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Original Article

Severity and immediate neurodevelopmental outcome in term neonates with hypoxic-ischemic encephalopathy admitted in NICU at a tertiary hospital in Bangladesh.

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Abstract:

Background: *Neonatal hypoxic ischemic encephalopathy (HIE) is a major cause of mortality, morbidity and long-term neurological deficits.*

Objective: *The aim of the study was to determine the severity of encephalopathy and immediate neurodevelopmental outcomes in term neonates with HIE admitted in NICU at a tertiary care hospital.*

Materials and Methods: *This was a Prospective Cohort study conducted between July 2016 and June 2017 at Dhaka Medical college Hospital, Dhaka. Asphyxiated term newborns who came within 12 hours of birth were enrolled in this study. Sarnat and Sarnat score was used to assess newborns immediately after birth to classify HIE. Neurodevelopmental assessment was performed using age specific rapid neurodevelopmental assessment tool (RNDA) at and 3 months after discharge to identify impairment in specific developmental domains. We determined the relation between severity of HIE and clinical outcome.*

Results: *60 patients were included in this study and their mean duration of hospital stay was 7.19 ± 5.26 days. The majority, 40% had moderate HIE, followed by 33.33%, 26.67% that had mild and severe HIE respectively. A total of 20% died, and most of them had severe HIE (83.33%). Normal development was found in only 11.67% cases. Moderate and severe neurodevelopmental impairment (NDI) was found in 33.33% and 25% cases respectively. At discharge, the most severely impaired domains were speech, seizure, primitive reflex and behaviour whereas at 3 months of age it was gross motor and seizure. When neurodevelopmental outcome was compared with different stages of encephalopathy, significant association was found between moderate to severe impairment/death with stage III of HIE.*

Conclusion: *Apart from mortality, a significant proportion of term neonates with HIE developed NDIs and adverse neurodevelopmental outcomes was significantly associated with severity of encephalopathy.*

Key words: *Hypoxic-ischemic encephalopathy (HIE), Neurodevelopmental outcome, Rapid neurodevelopmental assessment (RNDA), Neurodevelopmental impairment (NDI). Developmental domain.*

Introduction:

Perinatal asphyxia is one of the leading causes of neonatal mortality and morbidity worldwide and the outcomes of hypoxic - ischemic encephalopathy (HIE) are devastating and permanent, making it a major burden for the patient, the family and society. In Bangladesh, 26% of neonatal deaths are caused by perinatal asphyxia and it is one of the major public health problems.[1] Apart from increased mortality, perinatal asphyxia results in serious neurological consequences ranging from cerebral palsy and mental retardation to epilepsy.[2]

The main consequence of perinatal asphyxia is HIE and diagnosis of HIE requires abnormal findings on neurological examination on day after birth. HIE in term infants occurs at a rate of about three per thousand live-born infants in developed countries, but the rate is estimated to be higher in the developing world.[3,4] According to the Sarnat and Sarnat stages, the clinical spectrum of HIE is classified as mild, moderate or severe. Infants can progress from mild to moderate and/or severe encephalopathy over the 72 hours following the hypoxic-ischaemic insult.[5] Significant proportions of these infants die or survive with severe long-term morbidity.

In addition, identification of HIE and accurate classification of severity are important for reliable prediction of clinical outcome and long-term planning. Predictions of long-term

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outcome in the immediate neonatal period are based on clinical,[6-8] biochemical,[9,10] electrophysiological,[11,12] and imaging findings.[13] Therefore, this study was aimed at determining the severity of encephalopathy and to identify impairment in specific developmental domains among babies having HIE admitted in NICU at a tertiary care hospital. This study also explored the effect of HIE on achieving the neuro-developmental skill within very short time.

Methodology:

This was a prospective observational hospital based study. It was conducted in the Department of Neonatal Intensive Care Unit (NICU), Dhaka Medical College Hospital, Dhaka during the period July 2016 to June 2017.

All the admitted term newborns (delivered at ≥37completed weeks of gestation) that came within 12 hours of birth with history of perinatal asphyxia having features of HIE were enrolled in this study.

