



Outcome of Birth Asphyxia Managed With Magnesium

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ABSTRACT

INTRODUCTION:

Until recently, management strategies of birth asphyxia were supportive and not targeted toward the processes of ongoing injury. In view of conflicting reports about the role of magnesium in birth asphyxia and also due to the paucity of Indian studies in this part of Telangana, the present study was undertaken.

OBJECTIVE:

To study the outcome and complications of term asphyxiated neonates in first 10 days of life who are supplemented with Magnesium.

METHODOLOGY:

Randomized case control study on 85 term neonates with birth asphyxia (45 cases and 40 controls). All the term neonates with Apgar score of 3 or less at 1 minute and 6 or less at 5 minutes were included in the study. Cases had received Magnesium Sulfate intravenous infusion at a dose of 250 mg/kg in first hour of life and 2 additional doses of 125 mg/kg at intervals of 24 hours. Serum Magnesium was estimated at birth and then on 12, 24, 48 and 72 hours of life in both groups.

RESULTS:

Mean number of convulsions was 4.6 in cases and 7.2 in control group. Time interval between the first and last convulsion was less in cases as compared to control group. Duration of Oxygen supplementation and NICU stay were significantly shorter in cases. Direct breast feeding was able to initiate early in case as compared to controls group. Significant differences in Magnesium level were seen in cases after supplementation. Clinical or Serum Magnesium toxicity were detected in any of the cases. There was no difference in incidence of complications among the two groups.

CONCLUSION:

Decrease in the number of convulsion and duration of convulsion shows the neuroprotective effect of Magnesium in treatment of birth asphyxia. In the present study magnesium supplementation regimen was not associated with toxicity.

KEYWORDS : Birth Asphyxia, Magnesium supplementation, Neuroprotection

INTRODUCTION

In spite of major advances in monitoring technology and knowledge of fetal and perinatal medicine; birth asphyxia is one of the significant causes of mortality and long term morbidity. Data from National Neonatal Perinatal database suggests that birth asphyxia contributes to almost 20% of neonatal deaths in India. It defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age. Severe asphyxia was defined as no breathing or an Apgar score of 0-3 at 1 minute of age. "Failure to initiate or sustain respiration after birth" is define as criteria for the diagnosis of asphyxia by WHO.

Strict monitoring and prompt correction is needed for common problems including temperature maintenance, blood sugar, blood pressure and oxygenation Birth asphyxia may occur in utero, during labour and delivery, or in the immediate postnatal period. The clinical and neurological sequelae following perinatal asphyxia is referred to as Hypoxic-Ischemic Encephalopathy (HIE). Most widely used classification of HIE is that of Sarnat and Sarnat which divides affected infants into Stage I, Stage II and Stage III.

OBJECTIVES

To study neonatal outcome and advantages of early supplementation of magnesium in birth asphyxia.

To study the complications of term asphyxiated neonates in the first 10 days of life.

METHODOLOGY

SOURCE OF DATA:

Term neonates (gestational age of more than 37 to less than 42 com-

pleted weeks) with birth asphyxia delivered in

The study was conducted from November 2012 to March 2014.

METHOD OF DATA COLLECTION:

After taking the informed consent from the parents or guardian and fulfilling inclusion and exclusion criteria, patients was included in the study.

Inclusion Criteria

All single term neonates with Apgar score of 3 or less at 1 minute and 6 or less at 5 minutes. (Term neonates with perinatal asphyxia as defined by WHO and NNPD).

Exclusion Criteria

All preterm and post term neonates.

Neonates with congenital malformations.

Neonates with meconium stained amniotic fluid.

Patients whose mothers received magnesium sulfate, pethidine, phenobarbitone or other durgs likely to influence the Apgar Score.

METHOD OF DATA COLLECTION:

Randomization of the study was done by; babies delivered on odd dates of a month will be taken as case group and babies delivered on even dates of a month were be taken as control group. i.e., a baby delivered on dates like 1,3,5,7 are included in case group and baby delivered on dates like 2,4,6,8 were be considered as control group. A day

was considered from 12AM to 11:59PM.

As soon as the baby is admitted to NICU, the details were be entered in a predesigned proforma. This includes 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 were also entered.

The examination finding including vital signs and detailed anthropometry were recorded and a complete examination of central nervous system, Respiratory system, cardio vascular system and Gastro-intestinal system was done and recorded in detail.

