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Outcome of Infants with Hypoxic-Ischemic Encephalopathy Treated by Whole Body Cooling and Magnesium Sulfate

Safwat M. Abdel-Aziz[1] Mohamed Sabry M. Abdel Rahman[1] Asmaa H. Shoreit[1] Moustafa Ez El Din[2] Enas A. Hamed[3] Eman Fathalla Gad[1]

[1] Department of Pediatrics and Neonatology, Assiut University Children's Hospital, Assiut, Egypt
[2] Department of Radiology, Faculty of Medicine, Assiut University, Assiut, Egypt
[3] Department of Medical Physiology, Faculty of Medicine, Assiut University, Assiut, Egypt

Address for correspondence Enas Ahmad Hamed, MD, PhD, Department of Medical Physiology, Faculty of Medicine, Assiut University, Assiut, P.O. Box 71516, Egypt (e-mail: eah3a2010@aun.edu.eg).

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Abstract

Therapeutic hypothermia (TH) either by selective head cooling or whole-body cooling decreases brain damage and provide neuroprotection and reduced mortality rate in cases of moderate-to-severe hypoxia-ischemia encephalopathy (HIE) of newborns, especially if started at first 6 hours after birth. Also, management with adjuvant therapies like magnesium sulfate (MS) provides more neuroprotection. The interventional randomized controlled research aimed to assess short-term actions of TH as sole therapy and in combination with MS as a neuroprotective agent for the treatment of HIE newborn infants. A total of 36 full-terms and near-term infants delivered at Assiut University Children's Hospital and fulfilled HIE criteria were enrolled. They were divided equally into three groups; Group 1 ($n = 12$) received whole body cooling during first 6 hours of life as a sole therapy; Group 2 ($n = 12$) received whole body cooling in addition to MS as adjuvant therapy; Group 3 ($n = 12$) received supportive intensive care measures as a control. TH plus MS group (group 2) had a significantly good short-term outcomes as short period of respiratory support and mechanical ventilation (p-value $=0.001$), less in incidence of convulsion (p-value $= 0.001$) and early in feeding initiation (p-value $= 0.009$), compared with other groups managed by TH (group 1) or by supportive treatment (group 3). In conclusion, whole body cooling in addition to MS as adjunctive therapy for the treatment of HIE neonates is safe therapy that improves short-term outcome both clinically and radiologically.

Keywords
- hypoxic-ischemic encephalopathy
- magnesium sulfate
- neuroprotective
- therapeutic hypothermia

Introduction

Hypoxic-ischemic encephalopathy (HIE) is an acquired syndrome manifested by a clinical, laboratory, and radiological evidence of acute brain injury.[1] Perinatal asphyxia affects two out of every 1,000 live births in wealthy countries, but it affects 10 times more people in developing countries when maternal and newborn care is inadequate. 15 to 20% of asphyxiated neonates will die during neonatal duration, and roughly 25% of survivors will have long-term neurological impairments.[2]

HIE is accompanied by two phases of pathologic events, primary and secondary energy failure. A decrease in cerebral

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blood flow and oxygen substrate, as well as significant tissue acidity, characterize primary energy failure.[3] Secondary energy failure includes several pathophysiologic actions as summation of excitatory brain neurotransmitters, oxidative stress, inflammation, apoptosis, changed growth factors, and protein formation.[4] There is a latent phase between primary and secondary energy failure, which corresponds to a therapeutic window of roughly 6 hours during which neuroprotective therapy should be started.[5]

Hypothermia of the brain is an example of a neuroprotective treatment that influences several processes in the events that lead to brain injury. In newborns, a slight drop in brain temperature (1 to 6°C) is linked to better cerebral energy maintenance during and immediately after birth ischemia. Other neuroprotective actions of brain hypothermia include stabilization of protein formation, decline of free oxygen radicals, and control of microglial activation and cytokine formation, as well as attenuation of excitatory neurotransmitter release and apoptosis.[6] Other neuroprotective therapies should be added to increase the benefits of therapeutic hypothermia (TH) and to minimize neonatal brain injury and make more neuroprotection; many researches support the safety and potency of magnesium sulfate (MS) as an adjuvant therapy to TH.[7–9]

