

# Study of Neurodevelopmental Outcomes at 10-14 Months of Age Using Bayley Scale of Infant and Toddler Development in Asphyxiated Newborns with Hypoxic Ischemic Encephalopathy Treated with and without Therapeutic Hypothermia

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## ABSTRACT

**Background:** Therapeutic hypothermia has become an established protocol for all neonates with moderate to severe Hypoxic Ischaemic Encephalopathy (HIE). There are very few studies comparing the neurodevelopmental outcomes in asphyxiated neonates who received therapeutic hypothermia or did not. This study aimed to assess the neurodevelopmental outcomes of asphyxiated neonates with features of HIE at 10-14 months of age using Bayley Scale of Infant and Toddler Development III (BSID III) and to compare this outcome between neonates who received therapeutic hypothermia and those who did not.

**Methods:** Term infants with HIE admitted in neonatal intensive care unit (NICU) at a tertiary referral hospital were followed up at 10-14 months of age from December 2013 to August 2015. Neurodevelopmental outcomes were assessed using BSID III.

**Results:** A total of 76 neonates with birth asphyxia were admitted to NICU between December 2012 and August 2014. These neonates were followed up from December 2013 to August 2015, and 34 of them were included in the study. At 10-14 months of age, 8 neonates (23.5%) had cognitive delay, 14 cases (41.17%) had motor delay, and 9 newborns (26.4%) had language delay using BSID III score of < 85 as cut off.

Twenty (58.82%) infants had normal development in all 3 domains. 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. Statistical analysis using Chi-square test showed P-value of 0.048 as statistically significant.

**Conclusion:** Neurodevelopment assessment at 10-14 months of age using BSID III of asphyxiated neonates with HIE showed significantly better outcome in infants who received therapeutic hypothermia than those who did not.

**Keywords:** Bayley scale of infant development III, Hypoxic ischemic encephalopathy, Hypothermia, Neonates

## Introduction

World Health Organization (WHO) has defined perinatal asphyxia as the failure to initiate or sustain breathing at birth (1). National Neonatal Perinatal Database (NNPD) has defined moderate asphyxia as "slow gasping breathing or as Apgar score of 4-6 at 1 minute of age" and severe asphyxia as "no breathing or as Apgar score of 0-3

at 1 minute of age" (2).

With regard to NNPD 2002-03 data, perinatal asphyxia was the commonest cause of stillbirths (accounting for a third of such cases) in India. It accounted for 28.8% of all neonatal deaths. The concept of a therapeutic window has allowed for the investigation of novel pharmaceutical products

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with neuroprotective properties; however, they are still under further investigation.

Mild hypothermia critically affects biological processes and has been widely investigated both in experimental models and neonates. Hypothermia acts as a neuroprotective agent in Hypoxic Ischaemic Encephalopathy (HIE) by reducing vasogenic edema, hemorrhage, and neutrophilic infiltration. It also acts by limiting the release of excitatory neurotransmitters, preventing intracellular accumulation of calcium and by reducing formation of free radicals, thereby decreasing reperfusion injury (3-5).

Two methods of cooling that have been evaluated so far are whole body and selective head cooling. Whole body cooling relies on the core temperature being equal to the deep brain temperature, while selective head cooling leads to a temperature gradient in the brain (6-8). Passive cooling involves shutting off all the external sources of warmth to the baby, including the incubators, radiant heat warmers, and baby cooling on his own. Target temperature can also be attained with the use of water bags, ice packs, ice mattresses or cooling caps.

In this study asphyxiated neonates with HIE were recruited from December 2012 to August 2014 when automated cooling was not available in the unit and passive cooling was done which was feasible (9). Extensive studies have been conducted in order to assess the feasibility, safety, and neurodevelopmental outcome of therapeutic hypothermia (9-13). There are very few studies on long term follow-up of asphyxiated neonates based on Bayley Scale of Infant and Toddler Development III (BSID III). Therefore, the purpose of this study was to assess the neurodevelopmental outcomes of asphyxiated neonates using BSID III and to compare this outcome between neonates who received therapeutic hypothermia and those who did not.

Several studies have followed up asphyxiated neonates for long term outcome by BSIDII (3-5). BSID II was developed in 1993 and modified into BSID III in 2006. Mental developmental index (MDI) and psychomotor developmental index (PDI) of BSID II were revised to obtain separate scores in cognitive, language, receptive, and expressive communication, and motor domains (14).

In this study neurodevelopmental outcomes of asphyxiated neonates using BSID III was assessed at 10-14 months of age and this outcome was compared between those who received therapeutic hypothermia protocol and those who

did not receive.

