How to Cite:
Nanda, A. K., Jalan, A., Pradhan, S. K., Kumar, T. V. R., & Pradhan, P. C. (2022). Effect of magnesium sulphate infusion on neonatal outcomes in babies with perinatal asphyxia: A randomized controlled trial. *International Journal of Health Sciences*, *6*(S2), 13064–13075. https://doi.org/10.53730/ijhs.v6nS2.8450

Effect of magnesium sulphate infusion on neonatal outcomes in babies with perinatal asphyxia: A randomized controlled trial

Dr. Ashok Kumar Nanda
Asst. Prof., Department of Pediatrics, MKCG Medical College, Berhampur

Dr. Arpita Jalan
Resident, Department of Pediatrics, MKCG Medical College, Berhampur

Dr. Santosh Kumar Pradhan
Asst. Prof., Department of Pediatrics, MKCG Medical College, Berhampur

Dr. T V Ram Kumar
Associate professor, Department of Pediatrics, PRM, MCH, Baripada

Dr Purna Chandra Pradhan
Assistant Professor, Community Medicine Department, SLN Medical College & Hospital, Koraput
Corresponding author email: purnapradhan71@gmail.com

***Abstract*---**Introduction- With a relatively scant evidence base in Indian population, this study aimed to determine the efficacy of intravenous magnesium sulphate in neonates with moderate to severe perinatal asphyxia on the severity of seizures, number of anticonvulsants used, duration of hospitalization and feeding pattern at discharge. Methodology- This was a non-blinded randomized controlled trial that was conducted among 227 neonates admitted to the SNCU of MKCG Medical College Hospital. Randomization and allocation of eligible neonates was done using software. The intervention used was magnesium sulfate given intravenously by trained pediatricians in a loading dose of 250 mg/kg/dose, given over 1 hour in 20 ml of 5% dextrose solution. This was given at the time of admission followed by two infusions of the same dosage after 24 and 48 hours of the first dose. Outcomes on neonatal feeding, survival, need for medications and seizure management were recorded and analysed using an intention to treat protocol. Results- The distribution of most clinico-social parameters were comparable between the 2 groups. The babies who received MgSO4 within 6 hours of life achieved earlier initiation of feeds (32 hours) as compared to

control groups (63 hrs). They also reached full feeding significantly earlier. The number of babies having shock and requiring ionotropic support was higher in the control group. Most of the babies in the intervention group responded to a single anticonvulsant, whereas the requirement of multiple types of antiepileptic drugs (AED) for seizure control were more in the control arm. The number of neonates who got discharged were significantly more in the intervention group. Babies in whom MgSO4 was initiated early (<6 hours), the mean duration of hospital stay was significantly reduced in intervention arm (9.09 days) as compared to control arms (6.22 days). Conclusion- IV magnesium sulphate is safe and effective in improving neonatal outcomes in babies with moderate to severe asphyxia birth asphyxia.

***Keywords*---**neonates, magnesium, seizures, RCT.

Introduction

Perinatal asphyxia (PA) is defined as a failure to initiate and sustain breathing at birth. (1) This asphyxia is primarily antepartum in origin in 50% of cases, intrapartum in 40%, and postpartum in the remaining 10% of cases, and is usually secondary to pulmonary, cardiovascular or neurologic insufficiency. (2) A common way to classify the severity of PA is using APGAR scores. Moderate PA is classified by slow/gasping breathing or an APGAR score of 4 to 6 at 1 minute of life and Severe PA by no breathing or an APGAR score of 0-3 at 1 minute of age. (3)

The incidence of PA is significant at around 8.4% of all live births and is directly related to a third of neonatal deaths and the most common cause of still births. (3) This is significantly lower in developed countries at 1.5 % of live births, indicating an inverse relationship to better obstetric/neonatal care, gestational age, and birth weight. A higher incidence is also reported in newborns of diabetic or toxemic mothers, those with intrauterine growth restriction, breech presentation, and newborns who are postdated. (4) PA is a major cause of neonatal and under-5 mortality in developing countries accounting for 9.4% of the total under-5 mortality worldwide. (5,6) Post-natal management of PA involves a set of strategies aimed to maintain oxygenation, stabilize vitals, controlling seizures, and other neuroprotective strategies. (7) An important tool that has multifaceted roles in the management of PA is Magnesium Sulfate (MgSO4). It has the following direct and indirect roles influencing PA:

