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Research Article

Beneficial effect of intravenous magnesium sulphate in term neonates with perinatal asphyxia

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ABSTRACT

Background: The objective of the study was to determine the role of intravenous magnesium sulphate therapy in promoting early recovery and favourable neurological outcome at discharge for asphyxiated term neonates.
Methods: Term neonates with birth asphyxia were assigned randomly, to either magnesium sulphate infusion (Study group) or Comparison group. Neonates in both the groups were treated according to routine NICU protocol for birth asphyxia. Study group in addition 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 with 2 additional doses repeated after 24 hours and later at 48 hours. Vitals were monitored continuously. Clinical assessments including detailed neurological examinations were done in both the groups till their discharge from NICU.
Results: Each group included 60 neonates. More number of neonates in the study group had their seizures controlled by a single anticonvulsant as against the comparison group. In the study group 92% neonates had seizure control within 2 days as compared to 70% in the comparison group which was statistically significant(p=0.048). There was early establishment of feeds amongst the study group as against comparison group which was statistically significant. In study group, 47 neonates (84%) recovered from abnormal neurological examination within 4 days as compared to 26 (53%) in comparison group which was statistically significant (p=0.0001).
Conclusions: Intravenous magnesium sulphate within 6 hours of life to term neonates with birth asphyxia helps in early seizure control, early recovery from abnormal neurological signs, early establishment of feeds and fewer chances of neurological abnormalities at discharge.

Keywords: Magnesium sulphate, Perinatal asphyxia, Neurological abnormalities

INTRODUCTION

Perinatal asphyxia is a major cause of early neonatal death. It refers to the impairment in the exchange of respiratory gases during delivery, and the ensuing adverse effect on the fetus. Perinatal asphyxia is determined by a complex interaction of various maternal, placental, uterine and fetal factors from pregnancy to delivery. In perinatal asphyxia, glutamate, the main excitatory amino acid neurotransmitter, is released in increased concentrations into the extracellular compartment of brain. High concentrations of glutamate open NMDA (N-methyl-D-aspartate) channels, allowing excessive calcium influx into the neurons and inducing irreversible neuronal injury.[1] Magnesium is a naturally occurring NMDA receptor antagonist and thus protecting the developing brain from the damage that is caused by glutamate. Thus magnesium sulphate is proposed for clinical use to combat glutamate excitotoxicity and brain damage.[2-4] Literatures regarding postnatal magnesium therapy after birth asphyxia revealed beneficial effects in some while no beneficial effects in others.[5-9] In view of

conflicting results about the role of magnesium in perinatal asphyxia and paucity of Indian studies, the present study was undertaken to determine the role of intravenous magnesium sulphate therapy in promoting early recovery and favorable neurological outcome at discharge for asphyxiated term neonates.

METHODS

The present study was a comparative study conducted on neonates with perinatal asphyxia delivered at Cheluvamba hospital attached to Mysore Medical College & Research Institute, Mysore, India from November 2011 to February 2012. A minimum sample size calculation of 120 term neonates (60 study group and 60 comparison group) with perinatal asphyxia was done with the incidence of perinatal asphyxia of 2/100 live births at our institution at a 0.05 significance level. The formula used was $n=z^2pq/d^2$ where z=1.96, p=0.02, q=1-p, d=0.05. Neonates were enrolled after informed consent from parents and the study was approved by the institutional ethical committee. The inclusion criteria was term neonates with perinatal asphyxia as defined by National Neonatal and perinatal database, which is APGAR score of less than 7 at 1 minute of age.[10] Neonates with history of maternal magnesium administration prior to delivery and mothers receiving Pethidine, Phenobarbitone which are likely to depress the baby and any obvious external congenital malformations in neonates were excluded from the study.

As soon as the baby is admitted to Neonatal intensive care unit (NICU), the details were entered in a predesigned proforma. This included history regarding antenatal risk factors for perinatal asphyxia like age of mother, history of pregnancy induced hypertension, anemia, bleeding, infection and systemic disease. Intrapartum factors like mode of delivery, history of prolonged rupture of membrane, meconium stained amniotic fluid, malpresentation and cord prolapse was also entered. The examination findings including vitals and detailed anthropometry were recorded and a complete neurological examination and other systemic examination were done. The selected neonates were assigned randomly, with computer generated random numbers, to receive either magnesium sulphate infusion (Study group) or Comparison group by investigator 1. The neonates in both the groups were treated according to the routine NICU protocol for birth asphyxia. Study group in addition 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 with 2 additional doses repeated after 24 hours and later at 48 hours. Vitals were monitored continuously. Clinical assessments were done by investigator number 2 who was blinded for assignment of patients. During the initial 72 hours of life, heart rate, respiratory rate, blood pressure and oxygen saturation were monitored continuously. Clinical assessments included assessments of the neurologic status twice daily during the stay, the grade of Hypoxic ischemic encephalopathy (Stage I, Stage II or Stage III), the type of respiratory support needed, the presence of seizures, involvement of multiorgan dysfunction, the time for establishment of full oral feedings through sucking, and neurologic examination at discharge. Baseline serum magnesium was measured soon after delivery and two more serum magnesium levels were measured at 24 hours and at 48 hours in both the groups. Serum magnesium was measured using magnesium kit provided by CREST biosystems using Calmagite method. All the statistical methods(descriptive statistics, chi square/contingency co-efficient analysis, independent samples t test) were carried out through the SPSS for windows(version 16.0). The p value <0.05 was taken as statistically significant.

