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An Echocardiographic Observation of Hypoxic Ischemic Encephalopathy (HIE) with Cardiac Functional Status in Neonates

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Abstract **Original Research Article**

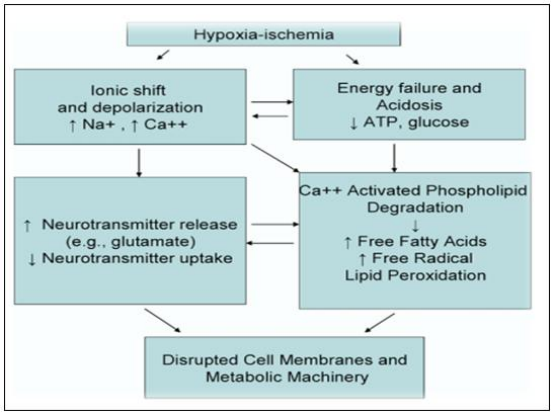
This was an observational prospective experimental study was distributed in Dhaka Shishu Hospital (DSH) from July 2015 to June 2017. Our aim was to observe echocardiographic findings of Hypoxic Ischemic Encephalopathy (HIE) with cardiac functional status in neonates. A total of 75 cases were selected during the study period. These cases were found to have different stages of Hypoxic Ischemic Encephalopathy. A total of 20 cases were found to be in HIE Stage-I, 24 cases in HIE stage-II and 31 Cases in HIE stage-III. Occurrence of myocardial dysfunction in different stages of HIE. Difference between Stage-I and stage-II was not found significant statistically. Various cardiac changes determined by echocardiography. Common cardiac abnormalities seen were Pulmonary hypertension, Tricuspid regurgitation, right atrial and right ventricular dilatations, left atrial and left ventricular dilatations and myocardial dysfunctional. Occurrence of myocardial dysfunction in different stages of HIE. Myocardial dysfunction was seen mainly in patients with HIE stage-II and stage-III and only one case in Stage-I. For comparison of systolic and diastolic dysfunction in different stage of HIE patients, ANOVA with post hoc multiple comparison analysis test was done. Analysis revealed significant deterioration of myocardial function (except RV diastolic function) between stage-II and stage-III, Stage-III and Stage-I but not between Stage-I and stage-II. Combined ventricular function assessed by myocardial performance index (Tei index) also showed increasing deterioration of myocardial function between stage-II and stage-III, Stage-III and Stage-I, and not between Stage-I and stage-II. Showing association of myocardial dysfunction among the cases with different stages of HIE. Analysis done by Chi squire test revealed that there was significant association myocardial dysfunction with hypoxic ischemic encephalopathy (p-value<.001). Risk estimation of myocardial dysfunction for prolonged hospital stay assessed by using odds ratio showed that myocardial dysfunction is a risk factor for prolong hospital stay.

Key word: Hypoxic Ischemic Encephalopathy (HIE), Dysfunctional, Myocardial, Cardiac, Abnormalities.

INRTODUCTION

Perinatal asphyxia, more appropriately called hypoxic ischemic encephalopathy (HIE) is a major cause of mortality and morbidity in neonates. There is no gold standard test for detection of HIE. Fetal distress, acidemia, Apgar score and other markers of possible intrapartum injury have low positive predictive value. Brain hypoxia and ischemia occurs due to systemic hypoxemia, reduced cerebral blood flow (CBF) or both. These are the primary physiological processes that lead to hypoxic-ischemic encephalopathy. Sarnat and Sarnat proposed a staging system useful in classifying the encephalopathy associated with perinatal asphyxia. They classify HIE into Stage-I, Stage-II and Stag-III. HIE Stages-I, II and III correlates clinically with mild, moderate, and severe encephalopathy [2, 7]. Perinatal asphyxia is the most important cause of HIE, resulting in hypoxemia and hypercapnia. The major manifestations of asphyxia occur due to combined effect of hypoxia and ischemia of the brain and other vital organs. In term infants with acute encephalopathy due to perinatal asphyxia the cerebral hemodynamics is deranged in the first few days. After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generate increased amount of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamate, accumulate in the damage tissue. Subsequently activation of glutamate cell-surface receptors occurs which results in an influx of Na^+ and Ca^{2+} ions. Increased amounts of intracellular sodium and calcium may result in tissue swelling and cerebral edema [2, 8]. Free fatty acids accumulate in the cytosol, due to increased membrane phospholipid turnover. Free fatty

acids undergo peroxidation by oxygen-free radicals arising from the reductive process within mitochondria. Ca^{2+} ions accumulate within the cytosol as a result of increased plasma membrane influx via voltage-sensitive and agonist-operated calcium channels. Also there occurs decreased efflux of Ca^{2+} across the plasma membrane along with release from mitochondria and the endoplasmic reticulum [2,8]. Nitric oxide, a free-radical gas, is generated via Ca^{2+} activation in selected neurons. Generated nitric oxide then diffuses to adjacent cells that are susceptible to nitric oxide toxicity. The combined effects of cellular energy failure, acidosis, glutamate, and nitric oxide neurotoxicity, free-radical formation, Ca^{2+} accumulation, and lipid peroxidation serve to disrupt structural components of the cell with its ultimate death[2,8].



