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Original Research Article

Cardiac Function in Perinatal Asphyxia

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Abstract: At present no clear-cut physiologic/serological parameter exist which enable an early identification of neonates who are at increased risk to develop myocardial dysfunction in perinatal asphyxia. This study was conducted to find out the incidence and features of cardiac dysfunction in perinatal asphyxia The present study was carried out on 48 neonates ,17 healthy neonates were taken as controls while 31 neonates with perinatal asphyxia enrolled within 72 hours of birth as cases. Electrocardiographic, echocardiographic and biochemical parameters were obtained in all subjects and were correlated with the severity of disease and its outcome. Mean CK-MB level in neonates with perinatal asphyxia was 15.18 ng/ml while mean value in control group was 2.9 ng/ml($p< 0.001$). Mean CK-MB values in Stage 1, stage 2 and stage 3 of Hypoxic Ischemic Encephalopathy (HIE) were 8.69 ± 2.85 ng/ml, 11.03 ± 4.46 ng/ml and 24.85 ± 19.13 ng/ml, respectively($p< 0.001$). Mean Troponin-I value in neonates with perinatal asphyxia was 0.18 ng/ml, while mean value in control group was 0.02 ng/ml ($p< 0.001$) Mean Troponin I values in Stage 1, stage 2 and stage 3 were 0.09 ± 0.04 ng/ml, 0.17 ± 0.07 ng/ml and 0 .26 ± 0.08 ng/ml, respectively ($p< 0.001$). Mean BNP level in neonates with perinatal asphyxia was 1111.2 ± 663.1 pg/ml while in control group it was 253.2 ± 86.1 pg/ml($p< 0.001$). Mean BNP Values in Stage 1, stage 2 and stage 3 were 482.40 ± 114.83 pg/ml, 957.00 ± 336.94 pg/ml and 1823.27 ± 477.91 pg/ml**,** respectively($p< 0.001$). CK-MB, cTnI and BNP levels were significantly higher among vasopressor recipients as compared to the non-recipients (p value < 0.01, <0.001, and < 0.001, respectively) Neonates who died had significantly higher level of CK-MB, cTnI and BNP (p value <0.001, <0.05 and <0.05 respectively) in comparison to patients who recovered and discharged. Significantly lower values of RVEF and LVEF were found with increasing grades of HIE ($p<0.05$ and <0.05 respectively). Myocardial dysfunction secondary to perinatal asphyxia is much more frequent than thought and it requires high index of suspicion. Thus, an early detection of myocardial dysfunction and prompt cardiovascular support will help in improving prognosis of these asphyxiated newborns.
Keywords: perinatal asphyxia; cardiac dysfunction; CK-MB; Troponin I; BNP.

INTRODUCTION

Birth asphyxia is defined by the World Health Organization as "the failure to initiate and sustain breathing at birth immediately after delivery" (WHO) [1].This has been associated with hypoxic-ischemic injury to the central nervous system (CNS) and the clinical manifestations of this injury have been termed as Hypoxic Ischemic Encephalopathy (HIE). Perinatal asphyxia is a common problem with the incidence varying from 0.5 – 2% of live births [2,3]. It is an important cause of morbidity and mortality and a frequent cause of admission to neonatal intensive care units (NICU).

In India, in rural regions of the Uttar Pradesh [4] and Maharashtra [5] 23% and 25% of neonatal mortality were attributed to birth asphyxia, respectively. Hospital-based studies in Nepal [6] and South Africa [7] estimated that birth asphyxia accounted for 24% and 14% of perinatal mortality, respectively.

As per the statements by the American College of Obstetricians and Gynecologist and the American Academy of Pediatrics, a neonate is labeled to be asphyxiated if the following conditions are satisfied:

- Umbilical cord arterial pH less than 7;
- Apgar score of 0 to 3 for longer than 5 minutes;
- Neonatal neurologic manifestations (e.g. seizures, coma, or hypotonia); and

- Multisystem organ dysfunction, e.g. cardiovascular, gastrointestinal, hematologic, pulmonary, or renal system.

Hypoxic ischemic organ damage can occur at antepartum prenatal asphyxia (50%), at intrapartum perinatal (birth) asphyxia (40%) or after delivery as postpartum asphyxia (10%) [8]. Acute maternal infections, pre-maturity of a newborn and multiple births are the most frequent natural risk factors leading to hypoxic conditions in a fetus or newborn.