RESULTS

A total of 142 neonates were screened of which 22 neonates were excluded (14 neonates had exclusion criteria, 5 parents refused to participate and 3 neonates were discharged against medical advice before completion of intervention). Finally 60 neonates were randomly assigned to study group and 60 neonates to the comparison group. The baseline data of the groups before intervention is shown in Table 1. The male to female ratio was 1:1.5 and 2.15:1 for study group and comparison group respectively (p=0.341). Among study group mean age of mothers was 21.9 years and 73.3% were primiparas and rest multiparas. Amongst the comparison group the mean age of mothers was 21.5 years with 76.7% primiparas and rest multiparas. Meconium stained amniotic fluid was the most common risk factor for birth asphyxia followed by premature rupture of membranes and prolonged labor. Others included cord around the neck, pregnancy induced hypertension and antepartum hemorrhage. Majority of the neonates were delivered by normal vaginal delivery and were appropriate for gestational age. There was no significant difference in the mode of resuscitation in both the groups and most of the neonate's required endotracheal intubation while resuscitation. Majority of children were in hypoxic ischemic encephalopathy (HIE) stage 2 in both the groups. Hence, the baseline data in both the groups were comparable with each other. Post intervention comparison of study group and comparison group is shown in Table 2. Post intervention mean serum magnesium level of study group was more than 2.4 Meq/L which was in the therapeutic and neuroprotective range.[11] No adverse effects related to elevated levels of magnesium were noted in any of the neonates. During hospital stay, study group had better control of seizures. The mean duration of seizures was less in study group as compared to comparison group which was statistically significant. More number of neonates in the study group had their seizures controlled by a single anticonvulsant as against the comparison group. In the study group 92% neonates had seizure control within 2 days as compared to 70% in the comparison group which was statistically significant(p=0.048). There was early establishment of

nasogastric tube feeding (p=0.001), palladai feeding (p=0.0001) and direct breast feeds (p=0.0001) amongst the study group as against comparison group which was statistically significant. In study group, 47 neonates (84%) recovered from abnormal neurological examination within 4 days as compared to 26(53%) in comparison group which was statistically significant (p=0.0001). Normal neuromotor tone was established in 32 neonates in study group as opposed to 22 neonates in comparison group which was statistically significant (p=0.019). The incidence of shock (5 amongst study group and 6 in placebo group), requirement of ventilator support (1 in study and 2 in placebo group), acute kidney injury (6 in study and 12 in placebo group) and mortality (one each in study and placebo group) were not statistically significant.

Table 1: baseline characteristics of the study group and comparison group before intervention.

Baseline characteristics	Study group Number (percentage)	Comparison group Number (percentage)	'P' value
1.Male: Female	1:1.5	2.15:1	0.341
2. Mean age of mothers(years)	21.9	21.5	
3.Primipara	73.3%	76.7%	
4. Mode of delivery			
a. Normal vaginal	40(66.7)	41(68.3)	0.845
b. Cesarean section	11(18.3)	11(18.3)	1.00
c. Assisted vaginal delivery	9 (15.0)	8 (13.3)	0.794
5.Major risk factors			
a. Meconium stained amniotic fluid	27(45)	29(48.3)	0.714
b. Premature rupture of membranes	12(20.0)	15 (25.0)	0.512
c. Prolonged labor	13(21.7)	7 (11.7)	0.142
d. Others(cord around the neck, pregnancy induced hypertension and antepartum hemorrhage)	12(20.0)	10(16.7)	0.637
6.Weight for gestational age			
a. Appropriate for gestational age(AGA)	56(93.3)	58(96.7)	
b. Small for gestational age(SGA)	3 (5.0)	2 (3.3)	0.539
c. Large for gestational age(LGA)	1 (1.7)	0	
7. Physiological variables	Mean±SD	Mean±SD	
a.Non-invasive BP(mm Hg)	45.6±3.22	45.5±2.98	0.860
b. Heart rate(per min)	147±14.57	148±3.21	0.535
c. Respiratory rate(per min)	46±7.89	46±5.92	0.620
d. Oxygen saturation(percentage)	96.6±3.40	97.5±1.82	0.238
8.Methods of resuscitation	Number(percentage)	Number(percentage)	
a. Bag and mask ventilation	21(35.0)	19(31.7)	
b. Endotracheal intubation+ Positive pressure ventilation	38(63.3)	41(68.3)	
c. Endotracheal intubation + Positive pressure ventilation + chest compression	1 (1.7)	0	0.545
9.Sarnat and Sarnat HIE staging			
Mild (HIE stage 1)	24(40.0)	27(45.0)	
Moderate(HIE stage 2)	34(56.7)	32(53.3)	0.752
Severe(HIE stage 3)	2 (3.3)	1 (1.7)	