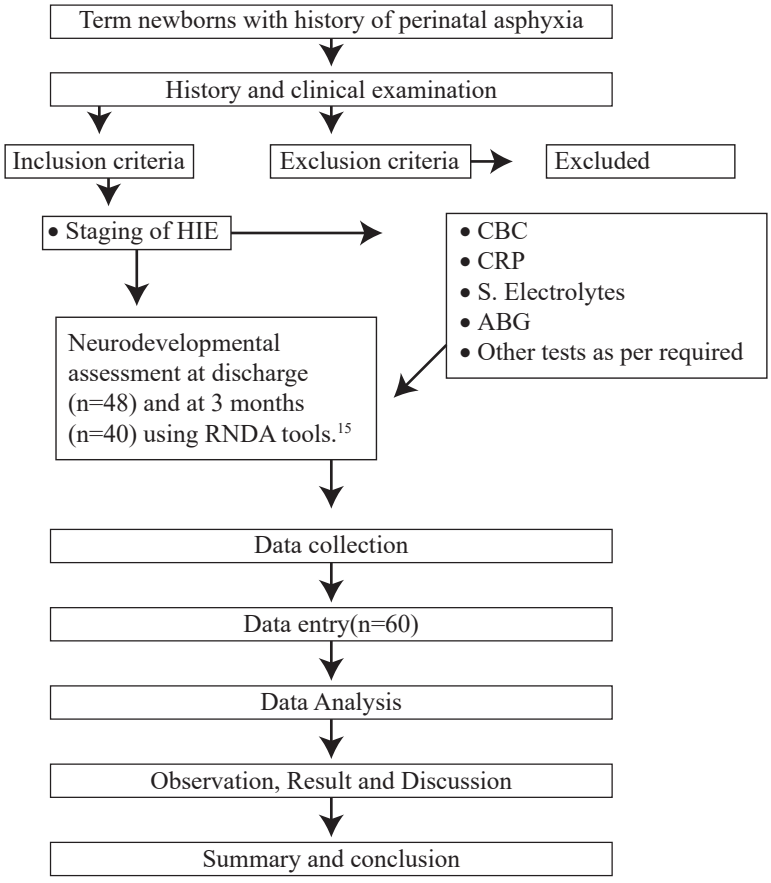
Newborns presenting with IUGR, congenital malformation and who developed other illness like septicemia, pneumonia, meningitis were excluded from the study.

Total 60 patients were included in this study. Detailed history was taken and thorough physical examination of the newborn was carried out and findings were noted on the questionnaire. Newborns who were born with perinatal asphyxia were classified according to the Sarnat and Sarnat scoring criteria for HIE. On the scale there are three stages of Hypoxic-Ischemic Encephalopathy (HIE): Stage I is characterized by mild symptoms, Stage II is characterized by moderate symptoms & Stage III is characterized by severe symptoms.[14]

Neonates were treated according to standard protocol of the institution. Blood specimens were taken at admission for complete blood count, serum electrolyte, CRP, ABG. All the blood specimens were tested by the same procedure. Follow up is given every day till discharge or death. At discharge and 3 months after discharge neurodevelopmental assessments were done by a Developmental therapist using RNDA tools for neonates[15]. Intervention (developmental therapy and stimulation) was given to each neonate at discharge and also at 3 months. All the findings were noted in the case collection sheet.

All data were entered in SPSS 16 for Windows statistical software and analyzed. A p value of ≤0.05 indicated statistical significance. A written consent for enrollment, treatment and follow up was taken from every parents. The study was given ethical clearance by the ethical review committee (ERC) of the hospital.

Study Flow Chart



Results:

In this study, there was male predominance (61.7%) with male to female ratio 1.6:1. Their mean duration of hospital stay was 7.19 ± 5.26 days. At the time of enrollment the mean age, weight, length and occipital-frontal circumference (OFC) & gestational age of neonates were shown in Table I.

Table I: Clinical characteristics of newborns on enrolment (n=60)

Characteristics	Mean(n=60)	SD
Age (hours)	6.42	±4.38
Weight (gm)	2813	±387
Length (cm)	50.45	±1.47
OFC (cm)	33.63	±1.2
Gestational age (weeks)	38.73	±1.03

Among 60 neonates, 33.33% had stage I, 40% had stage II and 26.67% had stage III of HIE (Figure I). Most of the neonates were inborn (58.3%). Caesarean Section was done only in 16 (26.7%) cases. No significant statistical difference was found among the groups of HIE in terms of bad obstetric history and mode of delivery. But when place of delivery (inborn and outborn) was compared with neonates having different stages of HIE, it showed significant statistical association (p value- <0.002) (Table II).