Postnatally after birth asphyxia, infusion of magnesium sulfate (250 mg/kg per day for 3 days) in combination with dopamine (5 ug/kg per minute) associated with a good neurodevelopmental outcome as it acts as non-competitive antagonization effect at N-methyl D-aspartate (NAMDA) glutamate receptors, stabilization of many critical enzymatic reactions, plasma membrane and anticonvulsant actions. Combination therapies as MS plus TH provide more synergistic neuroprotective effects and improve outcomes.[10–12]

Thus, the present research aimed to assess the neuroprotective actions of TH in addition to MS as adjunctive therapy in management of neonates with HIE.

Methods

The interventional randomized controlled research was made on 36 neonates delivered at the neonatal intensive care unit (NICU) of Assiut University Children's hospital, fulfilling the physiological and neurological inclusion criteria during period from January 2019 to June 2020. Physiologic criteria were infants ≥36 weeks gestation administered to NICU with at least one of the followings: Apgar score at 5 minutes following birth ≤5; continued requirement for resuscitation as mask or endotracheal ventilation, at 10 minutes following birth; acidosis within 60 minutes of birth with an arterial, umbilical cord, or capillary pH <7.1 or base deficit ≥16 mmol/L.; manifestations of fetal distress before delivery (as meconium-stained amniotic fluid or tachycardia >160/bpm or bradycardia <100/bpm). Neurological criteria were changes of consciousness (lethargy, stupor, or coma) and at least one of the following: clinical seizures; abnormal pupillary reflexes; abnormal oculomotor reflex; absent or weak suckling; absent or weak Moro reflex, and hypertonia. Excluded from the study were preterm infants, infants with congenital anomalies, and infants of mothers received medications that caused neonatal depression as phenobarbitone or pethidine.

Study Population and Sampling Size

All newborn that admitted to NICU of Assiut University Children's Hospital, Assiut, Egypt with moderate to severe HIE graded as Sarnat modified score system[13] during the research period were included. The patients were separated into two subgroups before randomly assigning them to moderate and severe HIE, then each group divided into three groups. The researchers randomly assigned the neonates into three groups according to severity of HIE, priority of admission and available places in NICU by utilizing random number tables generated by computer according to the inclusion and exclusion characteristics. Not any of the NICU's nurses or the attending neonatologists was aware of this randomization.

Data Collection Tools

Complete maternal, obstetric, and neonatal histories, full clinical examination including neurological examination, full laboratory assessment including complete blood count, serum urea, creatinine, magnesium, calcium and potassium and blood glucose were done.

Patients

Group 1 ($n = 12$) included HIE neonates treated by whole body cooling within 6 hours after birth for 72 hours as a sole therapy. Group 2 ($n = 12$) included HIE neonates treated by whole body cooling within 6 hours after birth for 72 hours in addition to a prophylactic dose of intravenous MS (250 mg/kg) with dopamine (5 µg/kg/min) over 1 hour for 3 days. Group 3 ($n = 12$) included HIE neonates received supportive treatment and served as a control. In the control group, the traditional treatment (supportive measures) only was used for management of HIE cases due to lack of capabilities, availability of places of newborn, and cooling device (relying solely on gel mattresses and passive cooling) in our NICU. Also, lack of nursing assistant staff in close monitoring and follow-up of these cases led to use of traditional treatment for management of these cases in spite of the beneficial effect of TH. Cooling was initiated within 6 hours after birth and continued for 72 hours, and all newborns were closely monitored and treated in a standard manner with attention to maintenance of oxygen saturation, blood pressure, normal blood gases, fluid balance, and kidney functions, with management of seizure, hypoglycemia, and jaundice. The target temperature during cooling must be 33 to 34°C during hypothermic therapy and rewarming; the temperature was registered continuously, and the temperature was registered every hour. The aim was to get the target temperature by 1 hour of starting cooling. TH was begun with passive cooling first, but if the temperature did not drop below 35°C after 30 minutes, active cooling was used. The newborn was kept naked in an open incubator at room temperature with the radiant heater turned off, while active cooling was achieved by utilizing a cool mattress at a

