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A Randomized Controlled Trial on the Efficacy of Intravenous Magnesium Therapy in Perinatal Asphyxia in a Resource-poor Setting

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Abstract:
Objective: *This study was conducted in the Neonatal Intensive Care Unit (NICU) of a teaching hospital situated in a rural area of Bihar to ascertain the impact of postnatal magnesium sulfate ($MgSO_4$) infusion on moderately to severely asphyxiated neonates.*
Methods: *This single-blind, parallel-group, prospective, longitudinal, randomized controlled trial (RCT) was carried out to study the effect of postnatal magnesium sulfate ($MgSO_4$) infusion on the mortality and neurological morbidity of term (born at 37-42 weeks of gestation) and post-term (>42 weeks of gestation) neonates with severe perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE) stage II (moderate) or III (severe) (Sarnat & Sarnat staging) at 24 hours,at 7 days andat discharge. Fifty (50) patients of severe perinatal asphyxia with HIE stage II or above admitted over a period of 6 months were included in the study. The patients were assigned randomly in two groups- one group of 25 neonates received 3 doses of intravenous $MgSO_4$ infusion at 250 mg/kg/dose (0.5 mL/Kg/dose of inj. $MgSO_4$ (50% w/v) 24 hours apart, and the other 25 neonates did not receive this treatment. Other supportive care as per protocol for perinatal asphyxia was given to the patients in both the groups equally.*
Outcomes: *The incidence of moderate (stage II) and severe (stage III) encephalopathy at NICU admission was the same in both the groups, that is, 18 (72.0%) and 7 (28.0%), respectively. The $MgSO_4$-treated group had an eventual mortality rate of 5.6% (1 out of 18) for neonates with stage II (moderate) encephalopathy and 42.8% (3 out of 7) for those with stage III (severe) encephalopathy. On the other hand, the group that was not given $MgSO_4$ suffered a mortality of 22.2% (4 out of 18) among newborns with HIE stage II (moderate encephalopathy) and 85.7% (6 out of 7) for stage III (severe) encephalopathy.Seizures were present on day 1 in all the 18 patients (100%) with stage II (moderate) encephalopathy in both the control and the treatment groups, but while only 2 (11.1%) of them in the treatment arm still had seizures at 24 hours of admission, 6 (33.3%) of neonates with moderate encephalopathy (HIE stage II) in the control arm had electroencephalographic (EEG) evidence of active seizures at 24 hours, even though all the patients with seizures were treated according to the same standard protocol for neonatal seizures due to perinatal asphyxia. Similarly, the proportion of neonates able to feed orally by day 7 of admission was 71.4% (15 out of the surviving 21) in the $MgSO_4$-treated group, whereas only 33.3% (5 out of the surviving 15) could suckle orally by that time in the control group. At discharge, abnormal neurological findings upon examination using the NeoNeuro& Up scoring by Ellison were present in 28.6% of the surviving newborns (6 out of 21 surviving) and 24.0% (6 out of 25) of the total in the treatment group. The control group had abnormal neurological findingsin 60.0% of surviving neonates (9 out of 15 surviving) and 36.0% (9 out of 25) of the total number of babies in the control group. No significant adverse effects of $MgSO_4$ were observed at the used dosage on hemodynamic parameters and respiration.*
Conclusion: *Intravenous $MgSO_4$ therapy decreases mortality and neurological morbidity in neonates with moderate (stage II) to severe (stage III) perinatal asphyxia and improves short-term outcomes.*

I. Introduction

Perinatal asphyxia is one of the major causes of neonatalmortality and long-term morbidity (1). It causes about 18.8% of all the neonatal deaths in India, about 0.19 million per year in number (2). Improving obstetric care delivery, including antenatal check-ups, timely transportation of mothers to properly equipped hospitals and peripartum monitoring of fetal well-being, is the only way to decrease the incidence of birth asphyxia. Unfortunately, due to logistic constraints and a large, quickly growing population, improving and modernizing the obstetric care infrastructure remains very challenging in a developing country like India. Low-cost and effective interventions to decrease the mortality and short- and long-term adverse neurological

morbidity due to perinatal asphyxia are the pressing need of the hour and a hot topic for active research worldwide.

