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ROLE OF LACTATE DEHYDROGENASE IN ASSESSING THE LIVER DYSFUNCTION AND PREDICTING THE NEUROLOGICAL OUTCOME AND SEQUELAE IN NEONATES ≥ 36 WEEKS WITH BIRTH ASPHYXIA

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ABSTRACT Birth asphyxia (BA) stands as common etiology for neonatal morbidity and mortality. In worldwide approximately 17.2% of neonatal deaths are due Perinatal asphyxia or BA1 Prolonged perinatal asphyxia may lead to Hypoxic Ischemic Encephalopathy (HIE). It has damaging effects on several body organ systems or even death at times. Hepatic comorbidity is highly prevalent in these subjects because of its role in functioning of many metabolic activities. In this prospective study a total of 84 patients have been enrolled and were categorised in to different grades of HIE based on NICHD assessment. Liver enzymes such as Lactate Dehydrogenase(LDH), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), activated Partial Thromboplastin Time (aPTT),Prothrombin Time Test (PT) were measured at baseline in patients enrolled to all three grades of HIE. Serum LDH levels were also measured in abnormal patients as assessed by MRI findings and Hammersmith neurological examination. This study observed a clinically significant correlation between the concentration of liver biomarkers with the severity of HIE. All the subjects in grade 3 HIE has elevated concentrations of Serum LDH, from admission to 72 hrs after admission. This study infers that elevation in concentration of Serum LDH along with SGOT, SGPT, aPTT can be used as a significant biomarker for hepatic dysfunction and its severity. ROC curve analysis of Serum LDH suggests it as a poorly prognostic biomarker in predicting neurological sequelae in neonates > 36 weeks with birth asphyxia

KEYWORDS : *Hypoxic-Ischemic Encephalopathy, Lactate dehydrogenase*

INTRODUCTION

Perinatal asphyxia stands as a major cause of morbidity and mortality in neonates. Statistics from World Health Organisation says four to nine million newborns develop birth asphyxia each year out of which estimated 1.2 million die and at least the same number develop severe neurological consequences such as cerebral palsy, epilepsy, and developmental delay[2] and multi-organ dysfunction (MODS) as result of prolonged hypoxia in the body. In response to this hypoxic ischemic condition a cascade of events happens in the body to prevent the vital organs such as Brain, heart and adrenals called as diving sea reflexes in which body circulates more volume of blood to these vital organs than to Kidney, liver, GI spleen etc[3] As liver is the site for various metabolic activities, when there is an ischemic condition due to hypoxia it may lead to increase in different hepatic enzymes like Lactate Dehydrogenase(LDH), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase(SGPT), activated partial thromboplastin time (aPTT),Prothrombin Time Test (PT) indicating liver dysfunction[4] As newborns are often assessed outside of tertiary-care centres, easilyaccessible biomarkers like liver enzymes are useful for an early diagnosis and prediction of outcomes. These markers will help in identifying infants that are more suitable for intervention in the first few hours of life.

In this prospective cohort study we assessed liver dysfunction and its correlation with the different grades of HIE. Clinical assessment and grading of HIE are done by using National Institute of Child Health and Human Development (NICHD) score.[5] Magnetic resonance imaging (MRI) and spectroscopy were used to predict the neurological outcomes of brain injury. MRI is proven to detect ischaemic brain areas and to assess the extent of the damage.[6]MRI confers a positive predictive value of 100% in detecting histological brain injury. Liver enzymes are investigated by comparing serum LDH, SGOT, SGPT, aPTT, PT values in 3 grades of HIE upon admission, at 24hrs and at 72hrs after admission in asphyxiated neonates. We also studied the correlation between LHD and MRI findings for predicting the neurological outcomes both in normal and abnormal subjects and the serum LDH levels were also compared to Hammersmith neurological examination both in normal and abnormal subjects at 14 days or later after birth asphyxia and at three months of age to predict the neurological sequelae.