- In treatment of neonatal hypomagnesemia and refractory neonatal hypocalcemia. (8)
- Antenatal MgSO4 therapy in mothers for eclampsia and preterm labour showed a lower incidence of cerebral palsy and intra-ventricular hemorrhage. (9–11)
- In treatment of persistent pulmonary hypertension of the newborn. (12)
- As an effective acute bronchodilator in severe acute asthma. (13)
- MgSO4 si linked to neuronal protection through a wide array of possible mechanisms of action. (14–17)

There is significant evidence, mostly in western settings, on the effect of injection MgSO4 in term neonates with PA inproviding neurologic benefit, reducing seizures, better feeding and survival indicators. (18–21) However, a systematic review and meta-analysis has shown that improvements in short-term outcomes without significant increase in side effects indicate the need for further trials to determine. (22) Importantly, evidence on the role of the neonate's age at initiation of MgSO4 therapy is not clear. With a relatively scant evidence base in Indian population, this study was planned with an objective to determine the efficacy of intravenous magnesium sulphate in neonates with moderate to severe perinatal asphyxia on the severity of seizures, number of anticonvulsants used, duration of hospitalization and feeding pattern at discharge.

Methodology

Research question

Our research question was to test whether IV MgSO4 among neonates with PA improved outcomes mentioned above and what, if any, is the role of age at initiation of therapy in effecting these outcomes.

Design and setting

We used a non-blinded randomized controlled design to test the efficacy of the intervention detailed below. The study was carried out at the Small Newborn Care Unit (SNCU) of the Department of pediatrics at MKCG Medical College, Berhampur, between 2019 – 2022.

Participants

The participants in the trial were recruited from among neonates admitted to the SNCU with moderate to severe perinatal asphyxia. We included neonates with moderate to severe perinatal asphyxia as manifested by one of the followings : an APGAR score of < 3 at 1 minute or <7 at 5 minutes or with moderate to severe encephalopathy in the form of lethargy, stupor, coma, abnormal reflexes, weak suck or seizure within 24 hours of birth along with a history of delayed cry at birth. We excluded neonates with evident congenital malformations or proven chromosomal disorders as well as those with proven inborn errors of metabolism. Parents who refused informed consent were also excluded from the trial.

Sample Size

On the basis of previous studies, it was estimated that at least 40 neonates with moderate/ severe PA had to be studied for detecting a 50% reduction in the rate of adverse outcomes with 80% power. (23) To allow for sufficient power for performing subgroup analyses based on age groups, this sample size was replicated in each of the three subgroups, thereby requiring 120 participants in each arm.

Intervention and control

In the intervention group, magnesium sulfate was given intravenously by trained pediatricians in a loading dose of 250 mg/kg/dose, given over 1 hour in 20 ml of 5% dextrose solution. This was given at the time of admission followed by two infusions of the same dosage after 24 and 48 hours of the first dose. This intervention was given in addition to the standard treatment for PA followed at the institute. In the control group, neonates received the standard treatment alone.

Randomization and allocation

We followed individual participant randomization and allocation for the trial. Upon admission, the admission registration numbers of the babies who were assessed for eligibility and included in the trial were allocated into the intervention or control group using an R-software based computer program. (24)

Outcomes

The primary outcome assessed in the trial was the severity of seizures in neonates measured by the frequency of convulsions. The secondary outcomes assessed were the number and types of anticonvulsants used, duration of and events during hospitalization, death or discharge status, and feeding pattern at discharge (classified into Oro-Gastric Tube feeding-OGTF, Katori Spoon feeding-KSF and Direct Breast Feeding- DBF).

