaged cellsopen the N-methyl-D-aspartate receptor channels, allowing an excessive influx of calcium and inducing irreversible neuronal injury.[4]Magnesium being the NMDA receptor antagonist gate the channel in a voltage dependent manner and blocking the influx of calcium.[5] But during asphyxia, this gate is overcome due to excess neuronal depolarisation. Thus, on increasing the extracellular concentration of magnesium ions can also restore the block. Magnesium is also known for its antioxidant action. So, magnesium sulphate is being proposed for therapeutic use to curb the brain injury. Antenatal MgSO4 therapy in mothers for eclampsia and preterm labour showed a lower incidence of cerebral palsy and intra-ventricular haemorrhage in the neonates.[6-8] Review of literature regarding studies on postnatal infusion have shown beneficial effects of neuroprotection in some while no effects in others.[9-14] Currently, therapeutic hypothermia has proven to be a definitive treatment and have improved the outcome in asphyxiated neonates. However, a substantial number of infants are still suffering from brain injury, and it is an expensive treatment for resource limited settings.[15-17] Thus, additional neuroprotective strategies are continuously searched for minimizing the secondary neuronal injury. Magnesium sulphate drug being easily accessible, easy implementation and feasible for monitoring in low resource NICU settings can be used on those asphyxiated neonates.Thus, in view of conflicting results about the role of magnesium sulphate and scarcity of evidence of its application in Indian studies, the present study was done to study the role of intravenous magnesium sulphate therapy in terms of better control of seizures, early establishment of full enteral feeds, promoting early recovery, lessening the mortality, and improving favourable neurological outcome at discharge and on follow-upof the asphyxiated term neonates.

METHODS

This was a randomized, open labelled trial conducted over a period of 12 monthsin NICU of the department of Paediatrics at Veer Surendra Sai Institute of Medical Sciences and Research, Burla, India which is a tertiary-care hospital. The sample size was derived from study Savitha MR et al., [events associated with seizures [mean duration of seizures ± SD (days)][12] and the formula used was $n = \frac{\left(z_{1-\left(\frac{\alpha}{2}\right)}+z_{1-\beta}\right)^2\left(\sigma_1^2+\frac{\sigma_2^2}{r}\right)}{(\mu_1-\mu_2)^2}$, where$\alpha$ = 0.05, β = 0.2,μ_1= 1.52, σ_1= 0.653, μ_2= 2.29, σ_2= 1.56 and the minimum sample size for the study was estimated to be 108 term neonates (54 in study group and 54 in control arm). Neonates were enrolled after obtaining informed consent from parents and the study was approved by the institution ethical committee. The inclusion criteria for the study wereterm neonates born between gestational age of 37weeks 0days to 41weeks 6days as calculated from declared expected delivery date, delivered intramural or extramural and presented to the study setting within 6 hours of life, and had moderate or severe HIE. Moderate HIE was diagnosed for these neonates when more than one sign was present in 3 of the following 6 categories as lethargy, hypotonia, hyperactive tendon reflexes, weak moro reflex and seizures. Severe HIE was diagnosed when more than one sign was present in 3 of the following 6 categories as stuporous or coma, flaccid tone, absent tendon reflex and absentmoro reflex, decerebrate posture. The neonates born with severe life-threatening congenital malformations involving brain, lung kidney or heart, syndromes, inborn error of metabolism, affected by other known case of seizure like hypoglycaemia, hypocalcaemia, early onset neonatal sepsis, had received previous dose of calcium and/or magnesium after birth before presenting to triage of NICU and whose mother had received previous antenatal dose of magnesium sulphate for eclampsia prior to delivery were excluded from the study. The neonates as soon as admitted to neonatal intensive care unit screen the inclusion criteria were enrolled and a duly designed case report proforma was filled containing the information of both the neonates and his/her mother including registration number, gender, gestational age, history of antenatal risk factors like age of mother, PIH, bleeding, infection, systemic disease, diabetes mellitus, intrapartum risk factors like history of fever, history of mode of delivery, history of prolonged labor, prolonged/ premature rupture of membrane, Apgar score of neonates and SARNAT and SARNAT staging of encephalopathy at the time of admission.The parameters including vitals, anthropometry, and complete neurological and other systemic examination were done after enrolment. The selected neonates were assigned randomly with computer generated numbers to study arm and control arm. Infants in both the groups were kept on open-care beds with temperature set in servo-controlled mode at 36.5°C with strict monitoring of vitals in form of heart rate, respiration rate, blood pressure and oxygen saturation. All the neonates were treated by the routine protocols of NICU for birth asphyxia. On day 1 of life, 10% dextrose solution was administered as the maintenance intravenous fluid; electrolytes were added from day 3 of life. The supportive treatment with anticonvulsants, empirical antibiotics and respiratory and vasopressor support were given to every neonate. The study group (case group) in addition had received intravenous magnesium sulphate infusion250mg/kg/dose (1ml/kg/dose diluted in 20ml of 5% dextrose solution) over 1 hour within 6

