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Original Research Article

CK-MB and LDH as predictor of HIE in term babies born with perinatal asphyxia

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Abstract

Background: One prevalent issue affecting newborns is perinatal asphyxia, which has a substantial impact on the morbidity and mortality of newborns. Perinatal asphyxia can affect all the organ systems with a higher predilection for the nervous system resulting in neurological dysfunction which has been termed Hypoxic Ischemic Encephalopathy (HIE). It has been discovered that LDH and CK-MB have great sensitivity and specificity and that the results of these tests can be obtained right away at the bedside. Following asphyxia, there is a significant increase in LDH and CK-MB, which indicates that these enzymes may be useful in predicting the degree of hypoxic-ischaemic insult a newborn would experience.

Aims: 1: To evaluate the serum CK-MB and LDH levels among asphyxiated and non-asphyxiated term neonates; 2: To study whether these enzymes (if raised) can be used to predict the development of Hypoxic Ischaemic Encephalopathy (HIE) and its correlation with HIE staging.

Materials and Methods: Newborns with perinatal asphyxia were used as cases in this prospective case-control research, whereas healthy term neonates were used as controls. Blood for CK-MB had been drawn at 8 ± 2hrs. of birth as well as LDH at 72 ± 2 hrs of birth.

Results: When comparing the levels of CK-MB as well as LDH in cases versus controls, a significant p value of 0.001 was obtained. LDH was found to have more sensitivity & specificity than CK-MB and hence was found to have more diagnostic accuracy. Babies that died due to HIE 3 had marked elevation of both biomarker levels as compared to other cases of asphyxia.

Conclusion: 1. LDH at 72±2 hours of birth was found to be a better diagnostic test than CK-MB for detecting HIE in cases of perinatal asphyxia; 2. LDH and CK-MB can be utilized to correlate the degree of HIE in cases of birth asphyxia.

Keywords: Biochemical markers, Perinatal asphyxia, Brain injury, Neonatal mortality, Ischemic encephalopathy

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1. Introduction

One of the main causes of death and morbidity in our nation is perinatal asphyxia. It is responsible for over 30% of newborn deaths globally, making it the second most significant reason of death following infections.[1] Perinatal asphyxia causes multisystem involvement. However, it has a greater predilection towards the nervous system and results in neurological dysfunction which is termed HIE and which has been found to have long-term neurological sequelae like cerebral palsy or some degrees of intellectual disability.[2]

In 2017 data released by NNF mentioned that in India, between 250,000 - 350,000 infants died every year because of birth asphyxia, and mostly within the first 3 days of life. Myocardial damage after an asphyxial insult may cause leakage of certain intracellular enzymes like "CK-MB (creatine kinase muscle-brain fraction) and LDH (Lactate dehydrogenase) and hypoxia can further decrease the myocardial perfusion and cause myocardial injury. In these situations, a significant increase in the enzyme levels may suggest a poor prognosis, and a high serum CK-MB might be useful in assessing the degree of myocardial injury.[3]

To lower the rates of mortality and morbidity associated with neonatal HIE, this study on the use of biomarkers to detect brain injury may enable early intervention and therapy. In our nation, research on newborn brain biomarkers is still in its infancy and has yet to make significant strides. This study is a small step towards it.

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2. Aims and Objectives

1. To estimate the serum CK-MB and LDH levels among asphyxiated and non-asphyxiated term neonates.
2. To study whether these enzymes can be used to predict the development of Hypoxic Ischemic Encephalopathy (HIE).
3. To study the outcome of babies in the study group and correlate it with the biomarker levels.

3. Materials and Methods

This prospective hospital-based case-control research was carried out in a tertiary care facility of Assam, India. Neonates admitted to the Inborn Unit of the Special Newborn Care Unit of Gauhati Medical College and Hospital having" the clinical features of birth asphyxia or requiring resuscitation at birth were taken as cases and healthy term neonates from the post natal ward of GMCH were taken as controls.

A study population of 110 cases and 110 controls satisfying the inclusion criteria was taken for the research (convenience sampling). Prevalence of birth asphyxia in community-based studies in India varies from 2 to 16.2 %.[4] We have considered a 7% prevalence to calculate the sample size.

