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A COHORT STUDY OF THE LONG-TERM NEUROLOGICAL OUTCOMES IN HIE (HYPOXIC ISCHEMIC ENCEPHALOPATHY) INFANTS BASED ON THEIR T.H. RECIPIENTS STATUS AT BIRTH AT 18 MONTHS OF AGE.

Neonatology

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ABSTRACT

Introduction- Hypoxic-ischemic encephalopathy (HIE) following perinatal asphyxia is the most common cause of the accquired perinatal brain injury and may lead to death or long-term neurologic sequelae. Approximately 20–30% of infants with HIE (depending on the severity) die in the neonatal period, and 33–50% of survivors are left with permanent neuro developmental abnormalities. Use of therapeutic hypothermia has been gold standard care of therapy to treat hypoxic ischemic encephalopathy (HIE) infants. The present study was planned to compare the neuro developmental and neurobehavioural outcomes in cohort of HIE infants treated with therapeutic hypothermia V/S infants not received therapeutic hypothermia at the age of 18 month follow up by ASQ and ASQ:SE scale. **Aims and objective** – To compare the long term neurodevelopment and neurobehavioural outcomes in cohort of HIE infant treated with therapeutic hypothermia vs infants not with Therapeutic Hypothermia at the age of 18 month. **Material and method** - This prospective cohort study was done on HIE infants at 18 months of age, who attended HRC of Chacha Nehru Bal Chikitsalaya (CNBC) of Department of Pediatrics, MGM Medical College Indore and associated Maharaja Yashwant Rao Hospital (M.Y.H). The study was conducted for a period of 1 year. According to therapeutic hypothermia given to HIE infants, 2 cohorts of the study sample (infants who received T.H. v/s infants who did not received T.H.) were compared in different domains of neurodevelopment and neurobehaviour by using ASQ and ASQ: SE scale. **Results** - Total 166 were recruited for present study at 12 month of age and followed upto 18 month of age. Baseline characteristics in both the group are similar. Out of total HIE infants 74% were HIE 2 and 26% were HIE 3. Total therapeutic hypothermia recepients are 48% as compared to 52% of non recepients. At 18 month of age neurodevelopment and neurobehavioural outcomes in HIE infants is better in T.H. received group as compared to non recepients group, p value 0.000 which is statistically significant in all domains. **Conclusion** - For present study, neurodevelopment and neurobehavioral assessment was done by ASQ and ASQ SE scale in all the developmental domain and found that neurological outcome is statistically significant and better in therapeutic hypothermia recipients group as compared to non- recipients.

KEYWORDS

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) following perinatal asphyxia is the most common cause of the accquired perinatal brain injury and may lead to death or long-term neurologic sequelae.[1] According to WHO, **perinatal asphyxia** is defined as a failure to initiate and sustained respiration, occurring in **2 to 3 per 1000 newborn children**.[2-4] As per NNPD data perinatal asphyxia is the most common cause of stillbirth and accounts for 28.8% of all neonatal death.[5]

Approximately 20–30% of infants with HIE (depending on the severity) die in the neonatal period, and 33–50% of survivors are left with permanent neuro developmental abnormalities (cerebral palsy, decreased IQ, learning/ cognitive impairment). The developmental outcome of HIE ranges from motor delay to learning problems, cognitive impairment, neurodevelopmental disorders and visual and hearing impairment.[6]In India the rate of cerebral palsy is **2-2.8/1000 live birth.**[7]. As of today, the sole modality for treatment and a way to decrease future Morbidity in babies with perinatal asphyxia is that **the initiation of therapeutic Hypothermia within the first 6 hours** of life. Trials of whole body and selective head cooling in neonates with moderate to severe HIE have shown that therapeutic hypothermia (TH) **within 6 hours** of birth ameliorates the severity of injury and improves neurodevelopmental outcomes (NDs) in surviving infants.[8]

Use of therapeutic hypothermia has been gold standard care of therapy to treat hypoxic ischemic encephalopathy (HIE) infants in developed nations since last 20 year.[9]Although, it's still a new concept in developing countries like India to treat HIE infants and very few government hospital in India are using therapeutic hypothermia as standard therapy as its efficacy in limited resource settings is still not well documented. There is a paucity of studies which have reported outcome in neonates managed with TH in India.