Data collection

Data from the participants was collected using a standardized electronic data capture tool through direct clinical examinations, history taking, laboratory investigations, and medical records available. Apart from the outcome measures included, data related to maternal clinical profile such as age, parity, mode of delivery, maternal risk factors and prenatal magnesium sulphate in mothers was collected. We also collected data on the clinical profile and progress of neonates at and during admission, APGAR scores at 1 and & 5 minutes, grading for hypoxic ischemic encephalopathy, treatment history, and anthropometric and vital measurements. Additionally, all participants underwent laboratory panel of investigations that included sepsis screen, serum creatinine, sodium and potassium.

Subgroup analysis

The enrolled babies were grouped further into three categories based on the age at enrolment in hours into the study. The groups included were- less than 6 hours, 6 to 24 hours and beyond 24 hours of life.

Analysis plan

The data was exported into excel sheets and were checked for completeness and major entry errors. The cleaned data were analyzed by Intention To Treat (ITT) analysis using R software packages. Appropriate tests of significance were used to

compare various parameters. Summary measures for continuous data were expressed as means with standard deviations and for categorical data, frequencies were used. The level of statistical significance was pre-set at a p-value of less than 0.05.

Ethical concerns

Written informed consent was obtained from all mothers/parents of the participating babies. Parents were free to withdraw from the trial at any point of time without affecting the treatment procedures. Institutional Ethical Committee clearance was taken before starting this trial.

Results

A total of 250 neonates were eligible to participate in the trial among 227 were distributed between the intervention(n=116) and control(n=111) group. The study flow diagram is provided in figure-1.

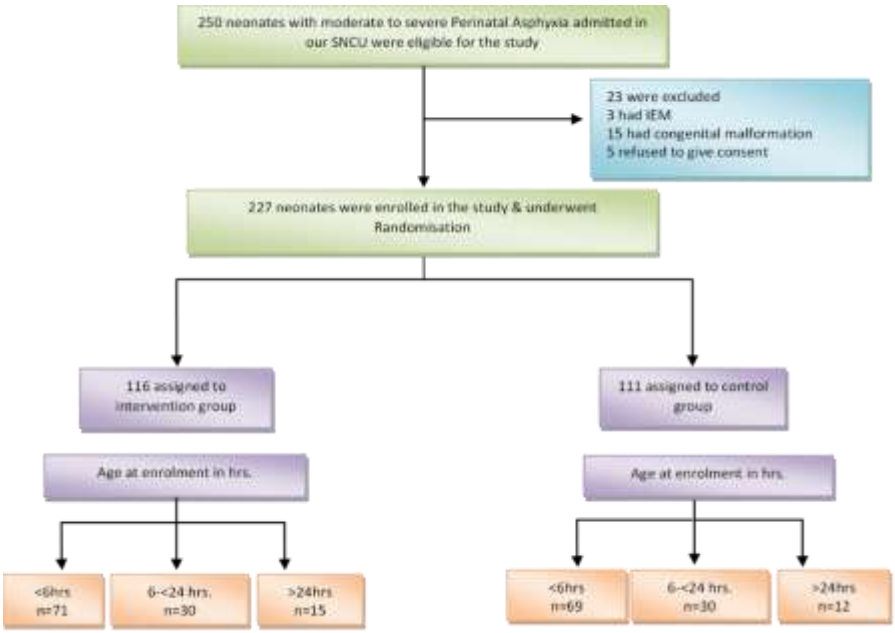

Figure 1. Study flow diagram for selection of intervention and control group participants

Most of the mothers were primis with a mean age of 23.7 years (± 2.2 years) and vaginal delivery was the most common mode of delivery in both in the intervention (73.3%) and control (70.3%) arms. The distribution of gender ratios, gestational age, birth weight, APGAR scores, and perinatal risk factors was comparable between the groups as shown in the table-1 below. Similarly, all bio-physiological and laboratory parameters were also similar across groups and sub-groups with statistically non-significant p-values.

