

Research Article

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Evaluation of safety of magnesium sulphate therapy in neonates with birth asphyxia

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ABSTRACT

Background: Incidence of perinatal asphyxia is about 1 to 1.5% in most centres of world and is usually related to gestational age and birth weight. The incidence is higher in term infants of diabetic and toxæmic mothers. Intrauterine growth retardation, antepartum hemorrhage and breech presentation are also associated with an increased incidence of asphyxia.

Methods: This is a prospective study carried out in Basveshwar & Sangmeshwar Teaching & General Hospitals from 1.12.2007 to 31.5.2009 on 80 terms, appropriate for gestational age babies. They all suffered severe birth asphyxia, of whom 40 formed control group & 40 formed study group. All were treated for birth asphyxia and its complications, except that the study group received injection of magnesium sulphate 250 mg/kg within half an hour of birth and subsequently 125 mg/kg at 24 & 48 hrs of life. Thereafter, they were monitored for effects on vital parameters and immediate outcome.

Results: The mean cord blood serum magnesium level in control and study group was 0.85±0.12 and 0.83±0.10. The serum magnesium levels at 12, 24, 48 and 72 hours were 1.80±0.16, 1.82±0.16, 1.81±0.18, 1.82±0.17 in the study group, which were significantly higher than those in control group. The serum magnesium levels in study group ranged between 1.50 mmol/L & 2.20 mmol/L which are considered to be neuroprotective range. No significant alteration in vital parameters was seen following magnesium infusion. Evidence of HIE was seen more frequently in the control group with 26 (65%) babies showing HIE versus 22 (55%) in the study group. The incidence of HIE, neonatal seizures, & apnoeic spells were lesser in the study group compared to control group.

Conclusions: Injection MgSO₄ administered in a dose of 250 mg/kg & 125mg/kg as intravenous infusion is safe, Mg level obtained are in neuroprotective range & it causes better immediate outcome.

Keywords: Birth asphyxia, Magnesium sulphate, HIE

INTRODUCTION

The overall incidence of perinatal asphyxia is 1.0-1.5% of live births.¹ It occurs in 0.5% of live born infants of more than 36 weeks of gestational age. Perinatal asphyxia causes 15-20% of deaths in neonatal period and 25-30% of the survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation).²

Neurobiological research has unravelled the mechanisms that culminate into neuronal loss after a hypoxic-ischaemic insult. Magnesium has been proved as a neuroprotective agent as it blocks receptors through which neuronal injury occurs.³

Due to the significant morbidity and mortality of HIE, challenging and newer therapeutic modalities are to be studied to counteract the progression of HIE.

However, before embarking on to use of magnesium for neuronal protection, it is important to study the effects of magnesium sulphate administration on physiological functions such as blood pressure, heart rate and respiration. The present study is aimed at evaluating the safety of magnesium sulphate in neonates with birth asphyxia.

To evaluate the neuroprotective role of $MgSO_4$, the patient's neurological development should be assessed at regular interval till the age of 1½-2 years.

METHODS

This prospective study was carried out in labour room and NICU of Sangameshwar Hospital and Basaveshwar Teaching & General Hospital attached to M. R. Medical College, Gulbarga in 80 inborn babies between 01.12.2007 to 31.05.2009. Babies were randomly allotted to one of the study or the control groups, using the randomization table. A written informed consent was taken from the parents of the babies in the study group. Neonate was labelled as term neonate on the basis of assessment of gestational age by maternal dates and confirmed by clinical examination as described by Ballard.

Exclusion criteria

1. Preterm.
2. Small for gestational age or large for gestational age.
3. General anesthesia to mother, during cesarean section.
4. Treatment of mother with $MgSO_4$ for pregnancy induced hypertension.
5. History of mother, having been given pethidine, phenobarbitone and other sedative drugs, likely to depress the CNS of baby.
6. Gross congenital malformation in baby.
7. Intracranial bleed in the neonate.
8. Babies with pathological jaundice.
9. Clinical or laboratory evidence of intra-uterine infections.
10. Abnormal head size at birth ($<5^{\text{th}}$ or $> 95^{\text{th}}$ percentile).