## Methods

This prospective cohort study was conducted in the hospital after the approval of the Institutional Ethics Committee (IEC). The study population included 10-14 months followed up term neonates with hypoxic ischemic encephalopathy who were admitted in NICU at a tertiary referral hospital. The study population was followed up during the study period from December 2013 to August 2015. The inclusion criteria were: 1) significant perinatal asphyxia, requiring assistance for breathing at birth, 2) Apgar score of  $\leq 5$  at 5 minutes (if available), and 3) the features suggestive of hypoxic encephalopathy as per Sarnat and Sarnat staging of HIE. Term neonates were included in the study if they satisfied at least criteria (1) and (3).

On the other hand the Exclusion criteria were, 1) Infants with major congenital malformations, 2) Neonates weighing less than 1800 grams at birth, and 3) Preterm infants < 37 weeks.

The neonates fulfilling the inclusion criteria were enrolled in the study. Neonates were classified according to Sarnat and Sarnat staging by a neonatologist (15). Neonates with hypoxic ischemic encephalopathy who were admitted within 6 hours of delivery (early referrals) were included in the hypothermia protocol, whereas neonates who were admitted after 6 hours of delivery were not included in the hypothermia protocol.

Asphyxiated neonates with hypoxic ischemic encephalopathy, who underwent hypothermia were subjected to passive cooling for a period of 72 hours. Hypothermia was achieved by placing the neonate under radiant warmer (Fisher and Paykel) with heater output at 0. The neonates were cooled to a target core temperature range of 33-34°C. In addition, the neonates were continuously monitored for core temperature (using a rectal probe) and skin temperature (probe over the upper abdomen). If target temperature could not be attained by switching off the warmer source, then pre cooled cloth covered gel ice packs were placed around the infants and were removed one by one when rectal temperature dropped to 33.5°C.

Moreover, neonates undergoing hypothermia as a modality of treatment were monitored for complications and managed with appropriate measures. At the end of 72 hours, the neonates were gradually rewarmed by 0.5°C / 2 hour. By 10 hours, the neonates were rewarmed to 36-36.5°C.

All neonates were managed as per the standard treatment protocol.

Furthermore, a brain MRI and neurological examination were done at 7 days of age (if feasible) and during the hospital stay and at discharge, respectively. Maternal details were obtained from the hospital records. Out of the 76 asphyxiated neonates, 34 cases were followed up at 10-14 months of age, 11 infants excluded before the follow up, 12 cases were not willing to continue, and 19 cases could not be contacted. Consent from the respective parents were obtained prior to examination. Neurodevelopmental assessment at follow up and statistical analysis using BSID III and Chi-square test was performed, respectively.

### **Bayley Scale of Infant and Toddler Development III**

The Bayley scale of Infant and Toddler Development (BSID III) (14) is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age. It assesses the child development regarding five domains, such as cognition, language, and motor, social, emotional, and adaptive behaviour. Assessment of cognitive, language and motor domains are conducted using items administered to the child.

The cognitive scale includes items that assess sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory and other aspects of cognitive processing. On the other hand, the language scale is composed of receptive communication and expressive communication items. Fine and gross motor subtests are included in the motor scale whereas the acquisition of social and emotional milestones in infants and young children are assessed in the social emotional scale

The Bayley III provides 4 types of norm-referenced scores, including scaled, growth, and composite scores, and percentile ranks. Raw scores of successfully completed items were converted to scaled and composite scores. These scores were used to determine the children's performance compared with normal child development factors and normal children of their age (in months).

These scores are interpreted as three groups, such as normal development, moderate, and severe delay. The normal development BSID III score is > 85 in all the three domains of cognitive, language and motor. The moderate delay is defined as BSID III score 1-2 standard deviation

(SD) below the normal, that is, the lowest composite score of 70-84 in any of the cognitive, language and motor domain. BSID III composite score > 2 standard deviation below the normal is regarded as a severe delay. It is whether < 70 on any of the three tested domains or a complete inability to assign a score owing to severe mental deficiency or cerebral palsy (14).

### **Results**

A total of 76 neonates with birth asphyxia and hypoxic ischaemic encephalopathy were admitted between December 2012 and August 2014. Out of them, 34 infants were included in the study as they completed 1-year follow-up protocol (Figure 1). Among neonates who received hypothermia protocol, 6 cases out of 19 neonates were between 37-38 week gestations; whereas 13 neonates were between 39-41 weeks gestation. Concerning the neonates who did not receive hypothermia, 6 out of 15 cases were between 37-38 weeks gestation; whereas 9 of them were between 39- 41 weeks gestation. Most of the neonates had birth weight between 2501 and 3000grams. All the 34 followed up infants were out born with birth asphyxia, and they had hypoxic ischemic encephalopathy.