Table-1. Comparison of descriptive variables between intervention and control groups							
Parameters		Age at enrollment in hrs.					
		<6hrs		6-24hrs		>24hrs	
Groups		I (n=71)	C (n=69)	I (n=30)	C (n=30)	I (n=15)	C (n=12)
1.Age of mother in years(mean)		23	24	25	24	23	23
2.Parity	Primi	40	45	15	18	10	6
	Multi	25	16	13	12	4	3
	Grand multi	6	8	2	0	1	3
3.Mode of delivery	Vaginal	52	47	24	22	9	9
	Assisted vaginal	7	7	4	5	4	2
	LSCS	12	15	2	3	2	1
4.Gender	Male	51	37	21	14	10	10
	Female	20	32	9	16	5	2
5.Gestational age	Preterm	12	11	7	7	0	2
	Term	55	52	21	21	14	9
	Post term	4	6	2	2	1	1
6.Mean birth weight(mean in grams)		2703	2750	2690	2848	2840	2511
7.Growth	Average for Gestaional Age	52	55	25	26	11	19
	Small for Gestational Age	19	14	5	4	3	3
	Large for Gestational Age	0	0	0	0	1	0
8. Place of delivery	Same hospital	40	41	4	3	2	0
	Referred from outside	31	28	26	27	13	12
9.APGAR score at 1 mins	<3	15	16	4	4	1	1
10.APGAR score at 5 mins	≤3	9	19	0	5	1	1
	≤7	32	14	54	9	4	3
11.Baseline vitals (Mean)	Respiratory Rate/min	59	62	67	71	59	60
	Heart Rate/min	142	146	142	141	141	135
	SpO_2 (%)	87	81	92	88	86	73
	NIBP (mm Hg)	46	40	43	44	45	40
12.Sepsis screen	Positive	47	44	15	18	10	4
	Negative	18	21	13	9	3	3
13.Serum creatinine(mg/dl) (mean)		1.00	1.11	0.65	1.69	0.98	1.20
14.Serum sodium(mg/dl) (mean)		138	142	140.5	145.5	139	141
15. Serum potassium(mg/dl) (mean)		4.89	5.20	4.80	5.66	4.95	5.12
I= Intervention group, C= Control group							

Overall, favourable outcomes were more frequent in the intervention group. The babies who received MgSO4 within 6 hours of life achieved earlier initiation of feeds (32 hours) as compared to control groups (63 hrs). They also reached full feeding significantly earlier. The number of babies having shock and requiring

ionotropic support was higher in the control group. Most of the babies in the intervention group responded to a single anticonvulsant, whereas the requirement of multiple types of antiepileptic drugs (AED) for seizure control were more in the control arm. The detailed clinical profile and outcome metrics are shown in table-2 below.

Table-2. Comparison of clinical profile and outcomes of the participants from each group