Table 1 Demographic features of the studied groups

Parameters	Total ($n = 36$)	TH group ($n = 12$)	TH and MS group ($n = 12$)	Control group ($n = 12$)	*p*-Value
Gender					0.441
Males	22 (61.11%)	6 (50.0%)	7 (58.3%)	9 (75.0%)	
Females	14 (38.89%)	6 (50.0%)	5 (41.7%)	3 (25.0%)	
Birth weight (kg)	3.42 ± 0.55	3.31 ± 0.54	3.44 ± 0.42	3.52 ± 0.70	0.419
Gestational age (weeks)	38.31 ± 1.66	38.24 ± 1.42	38.60 ± 1.76	38.1 ± 1.80	0.207
Mode of delivery					
Normal vaginal delivery	16 (44.44%)	5 (41.7%)	6 (50.0%)	5 (41.7%)	0.939
Cesarean section	11 (30.56%)	3 (25.0%)	4 (33.3%)	4 (33.3%)	0.913
Forceps delivery	3 (8.33%)	2 (16.7%)	–	1 (8.3%)	0.998
Ventose delivery	4 (11.11%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	0.778
Assisted breech	2 (5.56%)	1 (8.3%)	1 (8.3%)	–	0.479

Abbreviations: MS, magnesium sulfate; TH, therapeutic hypothermia.
Note: Comparison between groups was made using Pearson Chi-Square test.

temperature of around 10°C. If the temperature of the newborn drops below 33°C, the cooling mattress or packs are withdrawn. If that was not enough, the radiant heater is turned on to the lowest setting until the temperature reaches 33°C.[14] Rewarming to a temperature of 37°C was done slowly after 72 hours of TH.

This was accomplished by regulating the radiant heater's temperature to raise the patient's temperature by no more than 0.5°C every hour.[15] Assessment of cases was done by both clinical and radiological evaluation. Clinical evaluation was made using Thompson and Sarnat scoring systems. Magnetic resonance imaging (MRI)[16] scans were used to assess radiological evaluation; the babies were examined when they were stable to be carried securely to MRI scanner.[17]

The incidence of convulsion and neurological status, the period of mechanical ventilation and respiratory support, neurological finding in MRI, and the time of starting feeding were recorded.

Ethical Issues

Research was approved by Local Ethical Committee Institutional Review Board (IRB) of Assiut University Hospital, Assiut, Egypt (IRB: 17200592, December 26, 2018) which was according to Declaration of Helsinki. Informed written consent was got from mothers or guaranteed of every participant before inclusion and after explaining research aim to them at admission time.

Statistical Analysis

Descriptive statistical analysis was made by IBM SPSS statistics software version 25; SPSS inc. for Windows Microsoft. Shapiro – Wilk test was utilized to evaluate normal value distribution. Data were collected, checked, coded, and entered. Statistical methods included descriptive analysis like mean, standard deviation, number and Pearson Chi-square test percentage. Significance between groups was done using Chi-Square test for categorized data and one-way ANOVA test then by post hoc least significant difference for parametric variables. $p < 0.05$ was considered statistically significant.

Results

►**Table 1** showed the demographic features between the studied groups. Where six (50%) of the cases were males and also six (50%) were females in the neonates with hypothermia group and seven (58.3%) males and five (41.7%) females in hypothermia and MS group, while in control group nine (75%) were males and three (25%) were females with insignificant difference between groups ($p = 0.441$). Among hypothermia, hypothermia plus MS and control groups, there were insignificant difference between groups regarding birth weight (3.31 ± 0.54 kg; 3.44 ± 0.42 kg, and 3.52 ± 0.7 kg, respectively, $p = 0.419$) and gestational age (38.24 ± 1.42; 38.60 ± 1.76; and 38.1 ± 1.8 weeks, respectively; $p = 0.207$). The modes of delivery for the hypothermia; hypothermia and MS and control groups were vaginal (41.7, 50.0, and 41.7%, $p = 0.939$), CS (25.0, 33.3, and 33.3%, $p = 0.913$), forceps (16.7, 0, 8.3%, $p = 0.998$), ventose (8.3, 8.3, and 16.7%, $p = 0.778$) and assisted breech (8.3, 8.3, and 0%, $p = 0.479$).