MATERIALS AND METHODS

Study design and setting

This was an observational correlational clinical study carried on from September 2016 to march 2017 at Department of neonatology, Madras Medical College (MMC), Chennai. Also involved are out-born unit of Institute of Child health and hospital for children (part of MMC) and inborn unit of Institute of Obstetrics and Gynaecology, Chennai (part of MMC). A written consent of willingness for enrolment of the infants in the study was obtained from the parents / care-givers of the infants selected. All 84 infants selected belonged to any of the three stages of Hypoxemic ischemic encephalopathy (HIE).

Eligibility

All new borns admitted in the intramural and extramural, with perinatal asphyxia were eligible for this study

Inclusion criteria

Neonates born at ≥36 weeks of gestation and of >1800 g birth-weight, and with perinatal asphyxia were eligible. Perinatal asphyxia in patients born at the study hospital was defined as the need for resuscitation at birth, along with the presence of one or more of the following:

1. Apgar score of <6 – at 5 min after birth,
2. Continued need for resuscitation, for > 5 mins
3. umbilical cord pH or any arterial pH of <7.00 within 60 mins of birth, and base deficit of >16 mmol/L within 60 mins of birthWritten consent was obtained from the parents/caregivers of the infants selected for willingness for enrolment in the study (Annexure I).

Exclusion criteria

1. Neonates with major congenital anomalies
2. Neonates presenting after 24 hours of birth
3. Neonates enrolled in the therapeutic Cooling Study

Primary outcome measure is to study the role of Serum Lactate dehydrogenase in assessing live dysfunction along with other liver enzymes in Perinatal asphyxia subjects ans its role in prediction of neurological sequelae.

Non-parametric setting for Qualitative data analysis

Pearson correlation between study variables is performed to find the degree of relationship, Pearson correlation co-efficient ranging between -1 (weak correlation) to 1 (strong correlation) between two biomarkers. The stronger the correlation, stronger is the ability to influence the other biomarker with which there is a correlation.

Classification of Correlation Co-efficient (r)

Up to 0.1	Trivial Correlation
0.1-0.3	Small Correlation
0.3-0.5	Moderate Correlation
0.5-0.7	Large Correlation

0.7-0.9	V.Large Correlation
0.9- 1.0	Nearly Perfect correlation
1	Perfect correlation

ROC curve analysis is performed to find the predictability of study variables (biomarkers) in prognosis of advanced HIE stage. The biomarkers with higher sensitivity and specificity, PPV (Positive Predictive Value) and NPV (Negative Predictive Value) suggest their correlation beyond their individual cut-off values to be prognostic markers for the neurological sequelae. Diagnostic markers based on Area under curve AUROC signifies the following result –

0.9 - 1.0	Excellent test
0.8 - 0.9	Good test
0.7 - 0.8	Fair test
0.6 - 0.7	Poor test
0.5 - 0.6	Fail

Statistical Methods:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made

1. Dependent variables should be normally distributed,
2. Samples drawn from the population should be random,
3. Cases of the samples should be independent

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software:

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS AND DISCUSSION

84 infants with a gestation age of ≥ 36 weeks of gestation were included in the study. 19% (16/84) of infants were delivered through LSCS mode of delivery while the remaining infants delivered through normal route. 90% (76/84) of infants are of birthweight 2.5kg-3.5kg and 79 infants were AGA. Respiratory support was given 79 infants.

Demographic data of the patients

Patients enrolled are of both genders – 35 male and 49 female. 39/84 patients were of gestational age less than 38 weeks. Except 8 neonates who are below 2500g, remaining 76 neonates enrolled have a birth weight between ≥2500g and 3500g. Only five were small for gestational age. 79 neonates required respiratory support on admission (CPAP or mechanical ventilation or O2). Oxygen saturation was still less than 90 in case of 42 neonates upon admission and in 76 neonates mean arterial pressure upon admission is <30 mm to 40 mm of Hg. Upon admission, patients were categorised based on the severity of encephalopathy – 34 patients were assessed mild (HIE1), 37 were assessed moderate (HIE2) and 13 were assessed severe (HIE3). All three grades of encephalopathy are identified among neonates upon admission – 34 neonates with mild encephalopathy (HIE1), 37 neonates with moderate encephalopathy (HIE2), 13 neonates with severe encephalopathy (HIE3). All patients were assessed with APGAR score at 1 minute, as <7 and at 5 minutes the score is <7 in 28 patients. Around 54% of patients in both HIE2 and HIE3 groups still have APGAR score <7 at 5 min. The demographic data is summarised in Table 1.