One min of life, an APGAR score of less than seven, resuscitation with more than a minute of positive pressure ventilation prior to stable spontaneous respiration, clinical neurological manifestations such as seizures, hypotonia, and coma for babies born with birth asphyxia, and indications of multi-organ system dysfunction throughout the first few months of life were among the 110 cases of term babies with appropriate gestational age who met one or more criteria for having birth asphyxia. The control group consisted of 110-term, seemingly healthy newborns who did not exhibit any signs of perinatal hypoxia. They had normal fetal cardiac rhythms prior to delivery, clear liquor, and an Apgar score of at least 7 at one minute after birth. The study excluded infants with significant congenital malformations and infants born to moms who had taken magnesium sulfate a few hours before giving birth. Parents' signed, informed consent was required before subjects could be enrolled.

Maternal and neonatal details were noted down in a proforma. A comprehensive neurological and clinical assessment was performed on every infant participating in the research. During the initial neonatal period "in the NICU, the asphyxiated babies (case group) had been observed for seizures and their sequelae. To assess the severity of HIE, a clinical grading system developed by Modified Sarnat and Sarnat was employed.[5] Blood was taken for LDH at 72 ± 2hrs. of age and for CK-MB at 8 ±2 hrs. The identification and birth history of the newborn with asphyxia were concealed from the laboratory technicians doing the tests. The laboratory reference values were used to determine the cut-off level, which was a CK-MB value of >3.38 ng/mL.[4] For newborns and infants, the usual reference value of LDH is 170–580U/L. A cut-off level of > 580U/L at 72±2 hours was considered.[5]

Descriptive statistics were utilized to characterize baseline parameters as well as clinical and laboratory data. To describe nominal data, simple percentages were used. Chi-square tests were used to establish a relationship between the study groups. ROC curves and scatter plots were generated wherever needed. The tests' predictive values, specificity, and sensitivity were computed.

4. Results

Cases (n = 110) as well as controls (n = 110) had comparable rates of sex distribution in males (61% vs 59%) and females (49% vs 51%), a similar birth weight distribution with the majority of them belonging to 2.5 to 3 kg category (76% vs 71%), primigravida (79% vs 68%) and age distribution of mothers mostly belonging to 21 to 30 years (65% vs 77%).

Notably greater number of cases as compared to controls had anemia (51.8% vs 33.6%; p = 0.006), and prolonged labour (29% vs 0%; p < 0.001). The incidence of instrumental delivery and cesarean section was observed to be greater in cases (65.4%) in contrast to controls (37.2%), with a significant p-value of less than 0.001.

76(69%) cases were born through meconium-stained liquor. Of the 110 newborns in the case group, 38 (34.5%) cases had an Apgar score of less than three at one minute, while the remaining 72 (65.5%) cases had an Apgar score of less than seven at the same time. 46 (48%) neonates had an Apgar score of 4 - 6 at 5 min of birth even after resuscitation.

HIE staging was done for all the cases. 11 (10%) cases had no HIE, 14 (12.7%) had stage I HIE, 47 (42.8%) had stage II HIE" & 38 (34.5%) had stage III HIE during their course of stay in NICU. Tone abnormalities were present in 99 (90%) of the newborns. When a neurological examination was performed eight hours after admission on 99 infants with tone abnormalities, 61 (61.1%) had mild as well as significant hypotonia and 38 (38.4%) had been flaccid having severe hypotonia (p < 0.001).**Table 1**

Table 2 shows differentiation of the cut off levels of CK-MB as well as LDH in the study group. The mean CK-MB level at 8 ± 2 hours was 14.9 ±18.07ng/mL in case group and 1.4 ± 0.64ng/mL in the control group. The mean level of LDH at 72 ± 2hrs. had been 1014 ± 445 U/L in case group and 374.4 ± 138.7U/L in the control group. The mean value is notably greater in cases compared as to controls with *p"* <0.001.