Case group had received Magnesium sulfate infusion at 250 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour within first hour of birth, and 2 additional doses 125 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour at intervals of 24 hours. This extra fluid was considered along with total daily fluid maintenance dose of the neonates. The neonates of the control group were not received any proposed Magnesium supplementation. Further neonates of both groups were treated as per the routine NICU treatment protocol for birth asphyxia.

Clinical assessments include assessments of the neurologic status twice daily for the first 10 days of life using Sarnat and Sarnat classification of Hypoxic-Ischemic Encephalopathy (HIE) into Stage I, Stage II or Stage III.

Parameters like type of respiratory support needed, the presence of seizures, the time for establishment of full oral feedings, duration of stay in hospital. The assessment of the child was done in NICU and will be continued in wards if the child is transferred for mother side admission.

PROCEDURE

Wavelength / filter : 510 nm (Hg 546 nm)/Green.

Temperature : Room Temperature.

Light Path : 1 cm.

OBSERVATIONS AND RESULTS:-

The duration of study period was from November, 2014 to March, 2016.

85 patients of birth asphyxia were enrolled in the study of which 45 cases and 40 control group.

Total number of deliveries during the study period was 2537

Incidence of birth asphyxia during the present study period was 3.35

Statistical analysis was done using significance of serum Magnesium and outcome. This was analyzed using t-test in the present study.

The observations are as follows:-

Table 1. Gender distribution of the study Population

SEX	CASE	CONTROL	TOTAL
MALE	28(33%)	24(28%)	52(61%)
FEMALE	17(20%)	16(19%)	33(39%)
TOTAL	45(53%)	40(47%)	100(100%)

There were 52 (61%) male babies in the total study population. In the study population, case group comprised of 45(53%) babies. Male neonates were more in both the study group.

Table 2. Distribution of study groups according to Sarnet and Sarnet HIE classification.

	CASE	CONTROL	Total
HIE Stage 1	20(24%)	18(21%)	38(45%)
HIE Stage 2	18(21%)	17(20%)	35(41%)
HIE Stage 3	7(8%)	5(6%)	12(14%)
TOTAL	45(53%)	40(47%)	85(100%)

38(45%) patients had Stage 1 HIE, 35(41%) patients had Stage 2 HIE and 12(14%) patients had Stage 3 HIE. Most number of patients came in HIE Stage 1 group, 20(24%) patients. Least number of patients were in HIE Stage 3 control group, 5(6%) patients.

Table 3. Distribution of mean Serum Magnesium level among the study groups

Hours of life	S. Magnesium (mg/dl)		P~value	
	Case	Control		
Birth	1.795	1.74	>0.05	Not Significant
12 hours	4.062	1.801	<0.05	Significant
24 hours	4.137	1.797	<0.05	Significant
48 hours	4.172	1.824	<0.05	Significant
72 hours	4.202	1.857	<0.05	Significant

Mean Serum Magnesium level was lowest during birth (Case-1.795 mg/dl; Control-1.740 mg/dl). Magnesium levels were 4.062 mg/dl, 4.137 mg/dl, 4.172 mg/dl, 4.202 m/dlin cases during 12, 24, 48 and 72 hours of life respectively. All the Serum Magnesium values in the cases were in the neuroprotective range during the 1st 72 hours of life.

Table 4. analysis of Convulsion in HIE Stage-2

MEAN DURATION	CASE	CONTROL	P~ value	
Number of Convulsion	4.61	7.29	<0.05	Significant
1 st Convulsion (Hours of Life)	2.39	3.24	>0.05	Not Significant
Duration (hours)	10	20.75	<0.05	Significant

There was significant reduction in number of convulsions and interval between 1st and last convulsion among the two groups. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups.

Table 5: Analysis of Convulsion in HIE Stage 3

MEAN DURATION	CASE	CONTROL	P~value	
Number of Convulsion	5.29	3.40	>0.05	Not Significant
1 st Convulsion (Hours of life)	2.29	4.60	<0.05	Significant
Duration (Hours)	22.89	30.60	>0.05	Not Significant

There was significant reduction in time of presentation of 1st episode of convulsion among the two groups. There was no significant difference in number of convulsions and interval between 1st & last convulsion among the two groups.

