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Original Article

Effect of Postnatal Magnesium Sulfate Infusion on Neurological Outcome of Term Neonates with Severe Perinatal Asphyxia

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Abstract

Background : To compare magnesium sulfate with placebo in term neonates with moderate to severe ischemic encephalopathy due to severe perinatal asphyxia in term of improved neurological outcome.

Methods: In this randomized controlled trial a total of seventy term neonates of age less than six hours of either sex suffering from moderate and severe hypoxic ischemic encephalopathy were included. Neonates were assessed at two different ages , 2-3 hours and 4-5 hours, respectively. Each patient remained in the hospital for at least 14 days. Patients were randomly divided into two groups A and B. Group A received magnesium sulphate at 250 mg/kg/dose (1 ml/kg/ dose in 20 ml of 5% dextrose water) over one hour with the additional doses repeated at interval of 24 hours and 48 hours. Group B received 1 ml/kg/dose of normal saline in 20 ml of 5% dextrose water. (Three doses , 24 hours apart). Serum magnesium levels were carried out at seventy two hours of life. .Monitoring was also done for clinical course of encephalopathy, laboratory variables and adverse effects. At the time of discharge ,neurological examination was carried out and CT scan was done at fourteenth day of life.

Results:- More infants in group A were sucking at discharge as compared to group B (71.4% vs 40%; p=0.008). Neuroimaging (CT scan on day 14th) yielded abnormal findings for fewer neonates in group A which was significantly low as compared to group B (11.4% vs 37.1% p= 0.012).

Conclusion: Postnatal magnesium sulfate infusion is effective in improving outcome for infants with severe perinatal asphyxia.

Key Words: Perinatal asphyxia, Magnesium sulfate, Ischemic encephalopathy

Introduction

Perinatal asphyxia is the fifth largest cause of child death. Perinatal asphyxia with metabolic acidosis in the cord blood may be followed by a moderate or severe neonatal encephalopathy. Magnesium is a naturally occurring N-methyl D-Aspartate(NMDA) receptor antagonist that blocks neuronal influx of calcium within the ionic channel. [1] In developed countries, perinatal asphyxia occurs in 1 to 1.5% of the live births. In developing countries, like India, the incidence of perinatal asphyxia was 5%, in different studies conducted in 16 different medical institutions.

Severe perinatal asphyxia leads to encephalopathy in 50 to 60% of the neonates. Neurological abnormality at discharge was found to be predictive of long term neuro-developmental delay.[2] Perinatal asphyxia with metabolic acidosis in the cord blood (pH<7and base deficit >12mmo/L) may be followed by a moderate or severe neonatal encephalopathy within 24 hrs and further neurological impairment characterized by spastic quadriplegia and dyskinesia /dystonia.[3]

In the CNS, inotropic glutamate receptors are the major excitatory neurotransmitter receptors that mediate almost all excitatory synaptic transmission in brain. Neuronal injuries like cerebral hypoxic ischemic encephalopathy are due to the overstimulation of NMDA receptors of glutamate type. Glutamate acts on the N-methyl-d-aspartate receptors, a postsynaptic channel in brain. High concentration of glutamate open NMDA channels, allowing excessive calcium influx into the neurons, inducing reversible neuronal injury.[4] Magnesium is a naturally occurring NMDA receptor antagonist that blocks neuronal influx of calcium within the ionic channel.[2]

A neuroprotective effect of magnesium sulfate has been shown in some animal models of perinatal hypoxic-ischemic brain damage.[5] A study carried out in India showed that postnatal magnesium sulfate treatment improved neurological outcome at discharge for term neonates with severe perinatal asphyxia. Neuroimaging (CT scan on day 14th) yielded abnormal findings for fewer neonates in the treatment group as compared to placebo group (16 % vs. 44%).Infants in treatment group were more likely to be sucking at discharge than those in placebo group (77% vs. 37%). Good short term outcomes at discharge occurred for

77% of the patients in treatment group as compared with the placebo group.[2]

In our setup magnesium sulfate is not routinely used as treatment option in severe birth asphyxia. This study is being carried out to find out the effectiveness of this drug, on the neurological outcome of term neonates, with severe perinatal asphyxia.