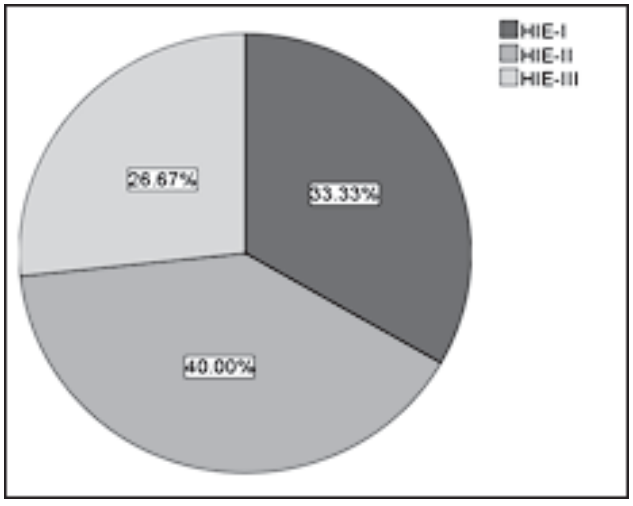


Figure I: Distribution HIE

Table II: Perinatal information of enrolled neonates (n=60)

Characters	(n)(%)	HIE-I (n)(%)	HIE-II (n)(%)	HIE-III (n)(%)	P-value
Bad obstetric history	No 39(65)	11(28.2)	17(43.6)	11(28.2)	0.51
	Yes 21(35)	9(42.9)	7(33.3)	5(23.8)	
Place of delivery	Outborn 25 (41.7)	2 (8)	16 (64)	7(28)	0.002
	Inborn 35(58.3)	18 (51.4)	8(22.9)	9(25.7)	
Mode of delivery	NVD 44(73.3)	11(25)	20(45.5)	13(29.5)	0.075
	C/S 16 (26.7)	9(56.2)	4(25)	3(18.8)	

Among enrolled neonates, 12(20%) neonates died before discharge. Majority of the newborns who died were those with stage III, than those with stage II of HIE. However no deaths were observed among neonates with stage I encephalopathy. Neurodevelopmental assessment was done in 48 neonates at discharge using RNDA[15] tools for neonates. Normal development and mild impairment were found in 21.67% cases, all of them having stage I and stage II of HIE. Moderate and severe neurodevelopmental impairment was found in 33.33% and 25% cases respectively (Table III). The most severely impaired domains were speech, seizure, primitive reflex and behaviour (Table IV). Among 48 neonates, 40 infants came after three months for follow up. Again assessment was done by the same developmental therapists. This time, the severely impaired domains were gross motor and seizure (Table V).

Table III: Neurodevelopmental outcome at discharge (n=60)

Variables	HIE I (n)(%)	HIE II (n)(%)	HIE III (n)(%)	Total (n)(%)	P value
Normal	5 (8.34)	2(3.33)	0	7 (11.67)	0.00
Mild impairment	2(2.33)	4(6.67)	0	6 (10)	
Moderate impairment	11(18.33)	9(15)	0	20 (33.33)	
Severe impairment	2(2.33)	7(11.67)	6(10)	15 (25)	
Death	0	2(2.33)	10(16.67)	12 (20)	

Table IV: Neurodevelopmental outcome in specific domains at discharge (n=48)

Domains	Normal n(%)	Mild n(%)	Moderate n(%)	Severe n(%)
Primitive reflex	13(27.1)	19 (39.6)	9 (18.8)	7 (14.6)
Gross motor	17 (35.4)	15 (31.2)	11 (22.9)	5 (10.4)
Fine motor	40 (83.3)	4 (8.3)	4 (8.3)	0
Vision	35 (72.9)	3 (6.2)	8 (16.7)	2 (4.2)
Hearing	40 (83.3)	3 (6.2)	1 (2.1)	4 (8.3)
Speech	28 (58.3)	2 (4.2)	7 (14.6)	11 (22.9)
Cognition	33 (68.8)	4 (8.3)	7 (14.6)	4 (8.3)
Behaviour	28 (58.3)	10 (20.8)	4 (8.3)	6 (12.5)
Seizure	26 (54.2)	4 (8.3)	8 (16.7)	10 (20.8)

Table V: Neurodevelopmental outcome in specific domains at 3 months (n=40)

Domains	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Primitive reflex	17 (42.5)	19 (47.5)	4 (10)	0
Gross motor	12 (30)	20 (50)	6 (15)	2 (5)
Fine motor	28 (70)	10 (25)	2 (5)	0
Vision	31 (77.5)	4 (10)	5(12.5)	0
Hearing	34 (85)	3 (7.5)	3 (7.5)	0
Speech	25 (62.5)	12 (30)	3 (7.5)	0
Cognition	21 (52.5)	16 (40)	3 (7.5)	0
Behaviour	23 (57.5)	14 (35)	3 (7.5)	0
Seizure	28 (70)	6 (15)	4 (10)	2 (5)

When neurodevelopmental outcome was compared with different stages of encephalopathy, significant association was found between moderate to severe impairment/death with stage III of HIE (p value 0.01) (Table VI).