Parameters		Age at enrollment in hrs.					
		<6hrs		6-24hrs		>24hrs	
Groups		Intervention N, (%)	Control N, (%)	Intervention N, (%)	Control N, (%)	Intervention N, (%)	Control N, (%)
1. HIE Grade	HIE-2	56 (78.9%)	32 (46.4%)	26 (86.7%)	23 (76.7%)	13 (86.7%)	9 (75.0%)
	HIE-3	15 (21.1%)	37 (53.6%)	4 (13.3%)	7 (23.3%)	2 (13.3%)	3 (25.0%)
2.Age of feeding in hours (mean)	Initiation of 1st feeds	31.94	50.15*	35.6	47.7	32.66	56.5
	Full feeds	121.5	156.7*	123.8	159.5	120.00	149.166
3. Antibiotic required		69 (97.2%)	68 (98.6%)	28 (93.3%)	28 (93.3%)	14 (93.3%)	8 (66.7%)
4.Oxygen required		50 (70.4%)	62 (89.9%)	23 (76.7%)	25 (83.3%)	10 (66.7%)	8 (66.7%)
5.Shock (requiring inotropes)		23 (32.4%)	39 (56.5%)	11 (36.7%)	8 (26.7%)	2 (13.3%)	9 (75.0%)
6. No. of Ionotropes required	Dob	9 (12.7%)	7 (10.1%)	3 (10.0%)	4 (13.3%)	1 (6.7%)	2 (16.7%)
	Dob+Dop	8 (11.3%)	16 (23.2%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
	Dob+Dop+Adr	5 (7.0%)	15* (21.7%)	1 (3.3%)	2 (6.7%)	0 (0.0%)	1* (8.3%)
7. Mean NIBP at 72 hours (mmHg)		42	38	44	40	39	40
9. No. of convulsions	1	28 (39.4%)	6 (8.7%)	10 (33.3%)	1 (3.3%)	8 (53.3%)	0 (0.0%)
	2-5	35 (49.3%)	39 (56.5%)	18 (60.0%)	18 (60.0%)	4* (26.7%)	8 (66.7%)
	>5	1* (1.4%)	8 (11.6%)	1* (3.3%)	8 (26.7%)	3 (20.0%)	2 (16.7%)
10.AED used	Pheno	58 (81.7%)	28 (40.6%)	25 (83.3%)	7 (23.3%)	11 (73.3%)	1 (8.3%)
	Pheno+ Pheny	4 (5.6%)	17 (24.6%)	1 (3.3%)	12 (40.0%)	1 (6.7%)	3 (25.0%)
	Pheno+Pheny+ Lev	0 (0.0%)	5 (7.2%)	1 (3.3%)	2 (6.7%)	1 (6.7%)	1 (8.3%)
	Pheno+Pheny+ Lev+Midaz	1 (1.4%)	3 (4.3%)	0 (0.0%)	5 (16.7%)	1 (6.7%)	1 (8.3%)
11. Final Outcome	Discharge	57* (80.3%)	33 (47.8%)	22 (73.3%)	21 (70.0%)	13* (86.7%)	5 (41.7%)
	Death	14*	36	8	9	1*	3

		(19.7%)	(52.2%)	(26.7%)	(30.0%)	(6.7%)	(25.0%)
	LAMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
12. Feeding pattern at discharge	OGTF	3 (4.2%)	5 (7.2%)	4 (13.3%)	5 (16.7%)	1 (6.7%)	1 (8.3%)
	KSF	19 (26.8%)	13 (18.8%)	4 (13.3%)	12 (40.0%)	7 (46.7%)	2 (16.7%)
	DBF	34* (47.9%)	15 (21.7%)	14* (46.7%)	4 (13.3%)	6* (40.0%)	0 (0.0%)
13.Mean Duration of hospital stay in days		9.09	6.22	10.04	9.96	11.07	5.88
Total		71 (100%)	69 (100%)	30 (100%)	30 (100%)	15 (100%)	12 (100%)

*Legend- * Significant at p<0.05; Dob-Dobutamine,Dop-Dopamine,Adr-Adrenaline,Pheno-Phenobarbitone, Pheny-Phenytoin, Lev-Levetiracetam, Midaz-Midazolam, LAMA- Left against medical advice, OGTF- Oro-gastric tube feeding, KSF-Katori-Spoon feeding, DBF- Direct Breast Feeding*

In our study, the number of neonates who got discharged were significantly more in intervention group as compared to control, and this was seen across all subgroups as shown in figure-2.