There were no identifiable antenatal risk factors in 19 neonates who received hypothermia protocol and 15 neonates who did not receive hypothermia protocol. The most common intrapartum complication was meconium stained amniotic fluid (MSAF). The majority of the neonates required bag and mask resuscitation with oxygen. In neonates who were under hypothermia protocol, 11 cases (57.8%) were resuscitated using bag and endotracheal tube mode of ventilation. Out of 34 neonates who were included in the study, 5, 25, and 4 cases had HIE Stage -1, -2, and -3, respectively.

Among neonates who received hypothermia as a treatment modality, 13 cases had seizures during the hospital stay whereas among the infants who did not receive hypothermia, 11 neonates had seizures during the hospital stay. Totally, 5 infants developed hypotension requiring inotrope support and 15 cases had dyselectrolytemia during the hospital stay. Altered Liver function test (LFT) was used among 8 neonates in each group. The findings of MRI on 27 neonates showed that 18 neonates were abnormal whereas 9 cases were normal. The most common area involved was Basal Ganglia which was seen in 10 neonates. Cortical involvement was observed in 6 neonates and corpus callosum was involved in 3

**Table 1.** MRI findings

MRI findings ( areas involved)	Diffusion Restriction/T1,T2 changes
cortex	6
Corpus callosum	3
PLIC ( posterior Limb of interal capsule)	2
Thalamus	4
BasalGanglia	10
Perirolandic area	4

neonates. Thalamus and PeriRolandic areas were affected in 4 neonates each. Posterior limb of internal capsule (PLIC) was involved in 2 neonates (Table 1).

With regard to 34 neonates with hypoxic ischemic encephalopathy included in the study, 8 cases (23.5%) had moderate-severe developmental delay in Cognition (BSID score <85), 14 neonates (41.17%) had BSID score <85 in Motor domain, whereas 9 newborns (26.4%) had BSID score of <85 in Language domain. Of all domains the Motor domain was most affected. Concerning all 3 domains, 20 neonates (58.8%) were normal. Among the 5 neonates with HIE Stage 1, only 1 case had developmental delay in Motor domain.

Out of 25 neonates with HIE Stage 2, the majority of the infants had developmental delay in the motor domain (10 neonates). Of the 12 infants, 2 newborns (16.67%) who had received hypothermia, had abnormality in motor scale, whereas 8 out of 13 neonates (61.5%) who had not received hypothermia protocol had delay in motor domain. Developmental delay was observed more in the group who did not receive Therapeutic Hypothermia.

Out of 4 neonates with HIE Stage -3, 3 of them had developmental delay in all 3 domains. Out of 19 infants who were treated with hypothermia protocol, 3 infants ( 15.78%) had abnormality in cognition milestone, whereas 5 out of 15 infants (33.33%) who did not receive hypothermia treatment, had delay in cognition milestones. In the motor domain, 9 out of 15 neonates (60%) who did not receive hypothermia protocol had delay in motor milestones, whereas only 5 out of 19 infants (26.3%) who received hypothermia protocol had motor milestone delay.

Among the neonates who were treated with hypothermia protocol, 3 out of 19 infants (15.78%) had delay in language milestones, 6 out

of 15 neonates (40%) who were not treated with hypothermia protocol had language milestone delay. It was observed that 14 neonates (73.68%) who received hypothermia protocol and 6 neonates (40%) who did not receive hypothermia protocol had normal development at follow up. Among the study group, 8 neonates had severe developmental delay in all 3 domains, out of which 3 neonates (15.78%) received hypothermia protocol and 5 neonates (33.30%) did not receive hypothermia.

With regard to the neonates with HIE Stage 2, one out of 12 (8.3%) neonates who received hypothermia had severe developmental delay, whereas 4 out of 13 (30.7%) neonates who did not receive therapeutic hypothermia, had severe developmental delay. Among neonates with hypoxic ischemic encephalopathy, 73.68 % of neonates who received hypothermia protocol had normal BSID III score at follow up (BSID score >85), as compared to 40% newborns who did not receive hypothermia protocol. Statistical analysis using Chi-square test showed P-value of 0.048 as statistically significant (Table 2).

Among neonates with HIE stage 2 who received hypothermia, 83.33% cases had normal BSID III score at follow up, as compared to 38.46% neonates who did not receive hypothermia as a modality of treatment. Statistical analysis using Chi- square test showed P-value of 0.04 as statistically significant (Table 3).

