International Journal of Contemporary Pediatrics
Kachhwaha R et al. Int J Contemp Pediatr. 2023 Oct;10(10):1558-1565
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20232884

Original Research Article

Neurodevelopmental outcome of babies with moderate to severe birth asphyxia with hypoxic ischemic encephalopathy treated with and without therapeutic hypothermia followed up till 6-24 month of age at tertiary care hospital of Southern Rajasthan

Ritika Kachhwaha, Suresh Goyal, Juhi Mehrotra, Sakshi Sethia, Jeevan G. M.*

Department of Pediatrics, R. N. T. Medical College Udaipur, Rajasthan, India

Received: 27 July 2023
Revised: 02 September 2023
Accepted: 05 September 2023

***Correspondence:**
Dr. Jeevan G. M.,
E-mail: gmjeevanreddy@gmail.com

ABSTRACT

Background: Therapeutic hypothermia has become an established protocol for all neonates with moderate to severe hypoxic ischemic encephalopathy. There are very few studies comparing the neurodevelopmental outcomes in neonates with moderate to severe HIE who received and not received TH. Objective was assessment of neurodevelopmental outcome between TH and non-TH group till last follow-up.
Methods: Hospital Based Prospective study. All term neonates with Moderate to severe birth asphyxia with HIE who received TH and not received TH, admitted in NICU of BalChikitsalay, RNTMC, Udaipur, consenting for the study were followed up at age 3-6 month, 6-12 month, 12-18 month and 18-24 month from September 2018 to February 2021 and neurodevelopment outcome was assessed.
Results: 70 neonates with birth asphyxia HIE II / III were included in the study, 35 in TH group and 35 in non-TH group. Out of 70 babies enrolled 46 (65.7%) were having normal development and 24 (34.3%) were having development delay. Out of 46 who were having development delay 6 (17.4%) were of TH group and 18 (51.4%) were of non-TH group. Most of the babies of TH group i.e., 30 (85.7%) were neurodevelopmentally normal and 5 (14.3%) were having some neurodevelopmental abnormality. In non-TH group 15 (42.8%) were normal and 20 (57.2%) were having some neurodevelopmental abnormality.
Conclusions: Results of the study showed significantly better outcome in infant who received therapeutic hypothermia than those who did not.

Key words: Perinatal asphyxia, HIE, Therapeutic hypothermia, Neurodevelopment outcome

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay or learning disability and epilepsy.[1] HIE occurs in 1.5 per1000 full term births. Approximately 15-20% of infants with HIE die in the neonatal period, and 25% of survivors are left with permanent neurodevelopmental abnormalities. Surviving neonates with severe birth asphyxia and hypoxic ischemic encephalopathy has variable neurodevelopmental outcomes they may have microcephaly, intellectual disability, psychomotor retardation (Gross motor and coordination problem), disabling cerebral palsy, epilepsy, blindness and hearing impairment.

Table 1: ICMR Development scale age centile values.