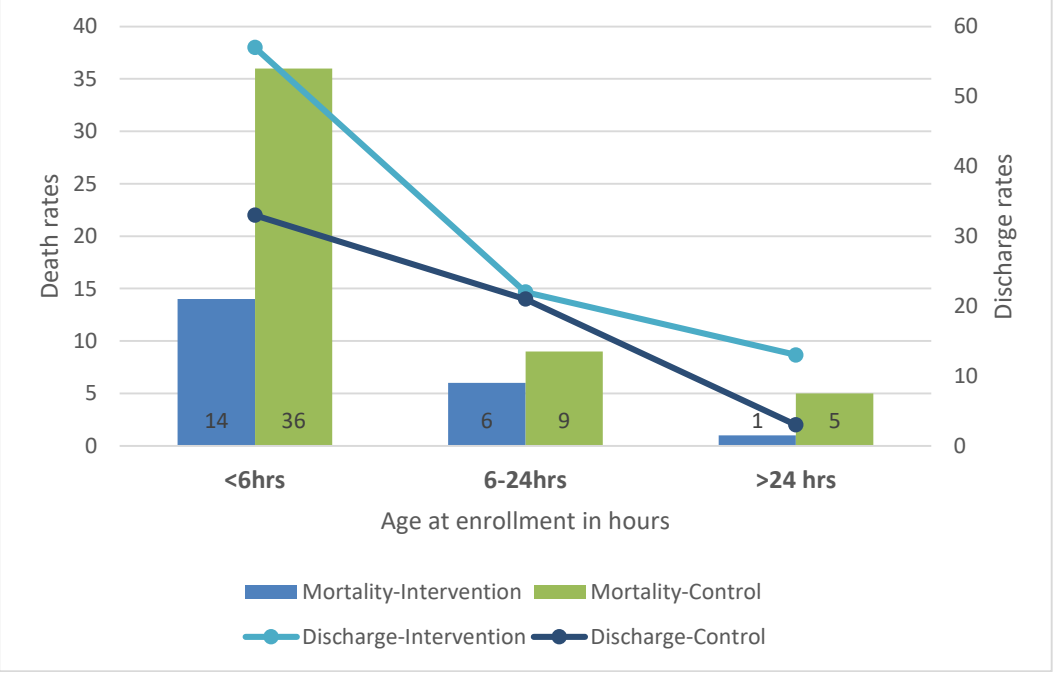

Figure 2. Mortality and Discharge rates of intervention and control groups

Our study also showed that the feeding pattern at discharge for babies was significantly favorable (establishment of breast feeding and/or Katori spoon feeding) for babies receiving MgSO4 irrespective of the age of enrolment. Among those babies in whom MgSO4 was initiated early (<6 hours), the mean duration of

hospital stay was significantly reduced in intervention arm (9.09 days) as compared to control arms (6.22 days).

Discussion

Perinatal asphyxia is an important cause of mortality and morbidity among children in the developing countries and this trial among 227 neonates reported the effects of IV MgSO4 in managing PA compared by age of the baby. MgSO4 did not adversely effect the babies vitals such as heart rate, oxygen saturation, respiratory rate or blood pressure. Other laboratory parameters such as serum sodium, potassium, creatinine and sepsis screen were similar across intervention and control groups. MgSO4 significantly improved outcomes in terms of convulsions, early feeding parameters, survival, hospital stay, requirements for ionotropes and antiepileptics.

While very few other studies have evaluated the effect of MgSO4 in neonates with PA, our study is unique in its approach for subgroup analysis based on age of MgSO4 administration. (21,25,26) A pilot study by Pius et.al had attempted a sub-group analysis, however, being a pilot trial, the findings were underpowered requiring further validations. As with most studies that assess adverse materno-fetal outcomes in developing countries, most of our babies' mothers were primigravidas. This is possibly due to a higher incidence of complications and adverse events following poorer knowledge and care seeking in primis.

Frequency of most descriptive characteristics, including APGAR scores at baseline and perinatal risk factors were comparable in 2 groups in our study. Delivery through meconium stained amniotic fluid was the most frequent risk factor, which has been previously reported as well. (21,26) No significant effect of MgSO4 on vitals of the babies during their hospital stay was seen, and similar findings have been reported previously. (21,26,27) The NIBP remained unchanged over 72 hours of magnesium sulphate administration. Some studies have reported hypotension associated with MgSO4 but we did not find any significant association in our study, perhaps due to a lower dose used here. (28,29)

In our study, magnesium sulphate was given in a loading dose of 250mg/kg at the time of admission followed by two infusions of same dose at 24 and 48 hours of first dose. This is the most common dosage regimen tested by others. We found this dose to be safe. Early administration of MgSO4 was associated with earlier initiation of feeds reached full feeding earlier. While similar results have been reported by others, very few studies have looked at feeding patterns in case of MgSO4 administration beyond 6 years of life. (18,21,26,30) We found a trend of achieving earlier feeding in the intervention group for babies receiving drug beyond 6 hrs of life as well, but this was not statistically significant.

