Original Research Article

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Effect of postnatal magnesium therapy on neonatal seizure in infants with moderate to severe hypoxic ischemic encephalopathy: a post-hoc subgroup analysis

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ABSTRACT

Background: Magnesium has got both neuroprotective and anticonvulsant effect on developing human brain. A post hoc subgroup analysis was done to determine the effect of magnesium on neonatal seizures in infants with moderate-severe hypoxic ischemic encephalopathy (HIE) who received postnatal magnesium therapy for perinatal asphyxia.

Methods: Term asphyxiated infants were randomly assigned to receive either magnesium sulphate infusion or placebo within 48 hours of life to maintain serum magnesium levels in neuroprotective range. Short term neurological outcome at discharge was evaluated. The post hoc analysis evaluated the effect of magnesium on neonatal seizures in infants with moderate-severe HIE. All statistical analysis was done through SPSS (version 19.0) for windows and p value <0.05 was taken as statistically significant.

Results: Sixty infants were included in magnesium and 60 in placebo group. Both groups were similar in baseline characteristics. Of 36 infants in magnesium group with moderate to severe HIE, 25 (69%) had neonatal seizures vs 27 (82%) of 33 infants in placebo group (p value 0.23). Among those with seizures, seizure control was achieved with single anticonvulsant in 24 infants (96%) in magnesium group vs 20 (74%) in placebo (p value 0.02). Seizures got controlled early in magnesium group compared to placebo, 36.5 hours vs 55 hours (p value 0.02). At discharge, anticonvulsant was required for 2 infants in magnesium group and 3 in placebo group.

Conclusions: Postnatal magnesium therapy as a neuroprotective agent in moderate-severe HIE may decrease the duration of clinical seizures and need for multiple anticonvulsants during the critical period of neuronal damage.

Keywords: Magnesium sulphate, Newborn, Seizure

INTRODUCTION

Glutamate is a potent and rapidly acting excitotoxic neurotransmitter which is accumulated in extracellular space in hypoxic ischemic encephalopathy (HIE) causing neuronal damage. Glutamate activates NMDA (N-methyl D-aspartate) subtype of receptors, opening a membrane channel that is highly permeable to calcium. The NMDA receptor-activated channel may be the major route by which glutamate induces a toxic calcium influx. Magnesium confers neuroprotective effect by

antagonizing NMDA receptors and thus blocking glutamate excitotoxicity in HIE.²

Several animal studies have demonstrated the role of magnesium in controlling hippocampal seizures.³⁻⁵ Studies in term infants have reported conflicting evidences regarding the neuroprotective role of magnesium when given postnatally to infants with HIE.⁶⁻⁸ We reported beneficial short term neuroprotective effect of magnesium sulphate in our randomized controlled trial.⁹ A post hoc subgroup analysis was done to evaluate

the effect of magnesium on neonatal seizures in infants with moderate to severe HIE.

METHODS

The study was a randomized controlled trial conducted in neonates with perinatal asphyxia delivered at the mother and child hospital attached to Mysore Medical College and Research Institute, Mysore, India from November 2011 to February 2012. A minimum sample size calculation of 120 infants 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 and a power of 80%. 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. The study was approved by the Institutional Ethical Committee.

Inclusion criteria

- A sentinel hypoxic event occurring immediately before or during labour
- Failure to initiate breath at birth or APGAR score < 7 at one minute
- Need for resuscitation at birth (positive pressure ventilation or chest compression)
- Early onset of features of hypoxic ischemic encephalopathy
- Exclusion of other etiologies of neonatal encephalopathy.

Excluding criteria

- Preterm infants
- Infants whose mothers received pethidine or phenobarbitone which might cause depression in baby
- Neonates with any obvious external congenital malformations.

All baseline characteristics of infants were entered in a predesigned performa. All 120 newborns were randomly assigned to either magnesium group or placebo group by a computer generated random number sequence. The neonates were treated according to the routine NICU protocol for perinatal asphyxia. Out of 120 infants, sixty infants received magnesium sulfate infusion at 250 mg/kg per dose (1 mL/kg per dose in 20 mL of 5% dextrose solution) over 1 hour within 6 hours of birth, with 2 additional doses repeated at intervals of 24 hours. While, 60 control infants received 3 doses (1 mL/kg per dose) of normal saline solution in 20 mL of 5% dextrose solution, 24 hours apart.

A base line serum magnesium level was measured soon after delivery and two more serum magnesium levels at 24 hour and at 48 hour was measured for both cases and controls. Clinical assessments included the grade of HIE

(mild, moderate and severe), the type of respiratory support needed, the presence of clinical seizures, involvement of multiorgan dysfunction, the time for establishment of full oral feed, and neurologic examination at discharge. Though neuroimaging with cranial ultrasound was performed for infants, MRI and EEG was not done due to resource limitations.

All the statistical methods (descriptive statistics, chi square/contingency coefficient analysis, independent samples t-test) were carried out through the SPSS for windows (version 19.0). 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 magnesium group and 60 neonates to the placebo group.

All baseline characteristic features of both groups were similar including sex, gestation, antenatal risk factors, mode of delivery, birth weight, APGAR score and methods of resuscitation (Table 1).