Parameters	3rd	5th	25th	50th	75th	95th	97th
Gross motor							
Lifts head when on stomach	1.8	2.1	3.1	3.7	4.6	5.9	6.5
No head lag in sitting position	1.9	2.2	3.1	3.8	4.7	5.9	6.5
Sits alone	4.2	4.5	5.8	6.6	7.7	9.4	10.0
Crawls	4.1	4.4	5.6	6.4	7.3	9.0	9.7
Stands alone	6.1	6.9	9.8	11.8	14.1	19.0	-
Stands on one foot with help	11.7	12.6	16.2	18.9	23.0	-	-
Hops on one foot	-	30.1	42.2	49.9	58.0	-	-
Walks backwards	-	12.5	19.2	24.1	30.7	-	-
Cames wooden block on head and walks 5 steps	-	-	27.0	35.2	44.6	-	-
Gets up from squatting position without help	-	-	19.2	25.3	33.4	-	-
Vision and fine motor							
Regards objects	-	-	0.1	0.6	2.0	2.1	-
Sustained attention	-	-	1.2	1.8	2.6	4.0	4.6
Reaches for objects	1.4	2.0	3.4	4.4	5.3	6.8	7.0
Grasps objects	2.0	2.2	3.4	4.2	5.0	6.9	7.6
Picks up cube/pebble	3.1	3.5	5.2	6.3	7.6	10.5	11.7
Attempts imitation of scribble	7.6	8.3	11.2	13.1	15.6	-	-
Puts 3 or more cubes/pebbles into cup	9.8	10.4	12.9	14.7	17.0	-	-
Draws straight line in imitation	15.3	16.4	20.8	24.2	29.5	-	-
Draws circle in imitation	-	21.3	31.5	39.3	49.9	-	-
Draws square in imitation	-	-	49.7	60.4	-	-	-
Movement of thumb	-	-	-	36.7	52.8	-	-
Can close one eye lid	-	-	-	43.1	57.3	-	-
Threads one bead with nylon wire	-	12.0	17.1	20.8	25.2	41.0	-
Makes ball from dough or clay	-	-	24.9	32.0	42.4	-	-
Thumb and finger snap test	-	-	21.9	29.6	41.3	-	-
Hearing, language and concept development							
Responds to sound	-	-	-	0.1	0.9	2.5	2.9
Manipualtes bell	-	4.2	6.3	7.8	9.6	14.0	-
Rings bell	-	-	7.7	9.9	12.6	-	-
Repeats a number or word	-	-	19.3	25.0	30.4	-	-
Says one word	11.3	12.0	14.9	17.3	20.l	-	-
Identified one object	-	-	13.5	18.6	23.6	31.0	33.7
Names one object	-	-	20.5	25.1	30.7	-	-
Enjoys looking at pictures	-	-	9.5	13.4	18.8	27.7	-
Points two parts of body	-	-	18.4	22.4	26.9	37.0	-
Says two words together	-	-	23.4	30.4	37.6	-	-
Names three objects	-	-	23.4	30.4	37.6	-	-
Relates two objects	-	-	20.5	25.4	31.6	-	-
Points to 4 parts of body	-	-	-	24.4	30.2	-	-
Concept of big and little	-	-	26.2	33.3	43.3	-	-
Concept of heavy and light	-	-	-	35.4	44.0	60.8	66.3
Repeats 2 numbers	-	-	27.3	35.4	44.5	-	-
Recognizes 3 colors	-	-	50.1	63.0	-	-	-
Understands prepositions	-	-	23.0	29.4	36.9	-	-
Completes sentence	-	-	40.6	50.4	61.3	-	-
Understands money	-	-	18.5	23.3	28.5	39.1	-
Signs 2 lines of song/folklore	-	-	43.6	60.7	-	-	-
Self help skills							
Feeds self in any way	3.7	4.3	6.3	7.6	8.9	11.3	12.0
Drinks from cup or glass	-	8.9	14.8	19.0	24.1	-	-
Feeds self appropriately	8.1	9.0	12.2	14.5	17.2	24.2	-
Bladder control during day	10.7	12.3	18.6	23.0	28.4	-	-

Continued.

Parameters	3rd	5th	25th	50th	75th	95th	97th
Bladder control during night	6.1	8.6	18.4	25.7	35.7	-	-
Bowel control during day	9.6	11.1	16.6	20.5	25.2	-	-
Bowel control during night	-	-	9.5	15.8	22.9	-	-
Cleans teeth	-	-	25.8	33.0	43.2	-	-
Washes hand	-	-	19.3	24.4	30.4	45.0	-
Washes face	-	-	21.2	26.7	33.3	-	-
Dresses self without help	-	32.9	44.6	55.9	-	-	-
Visits key places in villages	-	-	30.7	40.7	52.6	-	-
Social skills							
Smiles in response	-	-	-	1.7	2.7	4.2	4.8
Vocalizes in response	-	-	1.6	2.9	4.4	7.1	8.0
Awareness of strangers	-	-	6.7	9.4	12.7	-	-
Can tell hisiher name	-	-	24.7	30.1	36.4	-	-
Can tell gender	-	-	31.2	38.5	47.9	-	-
Plays with other children	-	-	15.5	20.4	26.3	-	-
Rules of games understood	-	33.3	47.0	62.4	-	-	-

