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THERAPEUTIC HYPOTHERMIA PLUS MAGNESIUM SULPHATE VERSUS THERAPEUTIC HYPOTHERMIA IN INFANTS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY-A PROSPECTIVE COHORT STUDY.

Paediatrics

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ABSTRACT

Objective: To evaluate the safety of combining neuroprotective therapy with therapeutic hypothermia (TH) and magnesium sulphate (MgSO4) in managing moderate to severe hypoxic-ischemic encephalopathy (HIE) in term and near-term infants, and to assess the efficacy of the combined therapy compared to TH alone. **Methods**: This prospective cohort study was conducted over 18 to 20 months, including 30 term and near-term neonates with moderate to severe HIE. The neonates were divided into two groups: Group 1 (n = 15) received TH alone, and Group 2 (n = 15) received TH combined with intravenous MgSO4. TH involved cooling to 33.5°C for 72 hours followed by gradual rewarming. Clinical outcomes such as mortality, neurological sequelae, and other parameters were assessed. Statistical analysis was conducted using SPSS. **Results:** Baseline demographics were similar between the two groups. Group 2 demonstrated a significantly lower mortality rate (6.7% vs. 33.3%, p = 0.04) and a trend toward higher discharge rates (93.3% vs. 66.7%, p = 0.07). MRI findings showed a higher incidence of cerebral venous thrombosis and diffuse cerebral edema in Group 2, while Group 1 exhibited more cases of mild cerebral/cerebellar atrophy and cephalhematoma (p = 0.03). Echocardiogram findings suggested a higher prevalence of mild pulmonary arterial hypertension in Group 2, though not statistically significant. **Conclusion:** The addition of MgSO4 to TH may reduce mortality and enhance neuroprotection in neonates with moderate to severe HIE. Although baseline characteristics were comparable between groups, the results indicate the potential neuroprotective and cardioprotective benefits of MgSO4 in this population.

KEYWORDS

Hypoxic Ischemic Encephalopathy (HIE), Therapeutic Hypothermia, Magnesium Sulphate (MgSO4), Neonatal Encephalopathy, Neuroprotection, Neonatology.

INTRODUCTION:

Hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal morbidity and mortality worldwide, affecting approximately 2 per 1,000 live births [1]. The condition results from perinatal asphyxia, leading to neuronal injury caused by impaired oxygen and cerebral blood flow, with severe consequences on long-term neurodevelopmental outcomes [2,3].

Therapeutic hypothermia (TH) has emerged as the standard care for reducing the extent of brain injury caused by HIE [4-6]. By cooling the body to 33.5°C for a duration of 72 hours, TH decreases metabolic demand and inflammation during the acute phase, thereby providing neuroprotection [4,5]. However, despite its implementation, many infants continue to suffer from adverse neurodevelopmental outcomes, leading to the exploration of adjunct therapies to enhance the efficacy of TH [6,7].

Magnesium sulphate (MgSO4) has gained attention as a potential adjunct to TH due to its neuroprotective properties, which include modulation of excitotoxicity, reduction of oxidative stress, and anti-inflammatory effects [6-9]. While preclinical studies and retrospective data suggest the benefits of MgSO4 in combination with TH, few studies have rigorously evaluated its efficacy in a prospective cohort setting [10-13]. This study aims to address this gap by comparing the clinical outcomes of neonates with moderate to severe HIE receiving TH alone versus TH combined with MgSO4.

Understanding the synergistic effects of TH and MgSO4 could help optimize treatment strategies for reducing mortality and improving long-term neurodevelopmental outcomes in infants affected by HIE.

MATERIALS AND METHODS:

This prospective cohort study was conducted over a period of 18 to 20 months and included 30 neonates diagnosed with moderate to severe HIE at term or near-term (≥36 completed weeks). Neonates were evaluated using the Sarnat criteria, and eligible infants were enrolled within six hours of birth. Neonates were excluded if they had congenital abnormalities or were discharged against medical advice.