The number of babies having shock and requiring ionotropic support was higher in the control group. Similarly, the number of ionotropes required to manage the shock was also higher in the control group. A higher requirement of pressor agents in intervention arms have been reported by Bhat et. al. and Ichiba et.al. (18,21) However, the significantly smaller sample sizes of these studies as compared to ours make generalizations difficult.

The number of babies having seizures was slightly more in the intervention arm in our study. The reason possibly is related to the higher number of babies with HIE-3 in this arm who were sick but had no convulsion. However, the total episodes of convulsions were significantly less in the MgSO4 group and consequently these babies required fewer number of antiepileptics for the control of seizure. While most of the previous studies have looked at the occurrence and duration of seizures, they have not included the total episodes of convulsions and the number of anticonvulsant drugs required. (18)

The mortality was significantly higher in the control arm in all subgroups of our study. Varying results in this outcome have been reported previously with most studies showing no difference between intervention and control groups. (18,21,25,26,28,30–32) A systematic review by Tagin et.al even reported a trend toward an increase in mortality in the magnesium group. (22) This difference could be attributed to the variation in the number of doses of magnesium in the studies included in the meta-analysis as well as the small sample sizes of all the studies. All previous studies had low sample sizes below 50 participants and subsequently the confidence on our findings is greater.

Our study showed that the feeding pattern at discharge for babies was significantly favourable for babies receiving MgSO4 irrespective of the age of starting the infusion. Similar findings have been noted by other studies for those receiving drug within 6 hours of life. (18,21,25,26,28,30) This is possibly related to neuroprotection offered by magnesium, resulting in earlier recovery from abnormal neurological features of ischemia. The mean duration of hospital stay was significantly lesser in intervention arm in the group getting MgSO4 within 6 hours of birth. However, this was not seen in other age groups, signifying that early initiation of therapy has more impact on hospital stay as compared to other outcomes.

A major strength of our study is the large sample size that powers all the subgroup analyses adequately. The subgroup analysis performed provide valuable data on previously ambiguous findings. Our study had some limitations. The care giver did have knowledge of the intervention, and this could potentially introduce bias. However, we have attempted to address this by relying on a blinded data collector and clinical evaluator. We used clinical definition for identification of our cases instead of laboratory markers such as umbilical cord pH and base deficit for diagnosis. We also did not collect the EEG and neuroimaging results in our study. As the availability of these tools is severely limited in low-income settings, which is our target population, our study's reliance on clinical diagnosis remains relevant.

Conclusion

IV magnesium sulphate is safe and effective in improving neonatal outcomes in babies with moderate to severe asphyxia birth asphyxia. This intervention is associated with improved feeding, lesser need of ionotropes or anti-epileptics, better control of seizures and improved rates of survival. The beneficial effect is most when administered within 6 hours of life, however, similar trend is evident even beyond 6 hours.