Table 6: Distribution of outcome analysis

Mean Duration	CASE (Hours of Life)	CON- TROL (Hours of Life)	P-Value	
O ₂ Dependence	94	123	0.00048511	Significant
Starting of DBF	136	165	0.000160049	Significant
NICU Stay	160	195	0.007867336	Significant

There was significant difference among the two groups in

Duration of Oxygen Supplementation

Initiation of DBF

Duration of NICU stay

Table 7: Analysis of Complications

	CASE	CONTROL	Total
Renal Failure	2	1	3
Feed Intolerance	3	3	6
PAH	3	4	7
GMH	3	3	6
IVH	2	3	5
Hyperbilirubinemia	3	2	5
Death	2	3	5

There was no significant difference in the incidence of complications of birth asphyxia.

DISCUSSION

Data from Nation Neonatal Perinatal database suggests that birth asphyxia contributes to almost 20% of neonatal deaths in Indian.[1] It defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age. Severe asphyxia was defined as no breathing or an Apgar score of 0-3 at 1 minute of age. "Failure to initiate or sustain respiration after birth" is defined as criteria for the diagnosis of asphyxia by WHO.[2]

In our study, the case and control groups had no differences in gestational age, birth weight, gender, mode and place of delivery, parity, antenatal checkup, liquor colour and hypoxic-ischemic encephalopathy (HIE) staging and mean age of intervention between the experimental and controlled groups. The serum magnesium levels at birth were 1,740 (± 0.286) mg/dl and 1.795 (± 0.237) mg/dl in the control and study group respectively. The normal reported values for serum Mg in neonatal on day 1 of life are 1.8 (± 0.15) mg/dl.[3] Geeta *et al*, Levene *et al* and Hossain *et al*, reported similar '0' hour serum Mg levels 1.867 mg/dl, 1-704 mg/dl and 1.6 mg/dl respectively in babies with severe birth asphyxia.[4,5,6] The values obtained in the present study are comparable to these. This is possible why the Mg levels at birth in the babies with birth asphyxia were not different from those reported in normal neonates.

We used 3 doses of MG -250 mg/kg given within an hour of birth, followed by 125 mg/kg given at 24 and 48 hours of life. The serum Mg levels obtained were between 4.062 (± 0.22) mg/dl. Geeta *et al* also used the same dosage and serum Magnesium were between 3.523 mg/dl and 4.598 mg/dl. Levene *et al* also used a single dosage of 250 mg/kg. the 12 hour value was 4.062 mg/dl which is similar to that reported by both the studies. 24-hours additional dose of 125 mg/kg of Mg, which was administered at 24 hours.

The normal serum Mg levels being 1.8 mg/dl to 2.5 mg/dl. Serum Magnesium levels between 3-5 mg/dl may be expected to be neuroprotective. With the dosage schedule used in the present study, Serum Mg levels obtained were in the range of 4.062 – 4.202 mg/dl over a period of 72 hours. The Mg levels reached were therefore in the neuroprotective range. Secondary neuronal injury to the post asphyxia neonatal brain can occur over a period that may last as long as 72 hours.[7] We administered the second and third doses of Magnesium at 24 and 48 hours with an aim to maintain increased serum Magnesium concentration for a period of 72 hours. With the dosage schedule used in the present study we were successful in the maintaining serum Mg levels in the neuroprotective range for a period of 72 hours.

Magnesium toxicity has been shown to relate to the serum Magnesium levels. Reportedly, symptoms of hypermagnesaemia manifest at serum Magnesium level above 5 mg/dl.[8] Babies in the study present group were monitored during Magnesium infusion and every 8 hours subsequently recorded the refilling time. There were no significant alterations in these parameters either these doses are safe. The maximum serum Mg level documented in the present series was 4.202 mg/dl. This can be possible reason why we did not see any side effects in the babies.

Hours of Life	Serum Magnesium (mg/dl)			
	Present Study	Geeta <i>et al</i>	Levene <i>et al</i>	Hossain <i>et al</i>
Birth	1.795	1.867	1.704	1.600
12 th	4.062	3.523	3.648	-
24 th	4.137	4.514	2.688	-
48 th	4.172	4.598	-	3.900
72 th	4.202	3.583	-	-

The mean number of convulsions in HIE Stage 2 cases and controls were 4.61 and 7.29 respectively. There was significant reduction in number of convulsions and duration between 1st & last convulsion among the two groups. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups in neonates with moderate encephalopathy. There are no major changes in analysis of convulsion or neurological outcome in patients with severe encephalopathy (HIE Stage 3).