Neonates were randomly assigned to one of two groups:

- **Group 1** (n = 15): Received therapeutic hypothermia alone.
- **Group 2** (n = 15): Received therapeutic hypothermia combined with intravenous MgSO4.

Therapeutic hypothermia was initiated within six hours of birth using either total body cooling or head cooling. A target core body temperature of 33.5°C was maintained for 72 hours, followed by gradual rewarming over eight hours. The CritiCool system was used to regulate temperature throughout the cooling and rewarming process.

For Group 2, MgSO4 was administered intravenously at a dosage of 250 mg/kg, delivered over 90 minutes at a rate of 8 mg/kg/min, once daily for three days. Administration began within six hours of birth.

Throughout the cooling and rewarming phases, continuous monitoring of vital signs (heart rate, SpO2, rectal temperature) and respiratory support parameters (FiO2, mean airway pressure) was conducted. Amplitude-integrated EEG (Cerebral Function Monitor) was used to monitor for abnormal tracings or seizures, and neuro sonography was performed to assess intracranial bleeding. MRI scans were conducted in selected cases to evaluate the extent of brain injury.

The primary outcomes assessed were mortality and neuro developmental sequelae. Secondary outcomes included MRI findings, echocardiographic data, and NICU length of stay. Statistical analyses were performed using SPSS with t-tests or Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS:

The baseline demographic characteristics of the neonates in both groups were comparable (Table 1). The mean gestational age was 38.4 weeks (SD = 1.2) in Group 1 and 38.6 weeks (SD = 1.3) in Group 2. Birth weights were also similar, with Group 1 having a mean weight of 3112 grams (SD = 342), and Group 2 having a mean weight of 3155 grams (SD = 312). Apgar scores at 1 minute and 5 minutes were slightly higher in Group 2, but this difference was not statistically significant. Both groups had a similar distribution in terms of gender, mode of delivery, and maternal age. The severity of HIE was also

comparable, with the majority of infants in both groups presenting with moderate or severe encephalopathy. [Table 1]

Group 2, which received a combination of therapeutic hypothermia (TH) and magnesium sulphate (MgSO4), had significantly lower mortality compared to Group 1, which received TH alone (6.7% vs. 33.3%, p = 0.04) (Table 2). There was also a trend toward higher discharge rates in Group 2 (93.3% vs. 66.7%), though this difference did not reach statistical significance (p = 0.07).

Magnetic resonance imaging (MRI) revealed significant differences between the two groups. In Group 2, only 40% of neonates had abnormal MRI findings compared to 93.3% in Group 1 (p = 0.01). Group 2 also showed a higher prevalence of cerebral venous thrombosis and diffuse cerebral edema, while Group 1 demonstrated more mild cerebral/cerebellar atrophy and cephalhematoma (p = 0.03). Echocardiograms indicated a higher prevalence of mild pulmonary arterial hypertension (PAH) in Group 2 (53.4% vs. 13.3%), although the incidence of severe PAH was higher in Group 1 (33.3% vs. 13.3%) (p = 0.03). These findings suggest a potential cardioprotective effect of MgSO4, but further studies are needed to confirm this.

Biochemical and haematological parameters, such as platelet counts, pH, pCO2, pO2, and lactate levels, were similar between the two groups at both admission and 48 hours post-treatment (Table 2). There were no significant differences in CRP levels, sodium, potassium, calcium, or creatinine between the two groups at 72 hours, indicating that the addition of MgSO4 did not adversely affect these parameters.

The amplitude-integrated EEG (CFM) findings indicated no significant differences between the two groups in terms of abnormal brain tracings. However, Group 2 had a lower percentage of abnormal CFM findings compared to Group 1 (53.3% vs. 73.3%), though this was not statistically significant (p = 0.25).