Severe birth asphyxia results in myocardial ischemic injury. The incidence of clinical cardiac dysfunction in perinatal asphyxia varies from 24-31 %. Myocardial involvement leading to cardiogenic shock remains one of the commonest challenges in management and significant cause of mortality in neonates suffering from perinatal asphyxia. Clinically cardiac dysfunction in perinatal asphyxia manifest as: respiratory distress, congestive heart failure, triscupid insufficiency and myocardial ischemia leading to cardiogenic shock.

Electrocardiographic and echocardiographic studies have been done to study cardiac dysfunction in perinatal asphyxia. Associated ECG changes are T wave inversion, T wave flattening, ST segment depression and significant Q wave indicating infarction. Echocardiographic findings include tricuspid regurgitation, mitral regurgitation, right and left ventricular hypokinesia and ventricular dilatation [9].

CPK-MB has been found to be both very specific and very sensitive for diagnosing acute MI in adults until recently being replaced by highly selective troponins [10, 11]. It has been found that levels of CK-MB correlate well with degree of myocardial involvement in perinatal asphyxia in neonatal period and associated with poor outcome [12].

Cardiac troponin I (cTnI) is thought to be an indicator of perinatalasphyxia-induced myocyte damage [13]. Cardiac troponin I (cTnI) concentration within 36 hr of birth correlate strongly with severity of myocardial dysfunction, clinical grade of HIE and with duration of inotropic support. It has been seen that early cTnI concentrations may provide a useful marker for the anticipated severity of myocardial dysfunction in asphyxiated neonates [14].

Btype natriuretic peptide (brain natriuretic peptide; BNP)is a cardiac hormone with diuretic, natriuretic, and vasodilator properties [15].This is secreted mainly in the ventricles inresponse to volume expansion and pressure load. Both BNP and troponin I are elevated in preterm infants with a significant patent ductusarteriosus [16, 17] and both have been used to evaluate the response to treatment of congenital heart disease [18]. BNP is elevated in persistent pulmonary hypertension of the newborn and correlates well with the pressure gradient across the tricuspid valve [19] and therefore is a useful marker in infants with persistent pulmonary hypertension of the newborn following perinatal asphyxia. Also cord blood BNP is significantly elevated in infants requiring inotropes following perinatal asphyxia [20].

Myocardial involvement in perinatal asphyxia remains one of the commonest challenges in management and significant cause of mortality. The exact incidence of occurrence of various electrocardiaographic and echocardiographic findings in studies done earlier by various authors differ markedly. Factors leading to respiratory distress per se, like transient tachypnea of newborn, birth trauma, increased intracranial tension and use of drugs which suppress myocardium, like phenobabitone given in high dose to control refractory seizure pose problem in finding out the exact incidence of cardiac dysfunction due to birth asphyxia. Also not much data is available whether the cardiac changes and mortality is affected by sex, birth weight or mode of delivery. CK-MB, cardiac troponin I and BNP testing is central to the diagnosis of acute myocardial infarction in adults. But there are few data in neonates about the efficacy of these enzymes as a marker of cardiac dysfunction in perinatal asphyxia and as a predictor of future outcome and/or mortality. At present no clear-cut physiologic/serological parameter exist which enable an early identification of neonates who are at increased risk to deveope myocardial dysfunction in perinatal asphyxia.

This study was conducted with following objectives :

1. To find out the incidence and features of cardiac dysfunction in perinatal asphyxia
2. To evaluate the role of cardiac enzyme CK-MB, Troponin I and BNP as a marker of cardiac dysfunction in perinatal asphyxia.

MATERIALS AND METHODS

This study was done at Department of Pediatrics, Institute of Medical Sciences & Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, India, 221005. This study is a prospective case control study. Subjects included 48 neonates born in labour room/ obstetric operation theatre at S.S. hospital from January 2012 to August 2013. The study was approved by the Institute Ethical Committee.