References

1. World Health Organization. Perinatal mortality: a listing of available information [Internet]. Available from: FRH/MSM.96.7.Geneva:WHO,1996.
2. Dilenge ME, Majnemer A, Shevell MI. Long-term developmental outcome of asphyxiated term neonates. J Child Neurol. 2001;16:781–92.
3. Report of the National Neonatal Perinatal Database. India: National Neonatology Forum; 2003.
4. Cloherty and Stark's manual of neonatal care. In: Chapter 55,Perinatal Asphyxia and Hypoxic -Ischemic Encephalopathy;p794. South Asian. Philadelphia: Wolters Kluwer; 2021. p. 800.
5. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;5;375(9730):1969-87.
6. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Lancet's Stillbirths Series steering committee. Stillbirths: Where?When? Why? How to make the data count? Lancet. 2011;23;377(9775):1448-63. Epub2011 Apr 13.
7. Volpe JJ. Neurology of the Newborn. Philadelphia: WB Saunders Co,1981,pp141-179;
8. Rouse DJ. Magnesium sulfate for the prevention of cerebralpalsy. AJOG 2009 (June);200(6):610.
9. Kuban KCK, Leviton A, M P. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. J Child. 1992;7:70–6.
10. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birth weight infants? Pediatrics. 1995;95(2):263–9.
11. Schendel DE, Berg CJ, Yeargin-Allsopp M, Boyle CA, Decoufle P. Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. JAMA. 1996;276(22):1805–10.
12. Teng RJ, Wu TJ. Persistent pulmonary hypertension of the newborn. Journal of the Formosan Medical Association. 2013;1;112(4):177-84.
13. Andrews T, Banks J. The use of magnesium sulfate in acute asthma: Rapid uptake of evidence in North American emergency departments. Pediatrics2007;120;S146-S147;
14. Berger R, Garnier Y. Perinatal brain injury. J Perinat Med. 2000;28(4):261–85.
15. Gathwala G. Neuronal protection with magnesium. Indian J Pediatr. 2001;68(5):417–9.
16. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. Nature. 1984;307:462–5.
17. Enomoto T, Osugi T, Satoh H, McIntosh TK, Nabeshima T. Pre-Injury magnesium treatment prevents traumatic brain injury-induced hippocampal ERK activation, neuronal loss, and cognitive dysfunction in the radial-arm maze test. J Neurotrauma. 2005;22:783–92.

18. Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int Off J Jpn Pediatr Soc. 2002;Oct;44(5):505–9.
19. Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. Pediatr Int. 2006;48(1):70–5.
20. Pius S, Bello M, Ambe JP, Machoko Y, Clement AY, Genesis R. Pilot Study: Magnesium Sulphate Administration and Early Resolution of Hypoxic Ischemic Encephalopathy in Severe Perinatal Asphyxia. Open J Pediatr. 2019 Jan;11;9(1):89–102.
21. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, M-U-H M. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. Pediatrics. 2009;May;123(5):e764-769.
22. Tagin M, Shah PS, Lee KS. Magnesium for newborns with hypoxic-ischemic encephalopathy: a systematic review and meta-analysis. J Perinatol. 2013;Sep;33(9:663–9.
23. Sample Size Calculator [Internet]. [cited 2022 May 22]. Available from: https://clincalc.com/stats/samplesize.aspx
24. randomize function - RDocumentation [Internet]. [cited 2022 May 21]. Available from: https://www.rdocumentation.org/packages/experiment/versions/1.2.1/topics/randomize
25. Siddiqui MA, Butt TK. Role of Intravenous Magnesium Sulphate in Term Neonates with Hypoxic Ischemic Encephalopathy (HIE) in a Low-income Country: A Randomised Clinical Trial. J Coll Physicians Surg–Pak JCPSP. 2021 Jul 30;
26. Savitha M, Rajprakash R. Beneficial effect of intravenous magnesium sulphate in term neonates with perinatal asphyxia. Int J Contemp Pediatr. 2016 Jan 1;
27. Farargy MS, Soliman NA. A randomized controlled trial on the use of magnesium sulfate and melatonin in neonatal hypoxic ischemic encephalopathy. J Neonatal-Perinat Med. 2019;12(4):379–84.
28. Gathwala G, Khera A, Singh J, Balhara B. Magnesium for neuroprotection in birth asphyxia. J Pediatr Neurosci. 2010;Jul;5(2):102–4.
29. Levene M, Blennow M, Whitelaw A, Hanko E, Fellman V, Hartley R. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. Arch Dis Child Fetal Neonatal Ed. 1995;73(3):174–7.
30. Iqbal N, Younus J, Malik M, Fatima B, Imran A, Maqbool S. The Neuroprotective Efficacy of Postnatal Magnesium Sulfate in Term or Near-Term Infants With Moderate-to-Severe Birth Asphyxia. Cureus. 2021;Aug;13(8):e16826. 30.
31. Anabrees J. Magnesium sulphate for newborns with HIE; synopsis of evidence from a systematic review. J Clin Neonatol. 2013;Jul;2(3):114–6.
32. Okonkwo IR, Okolo AA. Postnatal Magnesium Sulfate in Asphyxiated Newborns in Benin City Nigeria: Effect on Mortality.