Maternal details

Details of mother if booked (on regular follow up) or unbooked, parity, antenatal problems as APH, PIH, Eclampsia, diabetes, heart disease etc. were documented. Her period of gestation, duration of labour and method of delivery including instrumentation were also noted. Evidence of fetal distress e.g. meconium stained liquor in vertex position and occurrence of fetal bradycardia were recorded.

Birth details

Apgar scoring

APGAR scoring of the baby was done as per criteria described by Virginia Apgar⁷². They were scored at 1 & 5 min. An effort was made to find out any correlation between apgar score and outcome.

Cause of perinatal asphyxia

Cause of perinatal asphyxia was documented

Umbilical artery pH at birth

0.5 ml of blood was taken from umbilical artery by arterial puncture in a preheparinized glass syringe, immediately after birth and was sent to blood gas analysis laboratory for pH analysis. Umbilical cord arterial blood $pH \leq 7$ was taken as supportive evidence of birth asphyxia.

Selection of cord pH as evidence of birth asphyxia was based on the fact that in case of significant hypoxemia foetus utilized anaerobic glycolysis to meet its energy needs. The subsequent formation of non-volatile acids as lactic acid results in decrease of blood pH.

Details of magnesium therapy

Time of giving magnesium

Magnesium was given to the neonate within half an hour of birth in the form of diluted Magnesium Sulphate (clinical grade) at neutral pH. All neonates were infused with the chemical procured from a single source.

Source of magnesium

Magnesium was procured in the form of hydrated $MgSO_4$ injection (2 ml ampules containing 500 mg of $MgSO_4$ per ml).

Method of giving magnesium

Magnesium was given as infusion of magnesium sulfate diluted in 5% dextrose over a period of half-hour, through an infusion pump. The procedure was always done in the presence of a pediatrician, as an abundant precautionary measure, though the salt is known for its safety margin. The pediatrician monitored the baby for oxygen saturation, heart rate, respiratory rate, blood pressure and mean arterial pressure.

Dosage schedule of giving magnesium

Magnesium was given in a loading dose of 250 mg/kg body weight, within half hour of birth. It was followed by two further infusions in a dose of 125 mg/kg at 24 and 48

hours of birth. The dosage schedule was in accordance with the recommendations made by M Levine. The aim of the procedure was to bring magnesium concentration of blood in the range of 1.2-2.5 mmol/l⁶⁹.

Monitoring during magnesium infusion

During magnesium infusion, baby was kept in intensive care unit, with facilities of ventilator, pulse oximeter and neonatal blood-pressure measuring apparatus. Monitoring of heart rate and oxygen saturation using pulse oximeter was done continuously. Also blood pressure and mean arterial pressure were documented using non-invasive neonatal blood pressure instrument (BCI-Mini Torr-Plus), every 10 minutes for 1 hour and thereafter every hourly for 12 hours. Respiratory rate was also documented at 10 minute intervals. Baby was also monitored for changes in muscle tone, deep tendon reflexes, and for occurrence of apnoea. The aim of monitoring was to rule out occurrence of hypotension, and of respiratory depression, which are the expected complications of magnesium therapy with high doses.

Precautions during magnesium infusion

Facilities of dopamine and dobutamine infusion, endotracheal intubation and of ventilator were kept ready during the period of infusion, to prevent any untoward incident.

Monitoring of magnesium levels

Magnesium levels were documented at 0, 12, 24, 48, 72 hours of MgSO₄ infusion using the sensitive, atomic absorption spectrophotometer (AAS). Levels at 24 & 48 hours were documented 45 minutes after the Mg infusion. Each AAS measurement required 0.5 ml of serum. The samples were immediately treated with trichloracetic acid to precipitate organic materials from the serum. Samples were then taken as a batch for estimation of Mg content.

Method of measurement of magnesium levels

Magnesium levels were measured using method given by Sunderman and Carroll. In this method, to 0.5 ml of serum in a centrifuge tube was added 4.5 ml of 10% trichloracetic acid. The contents were mixed and allowed to stand for 10 minutes. It was then centrifuged at 2500 rpm for 15 minutes. The sample was then analysed with the help of atomic absorption spectrophotometer (model ECIL – AAS – 4129). The AAS machine was standardized prior to the estimation using standard methods.