►**Table 2** demonstrates the pregnancy-related risk factors of infants with HIE. There was statistically significant difference among the studied groups regarding pre-eclampsia, antepartum hemorrhage, and prolonged 2nd stage of labor ($p = 0.017$, $p = 0.019$, $p = 0.016$, respectively).

►**Fig. 1** demonstrates the short-term outcomes and MRI findings among the studied groups. There were statistically significant differences in hypothermia and MS group versus hypothermia and control groups and in hypothermia group versus control group regarding duration of respiratory support ($p = 0.023$; $p = 0.001$, and $p = 0.005$, respectively); frequency of convulsions ($p = 0.005$; $p = 0.002$, and $p = 0.002$, respectively); initiation of feeding ($p = 0.005$; $p = 0.001$, and $p = 0.008$, respectively); antiepileptic drugs at discharge ($p = 0.001$; $p = 0.007$, and $p = 0.031$, respectively). MRI finding in

Table 2 Pregnancy-related risk factors of infants with hypoxic ischemic encephalopathy

Pregnancy risk factors	Total ($n = 36$)	TH group ($n = 12$)	TH and MS group ($n = 12$)	Control group ($n = 12$)	*p*-Value
Eclampsia	4 (11.11%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	0.778
Pre-eclampsia	8 (22.22%)	4 (33.3%)	3 (25.0%)	1 (8.3%)	0.017
Previous stillbirth	2 (5.56%)	1 (8.3%)	1 (8.3%)	–	–
Cord prolapse and placental insufficiency	4 (11.11%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	0.778
Antepartum hemorrhage	5 (13.89%)	2 (16.7%)	1 (8.3%)	2 (16.7%)	0.019
Premature rupture of membrane.	5 (13.89%)	2 (16.7%)	2 (16.7%)	1 (8.3%)	0.819
Prolonged 2nd stage of labor	9 (25.0%)	2 (16.7%)	3 (25.0%)	4 (33.3%)	0.016

Abbreviations: MS, magnesium sulfate; TH, therapeutic hypothermia. Comparison between groups was made using Pearson Chi-Square test.

hypothermia group was normal in 11 cases (92.7%) and gray and white matter lesion in one case (8.3%); in hypothermia with MS group findings were normal in 11 cases (92.7%) and cortical lesion in one case (8.3%), in the control group it was normal in 10 cases (83.4%), cortical lesion in one case (8.3%) and gray and white matter lesion in one case (8.3%) with insignificant difference between different findings (normal, cortical lesion and gray, and white matter lesion) in different groups ($p = 0.307$, $p = 00.867$, and $p = 0.819$, respectively).

Discussion

Hypothermia is a standard-of-care for babies suffering from HIE but the hypothermia does not provide complete neuroprotection, so adding a pharmacological agent may improve outcomes. MS is a good example of these agents which are used in neonates, producing neuroprotective effects.[18] This prospective intervention research was designed to test short-term effect of whole body cooling alone and whole body cooling plus MS as a neuroprotective agent to infants with HIE admitted to NICU of Assiut University children's hospital and fulfilling the inclusion characteristics for the research.

In this study, there was an insignificant difference with regard to gender between the three studied groups. Meanwhile, the number of males ($n = 22$, 61.11%) was exceeding that of females where six (50%) of the cases were males and also six (50%) were females in neonates with hypothermia group and seven (58.3%) males and five (41.7%) females in hypothermia and MS group, while in control group nine (75.0%) were males and three (25.0%) were females. A study conducted by Siegel et al,[19] in Pakistan on 144 neonates with perinatal asphyxia had 68.8% of cases as males and 31.3% as females. This study reported that male sex adversely affected neonates outcome in cases with perinatal asphyxia.[19] Cerebral ischemia stimulates both caspase-independent and caspase-dependent cell death pathways. Stroke-led to cell death in males is triggered by mitochondrial release of apoptosis-inducing substances which results in cell death that is not dependent on caspase.