hours of life followed by 2 additional doses are repeated after 24 hours and later at 48 hours followed by monitoring of vitals and treatment according to the clinical condition of the patient. The control group would receive no such placebo drug. Full maintenance fluids were administered initially, and fluid restriction were done if SIADH was detected. Routine investigations including blood sugar, complete blood count, serum electrolytes and renal function tests were done with further repetition of lab tests were done as on required basis. Respiratory support in form of oxygen therapy or ventilation and circulatory support with inotropes were provided as and when needed. During the initial 72 hours of life, vitals were monitored continuously. The clinical assessments done wereneurological status at admission, during hospital stay, at discharge and on follow-up, grade of HIE (moderate or severe) and its progression, type of respiratory support and vasopressor support, complications related to HIE and other factors like sepsis, presence of seizure and time till control of seizure, time till establishment of full enteral feeds. The metabolic parameters assessed were complete blood count, serum electrolytes, renal function test, liver function test, neuroimaging by MRI at discharge and follow up after three months and electroencephalography at one month. All the statistical analysis (Fischer's exact test, chi square, independent samples t test) were done using n Master Version 2.0 software and SPSS v 26 software. The p value <0.05 was taken statistically significant.

RESULTS

A total of 178 babies eligible for the study were screened over 12 months from which 42 neonates were excluded (33 neonates had exclusion criteria and 9 dropped out from the study). 132 neonates who fulfilled the inclusion criteria were enrolled in the study. 62 neonates were assigned randomly to control group and 62 to the magnesium group (study group). After randomization, 8 neonates subsequently dropped out of study. Finally 54 neonates in study arm and 54 neonates in control arm were assigned. The baseline data of the groups before intervention is shown in table 1. There were no significant differences noted in maternal age, parity, place and mode of delivery, gender, gestational age, birth weight and Apgar score between the treatment group and placebo group. The studies showed most of the mothers were primiparas in both groups. Meconium stained amniotic fluid was found to be the most common risk factor associated with HIE followed by prolonged labor. Others included the factors like cord around the neck, antepartum haemorrhage, diabetes mellitus, malpresentation and pregnancy induced hypertension.Majority of neonates in both groups were delivered by normal vaginal delivery and were appropriate for gestational age and were diagnosed as hypoxic ischaemic encephalopathy stage 2 at admission. All the physiological variables (heart rate, respiratory rate, oxygen saturation and mean arterial pressure) and laboratory parameters recorded at admission were also similar in both groups with statistically non-significant p-values.

Table 1: Baseline Clinical Characteristics in neonates of study group and control group

	Study group [n=54]	Control group [n=54]	p value
1. Mean age of mother, in years	25.62	26.22	0.523
2. Primipara	45 (83.3%)	42 (77.8%)	0.627
3. Mode of delivery			0.714
a. normal vaginal delivery	43 (79.6%)	40 (74%)	
b. caesarean section	8 (14.8%)	9 (16.7%)	
c. assisted vaginal delivery	3 (5.6%)	5 (9.2%)	
4. Antenatal risk factors			
a. Meconium-stained amniotic fluid	29 (53.7%)	34 (62.9%)	0.497
b. Prolonged labor	15 (27.8%)	10 (18.5%)	
c. Others	10 (18.5%)	10 (18.5%)	
5. Male: female	1.7:1	2.1:1	0.420
6. Weight, in grams, mean±SD	2752.59±414.57	3056.48±130	0.48
7. Gestational age, in weeks, mean±SD	38.8±1.37	39.13±1.28	0.338
8. Grades of HIE			0.222
a. HIE stage 2	44 (82%)	39 (72%)	
b. HIE stage 3	10 (18.5%)	15 (28%)	
9. Vitals on admission, mean±SD			
a. Heart rate per minute	158.68±11.03	158.66±9.70	1
b. Respiratory rate per minute	49.42±3.88	51.31±5.04	0.33
c. Mean arterial pressure, mm hg	51.62±5.78	49.22±5.30	0.28
d. Oxygen saturation, %	97.68±2.22	94.96±2.62	0.322
10. Serum calcium, mean ± SD, mmol/L	1.08±0.12	1.07±0.10	0.676
11. Serum creatinine, mean ± SD, mg/dl	0.71±0.22	0.66±0.21	0.25
12. Random blood sugar, mean ± SD, mg/dl	122.4±29.8	129.3±36	0.278