Clinical details

A general as well as detailed neurological examination was done for all babies, in both groups. Neonates were examined for evidence of hypoxic-ischemic-encephalopathy (HIE) which was staged as HIE-I, HIE-II

& HIE-III as described by Sarnat and Sarnat¹⁵. Occurrence of seizures, their type, total number and the anticonvulsants used for controlling them were noted. An effort was made to correlate the occurrence of seizures, with outcome. Occurrence of apnoeic spells and their number was also documented. Other causes of apnoeic spells such as hypoglycemia, hypocalcemia, hyponatremia, hypothermia, sepsis and IVH were ruled out. We tried to correlate occurrence of apnoeic spells with the outcome.

Biochemical investigations

Blood sugar

Blood sugar levels were monitored 12 hourly in all the babies and glucose infusion rates were increased to maintain blood sugar in a range of 70-100 mg/dl.

Renal profile

An asphyxiated infant is at risk for ATN and for SIADH. Persistent oliguria (<1 ml/kg/hour) for first 36 hours is significantly associated with severe HIE and poor outcome. Urine output measurement, Urinalysis, serum electrolytes and daily weight charting were done to rule out these abnormalities.

Chest X-ray

Infants with birth asphyxia may have transient myocardial ischemia. They may show signs of congestive heart failure. Chest X-ray of babies was done whenever indicated to assess for cardiomegaly.

Serum calcium

Hypocalcemia is a common metabolic alteration in neonatal post asphyxial syndrome. Serum calcium level was determined in all babies and calcium supplementation was given to all asphyxiated babies for the first 72 hours as a unit protocol.

Statistical analysis

The data was entered in microsoft excel and analyzed in SPSS 21. The statistical tests used were Proportion, Mean, Standard Deviation, and Independent T test.

RESULTS

In this study, a total of 80 terms, appropriate for gestational age babies were enrolled. They all suffered severe birth asphyxia (defined as 1 minute Apgar score \leq 3 and 5 minute Apgar score \leq 6). Forty of these formed the control group and forty the study group. All were treated for birth asphyxia and its complications as per unit protocol, except that the study group received intravenous injection of MgSO₄ 250 mg/kg, within half

an hour of birth and subsequently 125 mg/kg at 24 and 48 hours of life.

Serum magnesium levels in the study and the control group were comparable at 0 hours but were significantly higher ($p<0.001$) than those in the control group at 12, 24, 48 and 72 hours. Serum magnesium levels in the study group ranged between 0.70 and 2.20 mmol/L with a Mean \pm SD of 0.83 \pm 0.10, 1.80 \pm 0.16, 1.82 \pm 0.16, 1.81 \pm 0.18 and 1.82 \pm 0.17 at 0, 12, 24, 48 and 72 hours respectively. Maximum level seen in the control group was 1.20 mmol/L.

Table 1: Serum Mg levels – Mean \pm SD (mmol/L).

Time	Control Group Mean (\pm SD), n = 40	Study Group Mean (\pm SD), n = 40	'P' Value
0 hour	0.85 \pm 0.12	0.83 \pm 0.10	p>0.05
12 hour	0.85 \pm 0.08	1.80 \pm 0.16	P<0.01
24 hour	0.81 \pm 0.10	1.82 \pm 0.16	P<0.01
48 hour	0.81 \pm 0.08	1.81 \pm 0.18	P<0.01
72 hour	0.86 \pm 0.09	1.82 \pm 0.17	P<0.01

Heart rate and oxygen saturation were monitored continuously with pulse oximeter and charted every 10 minute interval for first one hour and two hourly thereafter, for six hours. No significant difference was found between the initial heart rate and oxygen saturation, and that documented after magnesium infusion.

Table 2: Monitoring during Mg infusion; heart rate & oxygen saturation.

Criteria	Heart rate		Oxygen saturation	
	Mean \pm SD (n=40)	'P'	Mean \pm SD (n=40)	'P'
0 min	137.88 \pm 6.12	>0.05	0.92 \pm 0.03	>0.05
10 min	135.50 \pm 6.49	>0.05	0.92 \pm 0.03	>0.05
20 min	136.55 \pm 6.33	>0.05	0.92 \pm 0.03	>0.05
30 min	137.35 \pm 5.65	>0.05	0.91 \pm 0.02	>0.05
40 min	136.20 \pm 5.27	>0.05	0.92 \pm 0.03	>0.05
50 min	138.38 \pm 5.88	>0.05	0.92 \pm 0.03	>0.05
60 min	137.93 \pm 5.95	>0.05	0.92 \pm 0.03	>0.05
2 hours	137.80 \pm 6.26	>0.05	0.93 \pm 0.03	>0.05
4 hours	136.33 \pm 7.16	>0.05	0.92 \pm 0.03	>0.05
6 hours	136.80 \pm 7.14	>0.05	0.92 \pm 0.03	>0.05