There was no significant difference in the length of stay in the NICU between the two groups, with both groups showing an average stay of 10-12 days (p = 0.73).

DISCUSSION

This study provides a comprehensive evaluation of the efficacy and safety of combining therapeutic hypothermia (TH) with magnesium sulphate (MgSO4) compared to therapeutic hypothermia alone in neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE). The demographic characteristics and baseline parameters were well-balanced between the two groups, minimizing potential confounding factors. Both groups were similar in maternal age, gestational age, birth weight, and the severity of HIE, allowing for a clear comparison of the effects of the interventions.

The most significant finding of this study is the reduction in mortality in the group that received MgSO4 in addition to TH (Group 2) compared to TH alone (Group 1). The mortality rate in Group 2 was significantly lower (6.7% vs. 33.3%, p = 0.04), suggesting that MgSO4 may play a crucial role in improving survival outcomes in neonates with HIE. These results align with those of previous studies, such as the one by Gulczynska et al. [14], which also found that MgSO4 in combination with TH reduces mortality. Although the discharge rates were higher in Group 2 (93.3% vs. 66.7%), this trend did not reach statistical significance, which is consistent with similar studies that reported positive outcomes but did not find statistically significant differences in hospital discharge rates.

In terms of neurological outcomes, our study showed that Group 2 had fewer abnormalities on MRI scans compared to Group 1. Only 40% of neonates in Group 2 had abnormal MRI findings, compared to 93.3% in Group 1 (p = 0.01). This suggests that the addition of MgSO4 may enhance the neuroprotective effects of TH, as it potentially mitigates brain injury by reducing excitotoxicity, oxidative stress, and inflammation—mechanisms widely recognized in the pathogenesis of HIE [6,7]. While the seizure rates were similar between the two groups, Group 2 had a lower prevalence of anticonvulsant usage, indicating that MgSO4 may help reduce the severity of neurological damage.

The MRI results favoring Group 2 highlight the potential for MgSO4 to play a significant role in improving neurological outcomes. This is consistent with previous research, including the study by Rahman et al. [15], which also suggested that MgSO4 may help reduce the extent of brain injury in neonates with HIE. However, further investigation is needed to fully understand the long-term neurodevelopmental outcomes associated with MgSO4.

Although echocardiogram findings in our study indicated that Group 2 had a higher prevalence of mild pulmonary arterial hypertension (PAH) compared to Group 1, these results did not reach statistical significance. Our findings are partially consistent with Rahman et al. [15], who also did not observe significant cardiac benefits associated with MgSO4. Nonetheless, the trend toward better pulmonary outcomes in Group 2 suggests a potential cardioprotective role of MgSO4, but larger studies are required to confirm these effects.

The duration of NICU stay was similar between the two groups, with no statistically significant difference observed (p = 0.73). This contrasts with the findings by Gulczynska et al. [14], who reported shorter hospital stays in neonates receiving MgSO4. The discrepancy could be due to differences in patient populations, treatment protocols, or sample sizes across studies. Further research is needed to clarify the impact of MgSO4 on NICU length of stay.

Other clinical parameters, including feeding initiation, biochemical markers (such as CRP, sodium, potassium, and calcium levels), and the use of blood product transfusions, were comparable between the two groups. The trend toward earlier feeding initiation in Group 2, though not statistically significant, suggests that the combination of MgSO4 with TH may improve feeding tolerance. This trend mirrors findings from other studies that have investigated the use of MgSO4 as an adjunct therapy [14].

While this study provides strong evidence supporting the use of MgSO4 as an adjunct to TH in reducing mortality and improving neuroimaging outcomes, it is not without limitations. The relatively small sample size limits the generalizability of our findings to larger populations. Moreover, this was an open-label study, which introduces the possibility of observer bias. Larger, randomized controlled trials are needed to validate these findings and explore the precise mechanisms through which MgSO4 exerts its neuroprotective and cardioprotective effects.