Flow chart: Cellular mechanisms of hypoxic-ischemic brain damage

Hypoxic-ischemic encephalopathy (HIE) is the most common neurologic complication in the perinatal period. It is a major cause of chronic disability in childhood. HIE results from systemic hypoxemia and decreased cerebral perfusion causing ischemia. They may develop during antepartum (20%), intrapartum (30%), intrapartum and antepartum (35%), or postpartum (10%) period. HIE develops in the setting of perinatal asphyxia, and is a multi-organ system disease. Hypoxia and ischemia can cause damage to almost every tissue and organ of the body [2, 9]. Involvement of one or more organs occurs in 82% of the infants; the central nervous system (CNS) involves most frequently (72%). Other organ involvement occurs as follows: Renal involvement in 42%, pulmonary in 26%, cardiac in 29%, and gastrointestinal in 29% of the infants [3]. The criteria for involvement of each organ/system are as follows: Renal: Anuria or oliguria (<1 ml/kg/h) for 24 hours or more, and a serum creatinine concentration >100 mmol/ l; or anuria/oliguria for >36 hours; or serum creatinine >125 mmol/l; or increased level of serial serum creatinine values postnatally Cardiovascular: Hypotension treated with an inotrope for more than 24 hours to maintain blood pressure within the normal range, or electrocardiographic evidence of transient myocardial ischemia. Pulmonary: Need for ventilator support with oxygen requirement. 40% for at least the first four hours after birth Hepatic: Aspartate aminotransferase >100 IU/l or alanine aminotransferase >100 IU/l at any time during the first week after birth [2, 3, 5]. Along with other management, echocardiographic evaluation of the neonates having perinatal asphyxia with HIE will be useful for proper evaluation and appropriate management, thereby reducing mortality and morbidity.

OBJECTIVES

- **General objective**

To observe of Hypoxic Ischemic Encephalopathy (HIE) with Cardiac Functional Status in Neonates

- **Specific objectives**

To observe the cardiac function of the cases by measuring serum Troponin-I and Echocardiographic changes

METHODOLOGY AND MATERIALS

This was an observational prospective experimental study was conducted in Dhaka Shishu Hospital (DSH) from July 2015 to June 2017. Our aim was to observe of HIE with cardiac functional status in neonates. A total of 75 cases were selected during the study period. These cases were found to have different stages of Hypoxic Ischemic Encephalopathy. A total of 20 cases were found to be in HIE Stage-I, 24 cases in HIE stage-II and 31 Cases in HIE stage-III. A total of 94 cases were selected during the study period. Out of them parents or legal guardians of 6 neonates refused to remain with the study procedure, 2 cases left with DORB, 11 cases were excluded according to exclusion criteria. Remaining 75 cases were included for study. These cases were found to have different stages of Hypoxic Ischemic Encephalopathy. A total of 20 cases were found to be in HIE Stage-I, 24 cases in HIE stage-II and 31 Cases in HIE stage-III.

Inclusion criteria

- Age: Less than 72 hours
- Gestational age: Term neonates

- H/O failure to take spontaneous respiration immediately after birth and/or
- Perinatal asphyxia evidenced by documented Apgar score (if available)

Exclusion criteria

- Major congenital anomaly such as meningocele, meningoencephalocele, congenital hydrocephalus and congenital brain parenchymal anomalies.
- Presence of any structural congenital heart disease
- Clinical features consistent with congenital infection.