Cooling appears to reduce DNA damage induced by oxidative stress and improve neurodevelopmental outcome.[2,3] Therapeutic hypothermia act as neuroprotective agent in HIE by reducing vasogenic edema , hemorrhage and neutrophilic infiltration. The incidence of neonatal encephalopathy (NE) is 10-20 times higher in low resourced settings compared to industrialized countries. Therefore, a research priority involves developing low technology methods of neuroprotection and evaluating these through an extensive network of developing country partners. There has been considerable debate regarding the use of cooling in low- and middle-income countries. Use of therapeutic hypothermia in low resource settings should be considered experimental and should therefore be restricted to well equip level 2 and 3 neonatal units.

Microcephaly is a known consequence of severe birth asphyxia and may be accompanied by abnormalities such as cerebral palsy, seizures, developmental delay and intellectual disability.[4,5] Head circumference must be accurately checked at each visit up to 2 years must be checked with a non-stretchable tape. Children suffering from moderate to severe NE are 5.9 times more likely to be diagnosed with an autism spectrum disorder as compared to controls at 5 years.[6] Autism screening should be conducted universally in all children between 18-24 months.[7] Epilepsy occurs in up to 50% of newborn with HIE and usually start within 24hrs after HI insult. It is to be remembered that seizures in HIE are often subclinical (electrographic only) and may be manifested only by abrupt change in BP, HR and oxygenation. However, survivors of NE though apparently normal in early childhood may develop subtle cognitive and behavioral abnormalities later on.[8,9] Like other high-risk infants, it is necessary to follow up cases of TH till 8-10 years of age, if possible, throughout their school years, even if they appear to be normal in early childhood.[10,11] At the least, they should be followed up till 18-24 months of corrected age. Study on neurodevelopmental outcome of neonates with moderate to severe HIE treated with therapeutic hypothermia is not available from this part of country, hence this study was planned.

METHODS

This is a hospital based prospective study. All term and near-term neonates with moderate to severe birth asphyxia with HIE who received TH and not received TH, admitted in NICU of BalChikitsalay, RNTMC, Udaipur, consenting for the study were followed up at age 3–6-month, 6–12-month, 12-18 month and 18-24 month from September 2018 to February 2021 and neurodevelopment outcome was assessed. An informed and written consent was taken from all parents of patient prior to study after proper counseling.

Inclusion criteria

All the neonates of Moderate to severe birth asphyxia with HIE who underwent Therapeutic Hypothermia for its entire duration (72 hours) and survived after treatment with therapeutic hypothermia, were enrolled in the study and followed in follow up clinic till the age of 2 years. Equal numbers of neonates with moderate to severe birth asphyxia were taken as controls who were not treated by therapeutic hypothermia were included.

Exclusion criteria

Exclusion criteria were; not consenting for the study, Infants with congenital malformation, Premature infants <37 week, Neonates weighing <1800 gm at birth, lost to follow up.

The neonates fulfilling the inclusion criteria were enrolled in the study. Neonates were classified according to sarnat and sarnat staging. Neonates with HIE who were admitted within 6 hrs of delivery were included in the hypothermia protocol and Neonates with HIE who were admitted after 6 hrs of delivery were included in the non-hypothermia protocol. Asphyxiated neonates with grade II/III HIE were given hypothermia using non-servo controlled (Miracradle)/servo controlled (Neotherm) for a period of 72 hrs and were monitored and managed as per standard treatment protocol.

