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Paediatrics Section

Early Neurodevelopmental Outcome of Asphyxiated Newborns Treated with Therapeutic Hypothermia: A Non Randomised Cohort Study

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ABSTRACT

Introduction: Therapeutic Hypothermia (TH) is now a proven model of treatment to prevent complications in asphyxiated newborns. Perinatal asphyxia is the leading cause of mortality and disability in India and developing countries. The TH is still not the standard treatment protocol in developing India, and data regarding early neurological outcomes after TH is lacking.

Aim: To evaluate the early neurological outcome at three, six and nine months of asphyxiated newborns who received TH compared to non recipients.

Materials and Methods: This was a non randomised cohort study conducted at the tertiary care teaching hospital. A total of 190 asphyxiated newborns admitted to Neonatal Intensive Care Unit (NICU) within 24 hours of life, meeting the laboratory and/or clinical criteria of perinatal asphyxia were enrolled. Eligible newborns admitted within six hours of birth receiving TH were labelled as recipients, and those who received standard care were labelled as non-recipients. Neonates were assessed at three, six, and nine months and compared for neurodevelopment using the Hammersmith Infant Neurological Examination (HINE) optimality score and Denver Developmental Screening Test II. Both groups were compared using t-test and chi-square test.

Results: Out of the total 190 enrolled participants, 14 were excluded and 176 newborns were further divided into recipients and non recipients groups. Baseline demographic characters were similar in both groups. Seventy-five recipients were followed-up till three months, 72 at six months, and 69 at nine months vs 62, 60, and 56 non recipients, respectively. Lesser number of recipients scored suboptimal scores (HINE score <67) at three months vs non recipients (20% vs 35.4%, mean/SD 63 [3.43] vs 57 [4.55], [p<0.001]). At six months (HINE score <70), the incidence was 18% vs 21% (p=0.02), mean score 67 vs 61 (p<0.0001); and at nine months (HINE score <73) the incidence was 14.4% vs 30.3% (p=0.048), mean score 72 vs 65 among recipient vs non recipients (p<0.0001). Recipients also had less incidence of severe disability (HINE score <40) at six months (8.3% vs 21.6% p<0.02), and nine months (8.6% vs. 19.6%, p<0.04) as compared to non recipients. More recipients had a normal developmental screening at three, six, and nine months on the DDST scale. Recipients required fewer anti-epileptics at three and six months (3 vs 11) as compared to non recipients (p<0.05). Mortality was also less in recipients (7.8% vs 20.9%, p<0.05) as compared to non recipients.

Conclusion: There was a significant developmental and neurological improvement with decreased mortality, less episode of seizures, reduction in the need for antiepileptic among recipients of TH compared to non recipients at three, six, and nine months of age.

Keywords: Hammersmith infant neurological examination, Limited resource setting, Perinatal asphyxia

INTRODUCTION

According to the Lancet neonatal survival steering team, an estimated four million babies die annually during the neonatal period, and 99% of these deaths occur in developing countries [1]. Epidemiological studies have found the incidence of prenatal asphyxia as 2 per 1000 births in developing countries [1]. Still, the rate is 10 times higher in developing countries with limited access to maternal and neonatal care [2]. Perinatal asphyxia is responsible for 24% of neonatal mortality worldwide [1] and 15% of neonatal deaths in India; 97.8% of deaths due to perinatal asphyxia occur in the first week of life and 70% within the first 24 hours [2].

Hypoxic-ischaemic Encephalopathy (HIE) is characterised by neonatal encephalopathy, causing severe detrimental effects on the developing brain. Approximately 25% of survivors have permanent neurodisabilities, such as Cerebral Palsy (CP), cognitive impairment, and behavioural and seizure disorder [3]. In developing countries, estimates are as high as 50% in the absence of neuroprotection following perinatal asphyxia [4].

Therapeutic Hypothermia (TH) has been proven to reduce the severity of brain injury after an ischaemic insult, exert a favourable effect on neurological outcomes and is widely used as standard care therapy for asphyxiated newborns in developed nations [5]. A Cochrane (2013) review also concluded a significant reduction in the risk of death or major neurodevelopmental disability from HINE among infants receiving hypothermia without increasing significant adverse effects [6]. Still, in 2013 a systemic meta-analysis of pooled data from developing countries concluded that TH might not be effective in developing countries due to differences in demographic and socioeconomic profiles such as maternal age, parity, education, nutritional status, and family income and healthcare access from developed nations [7]. Nevertheless, a recent systemic review and meta-analysis (2021) of developing and developed countries' randomised controlled trials concluded that TH in term infants with perinatal asphyxia effectively reduces mortality, and is an achievable, safe, and inexpensive modality in low-resource settings. Moreover, low-income countries benefit the most from this therapy [8]. Previous

studies mainly focused on its feasibility, and only a few reported neurological outcomes [9-11]. Early neurological assessment of TH recipients is still not well documented.