Table 1: Showing baseline characteristics found in the study

Characteristics	Cases	Controls	p value
Birth weight			
• 2.5-3 kg	76(34.5%)	71(32.3%)	
• 3.1-3.5 kg	28(12.7%)	33(15%)	0.748
• >3.5 kg	6 (2.7%)	6 (2.7%)	
Sex			
• Male	61(27.7%)	59(26.8%)	0.787
• Female	49(22.3%)	51(23.2%)	
Age of mother			
• <= 20 years	10(9.1%)	6(5.5%)	
• 21-30 years	65(59.1%)	77(70%)	0.218
• >30 years	35(31.8%)	27(24.5%)	
Gravida			
• Primi	79(35.9%)	68(30.9%)	0.115
• Multi	31(14.1%)	42(19.1%)	
Mode of delivery			
• NVD	38(17.3%)	69(31.4%)	
• AVD	8(3.6%)	4(1.8%)	**0.001**
• LSCS	64(29.1%)	37(16.8%)	
Risk factors			
• Anemia	57(51.8%)	37(33.6%)	**0.006**
• Hypertension	16(14.5%)	14(12.7%)	0.694
• Prolonged labour	32(29.1%)	0(0%)	**0.001**
• Meconium stained liquor	76(34.5%)	0(0%)	**0.001**
APGAR score			
At 1 min of birth			
• 0-3	38(17.3%)	0(0%)	
• 4-6	72(32.7%)	0(0%)	**0.001**
• >=7	0(0%)	110(50%)	
At 5 mins of birth			
• 0-3	0(0%)	0(0%)	
• 4-6	46(20.9%)	0(0%)	**0.001**
• >=7	64(29.1%)	110(50%)	
HIE Staging			
• No HIE	11(10%)		
• HIE I	14(12.7%)	-	-
• HIE II	47(42.8%)		
• HIE III	38(34.5%)		
Neurological examination			
• Normal	11(5%)	110(50%)	**0.001**
• Abnormal	99(45%)	0(0%)	

Table 2: Showing mean "cut off levels of CK-MB and LDH

CK-MB	Cases	Control	p value
Mean ± SD	14.9 ±18.07	1.4 ± 0.64	< **0.001**
Median (Range)	6.35 (0.2-79.1)	1.4 (0.2-2.5)	
LDH	**Cases**	**Control**	**p value**
Mean ± SD	1014 ± 445	374.4 ± 138.7	< **0.001**
Median (Range)	958 (213-2117)	373.5 (120-579)	

Table 3: Showing levels of CK-MB and LDH in cases and controls and their sensitivity, specificity, PPV, and NPV

	CK-MB	LDH
Controls (Mean ± SD)	1.4 ± 0.64	374.4 ± 138.7
Cases (Mean ± SD) • HIE I • HIE II • HIE III	 0.54 ± 0.37 10.01 ± 9.52 25.03 ± 4.10	 626.37 ± 53.03 761.87 ± 171.82 1092.56 ± 424.26
Sensitivity	34.92%	23.16%
Specificity	100%	100%
PPV	100%	100%
NPV	79.29%	63.13%

Table 4: Showing CK-MB and LDH levels in relation to the outcome of the study group

Outcome	**CK-MB (ng/mL)**				**LDH (U/L)**			
		<=3.38	>3.38	Total		<=580	>580	Total
Discharged	N	157	41	198	N	125	73	198
	%	71.40%	18.60%	90.00%	%	56.80%	33.20%	90.00%
Expired	N	0	22	22	N	0	22	22
	%	0.00%	10.00%	10.00%	%	0.00%	10.00%	10.00%
Total	N	157	63	220	N	125	95	220
	%	71.40%	28.60%	100.00%	%	56.80%	43.20%	100.00%
Chi square test	60.91				32.16			
p value	**0.001**				**0.001**			