Neurological research has facilitated our understanding of the mechanisms by which perinatal asphyxia causes neuronal death and adverse consequences thereof. Asphyxia causes cerebral insult in two stages- the primaryneuronal injury that occurs at the time of the hypoxic-ischemic insult and the secondary neuronal injury that occurs over hours to days after the accumulation ofexcessive intraneuronal calcium (Ca^{2+}) through stimulation of the excitatory N-methyl–D-aspartate (NMDA) glutamate receptors, which triggers apoptosis of neurons (1). Experimental NMDA antagonist MK801 have been shown to protect the brains of animals against asphyxia, but it is so toxic that it cannot be used in human newborns (3). Mg^{2+} ion blocks the NMDA receptors in a voltage-dependent manner, prevents accumulation of calcium in the neuronal cells and cell death (4).

Studies in animal models of cerebral ischemia and hypoxia, such as adult rats (5), fetal lambs (6), and neonatal rats (7-11) have shown that $MgSO_4$ administration provided protection against both short- and long-term consequences of asphyxia. A biochemical study also showed beneficial effects of $MgSO_4$ on vital ATP-dependent enzymes (Ca^{2+}-ATPase and protein kinase A and C) and band 3 protein in the RBC membranes of asphyxiated human newborns (12). Magnesium has already been established as the therapeutic anticonvulsant of choice in maternal eclampsia on the basis of significant evidence (13). Beneficial effects of maternal administration of intravenous $MgSO_4$ on the survival of preterm babies $\leq$30 weeks of gestation and their neurological prognosis by the age of 2 years has also been validated in a large multicenter RCT (the Australasian Collaborative Trial of $MgSO_4$ (ACTO$MgSO_4$) (14). A recent Cochrane database review also suggested that prenatal magnesium administration to mothers at risk for preterm delivery was beneficial in the prevention of cerebral palsy in premature babies (15).

Hence, therapeutic trials of intravenous $MgSO_4$ in asphyxiated neonates have been conducted in many centers around the world (1, 16-20) and most of them have found it to be safe and effectivefor improving their survival and short-term and long-term neurological prognosis. Most systematic literature reviews have also corroborated this finding to various extents (21-26).

II. Aims And Objectives

This study was designed to assess the effects of intravenous $MgSO_4$ therapy on the survival and short-term neurological prognosis of term newborns with perinatal asphyxia in a tertiary teaching hospital in the rural area of Bihar, one of the poorest and most backward states of India, where a substantial number of neonates suffer from the morbidity and mortality due to birth asphyxia.

III. Material And Methods

This studywas conducted in the neonatal intensive care unit of a tertiary teaching institution (Narayan Medical College, Jamuhar)situated inRohtas district of Bihar, India, which is a rural area in one of the most backwardstates of the country.Fifty (50) patients of moderate to severe perinatal asphyxia with HIE stage II or above admitted over a period of 6 months were included. These patients were randomized into two groups of 25 each- one group (intervention group) received 3 doses of intravenous $MgSO_4$ infusion at 250 mg/kg/dose (0.5 mL/Kg/dose of inj. $MgSO_4$ (50% w/v) diluted in 5 mL/Kg of 5% dextrose infused slowly @ 25 mg/minute) 24 hours apart, and the other group (control) did not receive this treatment. Other supportive care as per standard protocol for perinatal asphyxia was given to the patients in both the groups equally. The baseline characteristics of the two groups, such as gender ratio, gestational ages, birth weights and the ratio of stage II (moderate) and stage III (severe) hypoxic-ischemic encephalopathy were matched. The Sarnat & Sarnat classification of hypoxic-ischemic encephalopathy (27) was used for this study. Only neonates admitted within 6 hours of birth were included in the study in both the $MgSO_4$ group and the control group and intravenous $MgSO_4$ infusion was started within 6 hours of birth in all the patients in the intervention arm.