RESULTS

Total 75 term neonates diagnosed as perinatal asphyxia with different grades of HIE were selected to evaluate the cardiac status in neonates. The enrolled patients were grouped into HIE Stage-I, HIE Stage-II, and HIE Stage-III. Level of Cardiac troponin I, ECG changes, and Echocardiographic parameters were observed in all groups and recorded. The significance of raised Cardiac Troponin I level and Echocardiographic parameters for diagnosis of myocardial dysfunctions were compared among the groups to see whether these two methods correlate in diagnosing myocardial dysfunction. Immediate outcomes were monitored in terms of mortality and prolonged hospital stay. Demographic data according to various stages of HIE is presented in (Table-I). No significant difference was seen among the neonates with HIE Stage-I, HIE stage-II and HIE stage-III groups with respect to parameters like birth weight, sex, gestational age, crown heel length (CHL), occipital frontal circumference (OFC), maternal age, and antenatal complications. (Table-II) Biochemical parameters (cardiac troponin I) in different stages of HIE with perinatal asphyxia shown in (Table-III). It is seen from the above table that cardiac troponin I level raises as the stages of HIE increases. Comparison of values in different groups were assessed by applying ANOVA with Post hoc multiple comparison test showing statistically significant difference in values between stage-II and stage-III and stage-III and Stage-I. Difference between Stage-I and stage-II was not found significant statistically. Table III showing various cardiac changes determined by echocardiography. Common cardiac abnormalities seen were pulmonary hypertension, tricuspid regurgitation, right atrial and right ventricular dilatations, left atrial and left ventricular dilatations and myocardial dysfunctional. (Table-IV) showing occurrence of myocardial dysfunction in different stages of HIE. Myocardial dysfunction was seen mainly in patients with HIE stage-II and stage-III and only one case in Stage-I. (Table-V) For comparison of systolic and diastolic dysfunction in different stage of HIE patients, ANOVA with post hoc multiple comparison analysis test was done. Analysis (table 5.3) revealed significant deterioration of myocardial function (except RV diastolic function) between stage-II and stage-III, Stage-III and Stage-I but not between Stage-I and stage-II. Combined ventricular function assessed by myocardial performance index (Tei index) also showed increasing deterioration of myocardial function between stage-II and stage-III, Stage-III and Stage-I, and not between Stage-I and stage-II (Table- VI). (Table-VII) Showing association of myocardial dysfunction among the cases with different stages of HIE. Analysis done by Chi squire test revealed that there was significant association myocardial dysfunction with hypoxic ischemic encephalopathy (p-value < .001). Risk estimation of myocardial dysfunction for mortality assessed by using odds ratio showed (Table-VIII) that there was significantly increased risk of mortality in cases with myocardial dysfunction. Risk estimation of myocardial dysfunction for prolonged hospital stay assessed by using odds ratio showed (Table- IX) that myocardial dysfunction is a risk factor for prolong hospital stay.

Table-I: Demographic data according to HIE stages (n=75)

Demographic parameters		HIE stages			Chi Value	F-Value	P-value
		Stage-I	Stage-II	Stage-III			
Sex	Male	9	15	21	.93		.62
	Female	11	9	10			
Gestational age (weeks)		38.40±1.09	38.35± .67	38.15± 2.11		.172	.84
Maternal age	≤ 20yrs	12	14	21	.41		.81
	>20 yrs.	8	10	10			
Parity	Primi	11	9	11	1.77		.41
	Multi	9	15	20			
Birth Weight (Kg)		2.85± .17	2.89± .16	2.97± .17		2.50	.09
Length (cm)		47.98± .56	47.88± .52	47.81± .52		.469	.62
OFC (cm)		33.87± .35	33.96± .31	33.92±.29		.471	.62
Antenatal checkup	Regular	10	8	17	.44		.80
	Irregular	10	17	14			
Mode of delivery	Vaginal delivery	11	15	21	.53		.76
	Caesarian section	9	9	10			

Table-II: Cardiac abnormalities among the study cases by echocardiography (n=75)

Echocardiographic changes	n	%
Pulmonary hypertension	21	28.00%
Tricuspid regurgitation (TR)	35	46.66%
RA/ RV dilatation	32	42.66%
LA/ LV dilatation	7	9.33%
Myocardial dysfunction	30	40.00%

Table-III: Presence of myocardial dysfunction in different stages of HIE (n=75)

Stages of HIE	Number of cases	Dysfunction present	Percentage
I	20	1	5.00%
II	24	8	33.33%
III	31	21	67.74%

Table-V: Comparison of systolic and diastolic myocardial dysfunctions among the different stages of HIE. (n=75)