As a tertiary care teaching hospital, we deal with a significant burden of perinatal asphyxia and its complications, so it was aimed to study the neuroprotective benefit of TH in asphyxiated newborns by analysing early neurodevelopmental outcomes as compared to non recipients. To the best of our knowledge, the present study is also one of few reporting early neurological outcomes and the first to use HINE in newborns receiving TH in India as early identification of neuro-disabilities enables clinicians to categorise high-risk newborns and focus on early intervention [12].

MATERIALS AND METHODS

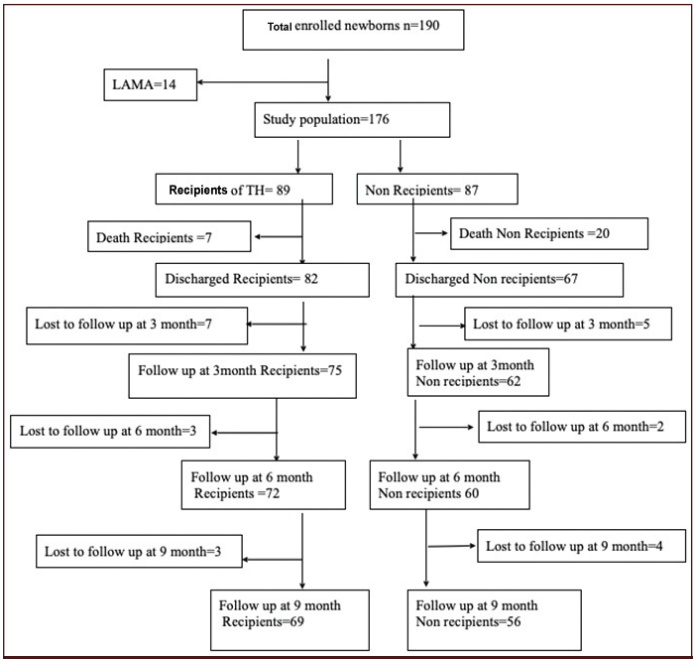
The non randomised prospective cohort study was conducted at a level three Neonatal Intensive Care Unit (NICU) of a tertiary care teaching institute from January 2019 to August 2020. The institutional ethical committee had approved the study (letter no-EC/MGM/march 19/07).

Sample size calculation: A minimum sample size of 50 in each group was calculated using the formula (Z*Z(P)(1-P)/C*C), with two-sided desired confidence level power of 95%, and with a minimum 15% incidence [4] of neurological abnormality among survivors (1.96×1.96×0.15×(1-0.15)/0.10×0.10=48.98~50). Considering 30-40% exiting institutional loss to follow-up, a minimum of 80 newborns were enrolled for the study.

Inclusion criteria: Asphyxiated newborns with the following laboratory and/or clinical evidence of severe birth asphyxia: 1) Moderate to severe encephalopathy at birth according to modified Sarnat criteria. 2) Persistence of low Appearance, Pulse, Grimace, Activity, Respiration (APGAR) ≤5 at 5 minutes or longer and/or acidosis and/or resuscitation/ventilation required 10 minutes after birth [13].

Exclusion criteria: Newborns <36 weeks, weight <2000 gm, hypotension (None Invasive Blood Pressure [NIBP] <40 mmHg) requiring adrenaline, persistent hypoxaemia on admission, and having significant congenital anomaly were excluded from the study [13].

A total of 190 newborns were enrolled for the study at the time of admission to the NICU [Table/Fig-1].



[Table/Fig-1]: Flowchart of the study.

Study Procedure

The neonates fulfilling the inclusion criteria were enrolled in the study after taking parental consent and were classified according to modified Sarnat and Sarnat [14] criteria by the treating paediatrician. Neonates with HIE, admitted within six hours of birth or early referrals were included in the hypothermia protocol, and TH was started and maintained for a period of 72 hours to target core temperature range of 33-34°C, followed by rewarming by 0.5°C/2 hour, using a low-cost cooling device based on phase-changing material (Mira Cradle Neonate Cooler). Asphyxiated newborns admitted after six hours of life were managed as per the standard protocol for HIE. The baseline demographic and neonatal data were recorded in a predesigned proforma, and neonates were followed-up regularly at the high-risk clinic at three, six, and nine months, as per the national neonatology forum guidelines [15]. At discharge, the recipients and non recipients were allotted a registration number at the 'high-risk clinic'. They were called at regular follow-ups, with travel arrangements under the Janani Suraksha Yojana scheme. Twenty-two recipients and 31 non recipients were lost to follow-up till nine months of age. Detailed neurological examination and development screening was done by a trained paediatrician using HINE and DDST II scale [16,17].