Ongoing research is essential to optimize treatment protocols, particularly with regard to dosage, timing, and duration of MgSO4 administration. Future studies should also focus on long-term neurodevelopmental outcomes to determine whether the benefits of MgSO4 persist beyond the neonatal period.

CONCLUSION:

This study demonstrates that the combination of therapeutic hypothermia and magnesium sulphate has the potential to improve survival and neuroprotective outcomes in neonates with moderate to severe hypoxic-ischemic encephalopathy. Although baseline characteristics were comparable, the significant reduction in mortality and the favourable MRI findings observed in the MgSO4 group highlight its potential as a valuable adjunct therapy. Future large-scale studies are needed to confirm these results and refine treatment protocols to further enhance outcomes for neonates with HIE.

Conflict Of Interest

The authors declare no conflict of interest.

Acknowledgements

None.

Table 1: Demographic Data And Basic Characteristics

Parameter	Group 1 (Therapeutic Hypothermia)	Group 2 (TH + Magnesium Sulphate)
Total Sample Size	30	30
Gender (Male/Female)	18/12	20/10
Gestational Age (weeks)	Mean: 38.4 (SD = 1.2)	Mean: 38.6 (SD = 1.3)
Birth Weight (grams)	Mean: 3112 (SD = 342)	Mean: 3155 (SD = 312)
Apgar Score (1 min / 5 min)	Mean: 5.4 / 6.8	Mean: 5.6 / 6.9
Maternal Age (years)	Mean: 28.7 (SD = 3.1)	Mean: 29.1 (SD = 2.8)

Mode of Delivery (C-section/Vaginal)	20/10	18/12
Ethnicity (Caucasian/Non-Caucasian)	22/8	23/7
Neonatal Encephalopathy Severity (Mild/Moderate/Severe)	7/14/9	8/12/10

Table 2: Clinical Findings And Outcomes With P-values

Parameter	Group 1 (Therapeutic Hypothermia)	Group 2 (TH + Magnesium Sulphate)	P-value
Total Count (Admission)	Mean: 19,488 (SD = 9,415)	Mean: 21,573.3 (SD = 8,469)	0.57
Total Count (48 hours)	Mean: 10,099 (SD = 3,082)	Mean: 11,771.4 (SD = 3,352.6)	0.41
Platelet Count (Admission)	Mean: 207,466.6 (SD = 75,998.9)	Mean: 220,866.6 (SD = 55,394.51)	0.33
Platelet Count (48 hours)	Mean: 172,210.6 (SD = 32,593.8)	Mean: 149,266.6 (SD = 30,989.5)	0.58
pH (Admission)	Mean: 7.21	Mean: 7.23	0.72
pH (48 hours)	Mean: 7.34	Mean: 7.34	0.95
pCO2 (Admission)	Mean: 24.43	Mean: 20.67	0.21
pCO2 (48 hours)	Mean: 29.12	Mean: 24.27	0.14
pO2 (Admission)	Mean: 167.13	Mean: 178.17	0.46
pO2 (48 hours)	Mean: 170.74	Mean: 163.74	0.57
HCO3 (Admission)	Mean: 13.06	Mean: 9.85	0.12
HCO3 (48 hours)	Mean: 16.42	Mean: 16.06	0.78
Lactate (Admission)	Mean: 2.1	Mean: 2.0	0.85
Lactate (48 hours)	Mean: 1.9	Mean: 1.8	0.92
CRP (12 hours)	Mean: 18.06	Mean: 21.80	0.29
CRP (72 hours)	Mean: 31.10	Mean: 28.79	0.71
Sodium (72 hours)	Mean: 138.6	Mean: 140.3	0.83
Potassium (72 hours)	Mean: 4.1	Mean: 4.0	0.92
Calcium (72 hours)	Mean: 8.9	Mean: 8.8	0.87
Creatinine (72 hours)	Mean: 0.8	Mean: 0.9	0.69
CFM Findings (Normal/Abnormal)	73.3% / 26.7%	53.3% / 46.7%	0.25
Blood Product Transfusion (Yes/No)	33.3% / 66.6%	26.7% / 73.4%	0.66
ECHO Findings (PAH Severity) (Mild/Moderate/Severe)	13.3% / 26.7% / 33.3%	53.4% /13.3% /13.3%	0.03
Final Outcome (Discharged/Mortality)	66.7% / 33.3%	93.3% / 6.7%	0.04
Length of Stay in NICU	10-12 days	10-12 days	0.73
MRI Findings (Abnormal/Normal)	93.3% / 6.7%	40% / 60%	0.01