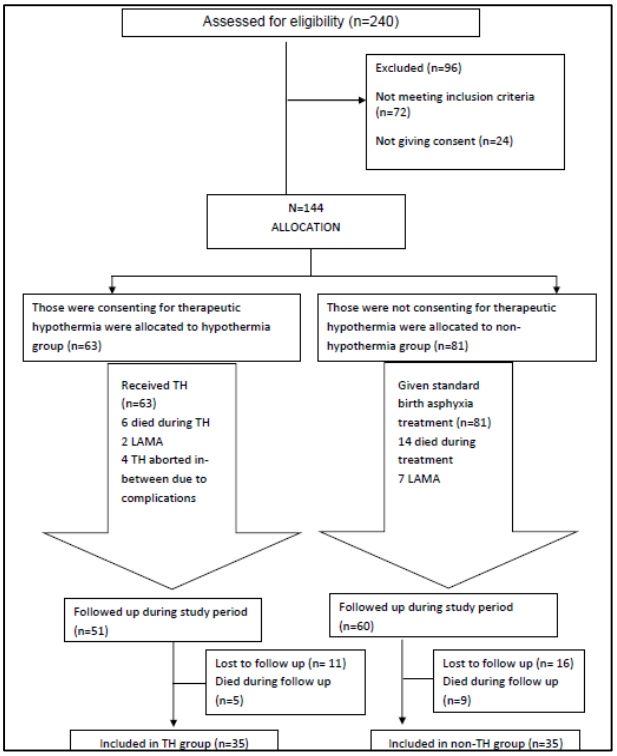

Figure 1: Diagram for enrolment and follow-up of infants.

Asphyxiated neonates with grade II/III HIE who were not given hypothermia were treated by standard ICU protocol under normothermic environment. Thompson scoring was done on admission and discharge of all neonates included in the study as part of neurological assessment. Demographic details, contact number were noted and general physical examination was done on admission of all included neonates. After discharge infants of both TH and non-TH group were followed up, at each follow up both groups were assessed for growth, development, neurological, hearing and vision. Development assessment was done on each follow up using ICMR (Indian council of medical research) development scale. This scale has been developed after a WHO-ICMR collaborative study on 28139 children in India, china and Thailand to develop culturally appropriate measures for monitoring child development at family and community level. The test has been standardized on Indian children's, comprises of culturally suitable items and is freely available for administration which made it ideal for screening. The test includes 66 items which measures abilities in 5 developmental area, namely gross motor (10), vision and fine motor (16), hearing, language and concept development (21), social skills (7), and personal skills (12). It has a very good correlation with more sophisticate, but time consuming and costly tests like Bayley's scale, which require investigators thorough education.

Advantages of ICMR scale include: simple low cost easily available items, items measure abilities which are relevant in context of the cultural expectation of social competence in the area and included items measures observable behaviour with a clear pass or fail score for the ability or skill being measured. 50th percentile is considered as average age. Children between 51st and 99th percentile are lagging behind in development and need suitable intervention. Children between 51st-90th percentile are most probably having development delay. Children between 90th-99th percentiles were reported to be at risk needing immediate intervention. While assessing two consecutive failures for the children were carefully scrutinized to rule out the possibility of stranger anxiety and other environmental factors that might contribute to child failure in performing some item. All the collected data managed and analyzed with standard software of Biostatistics (SPSS version 2.0). Statistical analysis of the data was done with Chi-square test (for quantitative analysis), Student t-test (for continuous data) with assistance of qualified statistician. A p value <0.05 was considered as statistically significant. Sampling technique used in study was purposive sampling (non-probability sampling). The study was approved by institutional ethical committee of RNT medical college and hospital, Udaipur.

RESULTS

Average Thompson score on admission of TH group was 15.51428571 and non-TH group was 15.71428571. Average Thompson score on discharge of TH group was 5.685714286 and of non-TH group was 9.8. Asphyxiated neonates with grade II/III HIE were given hypothermia using Non-Servo Controlled (Miracradle)/Servo Controlled (Neotherm) for a period of 72 hrs and were monitored and managed as per standard treatment protocol.

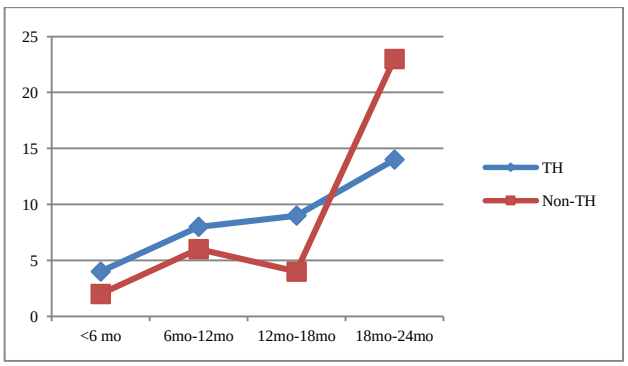

Figure 2: Follow-up duration of TH and non-TH group.