Criteria	Stage-I	Stage -II	Stage -III	F-Value	P-value
Left ventricular ejection fraction (LVEF)	64.4± 4.28	60.97± 5.42	54.05± 8.14	17.10	P= < .001 P_1= .22 P_2= .001 P_3= < .001
Left ventricular fractional shortening (LVFS)	44.42± 8.13	40.67±11.03	31.48±9.97	11.81	P= < .001 P_1= .46 P_2= .004 P_3= < .001
Left ventricular E/A Ratio	1.14±.15	1.07±.18	.88±.21	12.86	P= <.001 P_1= .54 P_2= .002 P_3= < .001
TAPSE	1.02±.21	1.07±.30	1.36±.48	6.28	P= < .003 P_1= .90 P_2= .02 P_3= < .01
Right ventricular E/A Ratio	.94±.05	.92±.04	.91±.03	1.97	P= .14 P_1= .29 P_2= .96 P_3= .06

P_1=Comparison between Stage -I and Stage -II, P_2= Comparison between Stage -II and Stage –III,
P3= Comparison between Stage -III and Stage -I.

- LVEF, LVFS and TAPSE represent systolic cardiac function
- Left and right ventricular E/A ratio represent diastolic function

Table-VI: Comparison of Myocardial Performance Index (Tei index) among different stages of HIE. (n=75).

Criteria	Stage –I	Stage –II	Stage -III	F-Value	P-value
Left ventricular Tei Index	.39±.02	.41±.03	.47±.05	22.21	P= <.001 P_1= .50 P_2= < .001 P_3= <.001
Right ventricular Tei Index	.29±.07	.33±.05	.42±.09	20.56	P= <.001 P_1= .12 P_2= <.001 P_3=< .001

P_1=Comparison between Stage -I and Stage -II, P_2=Comparison between Stage -II and Stage -III, P_3=Comparison between Stage -III and Stage -I.

Table-VII: Association between myocardial dysfunction and the cases with different stages of HIE (n=75).

Myocardial dysfunction	HIE Stage-I	HIE Stage-II	HIE Stage-III	Total	Chi Value	P- Value
Present	01	08	22	31	22.74	< .001
Absent	19	16	09	44		

Table-VIII: Risk measurement of myocardial dysfunction with mortality (n=75)

Factors	Death	No death	OR (95% Confidence Interval)
Myocardial dysfunction	21	9	22.66
No myocardial dysfunction	7	38	

Table-IX: Risk measurement of myocardial dysfunction with prolonged hospital stay (n=75)

Factors	Duration of hospital stay		OR (95% Confidence Interval)
	> 7 days	≤7 days	
Myocardial dysfunction	11	19	1.76
No myocardial dysfunction	13	32	

DISCUSSION

This observational study was carried out in the department of Paediatric Medicine and NICU of Dhaka Shishu Hospital during the period of July'2015 to June'2017. The main objective of this study was to observe Hypoxic Ischemic Encephalopathy (HIE) with cardiac functional status in neonates. A total of 75 cases were selected during the study period. A total of 75 neonates diagnosed as perinatal asphyxia with different stages of HIE (HIE Stage-I, HIE Stage-II, and HIE Stage-III) were included in the study. In this study, patients in different stages of HIE showed no significant difference regarding demographic parameters such as age, length, birth weight and Occipito frontal Circumference (OFC). All the patients in each group were within 72 hours of age, mean birth weight in different group were (in HIE Stage-I 2.85±.17 kg, in HIE stage-II 2.89± .16 kg and in HIE stage-III 2.97± .17 kg), mean length were (in HIE Stage-I 47.98± .56 cm, in HIE stage-II 47.88± .52cm in HIE stage-III 47.81± .52 cm), and mean OFC (in HIE Stage-I 33.87± .35 cm, in HIE stage-II 33.96± .31cm, and in HIE stage-III 33.92± .29 cm). A study by Jain DD *et al.* [3, 3] had demographic parameters as follows: Mean weight (g) in HIE Stage-I, II and III were 2646 ± 292, 2872 ±192, and 2912 ±237. Mean Length (cm) in HIE Stag-I, II, and III were 45.7± 6.5, 47.2± 1.6, 46.9± 0.6. Mean OFC (cm) in HIE Stage-I, II and III were 34± 1.5, 33.7± 0.5 and 33.7± 0.4. Their study subject had demographic characteristics similar to the present study. In this study Cardiac troponin, I was found to be high in patients with perinatal asphyxia. Mean catnip level (ngm/ml) in different stages of HIE were (.66±.21, .99±.52, and 1.47±.50 in HIE Stage-I, II, and III respectively). It is seen here that cTnI are rising significantly as the stages of HIE increases (P value < .001). Shastri *et al.*[4, 3]. Found in their study that cTnI concentrations correlate strongly with the clinical severity of HIE grades (0.04 lg/L in HIE-I, 0.12 lg/L in HIE-II and 0.67 lg/L in HIE-III). These findings are consistent with the current study. In the present study abnormal ECG changes seen in 32 (42.66%) neonates. Among them Grade-I ECG changes found in 7 (9.33%) patients, Grade-II changes seen in 16 (21.33%) patients, and Grade-III changes seen in 9 (12%) patients. In a study done by Rajakumar *et al.* [3, 9]. Grade I ECG changes were present in 6 (20%) cases, Grade II in 12 (40%) and Grade III in 4(13.3%) of asphyxiated neonates. Findings of this study were similar to the present study. Echocardiographic evaluation of the cases in the present study revealed multiple cardiac abnormalities including Pulmonary hypertension, Tricuspid Regurgitation (TR), Right atrium (RA), Right ventricular (RV), Left atrium (LA) and Left ventricular (LV) dilatation as well as myocardial functional abnormalities. Among them Tricuspid regurgitation was the commonest (47%) cardiac abnormality. These findings are consistent with studies done by Jain DD *et al.* [3, 3] and Rajaakumar *et al.* [12] except that the percentage of TR in their studies was 35.48% and 23.3% respectivey. Such differences may be due to- Presence or absence of pulmonary hypertension and Age of the neonates when echocardiography was done. Myocardial dysfunction was found in 30 (40.00%) cases in the current study. Raja kumar *et al.* [12] found myocardial dysfunction in 30% cases in their study. Comparison between HIE cases and myocardial dysfunction showed that myocardial dysfunctions were significantly associated with increasing stages of HIE. Rajakumar *et al.* also found a significant association between severity of HIE and myocardial impairment [12].