In high income countries have shown that TH resulted in improvement in long term neuro developmental outcome. In LMIC, however, the benefits of TH remain unclear.[9,10]A study in South Africa demonstrated that TH is feasible and safe in a resource-limited setting, provided there is adequate monitoring and support.

This is the first study in India as per our knowledge where we studied the long term neurological outcome of HIE infants treated with therapeutic hypothermia upto 18 month of age.

MATERIAL AND METHOD -

After approval from institutional and university ethical committee, this prospective cohort study was done on **166 HIE infants of 12 and 18 months of age,** who attended HRC of Chacha Nehru Bal Chikitsalaya (CNBC) of Department of Pediatrics, MGM Medical College Indore and associated Maharaja Yashwant Rao Hospital (M.Y.H.) and qualified the inclusion criteria as assessed by ASQ and ASQ: SE scale. The study was conducted for a period of 1 year. A written consent was obtained from the parents/ guardian of the subjects included.

HIE infants who fulfilled inclusion criteria[11-12] of T.H. protocol at NICU admission and registered in HRC clinic were recruited for the present study at the age of 12 month.

- **Recipients** – Patients who fulfilled the inclusion criteria of T.H. protocol and starting time of T.H. within 6 hours of birth.
- **Non-recipients-** neonates with perinatal asphyxia fulfilling above inclusion criteria who came after 6 hours of age or Mira cradle was not available.

Exclusion Criteria

1. History of meningitis and encephalitis.
2. Inborn error of metabolism.
3. Major congenital malformation.
4. Lost to follow up.

METHODOLOGY

Infant patients/newborns with perinatal asphyxia who met the inclusion criteria of T.H protocol were labelled as **RECIPIENTS** and after taking a written informed consent from their parents they were given **T.H by Mira cradle** for 72 hours. The newborns with perinatal asphyxia who did not receive therapeutic hypothermia were labelled as **NON- RECIPIENTS**, as described above. They were provided with routine supportive care. The neonates were categorized for HIE stage based on the modified Sarnat and Sarnat staging. {13}

After successful discharge, newborns were registered in high-risk clinic (HRC) as SNCU protocol and were followed up at 12 and 18

months of age for the present study. The neurological assessment was done by a trained pediatricians and principal investigator at high-risk clinic by **ASQ3 and ASQ: SE scale. {12,13}**

The Ages & Stages Questionnaires®, Third Edition (ASQ®-3)is a developmental screening tool that is designed to screen developmental progress in children between the ages of one month to 5 ½ years to identify those children who are in need of further evaluation. Each Questionnaire contained 30 questions grouped by developmental areas in relation to daily activities of the child. This scale evaluated the development of children in 5 domains (gross motor, fine motor, communication, personal social, problem solving) at different period of intervals between age one month to 5.5 Years. After completion of particular age questionnaires, the score was calculated in each domain and result was labeled as above, close or below according to the pre-decided cutoff score of that particular domain. Below cutoff in one or more areas:

- Score is 2 standard deviations or more below average
- Referred for further assessment
- Rescreened

ASQ:SE (The Ages and Stages Questionnaires: Social – Emotional) was meant to be used in conjunction with a general development tool (ASQ). It assessed cognitive, communicative and motor development and helped in identifying the need for further social behavior assessment in children. These questionnaires addressed seven behavioral areas: Self-regulation compliance, Adaptive functioning, Autonomy, Affect, Social-communication, and Interaction with people.

Sample Size, Data Collection And Analysis-

Sample size estimation –Minimum sample size of 50 in each group was calculate 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 of neurological abnormality among survivors.

According to therapeutic hypothermia given to HIE infants, **2 cohorts of the study sample (infants who received T.H. v/s infants who did not received T.H.)** were compared in different domains of neurodevelopment and neurobehaviour at the age of 18 months and categorized according to the cut off score.

We considered the normal development when score is above the cut off and delayed development when score is below or close the cutoff which is predefined in ASQ scale questionnaire and in ASQ: SE scale, we considered normal development when score is below to cutoff score and delayed development when score is close or above to cutoff score.