Patients and Methods

In this randomized controlled trial, carried out for six months (January-July 2013) in the department of Paediatrics Holy Family Hospital, Rawalpindi, a total of seventy term neonates of age less than six hours of either sex suffering from moderate and severe hypoxic ischemic encephalopathy were included in this study. Neonates were assessed at two different ages , 2-3 hours and 4-5 hours, respectively. Each patient remained in the hospital for at least fourteen days. Patients were randomly divided into two groups A and B. Group A(n=35) received magnesium sulphate at 250 mg/kg/dose (1 ml/kg/ dose in 20 ml of 5% dextrose water) over one hour with the additional doses repeated at interval of 24 hours and 48 hours. Group B (n=35) received 1 ml/kg/dose of normal saline in 20 ml of 5% dextrose water. (Three doses , 24 hours apart). Serum magnesium levels were carried out at seventy two hours of life. Monitoring was also done for clinical course of encephalopathy, laboratory variables and adverse effects. At the time of discharge ,neurological examination was carried out and CT scan was done at fourteenth day of life.Severe perinatal asphyxia was characterized by the history of fetal distress,need of immediate ventilation with a bag and mask or through ETT >2 min after delivery,5 minute APGAR score of <6 minutes and base deficit of >15 mEq/L or pH of <7 in arterial blood gases after birth. Moderate or severe Hypoxic Ischemic Encephalopathy (HIE) was established when one or more sign is present in three of the six categories, i.e., level of consciousness, spontaneous activity,tone,posture,primitive reflexes and autonomic nervous system in terms of pupils , heart rate and breathing pattern. Exclusion criteria included severe intrauterine growth retardation, any condition unrelated to asphyxia, age more than 6 hrs at admission, parental administration of magnesium to mother perinatally, chromosomal anomalies and congenital malformation

Frequencies and percentages were calculated for qualitative variables for good neurological outcome that is, presence of suck reflex and the CT scan findings of the head. Chi Square test was used to determine the difference in outcome, in term of frequencies of both variables, in two groups. P-value of<0.05 was considered significant. Stratification was done to control effect modifiers like age and gender to observe an outcome Chi-square test was also used. p≤0.05 was considered as significant for each stratified data.

Results

The average age of the neonates was 3.56±0.82 hours in group A and 3.58±0.73 in group B (Table 1). Out of 70 neonates, 48(68.6%) were male and 22(31.4%) female.Moderate hypoxic ischemic encephalopathy was observed in 58.6% and severe hypoxic ischemic encephalopathy in 41.4% . Significant difference was not observed between groups in grade of hypoxic ischemic encephalopathy (p=0.225) (Table 2).Postnatal magnesium sulfate treatment improved neurological outcome at discharge for term neonates with moderate to severe perinatal asphyxia. More infants in group A were sucking at discharge as compared to group B (71.4% vs 40%; p=0.008) (Table 3). Neuroimaging (CT scan on day 14th) yielded abnormal findings for fewer neonates in group A, as compared to group B (11.4% vs 37.1% p= 0.012) (Table 4).Sucking at discharge was high in group A but it was not statistically significant between groups (p=0.16) while for 4 to 5 hours age infant sucking was significantly high in group A as compared to group B (p=0.019)(Table 5). Similarly neuroimaging (CT scan on day 14th) yielded abnormal findings for fewer neonates in group A as compared to group B for 2 to 3 hours age infant, (p= 0.015) while for 4 to 5 hours age infants significant difference was not observed (Table 6). In neurological outcome suck reflex was better in group A as compared to group B (Table 7). CT scan, performed at 14th day revealed pronounced findings in group B as compared to group A (Table 8).

Table 1:Descriptive statistics of age and gestational age

Variables	Statistics	Group A n=35	Group B n=35
Age of neonate (hours)	Mean ± SD	3.56±0.82	3.58±0.73
Gestational Age (Weeks)	Mean ± SD	38.59±0.78	38.78±1.09
	Interquartile Range	1	1

Table 2:Grade of hypoxic ischemic encephalopathy with respect to groups

Grade of hypoxic ischemic encephalopathy	Group A(n=35)	Group B n=35	Total n=70
Moderate	18(51.4%)	23(65.7%)	41(58.6%)
Severe	17(48.6%)	12(34.3%)	29(41.4%)

Chi-Square= 1.47 p=0.225

Table 3:Comparison of neurological outcome in term of suck reflex at the time of discharge

Suck Reflex at discharge	Group A n=35	Group B n=35	Total n=70
Yes	25(71.4%)	14(40%)	39(55.7%)
No	10(28.6%)	21(60%)	31(44.3%)

Chi-Square= 7.006 p=0.008

Table 4:Comparison of neurological outcome in term of changes in CT scan at 14th day

Changes in CT scan at 14th day	Group A n=35	Group B n=35	Total n=70
Yes	4(11.4%)	13(37.1%)	17(24.3%)
No	31(88.6%)	22(62.9%)	53(75.7%)

Chi-Square= 6.29 p=0.012

Table 5:Comparison of neurological outcome in term of suck reflex at the time of discharge between groups for age of neonates