In this study parameters for left and right ventricular systolic and diastolic functions (LVEF, LVFS, TAPSE and E/A ratio) were impaired in perinatal asphyxia. These functional impairments were more evident as the stages of HIE increases. Right ventricular diastolic function was an exception, which showed no significant differences between patients with different stages of HIE. Khattab AAA *et al.* [4, 8] found significant systolic and diastolic dysfunction in perinatal asphyxia. These deteriorations were becoming more with increasing stages of HIE except in case of right ventricular diastolic dysfunction. Findings of their study were similar to the current study. Probable explanation regarding no significant difference of RV diastolic function may be due to-The increase in tricuspid E and a velocity after birth is probably associated with increased RV preload and decreased RV afterload [4, 5]. Right ventricular hemodynamic function is physiologically different than that of the LV including different RV versus LV myocardial fiber arrangements, lower RV after load (pulmonary vascular resistance), and lower systolic RV pressures compared with the LV [5, 4]. Diastolic function also may be affected in neonates with tachycardia because of merging of E and A velocity to various degrees, which are affected by loading conditions and heart rate [5, 5]. Myocardial performance index (Tei index) is an early

and reliable marker of global cardiac dysfunction. Both LV and RV Tei index were increased in the study cases. The Tei index values increasing with advancing stages of HIE (P < .001 for both LV and RV Tei index). Kai Jiang *et al*.[5, 7] in their study found that both LV and RV Tei index increases in patients with perinatal asphyxia with HIE and the increment correlate with increasing stages of HIE. Their findings were also similar to the present study. In this study levels of Myocardial performance index (Tei index) showed increasingly higher value with increasing severity of HIE, cTni levels also becoming higher in the same manner. Both LV and RV Tei index showed a positive correlation with cTn I (LV r value .30 and. RV r value .33 and P value .012 and .004 respectively). Khattab AAA *et al.* [4, 8]. Also found a positive correlation in this regard and having similar result with this study. In this study increased mortality and prolonged hospital stay were found to be the immediate outcome in patients with perinatal asphyxia with HIE. (Odds ratio for mortality was 22.66 and for prolonged hospital stay was 1.76.). PS Rajakumar *et al.* [12] found in their study that cardiac impairment was a risk factor of mortality in perinatal asphyxia. Result of their study support the current study.

LIMITATIONS OF THE STUDY

It was an observational prospective experimental study with small sample size, which doesn't reflect the scenario of the whole country.

CONCLUSION

Cardiac dysfunction is a common consequence that develops secondary to perinatal asphyxia and its frequency rises with increased severity of HIE. Cardiac abnormality in asphyxiated neonates with HIE is a risk factor that adversely affects the immediate outcome and thus increases the mortality and duration of hospital stay. Echocardiography is a noninvasive procedure that can be used for early and accurate evaluation of cardiac functional status. Along with other management, echocardiographic evaluation of the neonates having perinatal asphyxia with HIE will be useful for proper evaluation and appropriate management, thereby reducing mortality and morbidity.

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