Statistical Analysis

The data was collected and entered in Microsoft Excel 2010 (Microsoft corp.) and analyzed using the SPSS version 20.0 operating on Windows 10. All the descriptive data were presented as mean, standard deviation, frequency and percentages represented as the pie charts and bar diagrams. A P value of <0.05 is considered significant.

RESULTS

Total 166 patient recruited at 12 month of age who fulfill the inclusion criteria after parent/guardian consent. These patient were followed upto 18 month of age and neurological development assessed by using ASQ and ASQ:SE scale. Baseline demographic profile are similar in both the group (T.H. recepients and T.H. non recepients){ Table 1}. At 18 month of age out of 152 patients (16 patient lost to follow up), HIE 2 and HIE 3 were 74% and 26% , T.H. recepients and T.H. non recepients were 48% and 52% respectively.

At 18 month of age, we assessed the neurodevelopmental outcome by ASQ scale and found that in all domains the development is normal in T.H. recepients group as compared to non recepients where development was delayed, with statistically significant P value 0.000.

Table 1: Demographic profile of HIE infants.

S. No	Variables		Frequency	T.H. recepients	T.H. non recepients	P value
1	Birth weight	2-2.5 kg	133(58.55%)	68	65	0.111
		2.5-3 kg	44 (29%)	18	26	Non - sig
		>3 kg	18 (12%)	5	13	
2	Sex	Female	86(56.58%)	40	46	0.201
		Male	66(44.1%)	34	32	Non-Sig
3	HIE stage	HIE 2	127(78%)	64	63	0.123
		HIE 3	39 (21%)	17	22	Non-Sig
4	Admission	Inborn	92 (60.5%)	52	40	0.111
		Outborn	60 (40%)	22	38	Non-Sig
	Total(152)					

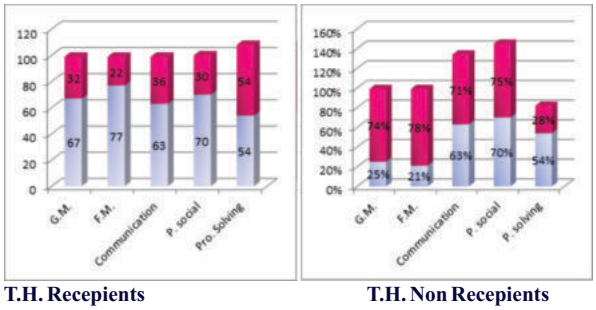
Table 2: Neurodevelopmental outcomes in HIE infants at 18 month of age by ASQ scale.

S.no.	Domain	T.H. Recepients (74)		T.H. non recepients (74)		P value
		Normal	Delayed	Normal	Delayed	
1	Gross motor	50 (67%)	24(32%)	20 (25%)	58 (74%)	0.000
2	Fine motor	57 (77%)	17 (22%)	17 (21%)	61 (78%)	0.000
3	Communication	47 (63%)	27 (36%)	22 (28%)	56 (71%)	0.000
4	Personal social	52(70%)	22 (30%)	20 (25%)	58 (75%)	0.000
5	Problem solving	40(54%)	34(45%)	22 (28%)	56(71%)	0.000
Interpretation-	Neurodevelopmental outcome is better in T.H. recepients group in all domains as compared to non recepients.					

Table 3: Neurobehavioural outcome of HIE infants at 18 month of age by ASQ:SE scale.

S.no.	Variable	T.H. Recipients		T. H. non recepients		P Value
		Normal	Delayed	Normal	Delayed	
	ASQ: SE scale	54 (73%)	20 (27%)	25(32%)	53 (67%)	0.000

Graph 1: Comparasion of Neurological outcomes in HIE infants at 18 month between T.H. recepients and T.H. non recepients.