Inclusion Criteria

1. Evidence of hypoxic ischemic encephalopathy as per Sarnat *et al.;* [21] clinical staging of hypoxic ischemic brain Injury
2. Written consent obtained from patients

Exclusion Criteria

1. Congenital heart disease
2. Neonates having other major congenital malformations
3. Use of therapeutic hypothermia

Parents or the guardians of neonates selected as subjects were explained about the study. Informed written consent was taken from the parents to enroll the neonate in the study.Neonates born in labour room/ obstetric operation theatre of S.S. hospital were included in study. Healthy neonates free from any clinical illness were taken as controls. Each delivery was attended by at least two skilled pediatric resident doctors. Resuscitation was performed as per NRP- AAP (Neonatal Resuscitation Program- American Academy of Pediatrics) 2010 guidelines. APGAR score of newborns was evaluated at 1 and 5 minutes.

A 12-lead ECG was recorded in every neonate within 72 hours of life.ECG changes were classified based on the criteria by Jedeikin *et al.;* [22].

Grade 1: Equivocal- Flat or inverted T wave in one lead only

Grade 2: Suggestive - Flat or inverted T in several leads with abnormal Q wave in any lead.

Grade 3: Moderate - Flat or inverted T in several leads or Bundle branch block with abnormal Q plus abnormal ST segments.

Grade 4: Severe- Classical segmental infarction pattern with abnormal Q waves and markedly elevated ST segments 2 D Echocardiography with color doppler study was performed bedside in each neonate within 72hrs of life. MicroMaxx© P 10/8-4 MHz ultrasonography system, Sono Site Inc. USA was used in this study. Right and left ventricular ejection fraction, tricuspid regurgitation (TR), mitral regurgitation (MR), presence of right and left ventricular dilatation was evaluated.

CK-MB, Troponin I, and B-type natriuretic peptide quantitative estimation was done using The Alere Triage® Cardio3 Panel kit and Alere Triage® Meter. Test Procedure is based on principles of fluorescence immunoassay. The test device contains murine monoclonal and polyclonal antibodies against CK-MB and BNP, murine monoclonal antibodies against troponin I and fluorescent dye. Blood specimen reacts with fluorescent murine antibody conjugates and meter detects the amount of fluorescence within a measurement zone. The concentration of the analyte(s) in the specimen is directly proportional to the fluorescence detected.

Two ml of venous blood was collected by venepuncture in EDTA vials. Whole blood specimens were tested within 1 hour of sample collection. If testing could not be completed within 1 hour, the plasma was separated and tested within 2 hours from the time of collection or frozen at ≤ -20 ºC until it could be tested. A chest X-ray was taken in all patients enrolled in this study. Blood from patient was also analyzed for other hematological and biochemical investigations like hemoglobin, total leucocyte count, urea, creatinine, sodium, potassium, calcium and blood sugar etc.

Data was collected in predesigned data sheet and entered in Microsoft Excel Worksheet 2007 and analyzed using SPSS 11.5 statistical software. Demographic parameters of neonates between case and controls were compared by Student's t test and proportions by Chi-Square test and Fischer exact test. Comparison of biochemical parameters and findings of 2D Echocardiography were made by analysis of variance (ANOVA). The parameters were compared between control and neonates having various stages of HIE. A p value of < 0.05 was considered as statistical significance.

RESULTS

The present study was carried out on 48 neonates ,17 healthy neonates were taken as controls while 31 neonates with perinatal asphyxia enrolled within 72 hours of birth as cases. Out of 31 neonates, 10 each was in HIE stage 1 and 2 while 11 were in HIE stage 3.

Demographic data

The demographic data of the study population along with control is presented in Table 1. No significant difference was seen between case and control with respect to parameters like sex, gestational age, crown heel length (CHL), occipital frontal circumference (OFC), maternal registration status, maternal age, maternal weight and antenatal complications. However, mean birth weight was significantly higher in perinatal asphyxia group($p< 0.05$).

Demographic data according to various stages of HIE is presented in Table 2. No significant difference was seen among the three HIE stage groups with respect to parameters like birth weight, sex, gestational age, crown heel length (CHL), occipital frontal circumference (OFC), maternal registration status, maternal age, maternal weight and antenatal complications.

