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A HOSPITAL BASED PROSPECTIVE STUDY TO COMPARE CK-MB, ECG AND 2-D ECHOCARDIOGRAPHIC FINDING IN ASPHYXIATED AND NON- ASPHYXIATED NEONATES AT TERTIARY CARE CENTER

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Abstract

Background: Perinatal asphyxia is a common perennial neonatal problem and contributes significantly to neonatal morbidity and mortality. Hence to detect the myocardium damage due to perinatal asphyxia present study was conducted to compare CK-MB, ECG and Echocardiographic finding among asphyxiated and non-asphyxiated neonates and their relation to the severity and stage of asphyxia and also try to establish an association between CK-MB and 2D echocardiography and ECG finding. **Materials and Methods:** This is a hospital based prospective study done on 120 neonates (>37 weeks) with perinatal asphyxia were admitted to Department of Paediatrics and Neonatology Rashtriya Mahila Chikitsalaya (RMC) JLNMC during one year period. The asphyxiated neonates were monitored for seizures, hypotonia and HIE in the immediate neonatal period in the NICU. Grading system used to grade the severity of HIE is SARNAT and SARNAT staging. 12 lead serial ECG were recorded in all neonates included in Study in first 72 hours of life to look for transient myocardial ischaemia. Echocardiography - were done in all cases and same cardiologist to evaluate for cardiac status after 24 hours and if patient have abnormal findings, then repeated after 6 weeks. **Results:** Our study showed that there was no statistically significant difference in distribution of weights among cases and controls (p=0.835). All the 26 cases with 2D Echo changes and 57 cases with normal 2D Echo had Ck-MB level >60U/L. Raised CK-MB level was found to be statistically significant in cases with Echocardiographic changes (p=0.01). Among the 3 cases of grade-1 ECG, 10 cases of grade-2, 12 case of grade-3 ECG and 1 case of grade-4 ECG having 2-D echo finding while 32 case of grade 1 ECG, 17 case of grade-2 ECG, 6 case of grade-3 ECG and no case of grade 4 ecg had normal echocardiogram. This shows that with increasing grading of ECG abnormality in echo finding were present which were significant. **Conclusion:** We conclude that severe ECG changes (Grades 3 and 4) occur only in the most critically ill neonates and should be considered a specific marker of severe myocardial injury. Because they can be detected even in mildly compromised neonates, CK-MB elevation and reduced systolic function should be considered the most reliable markers of ischemia.

INTRODUCTION

Perinatal asphyxia is a common perennial neonatal problem and contributes significantly to neonatal morbidity and mortality. Globally, hypoxia of the newborn (birth asphyxia) is estimated to account for 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year.[1] An estimated 1 million children who survive birth asphyxia live with chronic neuro-developmental morbidities - cerebral palsy, mental retardation, and learning disabilities. Due to a lack of resources, developing countries are worse off.

Data from National Neonatal Perinatal database (NNPD) suggests that perinatal asphyxia contributes to almost 20% of neonatal deaths in India.[2] Ante-partum and intra-partum asphyxia contributes to as many as 300,000 to 400,000 stillbirths.[2] In India, 8.4% of inborn babies have a one minute Apgar score less than 7 and 1.4% suffer from hypoxic ischemic encephalopathy (HIE).[2] Accurate estimates of the proportion of neonatal mortality attributable to birth

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asphyxia are limited by the lack of a consistent definition for use in community-based settings and the absence of vital registration in communities where the majority of neonatal deaths occur.

A variety of markers have been examined to identify perinatal hypoxia including electronic fetal heart monitoring, low Apgar scores, cord pH, electroencephalograms (EEG), computed tomography (CT) and magnetic resonance imaging (MRI) scans and Doppler flow studies. The current problem then is the inability to precisely distinguish the false positive affected from the true positive asphyxiated or compromised fetus. Several studies have been conducted to evaluate better markers that help distinguish an asphyxiated from a non-asphyxiated neonate.