T.H. Recepients **T.H. Non Recepients**

DISCUSSION

HIE is the most common cause of mortality and neurodisability among the newborn followed by perinatal asphyxia. HIE contribute up to 20-28% neonatal death and among survivors 30- 50% develop neurodevelopmental abnormality. 60- 80% neonates with severe encephalopathy develop neurodisability and Cerebral palsy.[1,2,14,15]

Several mechanisms have been postulated for neuro protection in birth asphyxia, TH has been widely studied since last 20 yrs and is being used in developed countries[3,4,9] as standard therapy of care in case of birth asphyxia to reduce mortality and neurodisability but in developing countries like India the data are still insufficient. Only few studies in India studied the benefit of T.H. in asphyxiated newborns.[8,10]

Present study is the first study to report long term neurological outcome in HIE infants at 18 months of age in therapeutic hypothermia recipients compared to non-recipients in India using detailed assessment of neurodevelopment and neurobehavior in each domain. This study was conducted after initial favorable results in previous recent study at present institute by **Nilesh Jain et al** which concluded that in HIE infants receiving T.H. exhibited improved survival and better neurological outcome using HINE scale at discharge from hospital.[16] We undertook the present study on 166 HIE infants attending High risk clinic at pediatric department with an aim to study long term neurodevelopmental and neurobehavioural outcome at 12 and 18 month of age.

The neonates fulfilling the inclusion criteria recruited for our study at 12 month of age and followed up to 18 months of age and results were compared between therapeutic hypothermia recipients and non-recipients. In India, **Basavaraj et al**. also described the long-term neurodevelopmental outcome in only T.H. recipients following

perinatal asphyxia by ASQ 3 scale in different domain up to 3,6 and 12 months. In Bosnia, **Smail Zubcevic et al.** done the neurological assessment at three different visit 3-6 month, 12 -18 month, 24-36month using ASQ 3 scale in HIE patients. Other studies **(J.M. Conway et al.,** also studied the long term neurodevelopment in HIE by using different methods.[17-20]

At present study, out of total participants female is higher as compared to male [56 v/s 44]. Most of the HIE infants had birth weight between 2.5 –3 kg. **Rajiv Prasad et al** also supported this proportion of higher female participants and mean birth weight in their study is 2.79 +/-0.8. Higher attendance rate was observed in T.H non recipients' group (53%) as compared to recipients (47%) at 18 month of age but difference was statistically insignificant]. Maximum HIE infants on follow up come under HIE 2 (79%) and HIE 3 (21%). A prospective cohort study **Rajiv Prasad et** al. also presents the different proportion of HIE stage HIE1 41%, HIE2 43% and HIE3 15%.[21]

Significant neurodevelopmental outcome difference is being noted between two groups at 18 months of age(p value 0.000). **Purkayastha J et al**. also reported that T.H. recipients had significant reduction in developmental delay at 10 and 14month of age and higher percentage of TH recipients had a normal BSID (Bayles score of infant development) score >85 as compared to non- recipients. **R Christina Catherine** randomized controlled trial also proved less neurological abnormality and more survivor. Other studies **(Smail Zubcevic et al, Mikael finder et al., Azzopardi D et al., Cochrane systemic review)** also supported the benefit of T.H. on neurodevelopmental outcomes.[22-27]

CONCLUSION

Perinatal asphyxia is a major contributor to global neonatal mortality and morbidity. The resultant complications of HIE are wide ranging. Brain injury following a period of hypoxia is a process that evolves hours to days providing an opportunity for neuro protective intervention.

The advent of therapeutic hypothermia as a standard neuroprotective treatment for moderate to severe encephalopathy has changed the prognosis and long-term neurodevelopment as compared to previous era in developed countries as per various studies, but in India very limited studies have concluded the long- term outcome of HIE survivors. Present study is the first study in India which follow up the HIE survivor at 18 months of age and development assessment is being done to detect abnormalities.

For present study, neurodevelopment and neurobehavioral assessment was done by ASQ and ASQ SE scale at 12 and 18 months of age in all the developmental domain (gross motor, fine motor, communication, personal social, problem solving) and found that neurological outcome is statistically significant and better in therapeutic hypothermia recipients group as compared to non- recipients at both the time (12 and 18 month).

Limitation

The limitation of present study that we used screening scale for development assessment which was based on parent recall, so developmental outcomes cannot be representative for actual neurodevelopment status. Further RCTs with larger sample size using more detailed confirmatory scales for neurodevelopment assessment are required to apply results to targeted population of affected children.

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