Details of intrapartum events are shown in Table 3. No significant difference was observed with respect to mode of delivery and color of liquor in case

and control groups. Mean Apgar scores at 1 min and 5 min were significantly lower among perinatal asphyxia group ($p< 0.05$ and<0.001, respectively)

Intrapartum events in relation to HIE stages are shown in table 4. No significant difference was seen among three HIE stages with respect to colour of liquor and mode of delivery. Mean Apgar score at 1 min in HIE stage 1, stage 2 and stage 3 were 6.1, 5.0 and 3.81 respectively ($p<0.05$). Mean Apgar score at 5 min in HIE stage 1, stage 2 and stage 3 were 7.9, 7.3 and 5.3 respectively ($p<0.001$).

Out of 31 cases, eight (25.80%) didn't require active resuscitation as depicted table-3. Twenty three (74.19%) neonates required active resuscitation. Twenty three (74.19%) neonates in present study required bag and mask ventilation during resuscitation. Nine (29.03%) neonates required endotracheal tube ventilation and only 2 (6.45%) required chest compression with ventilation.

Table 1: Demographic data among case and control group

Demographic data	Categories	Control	Case	p Value
Sex	Male	12	17	0.280
	Female	05	14	
Registration	Booked	08	13	0.732
	Unbooked	09	18	
Gestational age	Term	10	16	0.632
	Preterm	07	15	
ANC complications	No	12	13	0.205
	Yes	05	18	
Weight (g) Mean ±1 SD		2556.2 ± 577	2813 ± 270	< 0.05
Length (cm) Mean ±1 SD		46.9± 3.4	45.7± 6.5	0.508
OFC (cm) Mean±1 SD		33.2± 1.3	34± 1.5	0.114
Maternal age (yr) Mean±1 SD		29.5± 4.2	27.7± 3.7	0.124
Maternal weight (kg) Mean±1 SD		50.2± 3.9	50.5 ± 3.9	0.783

Table 2: Demographic data according to HIE stages.

Demographic data	Categories				
		Stage 1	Stage 2	Stage 3	p Value
Sex	Male	6	4	7	NS
	Female	4	6	4	
Registration	Booked	5	4	4	NS
	Unbooked	5	6	7	
Gestational age	Term	4	6	6	NS
	Preterm	6	4	5	
ANC complications	No	5	4	4	NS
	Yes	5	6	7	
Neonatal weight (g) Mean±1 SD		2646 ± 292	2872 ±192	2912 ±237	NS
Length (cm) Mean±1 SD		45.7± 6.5	47.2± 1.6	46.9± 0.6	NS
OFC (cm) Mean±1 SD		34± 1.5	33.7± 0.5	33.7± 0.4	NS
Maternal age (yr) Mean±1 SD		25± 3.7	27.6± 4.0	26..4± 3.2	NS
Maternal weight (kg) Mean±1 SD		47.7 ±3.7	51.6 ± 4.0	51.2 ±3.2	NS

NS= Non significant

Table 3: Intrapartum events among case and control group

Intrapartum Events	Category		Control	Case	p Value
Liquor	Clear		14	18	NS
	Meconium		3	13	
Mode of delivery	Normal vaginal		9	16	NS
	Caesarean section		8	14	
	Instrumental delivery		0	1	
Details of resuscitation	No		17	8	-
	Yes		0	23	
		B&M	0	23	
		B&T	0	9	
		CPR	0	2	
Apgar score-1min	≤3		0	4	<0.05
	4-7		4	27	
	>7		13	0	
Mean Apgar score - 1 min ± 1SD			7.76± 0.42	4.93± 1.24	-
Apgar score-5min	≤3		0	2	<0.001
	4-7		0	18	
	>7		17	11	
Mean Apgar score - 5 min ± 1SD			9.1±0.38	6.77±1.55	-

NS= Non significan

Table 4: Intrapartum events in relation to HIE stages

Intrapartum Events	Category		Stage 1	Stage 2	Stage 3	p Value
Liquor	Clear		8	5	5	NS
	Meconium		2	5	6	
Mode of delivery	Normal vaginal		4	6	6	NS
	Caeserean section		6	4	4	
	Instrumental delivery		0	0	1	
Details of resuscitation	No		5	3	0	-
	Yes		5	7	11	
		B&M	5	7	11	
		B&T	0	2	7	
		CPR	0	0	2	
Apgar score-1min	≤3		0	0	4	<0.05
	4-7		10	10	7	
	>7		0	0	0	
Mean Apgar score - 1 min ± 1 SD			6.1±0.7	5.00±0.77	3.81±0.44	-
Apgar score-5min	≤3		0	0	2	<0.001
	4-7		2	7	9	
	>7		8	3	0	
Mean Apgar score – 5 min ± 1 SD			7.9±0.56	7.3 ±0.82	5.3±0.92	