Table 2: Post intervention characteristics of the study group and the comparison group.

Characteristics	Study group	Comparison group	'P' value
1. **Mean serum magnesium levels (Meq/L)**	Mean±SD	Mean±SD	
a. Preintervention baseline level	1.52±0.3022	1.59±0.1384	0.0648
b. Post intervention at 24 hours	2.63±0.5584	1.58±0.1454	0.0001
c. Post intervention at 72 hours	2.72±0.4948	1.62±0.1338	0.0001
2. **Events associated with seizures**	Number (percentage)	Number (percentage)	
a. Seizures present	25 (69.4)	27 (81.8)	0.233
b. Mean duration of seizures±SD (days)	1.52±0.653	2.29±1.564	0.026
c. Seizure control with only one anticonvulsant	24 (96.0)	20 (74.0)	0.029
d. Seizure control within 2 days	23 (92.0)	19 (70)	0.048
3.Mean duration of recovery (days)±SD, from neurological abnormalities	Mean±SD 3.36±1.12	Mean±SD 4.96±1.54	0.0001
4. **Mean duration for initiation of feeding**			
a. Duration (days) for initiation of nasogastric tube feeding	3.02±0.985	3.9±1.254	0.001
b. Duration (days) for initiation of Palladai feeding	3.5±1.378	5.6±2.019	0.0001
c. Duration (days) for initiation of direct breast feeding	4.6±1.358	6.0±1.511	0.0001
5. **Feeding pattern and neurological findings at discharge**	Number(percentage)	Number(percentage)	
a. Normal suck and on direct breast feeding	32(91.4)	21(65.6)	0.009
b. Neurologically clinically normal	32(91.4)	21(65.6)	0.009
c. Normal neuromotor tone (Amiel Tison criteria)	32(91.4)	22(68.75)	0.019
d. Normal neuroimaging	28(80.0)	20 (62.5)	0.112

DISCUSSION

In the present study, comparisons of baseline parameters were similar in both the groups before intervention. We used a loading dose of 250 mg/kg magnesium, followed by two further infusions of same dose 24 hours apart. 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. The neuroprotective range of serum magnesium is 2.4-5 Meq/L.[11] 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. This was similar to the observation done in many other studies.[5-7,11,12] This is because complete neuromuscular blockade, cessation of respiration and loss of muscle tone was noticed only at 400mg/kg/dose.[11] The favorable outcome related to seizure control might be probably due to following properties of magnesium-its central anticonvulsant effect on hippocampal seizures, cerebral vasodilatory properties, reduction of calcium influx by gating NMDA receptor in brain, antagonizing glutamate excitotoxicity.[1-3] However, in contrast to our study, Ichiba H et al, found no significant difference in the clinical seizures between 2 groups.[5] This conflicting result could be because, they had a smaller sample size. This study adds that neonates in the study group recovered significantly early from abnormal neurological findings. Also, during hospital stay feeding could be started significantly early in study group. These findings support that magnesium has definite neuroprotection in asphyxiated neonates. Other studies have not evaluated the effect of magnesium on early initiation of feeding.

In the present study significantly less number of neonates had neurological abnormalities at discharge in study group. Similar results were obtained in other studies.[5,7] In the present study significantly more babies in study group could establish normal suck and feeding at discharge. Similar results were obtained by Bhat MA et al.[7] Mortality was less in the present study compared to other studies. It may be because of smaller sample size in other studies and also we had more number of neonates in HIE stage 1 in both the groups.[5-7]

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 diffusion weighted imaging (DWI), magnetic resonance spectroscopy (MRS) and amplitude integrated electroencephalography were not done. Also, lack of long

term follow up to assess future neurologic sequelae is another limitation.

CONCLUSION

We conclude that, intravenous magnesium sulphate within 6 hours of postnatal life to term neonates with birth asphyxia helps in early seizure control, early recovery from abnormal neurological signs, early establishment of feeds and fewer chances of neurological abnormalities at discharge.

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

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