The statistical details of the two groups are charted in table 1, which shows that the two groups were well-matched on several characteristics, including gestational age, gender ratio, Apgar scores at 1 minute and 5 minutes, cord arterial blood pH and the ratio of cases withmoderate (stage II) and severe (stage III) encephalopathy.

	Intervention group	**Control group**
Male:Female ratio	1.78 (16:9)	1.78 (16:9)
Ratio of HIE stage II and stage III	2.57 (18:7)	2.57 (18:7)
Male:Female ratioin cases with HIE stage II	1.25 (10:8)	1.25 (10:8)
Male:Female ratioin cases with HIE stage III	1.33 (4:3)	1.33 (4:3)
Mean gestational age	278.9 days (39 weeks 5.9 days)	275.5 days (39 weeks 2.5 days)
Range of gestational age	259-305 days (37 weeks-43 weeks 4 days)	259-300 days (37 weeks-42 weeks 6 days)
Median gestational age	275.0 days (39 weeks 2 days)	273.0 days (39 weeks)

Standard deviation	14.8 days	13. 1 days
25th percentile	266.0 days	264.0 days
75th percentile	292.5 days	284.0 days
Standard error of mean	2.96 days	2.62 days
Mean birth weight	2945 grams	2925 grams
Range of birth weight	2363-4038 grams	2323-3856 grams
Median birth weight	2894 grams	2853 grams
Standard deviation	440.0 grams	411.2 grams
25th percentile	2617 grams	2610 grams
75th percentile	3257 grams	3172 grams
Standard error of mean	88.0 grams	82.2 grams
Mean Apgar score at 1 minute (Range)	1.68 (1.45-1.91)	1.73 (1.56-1.93)
Mean Apgar score at 5 minutes (Range)	4.78 (4.68-4.88)	4.80 (4.70-4.90)
Mean cord arterial blood pH (Range)	6.85 (6.82-6.88)	6.87 (6.83-6.91)

Table 1

The vital parameters, circulatory and respiratory status and neurological status, including sensorium, tone, primitive, postural and deep tendon and superficial reflexes, especially rooting, sucking and suck-swallow co-ordination of all the newborns were monitored. All the patients were kept under continuous surveillance for clinical and/oraugmented electroencephalographic (aEEG) evidence of seizures. Oxygen therapy for respiratory distress, maintenance intravenous fluids, intramuscular vitamin K (1 mg) single dose at birth, correction of metabolic disturbances like hypoglycemia and hypocalcemia, intravenous antibiotics (ampicillin and cefotaxime) in case of evidence of sepsis, intravenous anticonvulsants for seizures (first phenobarbitone, then phenytoin if phenobarbitone failed, then levetiracetam as add-on therapy if phenytoin also failed and finally midazolam infusion), physiotherapy and enteral feedings when feasible were given to all the patients in both the groups on an as-needed basis.

The four main outcomes studied for the two groups were- mortality, presence or disappearance of clinical and/or electroencephalographic seizures at 24 hours of admission in patients with moderate (stage II) encephalopathy, ability to feed orally (suckling directly from the mother's breast where feasible or accepting formula feeds with spoon administered by nurses) by day 7 of life, andpresence or absence of neurological abnormalities upon detailed neurological examination using the NeoNeuro& Up scoring chart by Ellison (28)at the time of discharge.