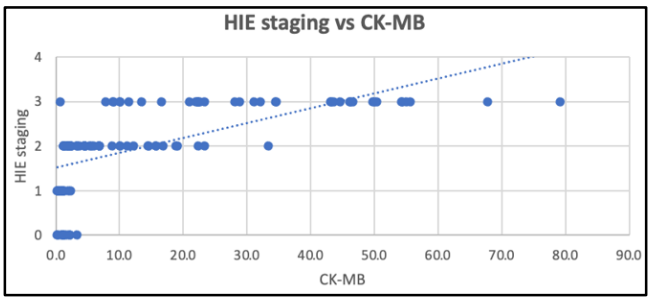

Figure 1: Showing scatter plots for correlation between HIE staging and CK-MB

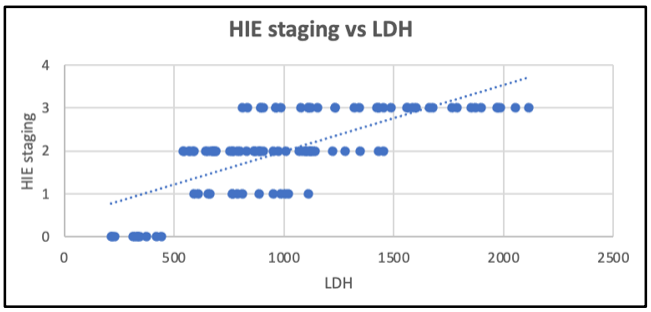

Figure 2: Showing scatter plots for correlation between HIE staging and LDH

Figure 1 and Figure 2 shows the correlation between HIE staging and biomarker levels. The cut-off value for CK-MB had been taken as 3.38 ng/mL and that of LDH was taken as 580 U/L. The correlation between HIE staging and biomarker levels was studied using scatter plots and both the scatter plots showed a positive correlation with results showing that increasing biomarker levels of CK-MB, as well as LDH had been seen with increasing Sarnat and Sarnat staging with highest levels of the biomarkers seen in HIE stage 3. Both CK-MB as well as LDH have a strong positive correlation with increasing HIE.

The correlation coefficient of CK-MB vs HIE is 0.6437 ($p < 0.001$) and LDH vs HIE is 0.7337 ($p < 0.001$).

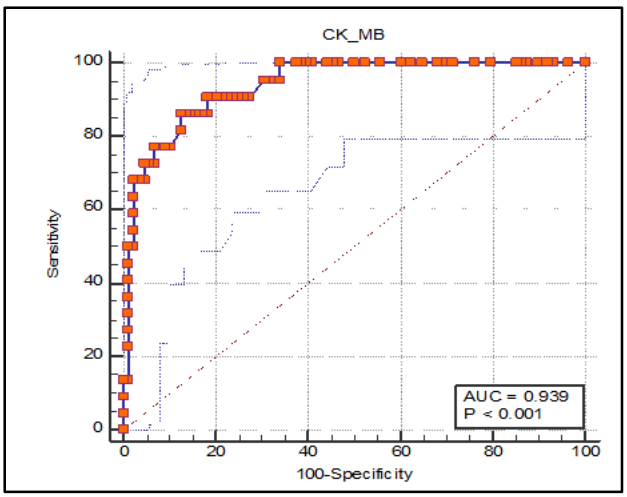

Figure 3 showing ROC (Receiver Operator Characteristics) of CK-MB

Figure 3 and 4 shows the "ROC curves for CK-MB as well as LDH that were generated. The region under the ROC had been highest for LDH (0.956) and then for CK-MB (0.939). The LDH had the greater ability to differentiate amongst cases and controls. Thus LDH is seen to have more

diagnostic value compared to CK-MB, but both are concluded to be excellent tests to discriminate asphyxiated from non-asphyxiated" newborns.