Table VI: Outcome at discharge in relation to Encephalopathy (n=60)

Stages of HIE	Normal or mild impairment(n)(%)	Moderate to severe impairment/Death(n)(%)	p-value
HIE I	7 (11.67)	13 (21.67)	0.077
HIE II	6 (10)	18 (30)	0.42
HIE III	0	16 (26.67)	0.01

DISCUSSION:

This was an observational study done among term neonates with HIE who were admitted in hospital within 12 hours of birth. They were getting usual care in neonatal intensive care unit. At and 3 months of discharge neurodevelopmental outcome was assessed using RNDA[15] tools for neonates. The tools are validated against the Baley scale for infant development where mental development index (MDI), physical devopment index (PDI) and behavioural regulation index(BRI) are correlated with the RNDA findings. The neuro-developmental intervention was started for all infants enrolled with or without identified NDI as potential neuroprotective strategies.

At the time of enrollment of neonates, the mean age, weight, length, OFC and gestational age were found similar with a base line parameter of a study conducted by Mushtaq et al.[16] Clinical classification of neonatal encephalopathy associated with perinatal asphyxia was done in this study as this was also found to be a helpful indicator of long-term outcome in many studies.[14,17]A study done by Qureshi et al[18], it was found that 23.4%, 40.4%, 36.2% term neonates developed HIE stage I, II and III respectively. Our study also found similar findings. A

study conducted in northern Tanzania found that majority of the new-borns with HIE had mild HIE (50.8%) whereas only 10.2% had severe HIE.[19]

Mortality observed in this study was 20%. Observations of previous studies at Dhaka Medical college Hospital was 16%[20], at Mulago Hospital in Uganda was 12.9%[21], in Cameroon 10%[22], at tertiary hospital in Johannesburg South Africa 14.3%[23], at Liaquat teaching hospital in Pakistan 15%[24] and at Ayub Teaching hospital in Pakistan 16%[25]. In a South African study, a mortality of 7.8% was reported. This was much lower than that found in our study, though most of the deaths were due to grade III HIE as was the case in our study[26]. Therapeutic cooling was used as part of the management for those with moderate and severe HIE which was not done in our study. Our study observed marked improvement in neonates who had mild to moderate HIE. These findings are consistent with a previous study.[19]

In a study, it was observed that majority (73.9%)) of newborns with HIE were discharged without short term complications by 1 week.[27] But on neurodevelopmental assessment, we found only 11.67% (7) neonate had normal development whereas development was mild, moderate and severely impaired in 10%, 33.33% and 20% neonates respectively. These findings are consistent with the findings of a study done by Banu et al[28]. In another study done by Khan et al[29] among preterm infants in Bangladesh, normal development was observed in 32%, mild impairments were found in 45%, and serious impairments were found in 23% of preterm infants.

At discharge, RNDA was done in 48 neonates. This study labelled the impairment at different domains and majority neonates had impairment in primitive reflex and gross motor domain. But the severely impaired domains were seizure, speech, behaviour, primitive reflex and gross motor. These results are consistent with a previous study.[30] After 3 months of discharge, 83.33% infants came for follow up. Final outcome was significantly better than the initial neurodevelopmental status at discharge. These findings are similar with a study published earlier.[28] Our study found significant association between moderate to severe impairment/death with stage III of HIE when neurodevelopmental outcome was compared with different stages of encephalopathy. The association could be attributable to the severity of the brain lesion. The risk of long term sequelae is high in this stage and this shows the need for long term follow up of children with HIE.

Apart from mortality, neonates who develops HIE have a risk of serious neuro-motor sequelae among the survivors. Hence improvement in monitoring of mothers in labor and of the newborns with HIE should be strengthened in our setting.

Conclusion:

This study demonstrated that many of term neonates with HIE developed moderate to severe encephalopathy. Apart from mortality, a significant proportion of them developed NDIs. Not only motor function but also cognition, behaviour, seizure, hearing and vision were impaired significantly. So the outcome should be measured in each new-born with HIE and intervention with developmental therapy and stimulation should be provided for every child.

Conflict of interest:

There is no conflict of interest to any of the authors of this article.

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