HINE: The assessment includes several aspects of neurological functions, including cranial nerve assessment, posture, movements, tone, reflexes, and behaviour. The overall global score ranges from a minimum of 0 to a maximum of 78. A total score below 67 and 70 at three months and six months are considered suboptimal. At nine to12 months, a global score of <73 is suboptimal with an excellent predictive value (96%) for developing CP at two years of age. Suboptimal global scores are also associated with a minor neurological disability when clinical signs of CP are absent [16].

DDST-II: It tests 125 items in four development domains; each object has 25th, 50th, 75th, and 90th percentile range. The age line plots infant age in a chart in each field. The test is interpreted commonly if the infant can pass three items on the left-side of the age line (above 75% mark) and the maximum number of one caution. The test is interpreted as abnormal if the child fails an item that falls on the left-side of the age line at the 90% mark or has two or more cautions in single or multiple domains [17].

STATISTICAL ANALYSIS

Data were entered in a Microsoft excel sheet, and analysis was done using SPSS software version 20.0. The continuous parameters were expressed as mean and median. Baseline characteristics were compared using t-tests for continuous data, categorical variables, and chi-square tests, and p-value was calculated wherever required. p-values <0.05 were considered significant.

RESULTS

Baseline demographic characters were similar in both groups. They had no statistical difference in maternal age, gender, place of birth, birth weight, gestational age, HIE grading, sepsis, and meconium aspiration syndrome during NICU stay (p>0.05). It was observed that non recipients of TH had significantly higher mortality than recipients (p<0.05) [Table/Fig-2].

Variables		TH recipients (n=89)	Non recipients (n=87)	p-value (chi square test)
Maternal age (years)	20-35	54 (60.7%)	49 (56%)	0.5
	>35	35 (39.3%)	38 (43.6%)	
	Mean (SD)	26 (4.55)	27 (4.67)	

Sex	Female	28 (31.4%)	36 (41.3%)	0.17
	Male	61 (68.5%)	51 (58.6%)	
Place of birth	Rural	32 (35.9%)	35 (40.2%)	0.55
	Urban	57 (64%)	52 (59.7)	
Birth weight	≤2.5 kg	18 (20.2%)	22 (25.2)	0.42
	>2.5 kg	71 (79.7%)	65 (74.7)	
	Mean (SD)	2.6 kg (0.52)	2.55 kg (0.35)	
Gestational age	36-38 wk	74 (83.1%)	75 (86.2)	0.57
	39-41 wk	15 (16.8%)	12 (13.7)	
	Mean, (SD)	278 days (9.88 days)	277 days (8.95 days)	
HIE grading	Stage 2	68 (76.4%)	60 (68.9)	0.26
	Stage 3	21 (23.5%)	27 (31%)	
Meconium aspiration syndrome		8 (8.9%)	14 (16)	0.06
Sepsis		14 (15.7%)	18 (20.6)	0.3
Mortality		7 (7.8%)	20 (22.9)	<0.005

[Table/Fig-2]: Baseline maternal and neonatal characteristics (n=176).

Seventy-five recipients were followed-up to three months, 72 at six months, and 69 at nine months vs 62, 60, and 56 non recipients, respectively. Lesser number of recipients scored suboptimal scores (HINE score <67) at three months vs non recipients 20% vs 35.4%, mean/SD 63 (3.43) vs 57 (4.55), (P<0.001). At six-month (HINE score <70), the difference was 18% vs 21% (p=0.02), mean score 67 vs 61 (p<0.0001), and nine month (HINE score <73) 14.4% vs 30.3% (p=0.048), mean score/SD 72 (3.45) vs 65 (4.88) among recipients vs non recipients, respectively (p<0.0001).

Recipients also had less incidence of severe disability (HINE score <40) at 6 (8.3% vs 21.6% p<0.02), and nine months (8.6% vs 19.6%, p<0.04) as compared to non recipients. The recipients also performed significantly better on developmental screening at three, six, and nine months as recipients had a normal developmental screening on the DDST scale. When compared to a seizure disorder, recipients required fewer antiepileptics at three and six months (11 vs. 4) as compared to non recipients (p<0.05). Overall mortality was also less among recipients (7.8% vs 20.9%, p<0.05) in comparison to non recipients [Table/Fig-3,4].