Twenty four infants in magnesium group (40%) and 27 infants in placebo group (45%) had mild HIE. Maximum number of infants, i.e. 34 infants in magnesium group (56.7%) and 32 infants in placebo group (53.3%), were having moderate HIE. Severe HIE was noted in two infants in magnesium group (3.3%) and one in placebo group (1.7%). Thus, moderate to severe HIE was reported in 36 infants (60%) in magnesium group and 33 infants (55%) in placebo group.

In infants of magnesium group, serum magnesium level increased from the baseline level of 1.52 meq/L to 2.72 meq/L at 48 hours. While in the control group serum magnesium level remained 1.62 meq/L at 48 hour. Based on the pharmacokinetics and estimates of plasma half life of magnesium sulphate as reported by Levene M et al in 1995, the neuroprotective range of serum magnesium is 2.4 - 5 Meq/L. In the present study, the post intervention mean serum magnesium level of study group was more than 2.4 Meq/L (1.2 mmol/L) which is in therapeutic and neuroprotective range. No adverse effects related to elevated levels of magnesium were noted in any of the cases.

Among infants with moderate to severe HIE, 25 infants in magnesium group (69%) and 27 infants in placebo group (82%) had clinical seizures requiring anticonvulsants during NICU stay. Though fewer infants in magnesium group had seizures, it was not statistically significant (p-value 0.23). Among infants who had convulsion, seizure control was achieved with one anticonvulsant

drug in 24 infants in magnesium group (96%) and 20 infants in placebo group (74%). Whereas, 1 infant in magnesium group (4%) and 7 infants in placebo group

(26%) required more than one anticonvulsant for seizure control which was statistically significant (p value=0.02).

Table 1: Characteristics of magnesium and placebo group of infants.

Characteristics	Magnesium group n = 60 no. (%)	Placebo group n = 60 no. (%)	P value
Female	24 (40)	19 (32)	0.34
Primi	44 (73)	46 (77)	0.67
Mode of delivery			
Normal vaginal	40 (67)	41 (68)	0.84
Cesarean	11 (18)	11 (18)	1
Assisted vaginal	9 (15)	8 (13)	0.79
Major risk factors			
Meconium- stained amniotic fluid	27 (45)	29 (48)	0.71
Premature rupture of membranes	12 (20)	15 (25)	0.51
Prolonged labor	13 (22)	7 (12)	0.14
Appropriate for gestation weight	56 (93)	58 (97)	0.54
Methods of resuscitation			
Bag and mask ventilation	21 (35)	19 (32)	
Endotracheal intubation+ Positive pressure Ventilation	38 (63)	41 (68)	0.56
Endotracheal intubation + Positive pressure ventilation + chest compression	1 (1.7)	0	
Sarnat and Sarnat HIE staging			
Mild HIE	24 (40)	27 (45)	0.75
Moderate HIE	34 (56.7)	32 (53.3)	0.73
severe HIE	2 (3.3)	1 (1.7)	

Table 2: Events associated with clinical seizures in infants with moderate and severe hypoxic ischemic encephalopathy.

Events associated with clinical seizures	Magnesium group n =36 no.(%)	Placebo group n = 33 no.(%)	p-value
Seizures	25 (69.4)	27 (81.8)	- 0.23
No seizures	11 (30.6)	6 (18.2)	
Seizure control with one anticonvulsant	24 (96)	20 (74)	0.02
Seizure control with more than one anticonvulsant	1 (4)	7 (26)	
Duration for seizure control (hours) mean±SD	36.5±15	55±37.5	0.02
Seizure control within 2days	23 (92)	19 (70)	0.04
Anticonvulsant need at discharge	2(8)	3(12)	0.63

In the present study seizure control was achieved early among magnesium group as compared to controls (mean 36.5 hours versus 55 hours) which was statistically significant. (p=0.02). Also, more number of babies among magnesium group achieved seizure control in less than 48 hours (p=0.04) compared to controls (92% versus 70%).

When analysis was done at discharge, it was found that 2 infants (8%) in magnesium group versus 3 infants (12%) in placebo group were discharged on anticonvulsants for

seizure control which was not statistically significant (p = 0.63) (Table 2).

DISCUSSION

Magnesium sulphate is widely used in obstetrics as a tocolytic agent for suppression of pregnancy-induced hypertension and to prevent convulsion in preeclampsia for more than 60 years.¹¹

Several observational studies reported that antenatal magnesium sulphate exposure for maternal indication

decreased incidence of cerebral palsy in preterm infants. A Cochrane systematic review (five studies including 6145 infants) investigated whether administration of magnesium sulfate to women at risk of preterm labour conferred neuroprotective advantage to the fetus. Infants exposed to magnesium sulfate were at reduced risk of substantial gross motor dysfunction compared to controls. The risk of cerebral palsy was also significantly reduced in the magnesium sulfate group. ¹²

In the present study 25 infants in magnesium group (69%) and 27 controls (82%) with moderate and severe hypoxic ischemic encephalopathy had clinical seizures during NICU stay. Though fewer infants in magnesium group had seizures, it was not statistically significant (p - value 0.23). This was similar to study done by Ichiba H et al in 2002 and 2006 as there was no statistically significant difference in the incidence of convulsion between cases and controls.^{6,7}

In the present study seizure control was achieved early among cases as compared to controls (mean 36.5 hours versus 55 hours) which were statistically significant. (p = 0.02). Also, more number of babies among magnesium group achieved seizure control in less than 48 hours compared to controls (92% versus 70%) (p = 0.04).