No significant increase in respiratory rate was documented in any case, in both the groups. No case required stoppage of magnesium infusion or any kind of ventilatory support. Statistically no significant difference was found between respiratory rates ($p>0.05$). Similarly no statistical difference was found in relation to mean arterial pressure at any time during the monitoring. No significant fall in blood pressure or mean arterial pressure was seen in any case. No case required dopamine or

dobutamine infusion to augment blood pressure, during magnesium infusion.

Four babies in both groups expired in the initial neonatal period. Two of these, in both groups, expired due to septicaemia, and two expired due to complication of asphyxia.

Table 3: Monitoring during Mg infusion; respiratory rate & mean arterial pressure.

Criteria	Respiratory rate		Mean arterial pressure	
	Mean \pm SD (n=40)	'P' Value	Mean \pm SD (n=40)	'P' Value
0 min	38.25 \pm 4.44	>0.05	45.20 \pm 3.20	>0.05
10 min	39.03 \pm 4.12	>0.05	46.03 \pm 3.95	>0.05
20 min	38.70 \pm 4.86	>0.05	44.18 \pm 2.99	>0.05
30 min	39.38 \pm 5.60	>0.05	45.00 \pm 2.84	>0.05
40 min	39.03 \pm 5.46	>0.05	44.45 \pm 3.07	>0.05
50 min	39.68 \pm 5.04	>0.05	43.80 \pm 3.07	>0.05
60 min	39.83 \pm 4.62	>0.05	45.15 \pm 2.37	>0.05
2 hours	39.45 \pm 5.24	>0.05	44.83 \pm 4.58	>0.05
4 hours	38.50 \pm 4.14	>0.05	45.33 \pm 2.90	>0.05
6 hours	39.20 \pm 5.50	>0.05	44.68 \pm 3.15	>0.05

Table 4: Immediate neurological outcome.

Criteria	Control Group (n=40)	Study Group (n=40)	Statistical Analysis
Deaths attributable to asphyxia	2 (5.0%)	2 (5.0%)	$\chi^2=0$ (p>0.05)
HIE-I	8 (20.0%)	10 (25.0%)	$\chi^2=0.143$ (p>0.05)
HIE-II	16 (40.0%)	10 (25.0%)	$\chi^2=1.025$ (p>0.05)
HIE-III	2 (5.0%)	2 (5.0%)	$\chi^2 = 0$ (p>0.05)
Neonatal seizures	16 (40.0%)	12 (30.0%)	$\chi^2 = 0.439$ (p>0.05)
Apnoeic spells	6 (15.0%)	4 (10.0%)	$\chi^2=0.228$ (p>0.05)

Details of death in control group attributable to septicemia

- Case-1: Expired on Day 5 of life, 98 hours of birth. Cause of death was Klebsiella septicemia, documented on day 3 of life.
- Case-4: Expired on Day 3 of life, 57 hours of birth. Cause of death was pseudomonas septicemia, documented on day 2 of life.

Details of death in control group attributable to complications of asphyxia

1. Case 5: Expired on Day 1 of life, 20 hours of birth.
2. Case 9: Expired on Day 2 of life, 43 hours of birth.

Details of death in study group attributed to septicemia

1. Case 4: Expired on Day 3 of life, 76 hours of birth. Cause of death was klebsiella septicemia, documented on day 2 of life.
2. Case 19: Expired on Day 6 of life, 137 hours of birth. Cause of death was klebsiella septicemia, documented on day 4 of life.

Details of death in study group attributable to complications of asphyxia

1. Case 8: Expired on Day 1 of life, 13 hours of birth.
2. Case 18: Expired on Day 1 of life, 18 hours of birth.

HIE was seen in 26 (65%) babies in control and 22 (55%) babies in study group. Although more babies had HIE in the control group versus the study group, the difference was statistically not significant ($p>0.05$).