Regarding the pregnancy-related risk factors of infants with HIE in total, nine (25.0%) had prolonged second stage of labor, eight women (22.22%) had pre-eclampsia, five (13.89%) had an antepartum hemorrhage, five (13.89%) had premature rupture of membranes, four (11.11%) had cord prolapse and placental insufficiency, four women (11.11%) had eclampsia, and two (5.56%) had a previous stillbirth. Prolonged 2nd stage of labor, preeclampsia, and antepartum hemorrhage showed significant difference between various studied groups ($p = 0.016$, $p = 0.017$, and $p = 0.019$). Torbenson et al[20] reported that prolonged second stage of labor and presence of meconium-stained amniotic fluid were risk factors for HIE development. In contrast to our results, a research conducted by Hashim et al[21] stated that significantly higher risk was associated with prolonged rupture of membranes that is a risk factor for fetal sepsis and associated with deterioration in the fetal acid-base status. Also, Peebles et al[22] reported that moderate-to-heavy meconium-stained amniotic fluid, placental abruption, ruptured uterus, and delivery by cesarean-section were independent intrapartum risk factors for HIE in newborn. An intrapartum risk factor was found in 70.3% of HIE group versus 29.6% in non-HIE group.

According to the mode of delivery, our research revealed that there was no statistically significant difference between the different modes of delivery among different studied groups of HIE. Among all HIE group, most of the deliveries were normal vaginal delivery ($n = 16$, 44.44%), then cesarean section ($n = 11$, 30.56%), ventose delivery ($n = 4$, 11.11%), forceps delivery ($n = 3$, 8.33%), and last assisted breech ($n = 2$, 5.56%). In line with the results of this study, Hill[23] and Badawi et al[24] reported that the normal vaginal delivery is associated with HIE. Dongol et al[25] reported that most vaginal deliveries are associated with perinatal and intrapartum asphyxia. In contrast, Seyal and Hanif[26] reported that most of infants with birth asphyxia were born by cesarean section. This could be explained by either internal hospital protocols that support CS or utilization of CS as ultimate mode of delivery after failed trials of normal vaginal delivery.