Age of neonate (hours)	Suck Reflex at discharge	Group A n=35	Group B n=35	p-Values
2-3 hours	Yes No Total	12(70.6%) 5(29.4%) 17	8(47.1%) 9(52.9%) 17	0.16
4-5 hours	Yes No Total	13(72.2%) 5(27.8%) 18	6(33.3%) 12(66.7%) 18	0.019

Table 6:Comparison of neurological outcome in term of changes in CT scan at 14th day between groups for age of neonates

Age of neonates (hours)	changes in CT scan at 14th day	Group A n=35	Group B n=35	p-Values
2-3 hours	Yes No Total	1(5.9%) 16(94.1%) 17	7(41.2%) 10(58.8%) 17	0.015
4-5 hours	Yes No Total	3(16.7%) 15(83.3%) 18	6(33.3%) 12(66.7%) 18	0.248

Table 7:Comparison of neurological outcome in term of suck reflex at the time of discharge between groups for male and female

Age of neonate (hours)	Suck Reflex at discharge	Group A n=35	Group B n=35	p-values
Male	Yes No Total	16(69.6%) 7(30.4%) 23	9(36%) 16(64%) 25	0.02
Female	Yes No Total	9(75%) 3(25%) 12	5(50%) 5(50%) 10	0.22

Table 8:Comparison of neurological outcome in term of changes in CT scan at 14th day between groups for male and female

Gender	Changes in CT scan at 14th day	Group A n=35	Group B n=35	p-Values
Male	Yes No Total	3(13%) 20(87%) 23	9(36%) 16(64%) 25	0.06
Female	Yes No Total	1(16.7%) 11(83.3%) 12	4(40%) 6(60%) 10	0.078

Discussion

Magnesium sulfate is neuroprotective because magnesium ions gate the NMDA receptor, thereby reducing the Calcium influx that can trigger cell death.[5] However, this block is voltage dependent and is overcome during the axonal depolarization that occurs with hypoxic-ischemia. If the extracellular magnesium concentration is increased, then this blockade can be restored.[6]Present study demonstrates role of magnesium sulphate. This was reflected by 11.4% neonates with neurologic abnormalities and 71.4% infants receiving oral feedings at discharge in the treatment group, which were significantly high as compared to control group. This is also supported by the neuroimaging results.

Ichibia et al. conducted a multicenter, randomized, controlled trial to determine whether postnatal magnesium sulfate infusion (250 mg/kg/day) for 3 days resulted in an improved outcome in babies with severe birth asphyxia. Enrolment criteria included a 5-min APGAR score of 7 or less and either failure to initiate spontaneous respiration at 10 min after birth or occurrence of clinically apparent seizures within 24 h of birth. Survival with normal results on cranial CT, EEG and establishment of oral feeding by day 14 of age occurred significantly more often in neonates who

were given magnesium sulfate as compared to control group. In the present study also, CT scan abnormalities occurred more frequently in the control group as compared to the magnesium group.[6]

The protective role of magnesium sulfate has been based largely on studies with animal models, many of which showed favourable results in terms of amelioration of secondary neuronal injury.[7] A few studies with pregnant women showed beneficial effects for neonates also. Nelson and Grether observed a lower incidence of cerebral palsy in preterm infants born to mothers who had received magnesium sulfate before delivery.[8] Schendel et al and Grether et al observed the relationship of intrapartum magnesium sulfate administration to mothers and cerebral palsy in newborns. [7,9] They showed statistically significant effect of magnesium sulfate in preventing cerebral palsy. Harrison et al reported lower incidences of fetal heart rate deceleration and term stillbirths for mothers who received magnesium supplementation during pregnancy. There was no effect on the incidence of HIE, because it was an underpowered study and compliance was poor among the study population.[10] Some other studies have also shown that postnatal magnesium suphate infusion is effective in improving short term outcome in neonates with birth asphyxia.[11-13]

The role of magnesium sulfate in neuroprotection also is being evaluated in acute traumatic brain injury, in both adults and children. In a recent study, magnesium sulfate administration to children with severe traumatic brain injuries did not decrease cerebral perfusion pressure or mean arterial pressure and had no adverse effects on cardiac conduction.[14] Although one study in adults showed no beneficial effects of magnesium sulfate after traumatic brain injury.[15]

Our study is the placebo-controlled trial that shows improved neurologic outcomes at discharge in the magnesium sulfate group. Good short term outcomes at discharge, the composite measure of all parameters, were statistically significant and individual components like neurologic abnormalities and oral feeding (sucking) were significant to support the positive role of magnesium sulfate infusion in improving the neurological outcome in term neonates with severe perinatal asphyxia.

Conclusions

Postnatal magnesium sulfate infusion is effective in improving outcomes for infants with severe perinatal asphyxia when it is given early (within 6 hours) and, in combination with other modalities of treatment during the therapeutic window.

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