Perinatal asphyxia may result in adverse effects on all major body systems. Many of these complications are potentially fatal. In a term infant with perinatal asphyxia renal, neurologic, cardiac and lung dysfunction occur in 50%, 28%, 25% and 23% cases respectively.[3] The extent of multi-organ dysfunction (MOD) determines the early outcome of an asphyxiated neonate with either the neonate succumbing as a consequence of organ damage or recovering completely. Generally, there are no long term sequelae associated with these organ system derangements. HIE refers to the central nervous system (CNS) dysfunction associated with perinatal asphyxia.

Transient myocardial ischemia is a recognized association of perinatal asphyxia, with an incidence from 30% to 80% in severely asphyxiated neonates.[4] Myocardium CK-MB is a cardiac enzyme which is leaked out due to this ischemia and hypoperfusion which is a marker of myocardium damage due to HIE. Previous study had been done for finding relationship b/w cardiac enzyme and HIE.

In myocardium ischaemia there is T wave inversion in Electrocardiography which is due to transient Myocardium damage and may lead to HIE related complications. Early damage is seen due to transient hypoperfusion, and this ECG finding is transient in nature.[5] Several studies are done earlier where there is correlation between higher HIE grade and Myocardial damage.[6]

Myocardium damage may also be determined by 2D Echo changes in ejection fraction (EF), fractional shortening (FS), Mitral or tricuspid regurgitation, ventricular hypokinesia. ECG also may depict changes in ST segment, T wave and Q wave changes. Although the myocardium in neonate is preferentially perfused during an episode of asphyxia, when such compensatory mechanism becomes compromised, the papillary muscle and subendocardial area appear to be particularly vulnerable to hypoxic injury.4 Transient myocardial ischemia is a recognized association of perinatal asphyxia, with an incidence from 30% to 80% in severely asphyxiated neonates Previous several study shows that investigations such as electrocardiogram (ECG), echocardiography (ECHO), and elevated levels of cardiac enzymes (CK-MB),[7,8] can detect ischemic insult to the heart. The recognition of myocardial ischemia is far more difficult in neonates than in adults. Hence to detect the myocardium damage due to perinatal asphyxia present study was conducted to compare CK-MB, ECG and Echocardiographic finding among asphyxiated and non-asphyxiated neonates and their relation to the severity and stage of asphyxia and also try to establish an association between CK-MB and 2D echocardiography and ECG finding.

MATERIALS AND METHODS

This is a hospital based prospective study done on 120 neonates (>37 weeks) with perinatal asphyxia were born in Rashtriya Mahila Chikitsalaya (RMC) and admitted to Department of Paediatrics and Neonatology Rashtriya Mahila Chikitsalaya (RMC) Jawaharlal Nehru Medical College from Jan 2021 to Dec 2021.

Data Collection

The study includes 2 groups:

The Case Group: It includes 120 HIE neonates who are fulfilling the inclusion criteria:

Inclusion criteria:

Gestational age > 37 weeks- Assessed by new ballard scoring system, Naegle's rule, 1st trimester USG.

Appropriate for gestational age- Assessed by foetal infant growth chart

The neonates will be identified to have experienced perinatal asphyxia when at least 3 of the following are present:

- Change in foetal heart as indicated by non-reassuring NST
- Apgar score of <7/10 at one minute of life
- Resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration.
- Mild, moderate or severe hypoxic ischemic encephalopathy (HlE), as defined by sarnat and sarnat ,1976.9
- E). Meconium-stained liquor

Exclusion criteria:

- Congenital malformations.
- Maternal drug addiction.
- Neonates born to mothers who would have received magnesium sulphate within 4 hours prior the delivery or opioids (pharmacologica‘ depression).
- Hemolytic disease of the newborn.
- Neonates born to mothers consuming alcohol.
- Neonates born to mothers who are smokers.
- Neonates born to mothers on anti-epileptics.

The Control Group: It includes 120 term apparently healthy neonates appropriate for gestational age without signs of perinatal asphyxia as evidenced by a normal fetal heart rate patterns clear liquor and apgar one minute score >7.

All neonate included in the study were subjected to the following:

1. Detailed maternal history, birth history with neonatal history, assessment of intrauterine fetal

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well-being by continuous electronic fetal monitoring, meconium staining of amniotic fluid, birth events, apgar score, sex of the baby and weight of the baby will record on the specially designed pretested proforma. Gestational age shall be assessed by a new ballard scoring system.