IV. Results

The $MgSO_4$-treated (intervention) group had an eventual mortality rate of 5.6% (1 out of 18) for neonates with stage II (moderate) encephalopathy and 42.8% (3 out of 7) for those with stage III (severe) encephalopathy, with a total mortality rate of 16.0% (4 out of 25). On the other hand, the control group that was not given $MgSO_4$ suffered a mortality of 22.2% (4 out of 18) among newborns with HIE stage II (moderate encephalopathy) and 85.7% (6 out of 7) for stage III (severe) encephalopathy, with a total mortality rate of 40.0% (10 out of 25), which was 2.5 times higher than the intervention group. The specific mortality rates for HIE stage II and III also were four times and twice as high, respectively, in the control group than the group treated with intravenous magnesium. However, as table 2 shows, these differences were not statistically significant because of the small sample sizes.

	Intervention group	**Control group**
Total patients with HIE stage II	18	18
Patients with HIE stage II who died	1	4
Mortality in patients with HIE stage II	5.6%	22.2%
Total patients with HIE stage III	7	7
Patients with HIE stage III who died	3	6
Mortality in patients with HIE stage III	42.8%	85.7%
Overall mortality	16.0% (4/25)	40.0% (10/25)
p-value by Fischer's exact test	0. 11(Not significant)	
Relative risk of mortality	0.40	

Table 2

All the 18 patients (100%) with stage II (moderate) encephalopathy had seizures on day 1 in both the control and the treatment groups, but while only 2 (11.1%) of them in the treatment arm still had seizures at 24 hours of admission, 6 (33.3%) of neonates with moderate encephalopathy (HIE stage II) in the control arm had active seizures at 24 hours, even though all the patients with seizures were given the same standard treatment. Similarly, the proportion of neonates able to feed orally by day 7 of admission was 71.4% (15 out of the surviving 21) in the $MgSO_4$-treated group, whereas only 33.3% (5 out of the surviving 15) could suckle orally by that time in the control group. At discharge, abnormal neurological findings upon examination using the NeoNeuro& Up scoring by Ellison were present in 28.6% of the surviving newborns (6 out of 21 surviving) and

24.0% (6 out of 25) of the total in the treatment group. The control group had abnormal neurological findings in 60.0% of surviving neonates (9 out of 15 surviving) and 36.0% (9 out of 25) of the total number of babies in the control group. The combined proportion of neonates with adverse outcome (death or neurological abnormality at discharge) was almost twice as high in the control group as in the $MgSO_4$-treated group (76% vs 40%). No significant adverse effects of $MgSO_4$ were observed at the used dosage on hemodynamic parameters and respiration. The data on the neurological outcome of the two groups is presented in table 3.

	Intervention group	**Control group**
Seizures on admission	100% (18/18)	100% (18/18)
Seizures continued at 24 hours	11. 1% (2/18)	33.3% (6/18)
Patients able to feed orally by day 7	71.4% (15/21)	33.3% (5/15)
Abnormal neurological findings at discharge (% of total neonates)	24.0% (6/25)	36.0% (9/25)
Abnormal neurological findings at discharge (% of surviving neonates)	28.6% (6/21)	60.0% (9/15)
Neonates with adverse outcome (death or neurological abnormality)	40.0% (10/25)	76.0% (19/25)

Table 3

As is obvious from the results of our study presented above, intravenous $MgSO_4$ therapy started within 6 hours of birth in term newborns with perinatal asphyxia and moderate (Sarnat stage II) to severe (Sarnat stage III) hypoxic-ischemic encephalopathy reduces mortality and short-term neurological morbidity (seizures and abnormal neurological signs).