Among the neonates with HIE who had abnormal Magnetic Resonance Imaging (MRI) brain (18 neonates), 8 neonates had cognitive impairment, 11 neonates had language delay and 8 neonates had motor involvement. Developmental delay was observed to be more common among the infants who did not receive therapeutic hypothermia with abnormal MRI brain in 17 neonates.

**Table 2.** Developmental outcome in infants treated with therapeutic hypothermia versus those who did not treat with hypothermia.

N =34	Hypothermia N=19	No Hypothermia N=15	P value
Normal BSID III	14(73.68%)	6(40%)	0.048(S)
Abnormal BSID III	5(26.32%)	9(60%)	

**Table 3.** Developmental outcome in infants treated with therapeutic hypothermia versus those who did not treat with hypothermia (HIE stage 2).

N =25	Hypothermia N=12	No Hypothermia N=13	P value (Sarnat Stage 2)
Normal BSID III	10(83.33)	5(38.46)	0.04(S)
Abnormal BSID III	2(16.67)	8(61.54)	

## Discussion

No comparison was made between BSID II and BSID III in the present study. Jary S et al. (16) in the UK and other studies compared BSID III with BSIDII (3-5). They state that fewer children are classified as severe delay in BSID III compared to BSIDII. In the current study, BSID score of <70 (severe developmental delay) was observed in all three domains in 8 children (23.5%) which was higher than the scores reported earlier by LF Chlak et al. (13%) (17). In a study conducted by Lina F Chalak et al. (17), 80 newborns underwent hypothermia. Regarding the total survivors, Bayley-III was performed on 89% neonates around 24 months of age. An abnormal outcome using Bayley-III <85 was observed in 50% of the neonates, while Bayley III <70 were observed in 13% of the newborns.

However, in the current study 20 neonates (58.8%) were normal in all domains and 14 cases (41.1%) had abnormality in one or more of the domains (BSID III <85). In the study conducted by Lina F Chalak et al. (17) on neonates with HIE Stage 2 who received hypothermia, severe developmental delay in cognition, motor and language milestones was observed in 13% (BSID III score of <70), 11%, and 10% of the study population, respectively.

In the aforementioned study cognition was more affected than the other domains. However, in the present study among those who underwent hypothermia protocol in HIE stage 2, only one (8.3%) child had severe developmental delay in all three domains. The majority of the neonates were noticed to have moderate to severe delay (BSID score of <85) in motor domain in the current study. BSID <70 (severe developmental delay) was seen in all domains in 8 newborns out of which 6 and 3 neonates were in HIE stage 2 and 3, respectively.

Neonates who had BSID score of <70 in cognitive domain had also <70 score in other domains. In the present study, abnormal MRI changes were most observed in basal ganglia (in 10 neonates) which were similar to other studies (18, 19).

Lina F Chalak et al. (17) commented that BSID <85 should be taken as the cut off. Therefore, their

study showed 50% disability with <85 as cut off while in the present study it was estimated as 41.1%. In the current study among neonates with HIE who received therapeutic hypothermia, 73.68% of infants had normal BSID score (>85); however, among those who did not receive hypothermia protocol only 40% of neonates had BSID score of >85. Statistical analysis using Chi-square test showed P-value of 0.048 as statistically significant.

Among neonates with HIE Stage 2, 83.33% of the cases had normal BSID III score in hypothermia group, whereas 38.46% neonates had BSID III score >85 who did not receive hypothermia as a modality of treatment. Statistical analysis using Chi-square test showed P-value of 0.04 as statistically significant.

In the current study, therapeutic hypothermia was found to be beneficial; however, in a study conducted by Battin et al (20), minimal head cooling was reported to be better than moderate cooling. In addition, therapeutic hypothermia was seen to be most beneficial to Stage 2 Sarnat staging of HIE which is in line with the study conducted by Robertson et al. (21).

Accurate HIE staging conducted at the time of admission by a neonatologist is regarded as one of the strength of this study. Moreover, strict hypothermia protocol was maintained, and the comparison between hypothermia group and non hypothermia group by BSID III assessment at follow up was made.

Limitations were the early age of follow up in that most studies followed up at 18 to 24 months while we followed up earlier because of fear of loss to follow-up and small sample size.

It is recommended that future studies aim at picking up early subtle cognitive changes and learning problems to make intervention at an early stages possible.

## Conclusion

Neurodevelopmental assessment at 10-14 months of age using BSID III of asphyxiated neonates with HIE showed significantly better outcome in newborns who received therapeutic hypothermia than those who did not receive

therapeutic hypothermia.

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## Conflicts of interests

None declared.

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