2. Thorough clinical and neurological examination was done for all the neonates included in the study. The asphyxiated neonates were monitored for seizures, hypotonia and HIE in the immediate neonatal period in the NICU. Grading system used to grade the severity of HIE is SARNAT and SARNAT staging.[9]
3. Serum CK-MB level - Venous blood 1 ml was drawn at 8±2 hours and 72±2 hours. A value of more than 92.6 U/L at 8 hour and 60 U/L at 24 hour was taken as cut off level.
4. 12 lead serial ECG were recorded in all neonates included in Study in first 72 hours of life to look for transient myocardial ischaemia. The grading was done as per criteria defined by Jedeikin et al.[10]
5. Echocardiography - were done in all cases and same cardiologist to evaluate for cardiac status after 24 hours and if patient have abnormal findings, then repeated after 6 weeks.

Statistical Analysis: Statistical data has been analyzed by SPSS windows 16.0 version software. Student t test, ANOVA and Pearson's correlation and Chi square tests were used for tests of significance.

RESULTS

Our study showed that gender distribution of neonates is statistically similar between two groups with P=0.990. There is no statistically significant difference in distribution of weights among cases and controls (p=0.835). Incidence of cesarean section and instrumental delivery are significantly more in case group (87%) compared to control group (40%) with P<0.001. Among the 120 neonates in case group, 27 (22%) had Reassuring NST and 93 (78%) had Non-Reassuring NST suggestive of fetal distress. All the 120(100%) neonates in control group had Reassuring NST. The incidence of Non-Reassuring NST is significantly more in case group (78.0%) against control group with P<0.001. MSAF is significantly more in cases when compared controls with P<0.001. The Apgar score <7 is significantly more in cases (100.0%) at 1 min & 5 min with P<0.001 & P=0.006 respectively [Table 1].

Abnormal neurological examination is significantly more in cases when compared to Controls with P<0.001. Among the 120 neonates in the case group, 76 (64%) had mild HIE, 34 (28%) had moderate HIE and 10 (8%) had severe HIE during the course in NICU [Table 1].

In neonates with mild HIE 46 cases had CK-MB >60U/L and 30 had CK-MB <60U/L. In neonates with moderate HIE 27 had CK-MB >60U/L and 7 had CK-MB <60U/L. In neonate with severe HIE all 10 had CK-MB >60U/L. Raised levels of CK-MB were significant in neonates with moderate and severe HIE (p<0.001) [Table 2].

Among the neonate with different grades of ECG mild HIE 34 had grade-1 ECG, 3 had grade-2 ECG, grade-3 and grade-4 had no neonate in mild HIE. In neonate with moderate HIE 1 had grade-1 ECG, 23 had grade-2 ECG, 10 had grade-3 ECG and no neonate had grade 4 ECG. In neonate with severe HIE, no neonate had grade 1 ECG, 1 had grade-2 ECG, 8 had grade 3 ECG and 1 had grade-4 ECG. Higher grade of ECG was significant in neonate with moderate and severe HIE (p<0.001) [Table 2].

Among the neonates with 2-D echo finding, mild HIE 5 had regurgitation lesion, 1 had pulmonary hypertension,1 had right atrial dilation and 1 had ejection fraction less than 60. In neonate with moderate HIE, 9 had TR/MR, 3 had pulmonary hypertension, 2 had right atrial dilation and 2 had ejection fraction ≤ 60. In neonate with severe HIE 12 had regurgitation lesion, 6 had pulmonary hypertension, 12 had dilation and 4 had ejection fraction≤60. Echocardiographic findings are more significant in moderate to severe HIE (p<0.01) [Table 2].

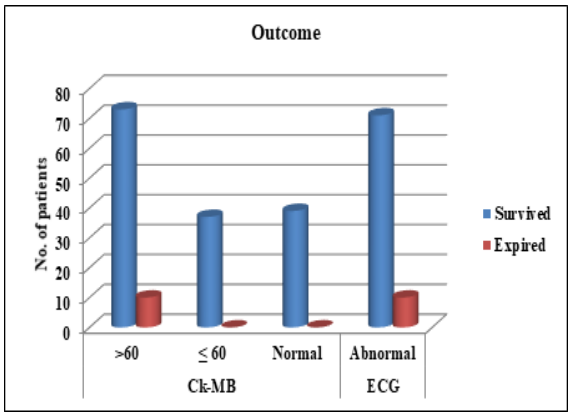

Figure 1: Correlation of CK-MB, ECG with Outcome.