V. Discussion And Conclusion

Many other studies have reported beneficial therapeutic effects of intravenous $MgSO_4$ in asphyxiated neonates with moderate to severe encephalopathy. Bhat et al (16) conducted a prospective, longitudinal, randomized placebo-controlled trial in 40 term infants with moderate and severe birth asphyxia, giving 3 doses of intravenous $MgSO_4$ (250 mg/Kg/dose)to half of them and 1 mL/Kg/dose of normal saline (NS) to the other half. Even though the proportion of moderate and severe encephalopathy was similar in both the groups and they were randomized to exclude confounding factors like birth weight and gender ratio, the incidence of neurologic abnormalities in the placebo group (56%) was about 2.5 times as high as in the $MgSO_4$- treated group (22%), abnormalities on CT scan of brain were observed in the placebo group in almost 3 times as many patients as in the intervention group (16% vs 44%) and favorable short-term neurologic outcome and the rate of resumption of oral feeding by discharge also was twice better in the treatment group (77% vs 37%). They did not detect any difference in mortality, however.

Similarly, in another single-blind RCT conducted by Hossain et al in Bangladesh (17), 50 term newborns aged less than 12 hours were randomized into two groups matched on gestational age, weight, mode and place of delivery, ANC, maternal parity, liquor colour, HIE stage and mean age of intervention- one receiving 3 doses of intravenous $MgSO_4$ and the other getting 3 doses of normal saline (NS). Even though the EEG characteristics were similar, the treatment group had less neurologic abnormalities at discharge (26% vs 61%), better short-term outcome (60% vs 32%) and more newborns feeding orally (78% vs 44%).

In yet another multicenter RCT conducted by Ichiba et al with the Kansai Magnesium Study Group (18), 33 neonates with severe birth asphyxia were assigned to two groups randomized and matched on perinatal factors and the severity of encephalopathy, one of them was treated with intravenous $MgSO_4$ (250 mg/Kg/dose) once daily for 3 days and the other was not given this treatment. Entry criteria included 5-minute Apgar score of seven or less and either failure to initiate spontaneous respiration at 10 minutes after birth because of asphyxia, or occurrence of clinically apparent seizures within 24 hours after birth. Survival with normal findings on cranial CT and EEG and establishment of oral feeding by day 14 was more in treatment group (70.6%, 12/17) than in the control group (5/16).

Gathwala et al (1) conducted an RCT at a tertiary teaching hospital in Rohtak, India upon 40 term neonates randomized into two groups of 20 each and administered 3 doses of intravenous $MgSO_4$ (first 250 mg/Kg, followed by two doses of 125 mg/Kg each, 24 hours apart). While there was no difference in mortality (10% for both) between the groups, they, too, found lower rates of abnormalities on CT brain (37.5%, 6/16 vs 62.5%, 10/16) and EEG (31.25%, 5/16 vs 43.75%, 7/16), lower incidence of seizures (35%, 5/16 vs 50%, 8/16) and abnormal findings on Denver II developmental scale (18.8%, 3/16 vs 31.2%, 5/16) in the group that was treated with $MgSO_4$. Maroszynska et al (20) also reached the same conclusion after their observational study of intravenous $MgSO_4$ therapy in 9 term newborns with birth asphyxia.

Systematic reviews by Marret et al (21), Westermaier et al (22), Vink et al (23), McGuire (24), Perlman (25) andBuonocore et al (26) have alsoshown that treatment of term newborns with moderate to severe birth asphyxia with intravenous $MgSO_4$ is safe and effective in significantly reducing the mortality and short- and long-term neurological morbidity in these patients. The results of our study, conducted in a hospital situated in a

rural area of one of the most backward states of India, agree with the conclusions by the above researchers and reviewers, even though the results might not have reached statistical significance due primarily to a relatively small sample size. Given the fact that birth asphyxia accounts for about 19% (0.19 million deaths annually) of all neonatal deaths (1.01 million annually) in India (29), and that our health infrastructure at the grassroots level is rudimentary at best with a huge shortage of funds and logistic support, a cheap and easily available treatment such as magnesium sulphate ($MgSO_4$) would be nothing short of a miraculous boon. More studies on the safety and efficacy of $MgSO_4$ in the treatment of perinatal asphyxia, preferably multicentre RCTs to maximize the number of subjects in order to erase statistical shortcomings are definitely the need of the hour.

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