Neurological outcome at 3 months (n=137)						
Variables		**TH recipients (n=75)**	**Non recipients (n=62)**	**p-value (chi square test)**	**95% CI**	**RR**
HINE score	Mean score/SD (z score)	63 (3.43)	57 (4.55)	<0.0001	-7.3-4.65	
	<67	15 (20%)	22 (35%)	0.05	0.44-1.05	0.067
	<40	8 (10.6%)	13 (20%)	0.07	0.37-1.16	0.65
Normal DDST*		63 (84%)	42 (67%)	0.027	0.3-1.0	0.62
Antiepileptics required		11 (14.6%)	18 (29%)	0.05	0.39-1.04	0.6
>1 antiepileptics required		4 (5%)	7 (11.2%)	0.201	0.14-1.53	0.472
Neurological outcome at 6 months (n=132)						
Variables		**TH recipients (n=72)**	**Non recipients (n=60)**	**p-value (chi square test)**	**95% CI**	**RR**
HINE score	Mean score/SD	67 (2.88)	61 (3.76)	<0.0001	-7.14 to-4.85	
	<70	13 (18%)	21 (35%)	0.02	0.4-1.0	0.63
	<40	6 (8.3%)	13 (21.6%)	0.04	0.12-0.96	1.08
DDST Normal*		63 (87%)	44 (73.3%)	0.04	0.15-0.98	0.46
Antiepileptics required		4 (5%)	11 (18.3%)	0.02	0.19-1.07	0.45
>1 antiepileptics required		2 (2.7%)	4 (6%)	0.28	0.07-2.19	0.41
Neurological outcome at 9 months (n=125)						
Variable		**TH recipients (n=69)**	**Non recipients (n=56)**	**p-value (chi square test)**	**95% CI**	**RR**
HINE score	Mean score/SD (z score)	72 (3.45)	65 (4.88)	<0.0001	-8.47 to -5.5	
	<73	10 (14.4%)	17 (30%)	0.048	0.36-1.03	0.61
	<40	6 (8.6%)	11 (19.6%)	0.03	0.28-1.11	0.56
Normal DDST*		61 (88.4%)	41 (73.2%)	0.02	0.19-0.94	0.43
Antiepileptics required		3 (4.3%)	6 (10%)	0.17	0.10-1.55	0.405
>1 antiepileptics required		0	2 (3.5%)	0.11	-1-1.0	0.00

[Table/Fig-3]: Neurological outcomes at 3, 6, and 9 months.
Suboptimal score at 3 months ≤67; 6 months ≤70; 9 months ≤73; *No delays or a maximum of 1 caution; CI: Confidence interval; RR: Relative risk

Mode	Age	Total (n)	Cranial nerve	Spontaneous movements	Posture	Tone	Reflexes	Total mean score (range)	Suboptimal score (n%)	Score <40 (n%)
TH recipients	3 month	75	13	5	14	20	9	63 (25-71)	15 (20%)	8 (10.6%)
	6 month	72	14	6	15	20	11	67 (28-76)	13 (18%)	6 (8.3%)
	9 month	69	15	6	16	21	14	72 (35-78)	10 (14.4%)	6 (8.6%)
Non recipients	3 month	62	12	5	14	16	8	57 (21-71)	22 (35.4%)	13 (20.9%)
	6 month	60	13	5	14	18	9	61 (27-76)	21 (35%)	13 (21.6%)
	9 month	56	15	4	15	20	11	65 (34-78)	17 (30.3%)	11 (19.6%)

[Table/Fig-4]: HINE subsection score.
Suboptimal score at 3 months ≤67; 6 months ≤70; 9 months ≤73

DISCUSSION

The TH is now used as standard therapy for perinatal asphyxia in developed countries for the last two decades and is also recommended by the American Academy of Paediatrics [18]. TH causes a reduction in DNA damage initiated by a direct attack of Reactive Oxygen Species (ROS) that are overproduced during secondary reperfusion injury. DNA damage by these ROS causes modification of genetic material and cell death, leading to various degrees of neurological disabilities and increased mortality among asphyxiated newborns. Tertiary damage to the neurons, such as reduced plasticity, myelin deficits, and altered cell numbers, may persist for months to years after the initial insult [19]. The neuroprotective role of TH in HIE is attributed to its inhibitory actions on these oxidative insults by preventing DNA damage [20].