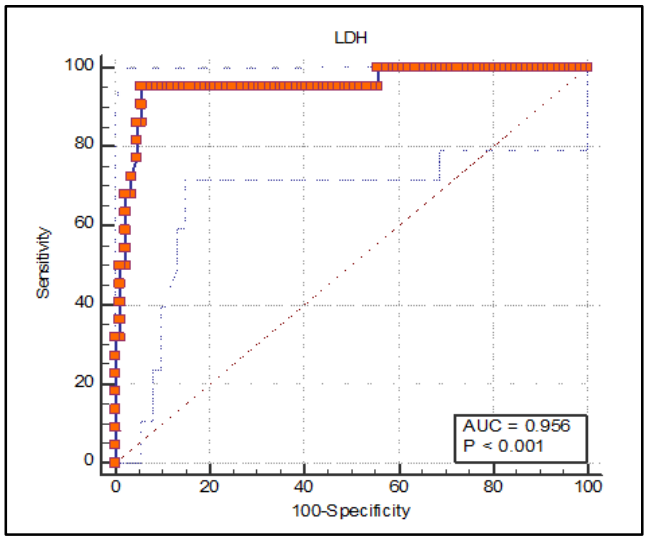

Figure 4 showing ROC (Receiver Operator Characteristics) of LDH

Table 4 shows the comparison between the levels of CK-MB as well as LDH in relation to the outcome of the study group. Out of 63 neonates with CK-MB levels > 3.38 ng/mL, 41 (18.60%) were discharged and the rest 22 (10%) expired. Out of 95 neonates with LDH levels > 580 U/L, 73 (33.20%) were discharged and the rest 22 had died. All the 22 neonates that died belonged to HIE Stage III. All newborns with HIE stage III (38) had notably raised levels of CK-MB as well as LDH levels and were found to have abnormal neurological examination on discharge.

5. Discussion

The current study evaluated the utility of biochemical markers like CK-MB & LDH in assessing the presence and progression of HIE in babies born with perinatal asphyxia. In our investigation we found that the level of biomarker had been greater in the cases as compared to controls, with the highest levels of CK-MB as well as LDH seen in HIE stage 3. Also, the ROC curves generated showed the highest AOC for LDH which is comparable to similar studies done in other centres both in India as well as outside the country.

Numerous other studies conducted to assess the function of biochemical markers in distinguishing between a newborn who is asphyxiated and one who is not, as well as to forecast the development of HIE, if any, in these infants have been carried out.

Reddy *et al*[8] in their study found that levels of CK-MB as well as LDH had been significantly raised in the case group as compared to the controls which are similar to the findings in our study. AOC was highest for LDH, which is consistent with our study, and ROC curves had been constructed for CK-MB at 8 hrs, 24 hrs, as well as LDH at 72 hrs.

Chawla *et al*[9] also in their study found statistically significant neonates with higher CK-MB as well as LDH levels in the case group as compared to the controls. Also, ROC curve of LDH was found to be more diagnostic as compared to CK-MB. They also concluded that LDH performed diagnostically better than CK-MB.

Meena *et al*[10] also compared cut-off levels of CK-MB as well as LDH in the study group and found them to be higher in cases than in controls. They also correlated the APGAR score, the level of CK-MB, as well as LDH to the severity of HIE and found a significant correlation as in our study with a significant *p*-value.

AbouZied H *et al*[11] conducted research in Egypt in 2021 to examine the function of creatine kinase MB in the identification of myocardial damage following newborn hypoxia-ischemia. Serum CK-MB levels in patients had been found to be substantially higher than in controls in the current investigation. Encephalopathy cases were found to be significantly associated with higher CKMB.

Prediction of perinatal asphyxia using serum lactate and other enzymes was studied in another study done in 2021 by Abdelbaseer K *et al*.[12] After taking 30 cases and 30 controls, the researchers discovered that the serum lactate levels, LDH levels, CK-MB levels, aspartate aminotransferase (AST) levels, as well as alanine aminotransferase (ALT) levels varied statistically significantly ($p < 0.001$).[13-15]

6. Conclusion

CK-MB & LDH are found to be good markers of HIE as well as its progression in cases born with perinatal asphyxia. The results of these potential biomarkers are usually available bedside within a few hours. These enzymes have the potential to be predictive of the degree of hypoxic-ischaemic insult in the neonate after birth due to the significant increase in LDH as well as CK-MB caused by organ damage after asphyxia. Early diagnosis allows for the aggressive and successful treatment of serious birth asphyxia in the very early neonatal period, which lowers the risk of death and morbidity.

7. Limitation

This study is a single-centre investigation with a limited sample size and further research would be needed to confirm its utility in daily practice. Also, this test might not be available in most peripheral centers and hence routine use might be a difficulty.

8. Declared Ethical Approval

The Institutional Ethics Committee gave the study its approval.

9. Source of Funding

None.

10. Conflict of Interest

None.

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