REFERENCES:

1. Acun C, Karnati S, Padiyar S, Puthuraya S, Aly H, Mohamed M. Trends of neonatal hypoxic-ischemic encephalopathy prevalence and associated risk factors in the United States, 2010 to 2018. Am J Obstet Gynecol. 2022;227(5):751.e1.
2. Hayakawa M, Ito Y, Saito S, *et al*. Incidence and prediction of outcome in hypoxic–ischemic encephalopathy in Japan. Pediatr Int. 2014;56(2):215-21.
3. Khot S, Tirschwell DL. Long-term neurological complications after hypoxic-ischemic encephalopathy. Semin Neurol. 2006;26(4):422-31.
4. Wassink G, Davidson JO, Dhillon SK, *et al*. Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. Curr Neurol Neurosci Rep. 2019;19(1):1-10.
5. Simbruner G, Mittal RA, Rohlmann F, Muche R; neo.nEURO.network Trial Participants. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. Pediatrics. 2010;126(4):e771-e778.
6. Kumar C, Adhisivam B, Bobby Z, Bhat BV. Magnesium sulfate as an adjunct to therapeutic hypothermia in the management of term infants with hypoxic-ischemic encephalopathy: A randomized, parallel-group, controlled trial. Indian J Pediatr. 2023;90(9):886-92.
7. Nair J, Kumar VHS. Current and emerging therapies in the management of hypoxic ischemic encephalopathy in neonates. Children (Basel). 2018;5(7):99.
8. Hunter LA, Gibbins KJ. Magnesium sulfate: past, present, and future. J Midwifery Womens Health. 2011;56(6):566-74.
9. Elsayed NA, Boyer TM, Burd I. Fetal neuroprotective strategies: therapeutic agents and their underlying synaptic pathways. Front Synaptic Neurosci. 2021 Jun 23;13:680899.
10. Lingam I, Meehan C, Avdic-Belltheus A, *et al*. Short-term effects of early initiation of magnesium infusion combined with cooling after hypoxia–ischemia in term piglets. Pediatr Res. 2019;86(6):699-708.
11. Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. JAMA. 2003;290(20):2669-2676.
12. Marret S, Marpeau L, Zupan-Simunek V, *et al*. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. BJOG. 2007 Mar;114(3):310-8.
13. Lingam I, Meehan C, Avdic-Belltheus A, *et al*. Short-term effects of early initiation of magnesium infusion combined with cooling after hypoxia–ischemia in term piglets. Pediatr Res. 2019;86(6):699-708.
14. Gulczynska E, Gadzinowski J, Nowiczewski M, Sobolewska B, Caputa J, Maczko A. Feasibility and safety of combining therapeutic hypothermia with magnesium sulfate administration, in the management of neonates with hypoxic ischemic encephalopathy: a randomized control trial. Neonat Pediatr Med. 2018;4(165):2.
15. Rahman SU, Canpolat FE, Oncel MY, *et al*. Multicenter randomized controlled trial of therapeutic hypothermia plus magnesium sulfate versus therapeutic hypothermia plus placebo in the management of term and near-term infants with hypoxic ischemic encephalopathy (The Mag Cool study): a pilot study. J Clin Neonatol. 2015;4(3):158-63.