Direct breast feeding was started on 136 hours (5days 16 hours) and 165 hours (6 days 21 hours) of life in cases and controls respectively and the difference was significant. This finding was similar to Bhat *et al* and Hossain *et al* studies.[9]

The duration of NICU stay was 160 hours (6 days 16 hours) in cases and 195 hours (8 days 3 hours) in control group. The mean duration of Oxygen supplementation was 94 hours (3 days 22 hours) and 123 hours (5 days 3 hours) in cases and controls respectively. These two variables showed a significant difference. These variables are not assessed by other studies.

One of the objectives of the present study was to monitor the complications of hypermagnesaemia in the study group. There was no significant alterations in heart rate, respiratory rate, oxygen saturation and capillary filling time were seen, following magnesium infusion with either 250 mg/kg or 125 mg/kg dose. This finding was similar to Geeta *et al*, Levene *et al*, Hossain *et al* and Ichiba *et al* studies.[10]

Neurological complications of birth asphyxia and improvement with Magnesium supplementation was studied in most of the above mentioned studies. The present study had also monitored complications of birth asphyxia in respiratory, cardiovascular, renal, hematological and gastro-intestinal system. Though the neurological outcomes were improved, there was no significant difference in the incidence of complications of birth asphyxia involving other systems were found in the present study.

CONCLUSION:

There were 52 (61%) male babies in the total study population. In the study population, case group comprised of 45(53%) babies. Male neonates were more in both the study group.

38(45%) patients had Stage 1 HIE, 35(41%) patients had stage 2 HIE and 12(14%) patients had Stage 3 HIE. Most number of patients came in HIE stage 1 group, 20(24%) patients. Least number of patients were in HIE stage 3 control group, 5(6%) patients.

Mean Serum Magnesium level was lowest during birth (Case-1.795 mg/dl; Control-1.740 mg/dl). Magnesium levels were 4.062 mg/dl, 4.137 mg/dl, 4.172 mg/dl, 4.202 mg/dl in cases during 12, 24, 48 and 72 hours of life respectively. All the serum Magnesium values in the case were in the neuroprotective range during the 1st 72 hours of life.

Patients with moderate encephalopathy showed significant reduction in number of convulsions (4.6 vs 7.2) and interval between 1st & last convulsion in case group (10 vs 20 hours) in case group. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups. These points out the neuroprotective effect of Magnesium supplementation.

Patients with severe encephalopathy showed significant reduction in time of presentation of 1st episode of convulsion among the two groups. But was no significant difference in number of convulsions and interval between 1st and last convulsion among the two groups.

Case group showed significant reduction duration of oxygen supplementation (94 vs 123 hours), time initiation of DBF (136 vs 165 hours of life) and duration of NICU stay (160 vs 195 hours) as compared to controls.

Complications of birth asphyxia (other than neurological system) were similar in both the groups.

References:

1. World Health Organization. Perinatal mortality: a listing of available information. FRM/MSM.96.7.Geneva: WHO, 1996.
2. Report of the National Neonatal Perinatal Database (National Neonatology forum, India) 2000.
3. Bajpai PC, Sugden D, Ramos A, Stern magnesium levels in the newborn and older child. *Arch. Dis Child* 1996; 41 : 424-427.
4. Levene MJ, Evans DJ, Mason S, Brown J. An international Network for evaluating neuroprotective therapy after severe birth asphyxia, *Seinars in Perinatal* 1999; 23; 223-233.
5. Geeta Gathwala, Khera A, Single I. Neuronal protection with Magnesium. *Indian J Pediatr* 2001; 68: 417-419.
6. Hossain MM, Mannam MA, Yeasmin. Short-term outcome of magnesium sulfate infusion in perinatal asphyxia. *Mymensingh Med J.* 2013 Oct; 22(4): 727-35.
7. Opelt WW, MacIntyre I and Rall DP. Magnesium exchange between blood and cerebrospinal fluid. *Am J Physiol* 1963; 205: 959-962.
8. Roth SC, Edwards AD, Cady EB, Depley DT, Wyatt JS, Azzopardi D Relation between cerebral oxidative metabolism following birth asphyxia and neurodevelopment outcome and brain growth at one year. *Dev Med Child Neurol* 1992; 34: 284-295
9. Bhat M A, Charoo B A, Bhat J I, Mushtaq Sulfate in Severe Perinatal Asphyxia: A Randomized placebo-Controlled Trial. *Pediatrics* 2009; 123: e764-e769.
10. Ichiba H, Yokoi T et al Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. *Pediatrics Int*, 2006; 48: 70-75.