However, in contrast to our study, in the study done by Ichiba H et al in 2002, there was no significant difference evident in the duration of clinical seizures between cases and controls. Rather, cases required more time for seizure control than controls. This conflicting result would have been probably because of their smaller sample size (17 versus 16).⁶

In the present study significantly more number of babies in case group could achieve seizure control with single anti-epileptic drug compared to control group. Of those subjects who had convulsion, seizure control was achieved with one anti-epileptic drug in 24 cases (96%) and 20 controls (74%).

The favorable outcome related to seizure control might be probably due to the following properties of magnesium:

- Its central anticonvulsant effect on hippocampal seizures¹³
- Its cerebral vasodilatory properties 14
- Reduction of calcium influx by gating N-methyl D-aspartate (NMDA) receptor in brain 14
- Neuroprotective effects by antagonizing glutamate exictotoxicity.¹

In the present study 8% infants in magnesium group versus 12% infants in placebo group who had clinical seizures required anticonvulsants for seizure control at discharge which was not statistically significant (p = 0.33). This was similar to study by Bhat MA et al in 2009 in which anticonvulsant at discharge was required for 17% versus 44% which was also not statistically

significant (p = 0.10). Thus, though there was a trend to decreased anticonvulsant need in magnesium group, it was not statistically significant.

Lack of EEG monitoring of seizure activity was a major limitation of our study as many subclinical electrographic seizures could have been missed. In addition it is nearly impossible to accurately identify and clarify subtle unexplained sudden stereotyped neonatal clinical events by visual inspection alone. The main practical barriers for implementation of EEG were the lack of availability of equipment, technical and interpretive personnel.

The analysis found that 69% vs 82% of infants with moderate to severe HIE in magnesium and placebo group respectively had clinical neonatal seizures. Our study was not adequately powered to detect this difference with 120 infants evaluated.

CONCLUSION

This post-hoc analysis concludes that postnatal magnesium therapy as a neuroprotective agent in infants with moderate-severe HIE may decrease the duration of clinical seizures and need for multiple anticonvulsants during the critical period of neuronal damage. Whether this effect has any long lasting benefit in those infants in magnesium group is a subject of further study.

The previous study reported beneficial short term neurological outcome in infants with HIE who were given postnatal magnesium compared to placebo. This effect of magnesium in neonatal seizure might also have contributed to the previous study finding.

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REFERENCES

- 1. Choi DW. The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. Annu Rev Neurosci. 1990;13:171-82.
- Haddad JJ. N-methyl-D-aspartate (NMDA) and the regulation of mitogen-activated protein kinase (MAPK) signaling pathways: A revolving neurochemical axis for therapeutic intervention? Progress Neurobio. 2005;77:252-82.

- 3. Cotton DB, Hallak M, Janusz C, Irtenkauf SM, Berman RF. Central anticonvulsant effects of magnesium sulfate on N-methyl-D-aspartate-induced seizures. Am J Obstet Gynecol. 1993;168(3):974-8.
- 4. Cotton DB, Janusz CA, Berman RF. Anticonvulsant effects of magnesium sulfate on hippocampal seizures: therapeutic implications in preeclampsia-eclampsia. Am J Obstet Gynecol. 1992;166(4):1127-34.
- 5. Standley CA, Irtenkauf SM, Cotton DB. Anticonvulsant effects of magnesium sulfate in hippocampal-kindled rats. J Biomed Sci. 1995;2(1):57-62.
- Ichiba H, Tamai H, Negishi H. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int. 2002;44:505-9.
- 7. Ichiba H, Yokoi T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. Pediatr Int. 2006;48:70-5.
- 8. Bhat MA, Charoo BA, Bhat JI, Mushtaq S. Magnesium sulfate in severe perinatal asphyxia: A randomized placebo-controlled trial. Pediatrics. 2009;123:764-9.

- 9. Savitha MR, Rajprakash. Beneficial effect of intravenous magnesium sulphate in term neonates with perinatal asphyxia. Int J Contemp Pediatr. 2016;3(1):150-4.
- 10. Levene M, Blennow M, Whitelaw A. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. Arch Dis Child Fetal Neonatal. 1995;73:174-7.
- 11. Crowther A, Janet EH, Lex WD. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. J Am Med Asso. 2003;290(20):2669-76.
- 12. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev. 2009;1:CD004661.
- 13. Gathwala G. Neuronal protection with magnesium. Indian J Pediatr. 2001;68(5):417-9.
- 14. Chahal H, Dsouza SW, Barson AJ. Modulation by magnesium of N-methyl-D-aspartate receptors in developing human brain. Arch Dis Child Fetal Neonatal. 1998;78:116-20.

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