NS= Non significant

Clinical details of the cases with perinatal asphyxia:

The clinical details of study subjects are presented in Table 5. According to Sarnat et al. 1976[21]HIE staging system, ten (32.25%) neonates were in HIE stage 1, 10(32.25%) were in HIE stage 2 and 11(35.48%) neonates were in HIE stage 3 group. Clinical Seizures were present in 16(51.61%) neonates. Respiratory distress was found in 17(54.83%) neonate. Acute renal failure was present in 13(41.93%) of the asphyxiated neonates. Congestive cardiac failure was present in none of the patients. Shock was present in 13(41.93%) asphyxiated neonates.

Vasopressor was given to all neonates with shock consisting of Dopamine, Dobutamine and Adrenaline and Hydrocortisone or combination of any of these drugs. Mean duration of vasopressor required was 55.38 hrs. Five neonates required vasopressor for <48 hours and 8 required it for >48 hours.

Hypoglycemia was present in 10(32.25%), hypocalcaemia was present in 13(41.93%) neonates. None of the neonates were hypothermic.

Table 5: Clinical details in asphyxiated neonates (n=31)

Clinical details	Category	No of Patients	Percentage
HIE Staging	1	10	32.25
	2	10	32.25
	3	11	35.48
Seizures	Absent	15	48.39
	Present	16	51.61
Respiratory Distress	Absent	14	45.17
	Present	17	54.83
Shock	Absent	18	58.07
	Present	13	41.93
Congestive Heart Failure	Absent	31	100
	Present	0	0
Hypoglycemia	Absent	21	67.75
	Present	10	32.25
Hypocalcemia	Absent	18	58.07
	Present	13	41.93
Hypothermia	Absent	31	100.00
	Present	0	0.00
Acute renal failure	Absent	18	58.07
	Present	13	41.93
Meconium aspiration syndrome	Absent	24	77.42
	Present	7	22.58

Details of Investigations done is shown in table 6. Chest x-ray was done in all neonates enrolled within 72 hrs of life; out of it was abnormal in 10(32.15%) neonates in asphyxia group. Meconium aspiration syndrome was most common finding, observed in 5 out of 10 neonates (50.0%) with abnormal chest x-rays

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ECG was abnormal in 20 (67.75%) neonates with perinatal asphyxia. Grade 1 changes were most common, present in 9 (29%), while grade 4 changes was present in only one case with HIE stage 3. Grading of abnormal ECG correlated with severity of HIE. Details of ECG grade according to HIE Stages is shown in table 7.

Table 6: Investigations

Investigation	Category	No of Patients	Percentage
Chest X-ray	Normal	21	67.15
	Abnormal	10	32.25
E.C.G	Abnormal	20	64.51
	Normal	11	35.48
Grading of E.C.G	Grade1	9	29.03
	Grade2	5	16.12
	Grade3	5	16.12
	Grade4	1	3.22

Table 7: ECG grade according to HIE Stages

ECG Grade	Stage 1	Stage 2	Stage 3
Grade 1	5	3	1
Grade 2	0	1	4
Grade 3	0	1	4
Grade 4	0	0	1

Table 8: Biochemical parameters in controls and cases with perinatal asphyxia.

Enzyme	Control (n=17)	Case (n=31)	pValue
CK-MB	2.90 ± 1.48	15.18±13.58	< 0.001
cTnI	0.02 ± 0.01	0.18±.098	< 0.001
BNP	253.2 ± 86.13	1111.2±663.1	< 0.001

CK-MB- Creatinine kinase MB
cTnI- Cardiac troponin I
BNP- Brain natriuretic peptide

Biochemical parameters in controls and cases in different stages of HIE with perinatal asphyxia is shown in table- 8 and 9. Levels of CK-MB, Troponin I and BNP correlated with severity of HIE.

Table 9: Enzyme levels in different stages of HIE.