The clinical characteristics of the neonates during hospital course and the outcome at discharge, after one 1 month and 3 months were mentioned in table no 2.There were no significant fluctuations of vitals were noted in both the groups in 72 hours during which 3 doses of magnesium sulphate were administered to the treatment(study) group. The common complications related to HIE developed in neonates during the hospital stay were vasopressor responding orrefractory shock, apnoea or irregular respiration requiring mechanical ventilation, oliguria leading to acute kidney injury (AKI), myocardial depression leading to PPHN, thrombocytopenia and DIC. The result between two groups were statistical insignificant but complications occurred less in the study arm in compared to the control arm. The post-interventional parameters showed favourable outcomes in the study group treated with magnesium. In the study group, a greater number of neonates had seizure control with one anti-epileptic drug and mean duration of seizure controlled in study group and control group were1.76 ± 0.689 days and 4.56 ± 1.37 days respectively (p = 0.001). There was early establishment of full enteral feed by day 3 in study group against control group (p = 0.001). The mean duration of recovery from neurological abnormalities was earlier in magnesium treated group (p = 0.001). The intervention group had lower mortality as compared to the control group (six deaths versus thirteen deaths) but was not statistically significant (p = 0.07). The combined outcome including both death and disability was 11(20.3%), less in the intervention group as compared to the 26(48.1%) in the placebo group suggesting an improved beneficial outcome of magnesium in term neonates with moderate to severe HIE. The mean age of discharge in the magnesium group which is significantly lower (p value= 0.03) than the age of discharge in the control group. The discharge status showed a greater number of neonates were discharged with normal suck and on direct breast feed in the interventional groupthan the control group (p=0.024) and a normal neuromotor tone in magnesium treated neonates (p= 0.017) which notes a more significant association of magnesium in early recovery of HIE neonates. Similarly, a greater number of neonates in the magnesium treated group (87.5%) had normal neuroimaging in MRI brain scan than the control group (65.3%) with a p value of 0.02.The infants on follow up at one month of age and at three months ofage showed an improved neurological outcome in magnesium treated neonates than the control group.

Table 2: Post-intervention outcomes of neonates in study group and control group

	Study group [n=54]	Control group [n=54]	p value
1. Clinical outcome of seizures			
a. Seizure present	37(68.5%)	44(81.4%)	0.181
b. Mean duration of seizure ± SD, days	1.766±0.689	4.56 ± 1.37	0.001
c. Seizure controlled within 2 days	33 (89.1%)	32 (72.7%)	0.06
2.Mean duration of recovery from neurological abnormalities ± SD, days	2.9±0.309	4.331±0.580	0.001
3. Time required for full enteral feed			
a. mean duration till OGTF ± SD, days	3.135±0.601	5.250±0.893	0.001
b. mean duration till DBF ± SD, days	4.61±1.350	5.34±3.07	0.02
4. Time till discharge, mean ± SD, days	4.83±1.6	5.98±3.47	0.03
5. Primary Outcome			
a. Death	6 (11%)	13(24%)	0.07
b. Discharge	48(89%)	41(75%)	0.07
6. Neurological outcome at discharge			
a. Normal suck and on direct breast feeding	44(91.6%)	30(73.1%)	0.024
b. Normal neuromotor tone	43(89.5%)	28(68.2%)	0.017
c. Normal neuro imaging on MRI	42 (87.5%)	27(65.6%)	0.021
7. Neurological outcome at 1 month of age			
a. Normal neurological examination	40 (83%)	29 (70%)	0.204
b. Normal EEG	38 (79%)	30 (73%)	0.302
8.Neurological outcome at 3 months of age			
a. Normal neurological examination	38 (79.1%)	30 (73.1%)	0.061
b. Seizures absent	38 (79.1%)	30 (73.1%)	0.618
c. Normal MRI brain	37 (77%)	30 (73.1%)	0.806