Table 2: Comparison of general data in two groups.

Parameters, N (%)		TH	Non-TH	P value
Gender	**Male**	22 (62.8)	21 (60)	0.8
	Female	13 (37.1)	14 (40)	
Follow-up duration (months)	**<6**	4 (11.4)	1 (2.8)	0.087
	6-12	7 (20)	7 (20)	
	12-18	10 (25)	4 (11.4)	
	18-24	14 (40)	23 (65)	
HIE grade (modified Sarnat and Sarnat grading)	**HIE II**	28 (80)	30 (85)	0.15
	HIE III	7 (20)	5 (15)	
Thompson score on admission	**1-10 (Mild)**	0	0	0.569
	11-14 (Moderate)	9 (25.71)	7 (20)	
	>15 (Severe)	26 (74.28)	28(80)	
Thompson score on discharge	**1-10**	34 (97.14)	22 (62.85)	0.0015
	11-14	1 (2.85)	10 (28.57)	
	>15	0	3 (8.57)	

Table 3: Development profile of children's according to ICMR tools.

ICMR development score	TH, N (%)	Non-TH, N (%)	Total, N (%)	P value
<25	0	0	0	0.00033
25-50	0	0	0	
50 (normal)	29 (82.85)	17 (48.75)	46 (65.4)	
50-75 (delayed)	4 (11.42)	0	4 (11)	
75 (delayed)	2 (5.71)	7 (20)	9 (12.85)	
75-95 (delayed)	0	6 (17.14)	6 (8.57)	
95 (abnormal)	0	5 (14.28)	5 (7.14)	
Total	35	35	70	

Among them 23 (65.7%) were given hypothermia by Non-Servo Controlled and 12 (34.3%) by servo controlled. In the study out of total 70 babies enrolled 46 (65.7%) were having normal development and 24 (34.3%) were having development delay according to ICMR development scale. Among 46 who were having development delay 6 (17.4%) were of TH group and 18 (51.4%) were of non-TH group.

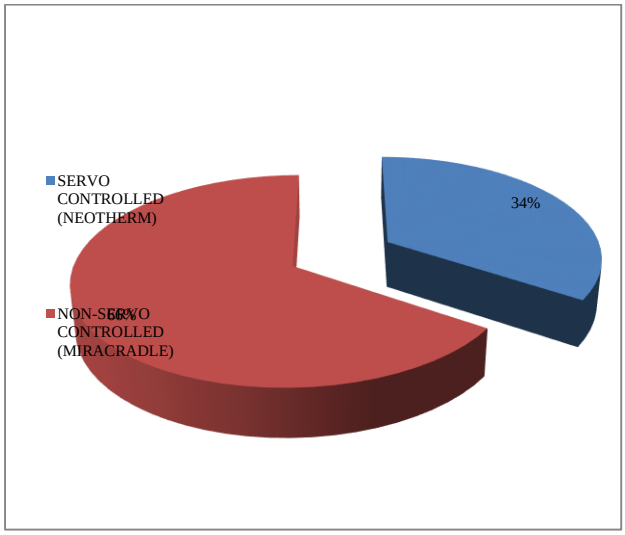

Figure 3: Distribution according to mode of hypothermia.

Among TH group 4 (11%) having b/w 50th-75th percentile and 2 (6%) having 75th percentile i.e., most likely development delay according to ICMR development scale. Among non-TH group 7 (20%) having 75th percentile & 6 (17%) having b/w 75th-95th percentile i.e., most likely development delay, 5 (14%) having 95th percentile i.e., high risk of development delay (abnormal) according to ICMR development scale. As per chi square test p value is <0.05 (0.0003) so null hypothesis can be rejected and difference in Development profile of children's according to ICMR tools till last follow-up between two groups was found to be significant. Development quotient was calculated as:

$$\frac{developmental\ age}{chronological\ age} * 100$$

In the study out of total 70 babies enrolled 46 (65.7%) were having >85% i.e., normal DQ, 12 (17.14%) were having DQ 71-84% i.e., below average, 6 (8.57%) having DQ between 51-70% i.e., mild development delay, 4 (5.71%) having DQ between 35-50% i.e., moderate development delay and 2 (5.71%) were having DQ < 35% i.e., severe development delay. Among TH group 28 (80%) were having normal DQ and 7 (20%) were having below average DQ. And among non-TH group 18 (51.4%) were having normal DQ, 5 (14.3%) were having DQ of 71-84% i.e., below average, 6 (8.57%) having DQ between 51-70%

i.e., mild development delay, 4 (5.71%) having DQ between 35-50% i.e., moderate development delay and 2 (5.71%) were having DQ < 35% i.e., severe development delay.