Out of the 26 babies which showed HIE in control group, 8 (20%) babies showed HIE-I, 16 (40%) babies showed HIE-II and 2 baby showed evidence of HIE-III. In case of study group 10 (25%) babies showed HIE-I, 10 (25%) showed HIE-II and 2 (5%) baby showed evidence of HIE-III. More babies had evidence of HIE-II, seen in the control group than in the study group, but the difference was not significant statistically ($p>0.05$).

Seizures were seen in 16 (40%) babies in control and 12 (30%) babies in study group. Although babies that received magnesium infusion had a lesser incidence of seizures than those who did not receive magnesium but again the results were not found to be statistically significant. All other probable causes of neonatal seizures like hypoglycemia and dyselectrolytemia were ruled out in both cases and control with seizures.

Apnoeic spells were seen in 6 (15%) babies in the control and 4 (10%) babies in study group. The observed difference between the two groups was also statistically not significant ($p>0.05$).

Thus, although incidence of HIE-I, HIE-II, seizures and apnoeic spells was higher in control group, as compared to study group, the differences had not reached a level to become statistically significant.

DISCUSSION

The two groups were found to be comparable for maternal age, parity, period of gestation, duration of labour, antenatal complications, regularity of maternal follow up, babies sex ratio, mean birth weight, mean gestational age, mean apgar scores and mean cord pH

One study has been published regarding use of Mg in human neonates with birth asphyxia from Poland, in 1999. In this study Maroszynska I et al infused Mg in 9 newborn babies with birth asphyxia. Brain damage was assessed by clinical examination. Babies were followed up for neurodevelopmental assessment till 12 months of age. In this study, no child with neurodevelopmental delay was found. No babies showed seizures. The findings of this study are limited by the use of very small number of cases ($n=9$), and the fact that enrolled babies had asphyxia which was anyway unlikely to produce neurological sequelae.⁴⁻⁵

Another study carried out by Gathwala G et al showed the neuroprotective range of serum magnesium in babies of birth asphyxia and the same level is safe. They also followed the study group and controls for 6 months period to assess neurodevelopment, which revealed comparatively better outcome in the study group.^{7,8}

In the present study, the short term outcome in babies receiving Mg Infusion was therefore better than those in the control group. They had a lesser incidence of HIE, seizures and apnoeic spells. Although the differences between the two groups did not reach statistical significance, Mg in the dosage schedule used by us dose appear to have some beneficial effects.

As many studies have proved the neuroprotective role of magnesium sulphate both in animals and human beings, but still there is apprehension regarding the adverse outcome of magnesium sulphate on vital parameters of babies. Only one study has been carried out in India by Geeta et al to prove the safety of magnesium sulphate in human babies.

Therefore, to regularize the use of $MgSO_4$ so as to avail its beneficial effects, its safety has to be proved on and on.

This study was therefore carried out to re-establish the safety of $MgSO_4$ infusion and to study the immediate neurological outcome in such babies.

The present study too has some limitations. Firstly, only a small number of cases were studied. Larger cases are required to document a significant reduction in adverse outcome with magnesium therapy.

Secondly, the earlier the magnesium infusion is given after asphyxial insult, the more likely that it will be beneficial/effective. We administered the initial dose of magnesium within half-an-hour at birth. Earlier administration, if feasible, would possibly be more effective.

Thirdly, because of limited period of study and other practical constraints, the babies were not followed up, to document the long-term effects of such therapy.

Therefore, as our present study mainly concentrated to prove the safety of magnesium sulphate infusion, we have documented that magnesium sulphate infusion given to babies with perinatal asphyxia in a dose of 250 mg/kg within half hour of life followed by 125 mg/kg at 24 and 48 hours respectively achieved serum magnesium levels considered to be in the neuroprotective range. Also this dosage schedule was safe and not associated with any significant side effects.

This study also observed better immediate neurological outcome in study group but the differences are less statistically significant because of drawbacks already monitored. Controlled trials with larger number of babies with follow-up for defined period to document long-term neurodevelopmental outcome is required to establish its neuroprotective role.

We recommend the dosage schedule of magnesium infusion used by us for further trials as the same has been documented to achieve serum magnesium levels in the neuroprotective range and is safe.

CONCLUSION

Short term outcome in babies given magnesium infusion was better in magnesium infused group, than those who did not receive it. The incidence of HIE, neonatal seizures and apnoeic spells were less in the magnesium infused group.

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

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