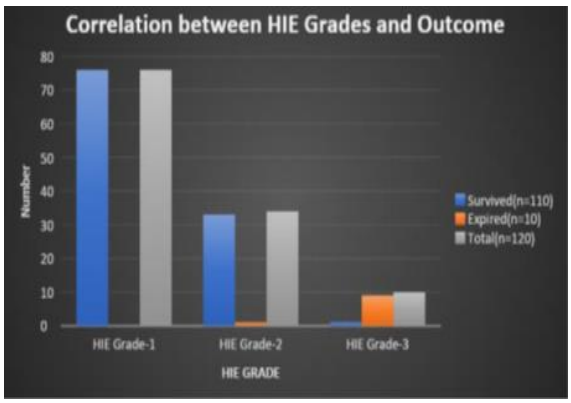

Figure 2: Correlation between HIE Grades and Outcome.

All the 26 cases with 2D Echo changes and 57 cases with normal 2D Echo had Ck-MB level >60U/L. Raised CK-MB level was found to be statistically significant in cases with Echocardiographic changes (p=0.01). Among the 3 cases of grade-1 ECG, 10

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cases of grade-2, 12 case of grade-3 ECG and 1 case of grade-4 ECG having 2-D echo finding while 32 case of grade 1 ECG, 17 case of grade-2 ECG, 6 case of grade-3 ECG and no case of grade 4 ecg had normal echocardiogram. This shows that with increasing grading of ECG abnormality in echo findings were present which were significant [Table 3].

Among the 10 cases which expired all 10 had CK-MB elevated, and had abnormal ECG. However, there is no statistically significant relation between levels of CK-MB grading of ECG and outcome of neonates. [Figure 1]

Among all the neonates with HIE higher grades of HIE was associated with statistically significant higher mortality ($p<0.001$). Among 10 neonates that expired 1 had Grade-2 HIE and 9 had Grade-3 HIE. [Figure 2]

Table 1: Distribution of cases and control in different variables.

Variables	Cases (N=120)	Control (N=120)	P value
GENDER			
Male	75 (62%)	66 (55%)	0.990
Female	45 (38%)	54 (45%)	
BIRTH WEIGHT (KG)			
2.50-2.99	66 (55%)	72 (60%)	0.835
3.00-3.49	40 (34%)	38 (32%)	
≥3.5	14 (11%)	10 (8%)	
Maternal History Of Neonates			
Primi	83 (69%)	72 (60%)	0.950
Multi	37 (31%)	48 (40%)	
MODE OF DELIVERY			
Normal	64 (53%)	72 (60%)	0.625
Instrumental	16 (13%)	4 (3%)	
Cesarean section (LSCS)	40 (34%)	44 (37%)	
NON-STRESS TEST (NST)			
Reassuring	27 (22%)	120 (100%)	<0.01**
Non-Reassuring	93 (78%)	0 (0%)	
MECONIUM-STAINED AMNIOTIC FLUID (MSAF)			
Present	82 (68%)	18 (15%)	<0.01**
Absent	38 (32%)	102 (85%)	
APGAR SCORE AT 1 MIN			
0-3	102 (85%)	0 (0%)	<0.01**
4-6	18 (15%)	0 (0%)	
≥7	0 (0%)	120 (100%)	
APGAR SCORE AT 5 MIN			
0-3	0 (0%)	0 (0%)	0.006*
4-6	24 (20%)	0 (0%)	
≥7	96 (80%)	120 (100%)	
NEUROLOGICAL EXAMINATION (TONE)			
Normal (N)	76 (64%)	120 (100%)	<0.01**
Decreased (↓)	34 (24%)	0 (0%)	
Flaccid (F)	10 (8%)	0 (0%)	