Enzyme	Stage 1 (n=10)	Stage 2 (n=10)	Stage 3 (n=11)	P Value (ANOVA)
CK-MB (ng/ml)	8.69 ± 2.85	11.03 ± 4.46	24.85 ± 19.13	< 0.001
cTnI (ng/ml)	0.09 ± 0.04	0.17 ± 0.07	0 .26 ± 0.08	< 0.001
BNP (pg/ml)	482.40 ± 114.83	957.00 ± 336.94	1823.27 ± 477.91	< 0.001

Table 10: Enzyme levels in different stages of HIE and Control group (Post hoc test)

Comparison group	CK-MB (p Value)	cTnI (p Value)	BNP (p Value)
Control vs Stage 1	NS	<0.01	<0.05
Control vs Stage 2	NS	< 0.001	< 0.001
Control vs Stage 3	< 0.001	< 0.001	< 0.001
Stage 1 vs Stage 2	NS	< 0.01	<0.001
Stage 2 vs Stage 3	<0.01	< 0.001	< 0.001
Stage 1 vs Stage 3	< 0.001	< 0.001	< 0.001

Comparison of CK-MB Values in different possible groups applied in Post hoc test(Table 10) showed statistically significant difference in values between stage 2 and stage 3; stage 1 and stage 3 but not between Stage 1 and stage 2. Also significant Values of CK-MB were found on comparing control group Stage 3 and but not between control and stage 1 or Stage 2.

Similarly, significant Values of Troponin I and BNP were found among three stages of asphyxia viz. Stage 1, Stage 2 and Stage 3. Significance was also found when these groups were compared with control group

As depicted in table 11, significantly higher values of CK-MB, cTnI and BNP were found in neonates who received vasopressor than non recipients (p value <0.01, <0.001 and <0.001)

Table 11: Enzyme levels according to need of vasopressor

Enzyme	Vasopressor	No. of Patients	Mean± SD	p Value
CK-MB (ng/ml)	Yes	13	23.24±17.97	<0.01
	No	18	9.35±3.45	
TNI (ng/ml)	Yes	13	0.26±0.07	<0.001
	No	18	0.11±0.05	
BNP (pg/ml)	Yes	13	1597.84±666.72	<0.001
	No	18	759.88±387.98	

Table 12: Echocardiographic finding in neonates with perinatal asphyxia

Parameter		Control	Case	p Value
RVEF		69.47 ± 2.35	68.54±4.91	NS
LVEF		68.71 ± 2.26	68.58±4.27	NS
TR	Present	0	11	<0.01
	Absent	17	20	
MR	Present	0	7	<0.05
	Absent	17	24	
RV Dilatation	Present	0	2	NS
	Absent	17	29	
LV Dilatation	Present	0	2	NS
	Absent	17	29	

RVEF= Right ventricular ejection fraction, LVEF= Left ventricular ejection fraction, TR= Tricuspid regurgitation, MR= Mitral regurgitation, NS= Non significant

As depicted in table 12, no significant difference was seen between cases and controls with respect to mean RVEF, Mean LVEF, RV dilation or LV dilation.

Table 13: Echocardiographic findings according to HIE stages

Parameter		Stage 1	Stage 2	Stage 3	p Value
RVEF		71.60 ± 2.99	68.00 ± 6.32	66.10 ± 3.11	<0.05
LVEF		70.90 ± 2.85	69.00 ± 4.90	65.80 ± 3.39	<0.05
TR	Present	3	3	5	NS
	Absent	7	7	6	
MR	Present	2	2	3	NS
	Absent	8	8	8	
RV Dilatation	Present	0	0	2	NS
	Absent	10	10	9	
LV Dilatation	Present	0	1	1	NS
	Absent	10	9	10	

NS= Non significant

As depicted in table 13, Mean RVEF was estimated as 71.60 % ± 2.99, 68.00 % ± 6.32 and 66.10 % ± 3.11 in Stage 1, Stage 2 and Stage 3, respectively (p< 0.05).Mean LVEF was estimated as 70.90 %± 2.85, 69.00 % ± 4.90 and 65.80 % ± 3.39 in Stage 1, Stage 2 and Stage 3, respectively(p Value <0.05). Tricuspid regurgitation (TR) was the most common finding, present in eleven (35.48%) neonates with perinatal asphyxia. No significant difference was found among neonates in three HIE groups with respect to tricuspid regurgitation (p = 0.71) or mitral regurgitation (p = 1)
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No significant difference was found among neonates in three groups with respect to RV dilation or LV dilation. Neonates who died had significantly higher level of CK-MB, cTnI and BNP (p value <0.001, <0.05 and <0.05 respectively) in comparison to patients who recovered and discharged(table 14).