DISCUSSION

Perinatal asphyxia defined by deprivation of oxygen around the time of birth, is one of the most predominant problems present globally. With the main purpose of improving quality of life for infants exposed to perinatal asphyxia and HIE, thistherapeuticintervention was tried in this trial. Many previous studies had concluded magnesium sulphate is neuroprotective because magnesium ions gate the NMDA receptor and prevent the neuronal

influx of calcium. This channel is voltage gated and thereby increasing extracellular magnesium concentration would restore the block.[5,6] There were no significant differences recorded in the initial demographic parameters of both the groups. We had used 3 doses of magnesium sulphate (250mg/kg per dose)infusion at 24 hours apart to maintain the plasma concentration in the neuroprotective range at 2.4-5 mEq/L as mentioned in the pharmacokinetics study by Levene M et al, because secondary injury can last as long as72 hours.[18] There were no significant changes noted in the vitals following the magnesium infusion. This observation was seenlike other studies. This was due to the neuromuscular blockade and stoppage of respiration noted at a higher dosage range of 400mg/kg/dose.[18] The present study recorded a favourable outcome in terms of early seizure control with decreased mean duration of seizure in days and better control with minimum number of antiepileptic medications. This might be because of magnesium acts as an anticonvulsant on hippocampal seizure, cerebral vasodilation, reduction of calcium influx by gating NMDA receptors and preventing glutamate mediated excitotoxicity injury to brain and most probable anti-inflammatory action by decreasing free radical injury. However, in contrast to our study, Ichiba H et al recorded no clinically significant difference in the events associated with seizures. This conflicting result may be due to small sample size.Our study also inferred on the early initiation of feeding in the magnesium treated neonates with decrease in hospital stay and promoting early discharge with normal neuroimaging in MRI brain and normal neuromotor tone. These findings support the neuroprotective effects of magnesium in improving good short-term outcome of HIE and added evidence to Bhat M A et al and Savitha MR et al study.[11-12]The review analysis by Tagin et al noted an increasing trend of mortality in magnesium treated group but, our study concluded a decrease in the mortality rate in magnesium treated infants in compared to control arm. However, a significant trend was not seen, and it may be attributed to our small sample size and more number infants in HIE stage 2.Our study included the special investigation techniques of MRI brain scan and electroencephalogram to study the progression and sequelae in HIE. The follow-up report on neurological outcome though not statistically significant had shown beneficial effects in terms of good seizure control with minimum anti-epileptics,normal neuromotor tone, normal brain neuroimaging and normal electroencephalogram at one months and 3 months of age in the magnesium treated neonates. This may be due to the small sample size of our study. The limitationsof our study included staging of HIE by clinical markers only without inclusion of umbilical cord pH and base deficit. A multicentric trial with larger sample size and long-term follow-up may yield more conclusive results.

CONCLUSION

Our study concluded that intravenous magnesium sulphate infusion when given within six hours of life had neuroprotective effect in term neonates with moderate to severe birth asphyxia. It is effective in early control of seizure with early full feeding establishment and promoting early discharge with fewer neurological impairment. The adverse effects following the drug infusion were less. Magnesium sulphate though not significant, had reduced the risk of morbidity and neurological handicap among the surviving neonates.

ABBREVIATIONS

DBF Direct breast feeding
DIC Disseminated Intravascular Coagulation
EEG Electroencephalogram
HIE Hypoxic Ischaemic Encephalopathy
MRI Magnetic Resonance Imaging
NICU Neonatal Intensive Care Unit
NMDA N-methyl-D-aspartate
OGTF Orogastric tube feeding
PPHN Persistent pulmonary hypertension of newborn
SIADH Syndrome of Inappropriate Antidiuretic hormone secretion

AUTHORS' CONTRIBUTIONS

SS collected the data, analysed the results of the two intervention groups and wrote the final manuscript. SD participated in patients' clinical assessment in addition to data analysis and interpretation. KPP contributed to the conception of the work and designed the frame of work of the initial draft. SP edited the manuscript with substantial revision.PCP contributed to work and revised the work substantially. All authors read and approved the final manuscript.

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No funds were sponsored for the study.

AVAILABILITY OF DATA AND MATERIALS

All the data supporting the results can be found within the article.

DECLARATIONS

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Research and Ethics Committee (090-2022/I-S-T/76), Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India. Guardians of the eligible neonates signed a duly written consent before participation in the study.

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