Various cooling devices have provided adequate neuroprotection in limited resource settings [8]. The results of the present study, which used a low-cost cooling device based on phase-changing material, are comparable with other studies using low-cost and high-cost cooling devices [4,5,9,10,11].

Severe HIE infants constituted 27.2% of the total study cohort in the present study, with 21 recipients and 27 non-recipient and moderate HIE newborns 72.8% of the study population. All the newborns who died during NICU stay were suffering from severe HIE. In the present study, the mortality rate among recipients was significantly lower (7.8%) than non recipients (22.9%), suggesting TH is an effective modality to reduce mortality in asphyxiated newborns ($p<0.005$) [Table/Fig-2]. Other studies using the same cooling devices also documented 6% to 21% differences in combined mortality and neurodevelopment among recipients and non recipients [21,22] but could not get statistical significance. However, a recent systemic review and meta-analysis of multiple RCTs observed that TH reduces the risk of death in neonates with moderate to severe HIE [8].

During follow-up, a slightly higher attendance rate was observed in the TH recipient group (84.5%) compared to non recipients (83.2%) at the nine-month visit. The present study recorded a significant decrease in neurological morbidity at nine months among recipients compared to non recipients. The recipients scored higher, and a lesser number of recipients scored suboptimal at three, six and nine months ($p<0.05$). Recipients were also significantly less likely to develop severe disability (HINE score <40) at 6 (8.3%) and nine months (8.6%) as compared to non recipients (21.6% and 19.6%) [Table/Fig-3,4]. This data is from a recent study by Romeo DM et al., using HINE. They demonstrated better neurodevelopmental and motor outcomes in TH recipients [23]. Purkayastha J et al., also reported that TH recipients had a significant reduction in developmental delay at 10 to 14 months of age, and a higher percentage of TH recipients (73.68%) had a normal Bayles scale of infant development score of >85 as compared to 40% non recipients [24]. Few other studies also concluded that TH reduced neurological abnormalities and resulted in more normal survival at six to 18 months [22,25].

The present study used the HINE scale, which has been reported to have good predictive value in identifying early neurodevelopment outcomes as early as three months. Although the early neurological development may not wholly predict the permanent outcome, a critical phase of rapid neurodevelopment continues till two years of age. Nonetheless, sub-optimal HINE scores at six and nine months of age have a 96% positive predictive value in identifying CP at two years of age, giving us more clinically relevant results [16].

Neonatal seizures are common morbidity following perinatal asphyxia. In the present study, the anti-epileptics requirement was significantly higher among non recipients than recipients when examined at three and six months [Table/Fig-3,4]. These results support the anti-seizure effect of TH among recipients. Lesser need for anti-epileptics further reduces the toxic effects of these drugs on the developing brain. TH is believed to protect against neural injury through multiple mechanisms that attenuate the excitatory environment in the injured brain [19]. Orbach SA et al., also concluded that the electrographic and clinical seizures were significantly lower among recipients of TH than non recipients [26]. Similarly, few other studies have also reported a reduced seizure burden, lower encephalopathy grade, and better electroencephalographic parameters with better neurodevelopment among recipients [5,21,24,25,27].

Observations made in the present study are comparable and consistent with other studies [5,6,8,14] done in developed countries as well as in limited resource settings [9,10,11,15]. Present study also provides important data regarding the early neurodevelopmental outcome of TH recipients, using HINE which has not been yet reported in HIE infants treated with TH provided at a resource-limited setting. Results of this study are highly encouraging for TH in neuroprotection and showed remarkable better neurological outcomes in recipients of TH than non recipients.

Limitation(s)

Follow-up of the study cohort had to be completed earlier with a relatively smaller sample size due to COVID-19-related operational constraints. The prospective observational design of the present study also makes the results less reliable as compared to a large RCT. Further, large RCTs with 18-24 month follow-up is necessary to confirm the observations of the present study, as the risk of developing CP may persist till the age of 2 years; some of these infants may show minor neurological signs that may not be detected earlier.

CONCLUSION(S)

Therapeutic Hyothermia leads to decreased mortality, less episode of seizures, reduction in the need for antiepileptics, and better neurological outcomes in survivors. Our findings will aid in existing knowledge and provide a better understanding of the safety and efficacy of TH in a limited resource setting to improve neurodevelopmental outcomes and reduce the burden of CP. It is recommended that future studies also aim at recognising early subtle neurological signs so that early intervention can be started early, which could allow further insight regarding the implementation of this novel therapeutic approach at the national level.

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