Table 14: Mean Enzyme levels (± 1 SD) in relation to outcome in neonates with perinatal asphyxia.

Enzyme	Outcome	Mean	P value
CK-MB	Death	33.66± 26.68	<0.001
	Discharge	11.62± 5.10	
cTnI	Death	0.26±0.07	<0.05
	Discharge	0.16±0.09	
BNP	Death	1888.6±598.6	< 0.01
	Discharge	961.8±571.2	

DISCUSSION

In present study was carried out 31 neonates with perinatal asphyxia admitted to the Neonatal Unit, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi. For delivery room resuscitation, the standard NRP AAP 2010 guidelines were followed. All the cases were enrolled within 72 hours of birth. The cases were further divided into HIE stage 1 (n=10), HIE stage 2 (n=10) and HIE stage 3 (n=11) according to Sarnat *et al.;* [21]staging.

Demographic parameters

Demographic parameters including maternal age and weight, antenatal care, gestational age, gender, crown rump length, and occipital-frontal circumference, was evenly distributed between case and control groups. Neonatal weight was higher among asphyxiated neonates ($p<0.05$). Probably larger sized babies were associated with more obstetric complications.

In present study, nine deliveries were by spontaneous vaginal delivery while 8 were by caesarean section among control group. Among cases, sixteen deliveries were by spontaneous vaginal delivery while 14 were by caesarean section and one was instrumental delivery. No significant difference was observed with respect to mode of delivery between case and control groups. Also no significant association of mode of delivery ($p= 0.123$) was found with different stages of HIE. Meconium stained amniotic fluid was present in 13 (41.93 %) cases. Similar incidence was found in the study of Martin-Ancel *et al.;* [23], where the authors documented an incidence of 42%.

Clinical presentation

In present study respiratory distress was most common finding to be present in seventeen (54.83%) neonates followed by cardiogenic shock in 13(41.93%) neonates. None of the neonates had congestive heart failure. In study done by Rajakumar *et al.;* [9] incidence of respiratory distress among asphyxiated neonates was 66.7% followed by congestive heart failure in 36.7% and shock in 16.7%. However, none of the neonate had congestive heart failure in study by Martin-Ancel *et al.;* [23] which is consistent with findings of present study. In present study, cardiogenic shock was present in 13 (41.93%) asphyxiated neonates which is comparable to 44 % incidence in study by Mandal *et al.;* [24].

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In presents tudy, chest X-ray was abnormal in 10 (32.25%) neonates. Features suggestive of meconium aspiration syndrome were most common finding to be present in 5 (16.12 %) neonates. Four neonates in HIE stage 3 group had X-ray features suggestive of meconium aspiration syndrome. Five chest X rays showed bilateral infiltrates suggestive of pneumonia.

In a study done by Martin-Ancel *et al.;* [23], 19% of neonates had clinical seizures, contradictory to Shah *et al.;* [25] who documented presence of seizure or coma in 87% neonates. In present study, clinical seizure was documented in 16 (51.61%) neonates and renal involvement was present in 13 (41.93%) neonates. Moderate to severe renal involvement was documented in 42% of neonates by Martin-Ancel *et al.;* [23], which is similar to present study.

Cretinine kinase-MB (CK-MB)

In present study, mean CK-MB level (15.18 ± 13.58 ng/ml) in cases was significantly higher than that of the controls (2.90 ± 1.48 ng/ml) ($p<0.001$). Mean value of CK-MB in Stage 3 was significantly higher as compared to stage 2 and stage 1 ($p< 0.01$ and <0.001, respectively), while it was comparable between Stage 2 and Stage 1. This finding is similar to previous study done by Rajakumar *et al.;* [9] who reported higher CK- MB values in asphyxiated neonates. Chauhan *et al.;* [26] also found very high correlation between clinical pattern of asphyxiated newborn infants and alterations of serum cardiac enzyme CK-MB.