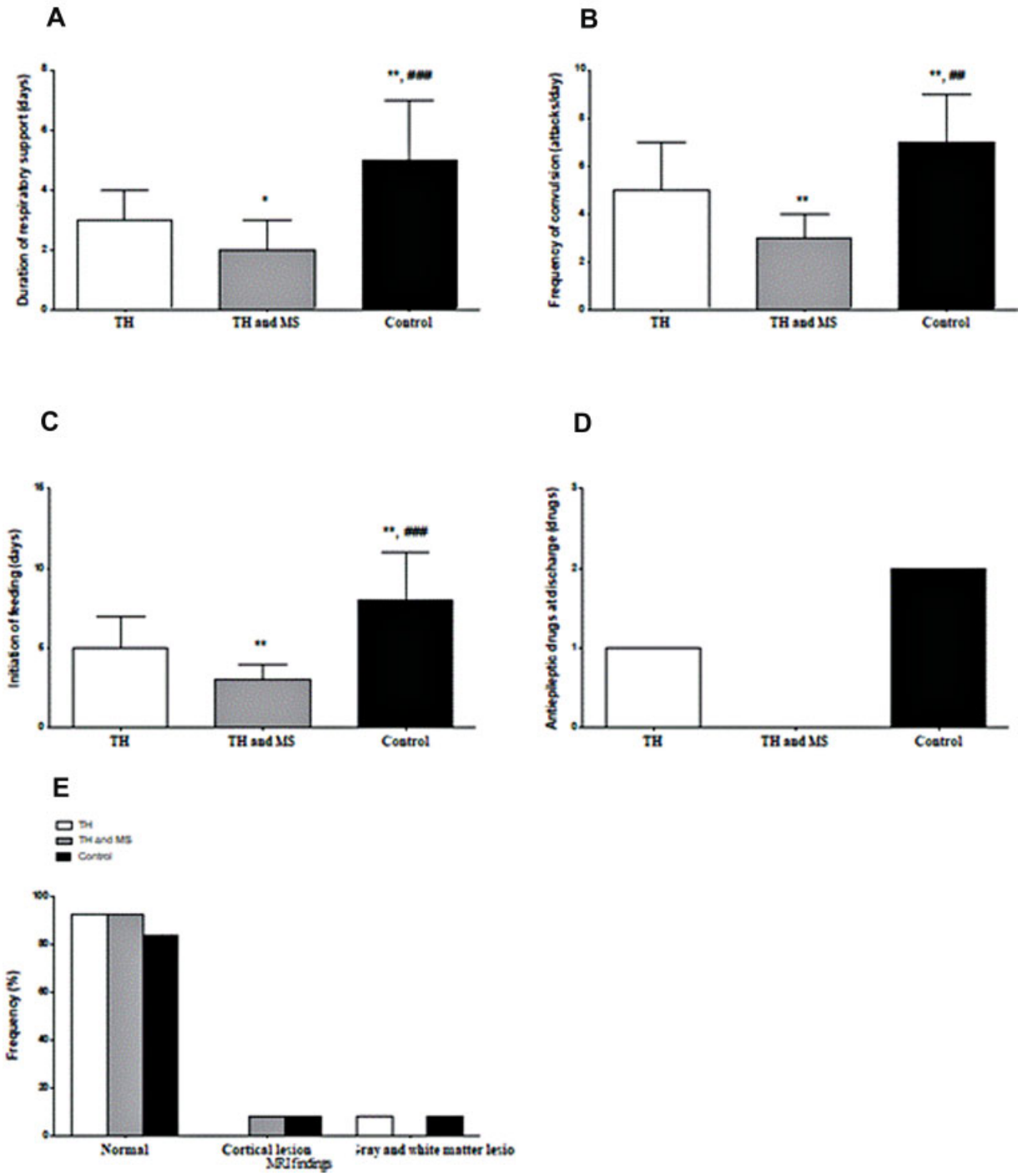

Fig. 1 Short-term outcomes among the studied groups. MS, magnesium sulfate; TH, therapeutic hypothermia; *Significance versus TH group; #Significance versus TH and MS group. $^{*}p < 0.05$; $^{**}p < 0.010$, and $^{***}p < 0.0001$. A: Duration of respiratory support (days); B: Frequency of convulsion (attacks/day); C: Initiation of feeding (days); D: Antiepileptic drugs at discharge (drugs); e: Frequency of MRI findings (%). Comparison between categorized data was made using Person Chi-Square test and using OneWay ANOVA test followed by LSD for parametric parameters.

According to the short-term outcomes among the studied groups, our results showed a significant statistical difference among three studied groups with regard to the incidence and frequency of clinical seizures ($p = 0.001$), respiratory support duration ($p = 0.001$), and time of enteral feeding initiation ($p = 0.009$). Our results reveal that, the group that received hypothermia with MS had a shorter length of mechanical ventilation and respiratory support versus group that received hypothermia alone, which was likewise shorter than the control group. In addition, the time it took to start feeding was less in the group that received hypothermia with MS than in the group that received hypothermia. A meta-analysis of five studies of infants with HIE found that TH had a substantial influence on the incidence of clinically identifiable seizures.[27,28] Sajid et al[29] found that neurological outcomes at discharge were improved with the treatment of

postnatal intravenous MS (250 mg/kg/dose, 24 hours interval for three doses) in neonates with severe birth asphyxia when given early after birth. In line with the present study, Abate et al[30] found that, TH decreased the mortality risk in neonates with moderate to severe HIE. Both selective head cooling and whole-body cooling methods were effective in decreasing mortality of HIE infants. Also, low-income countries benefit the most from therapy.