Table 4: Development profile of children's as per DQ.

Parameters (%)	TH, N (%)	Non-TH, N (%)	Total, N (%)	P value
115-85 (average)	28 (80)	18 (51.4)	46 (65.7)	0.021418
70-84 (below average)	7 (20)	5 (14.3)	12 (17.14)	
51-70 (mild)	-	6 (17.14)	6 (8.57)	
35-50 (moderate)	-	4 (11.42)	4 (5.71)	
<35 (severe)	-	2 (5.71)	2 (2.86)	
Total	35	35	70	

Table 5: Comparison of observed indicator between two groups.

Parameters		TH, N (%)	Non-TH, N (%)	P value
Development profile as per ICMR development assessment	Normal	30 (85.7)	18 (51.4)	0.0043
	Development delay	5 (14.28)	12 (34.3)	
	Abnormal development	0	5 (14.3)	
HC as per WHO chart	<3 (Microcephaly)	2 (5.7)	11 (31.4)	0.002046
	3-10	10 (28.5)	13 (27.14)	
	11-90	23 (65.7)	9 (25.7)	
	>97 (Macrocephaly)	0	2 (5.7)	
Tone	Hypertonia	0	14 (40)	<0.001
	Normal	35 (100)	8 (22.85)	
	Hypotonia	0	3 (8.6)	
Epilepsy	Present	2 (5.7)	14 (40)	0.00063
	Absent	33 (94.3)	21 (60)	
Vision	Normal	31 (88.57)	29 (82.85)	0.000118
	Abnormal	0	4 (11.42)	
	Cannot be assessed	4 (11.42)	2 (5.71)	
Hearing	Normal	31 (88.57)	30 (85.71)	0.158
	Abnormal	0	3 (8.57)	
	Can't be assessed	4 (11.42)	2 (5.71)	
Neurodisability	Absent	30 (85.7)	15 (42.8)	0.000183
	Present	5 (14.3)	20 (57.2)	
Neurological outcome	Epilepsy	2 (6)	14 (40)	
	Spastic CP	0	13 (37.1)	
	Hypotonic CP	0	3 (8.5)	
	Hydrocephalus	0	2 (5.7)	
	Hearing defect	0	3 (8.5)	
	Vision defect	0	4 (11.42)	

As per Chi square test p value is <0.05 (0.0214) so null hypothesis can be rejected and difference in DQ between two groups was found to be significant. Babies of TH group 30 (85.7%) were neurodevelopmentally normal and 5 (14.3%) were having some neurodevelopmental abnormality. Among neurodevelopmentally disabled 5 (14.3%) were having development delay, 2 (5.7%) developed epilepsy and 2 (5.7%) having microcephaly. In non-TH group 15 (42.8%) were normal and 20 (57.2%) were having some neurodevelopmental abnormality. Among neurodevelopmentally disabled 12 (34.3%) were having development delay, 5 (14.3%) abnormal development, 14 (40%) persistent seizures, 13 (37.1%) spastic CP, 3 (8.5%) hypotonic CP, 11 (31.4%) having microcephaly and 2 (5.7%) developed hydrocephalus. As per Chi square test p value is <0.05 (0.00018) so null

hypothesis can be rejected and difference in neurodevelopmental outcome between two groups was found to be significant.

DISCUSSION

Development assessment as per ICMR Scale

In this study out of total 70 babies enrolled 46 (65.7%) were having normal development and 24 (34.3%) were having development delay according to ICMR development scale. Among 46 who were having development delay 6 (17.4%) were of TH group and 18 (51.4%) were of non-TH group. As p value is <0.05 (0.0003) so difference in Development profile of children's according to ICMR tools till last follow-up between two groups was found to be significant.