Cardiac troponin I (cTnI)

Present study showed a statistically significant higher value of cTnI among asphyxiated neonates than control group ($p< 0.001$). Also significantly higher levels of cTnI were observed with increasing grades of HIE($p< 0.001$). This finding is consistent to observations of Simovic *et al.;* [27] and Shastri *et al.;* [14]. Trevisanuto *et al.;* [13] concluded in their study that in asphyxiated neonates, cTnI concentrations are higher with respect to healthy infants. Also Fang *et al.;* [28] demonstrated that CK-MB and cTnI levels were significantly higher in asphyxiated neonates than control group.

Brain natriuretic peptide (BNP)

In present study, mean BNP levels in asphyxia group was significantly higher than control group ($p< 0.001$). Moreover highest BNP levels were found in HIE stage 3 subgroup followed by HIE stage 2 and Stage 1 group ($p< 0.001$). In present study, mean BNP level in control group was 253.24 pg/ml which was similar to value of 231.6pg/ml as documented by Koch *et al.;* [29].

Mean BNP was highest in HIE stage 3 group suggesting the severity of myocardial injury. In this group, 7 neonates required vasopressor support (mean duration 68.14 hrs) while lowest value was found in HIE stage 1 group in which only 2 neonates required vasopresssor support (mean duration 37.5 hrs). BNP levels were significantly higher in vasopressor recipient neonates than non recipients ($p< 0.001$). Few studies have been done previously which correlate need of vasopressor support in asphyxiated neonates with BNP levels. This finding is consistent with previous studies by Moriichi *et al.;* [20] who found that cord blood BNP was significantly elevated in asphyxiated neonates requiring inotropes.

Thus findings of present study are consistent with previous reports that asphyxia in the newborns leads to myocardial injury as detected by CK-MB, cTnI and BNP. These markers may be useful in anticipating

cardiac dysfunction and providing appropriate cardiovascular support in addition to managing the primary condition.

ECG

ECG was abnormal in twenty one (67.75%) neonates in case group. Most ECG changes were of Grade 1 (29.03 %) followed by Grade 2 (16.12%) and grade 3 (12.90%). Grade 4 change was present in only one neonate in HIE stage 3 group. In study done by Rajakumar *et al.;* [9], ECG changes were present in 73.3% of asphyxiated neonates which is comparable to present study. However, Grade 2 ECG changes were most common abnormality reported by the authors

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Echocardiography

RVEF and LVEF were comparable in case and control population. However, values were significantly lower in HIE stage 3 as compared to HIE stage 2 and HIE stage 1 ($p<0.05$ and $p< 0.05$ respectively). In contrast, Rajakumar *et al.;* [9] reported significant differences in cardiac contractility between case and control group.

Ischemic injury to cardiac papillary muscle and PPHN both can lead to valvular regurgitation and regurgitant murmurs. In present study, tricuspid regurgitation was most common valvular lesion, present in 11 (35.48%) followed by mitral regurgitation in 7 (22.58%) neonates. The incidence of tricuspid regurgitation was 23.3% (most common) in study done by Rajakumar *et al.;* [9]. Incidences of TR as documented by Rowe *et al.;* [2], Flores *et al.;* [3] and Martin-Ancel *et al.;* [23] were 12%, 7% and 21%, respectively. The wide variation in the incidence of TR may be due to the type of cases selected, presence or absence of pulmonary hypertension and the timing of echocardiography.

CONCLUSION:

In general, cardiac abnormalities often are underdiagnosed and require a high index of suspicion. The measurement of CK-MB, cardiac troponin I and BNP as evidenced by present study may have a role in the early identification of neonates with myocardial damage secondary to ischemia.

In present study, there is a clear relationship between clinical pattern of asphyxiated newborn infants and alterations of enzymatic, electrocardiographic and echocardiographic parameters. Neonates with severe hypoxic damage was reflected in significant changes in ECG , echocardiography and enzyme levels.

Thus, it can be concluded that myocardial dysfunction secondary to perinatal asphyxia is much more frequent than thought, for which it will also be useful to submit asphyxiated patients to serial ECG monitoring, echocardiographic assessments and CK-MB, Troponin I and BNP level measurements. The early detection and prompt cardiovascular support will help in improving prognosis of these asphyxiated newborns.

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