Table 2: Correlation of CK-MB, ECG with stages of HIE

Variables		HIE stages			P-value sig.
		Mild (1)	Moderate (2)	Severe (3)	
CK- MB	>60	46	27	10	<0.001, VHS
	≤ 60	30	7	0	
ECG	Grade1	34	1	0	<0.05 (S)
	Grade2	3	23	1	
	Grade3	0	10	8	
	Grade4	0	0	1	
2-DECHO	MR/TR	5	9	12	<0.01 (S)
	PHTN	1	3	6	
	RA/RV dilation	1	2	12	
	EF≤60	1	2	4	

Table 3: Correlation of CK-MB, ECG with 2D Echo Changes (Presence of any of following is considered present- TR, Pulmonary hypertension, RA/RV dilatation, Ejection fraction <60)

Variables		2D Echo changes		P-value & sig.
		Present	Absent	
CK-MB	>60	26	57	
	≤ 60	0	37	P=0.01 HS
ECG	Grade 1	3	32	
	Grade 2	10	17	P=0.002 VHS
	Grade 3	12	6	
	Grade 4	1	0	

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DISCUSSION

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Birth asphyxia is a common and important cause of preventable cerebral injury occurring in the neonatal period. Although asphyxia at birth is a commonly made diagnosis, there is no accepted definition for it. Prediction of outcome of perinatal asphyxia is important. The Apgar score has a limited role in predicting the immediate outcome, such as that of HIE and the long-term sequelae.4 Only a third of deliveries in India are institutional and many asphyxiated babies are brought late to hospitals.[11] The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia. Several studies have been conducted to evaluate better markers that help to differentiate asphyxial and non-asphyxial etiology in neonates.

Gender distribution of neonates is statistically similar between two groups and the results are comparable to Reddy S et al.[12] The incidence of birth asphyxia is more in males in both the studies. Caesarean section and instrumental delivery were significantly more in cases compared to controls within the present study. This is comparable to Reddy S et al,[12] in which significantly more cases, as compared to controls, were delivered by emergency caesarean section [14 (58%) vs 3 (15%); P=0.003]. There were marked and significantly higher percentages of deliveries by emergency caesarean section among asphyxiated group compared to the control group (15% of asphyxiated group and 85% of severely asphyxiated groups in comparison with 6.8% of control group) in the study by Khreisat et al.[13]

The evidence of fetal distress in the form of non-reassuring NST was seen in 78% of cases in the present study compared to 92% in Reddy S et al,[12] and MSAF was seen in 68% of the cases in the present study and in only 8% in Reddy S et al.12 This difference could be attributed to differences in the inclusion criteria for the cases.

The incidence of HIE is 100% with 64% having mild HIE, 28% moderate HIE and 8% severe HIE. The incidence is comparable to Rajakumar PS et al,[14] in which 100% of the cases included had HIE. The incidence in the present study is higher when compared to Karunatilaka DH et al,[15] in which 25.71% of the cases had HIE. The differences in the incidence of HIE and involvement of other organ systems in birth asphyxia in different studies could be attributable to differences in the inclusion criteria for the cases, grading system used, meconium-stained amniotic fluid, a low 1 min Apgar score and mild to moderate acidemia in predicting the extent and severity of hypoxic-ischemic injury to brain and other organs, initiation and effectiveness of resuscitative measures at birth, level of neonatal intensive care, post asphyxial monitoring and management of the asphyxiated newborns.

The mean CK-MB levels were significantly higher in cases compared to controls with P<0.001 which is comparable to Reddy S et al.[12] Raised levels of CK-MB among asphyxiated neonates was also observed in studies conducted by Primhaket al,[16] Barberi et al.[17] The CK-MB activity increased from Group I to Group II and statistically significant difference was seen in controls and different groups as well as in between different groups. Thus, indicating CK-MB is a very sensitive marker of myocardial ischemia. Whereas Barberi et al,[17] observed that CK, CK-MB, CK-MB/CK ratio and lactate dehydrogenase were all increases in Group III, while only in Group II only CK-MB and the CK-MB/ CK ratio were abnormal.

CONCLUSION

We concluded that severe ECG changes (Grades3and4) occur only in the most critically ill neonates and should be considered a specific marker of severe myocardial injury. Because they can be detected even in mildly compromised neonates, CK-MB elevation and reduced systolic function should be considered the most reliable markers of ischemia.

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