Lingam et al[31] studied the neuroprotective effects of MS bolus and infusion over 48 hours (180 mg/kg bolus then 8 mg/kg/h infusion) and TH for 12 hours (33.5°C) and TH only in piglets' model of term neonatal encephalopathy. They reported that in MS plus TH versus TH only, there were overall decreased cell death ($p = 0.010$) and increased oligodendrocytes ($p = 0.002$). Meanwhile, there were no improvement on amplitude integrated electroencephalography recovery ($p = 0.084$) or magnetic resonance spectroscopy (Lac/NAA; PCr/Pi; NTP/epp) ($p > 0.05$) at 48 hours. Prakash[32] made a study on term asphyxiated infants that were received either MS infusion ($n = 60$) or placebo ($n = 60$) within 48 hours of life. MS infusion was administered at dose of 250 mg/kg/dose (1 mL/kg/dose in 20 mL of 5% dextrose solution) over 1 hour within 6 hours after birth, with two more doses repeated at intervals of 24 hours. The author reported that 25/36 infants in the magnesium group (69%) and 27/33 controls (82%) with moderate and severe HIE had clinical seizures during NICU admission. Among those with seizures, seizure control was achieved with single anticonvulsant in 24 infants (96%) in MS group compared with 20 (74%) in placebo ($p = 0.020$). Seizures got controlled early in MS group compared with placebo, 36.5 hours versus 55 hours ($p = 0.020$). At discharge, anticonvulsant was required for two infants in MS group and three in placebo group. Okonkwo and Okolo[33] reported that postnatal administration of MS alone or combined with respiratory support improves survival of asphyxiated neonates and neonates with encephalopathy. Bhat et al[10] found that postnatal MS treatment improved neurological outcomes at discharge for full-term neonates with severe perinatal asphyxia. Sreenivasa et al[34] reported that early (within 6 hours) postnatal intravenous MS infusion is effective in improving short-term outcomes for infants with perinatal asphyxia.

MRI patterns of brain injury vary because of differences in brain maturity at the time of insult, severity, and duration of the insult. Aun et al[35] reported that MRI imaging is considered a sensitive method in detecting various patterns of encephalopathy in newborns and used for early predictor of future development of neurological abnormalities in neonates with encephalopathy. Rutherford et al[36] stated that MRI is an excellent predictor of outcome following perinatal brain injury and can be used in interventional trials designed to decrease damage and enhance neurodevelopmental outcome. The results of this research showed the use of MS in addition to whole-body cooling associated with decline in cerebral damage seen on MRI which are characteristic of HIE.[37] Therefore, out of 36 cases that had MRI scans in the present study, 32 cases (88.89%) showed normal MRI in spite they had fulfilled the characteristics of hypoxic encephalopathy. Where in the hypothermia group, normal MRI was present in 11 cases (92.7%) and gray and white matter lesion in one case (8.3%). In hypothermia with MS group, normal MRI was present in 11 cases (92.7%) and cortical lesion in one case (8.3%). In the control group, normal MRI was present in 10 cases (83.4%), cortical lesion in one case (8.3%), and gray and white matter lesion in one case (8.3%). This supports our theory that cooling, with or without prophylactic MS, may have reduced the degree of hypoxic brain injury. Cheong et al[38] stated that brain injury on T1- and T2-weighted MRI decreased in hypothermia-treated newborns. Abnormal MRI are prognostic of long-term outcome in moderate to severe HIE regardless of hypothermia therapy.

Limitations of the Study

The study's neonatal sample was limited, separated into three groups, and the patients came from a single tertiary hospital. A high sample size is recommended.

Conclusion

Whole body cooling is a safe, effective, and inexpensive mode of intervention, which has become standard therapy for neonates with HIE and it is achievable, using simple and easily available cooling materials. Adding MS to cooling therapy for HIE significantly shortens the period of hospital stay, decreasing the incidence of convulsions and helps in early starting of feeding and decreasing the findings in MRI brain and uses of anticonvulsant therapy. Follow-up of HIE cases treated with TH is highly recommended to determine the long-term effects.

Author's Contributions

M.S.M.A.R. carried the study design, examined cases, and shared in writing of manuscript. A.H.S. selected the cases, did the validation, and coding, shared in writing manuscript. M.E.E.D. was involved in the selection of cases, MRI reading and interpretation and shared in writing manuscript and gathered references. E.A.H. did the validation, analysis of data and coding, shared in writing manuscript, reviewed and edited. S.M.A.-A. did the study design, conceptualization, writing manuscript, validation, and editing. All authors had read and approved manuscript for publication.

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Conflict of Interest

None declared.

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