Koshy et al in their study used Griffith mental developmental scales (GMDS) and Vineland social maturity scales (VSMS) and concluded that children who underwent therapeutic cooling for hypoxic ischemic encephalopathy, showed normal neurodevelopmental outcome with normal milestones and normal developmental quotient in a minimum of 60% of children at 18-24 months of age which is less than our study in which 29 (82.85%) who were given TH were developmentally normal.[14] Sowjanya et al in their study used developmental assessment scale for Indian infant-II and found that 5/11 (45.45%) had both motor and mental quotients below 85%.[15] Purkhayastha et al in their study used BSID- III and concluded that higher percentage of infants (73.68%) who received therapeutic hypothermia had normal BSID Score as compared to 40% of the neonates with normal BSID score (>85) who did not receive therapeutic hypothermia.[16] Gane et al in their study used developmental assessment scale for Indian infants (DASII), and concluded that Developmental delay at 12 months for the babies in the hypothermia group (9.4%) was significantly lower (p<0.05) than the control group (36%).[17] Azzopardi et al in their multicountry TOBY trial used the Wechsler preschool and primary scale of intelligence III (WPPSI-III) test or the Wechsler Intelligence Scale for Children IV (WISC-IV), and concluded that a total of 75 of 145 children (52%) in the hypothermia group versus 52 of 132 (39%) in the control group survived with an IQ score of 85 or more (relative risk, 1.31; p=0.04).[18] Chalak et al in their study used Bayley's III and concluded that of the 70 survivors, 62 (89%) of children had neurodevelopmental outcomes testing thirty-one (50%) children had normal Bayley-III scores of >85 in all domains (cognitive, language and motor).[19] Twenty-three (37%) children had scores of 70-84 on any one of the three domains, while an additional eight (13%) had scores of <70 indicative of severe delay. Zubcevic et al in their study used Ages & Stages Questionnaires (ASQ-3) and concluded that at the first assessment developmental categories of communication were normal in 78.9%, problem solving in 63.2%, personal-social in 68.4%, gross motor in 68.4%, and fine motor in 42.1% with a high need of retesting in this area.[20] Second assessment was done in 17 patients: developmental categories of communication normal in 58.8%, problem solving in 70.6%, personal-social in 64.7%, gross motor in 64.7%, and fine motor in 35.3%. Third evaluation was done in 14 patients: developmental categories of communication were normal in 64.3%, problem solving in 71.4%, personal-social in 57.1%, gross motor in 64.3%, and fine motor in 42.9%.

Neurodevelopmental outcome

In this study neurodevelopmental outcome was significantly affected in neonates without therapeutic hypothermia (p value is <0.05=0.00018). Most of the babies of TH group i.e., 30 (85.7%) were neurodevelopmentally normal and 5 (14.3%) were having some neurodevelopmental abnormality whereas in non-TH group 15 (42.8%) were normal and 20 (57.2%) were having some neurodevelopmental abnormality. Azzopardi et al in their multicountry TOBY trial concluded that among survivors, children in the hypothermia group, as compared with those in the control group, had significant reductions in the risk of cerebral palsy (21% vs. 36%, p=0.03) and the risk of moderate or severe disability (22% vs. 37%, p=0.03); they also had significantly better motor-function scores.[18]

Limitations

Less number of cases were enrolled as most of the outborn babies were received after 6 hours of birth so we could not start the therapy in those neonates and amplitude EEG was not done during hospital stay due to resource limitations.

CONCLUSION

After present study we could conclude that asphyxiated neonates with HIE II/III given therapeutic hypothermia have better developmental profile as compared to neonates not given hypothermia.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kachhwaha R, Goyal S, Mehrotra J, Sethia S, Jeevan GM. Neurodevelopmental outcome of babies with moderate to severe birth asphyxia with hypoxic ischemic encephalopathy treated with and without therapeutic hypothermia followed up till 6-24 month of age at tertiary care hospital of Southern Rajasthan. Int J Contemp Pediatr 2023;10:1558-65.