Table 1 Demographic data

	Final Diagnosis			P value
	HIE 1 (n=34)	HIE 2 (n=37)	HIE 3 (n=13)	
Gender				
• Female	24(70.6%)	19(51.4%)	6(46.2%)	0.162
• Male	10(29.4%)	18(48.6%)	7(53.8%)	
Gestation age (weeks)				
• 36-37	19(55.9%)	12(32.4%)	8(61.5%)	0.070+
• 38-40	15(44.1%)	25(67.6%)	5(38.5%)	
Birth weight (g.)				
• <2500	7(20.6%)	1(2.7%)	0(0%)	<0.001 **
• 2500-3000	21(61.8%)	17(45.9%)	9(69.2%)	
• 3000-3500	6(17.6%)	19(51.4%)	4(30.8%)	
Mode of delivery				
• LSCS	0(0%)	11(29.7%)	5(38.5%)	<0.001 **
• Vaginal	34(100%)	26(70.3%)	8(61.5%)	
APGAR score 1 min.				
• <7	34(100%)	37(100%)	13(100%)	1.000
• >7	0(0%)	0(0%)	0(0%)	
APGAR score 5 min.				
• <7	1(2.9%)	20(54.1%)	7(53.8%)	<0.001 **
• >7	33(97.1%)	17(45.9%)	6(46.2%)	
Cord ABG (pH, Base deficit)				
• <6.8	0(0%)	0(0%)	0(0%)	<0.001 **
• 6.8-7.2	20(58.8%)	26(70.3%)	13(100%)	
• >7.2	14(41.2%)	11(29.7%)	0(0%)	
Severity of encephalopathy @ admission (NICHD assessment)				
Mild	34(100%)	0(0%)	0(0%)	<0.001 **
Moderate	0(0%)	37(100%)	0(0%)	
Severe	0(0%)	0(0%)	13(100%)	

** Chi-Square test/Fisher Exact testAt base lines, blood samples were taken upon admission and after 24 hrs and 72 hrs to analyse for various prospective prognostic biomarkers such as Lactate degydrogenase, SGOT, SGPT, aPTT, PT. MRI findings and Hammersmith neurological examination have been done. Baseline investigations of biomarkers are presented in table 2.

Table 2: Baseline Investigations Of Serum Biomarkers

Marker	Up on admission			24 hrs after Admission			72 hrs after admission		
	HIE 1	HIE 2	HIE 3	HIE 1	HIE 2	HIE 3	HIE 1	HIE 2	HIE 3
Lactate Dehydrogenase	234.79 ±8.35	290.73 ±135.99	617.23 ±133.47	318.74±69.56	444.32 ±80.09	762.62 ±103.02	327.32±51.12	594.14 ±92.56	828.00 ±60.43
SGOT	107.32 +2.66	145.97 +47.21	215.38 +34.75	90.97 +8.86	186.97 +67.42	269.38 +28.50	74.38 +5.41	179.27 +76.29	300.62 +45.47
SGPT	39.00 +1.87	87.03 +30.24	86.00 +5.00	50.65 +18.16	88.27 +24.63	112.31 +13.38	47.47 +22.82	76.70 +17.83	152.23 +20.48
aPTT	27.06 ±1.43	26.11 ±1.51	37.69 ±3.47	26.35 ±1.54	30.05 ±2.69	41.62 ±1.80	30.71 ±1.06	32.76 ±1.79	38.38 ±6.81

P<0.001**, ANOVA test, P=0.03*

Lactate Dehydrogenase

An increase in mean concentration levels of Lactate dehydrogenase (34% increase in HIE3 group 104.26% in HIE 2 and 39.40% in HIE I group) was observed at 72 hours after admission. As the severity of HIE progressed the mean concentrations of lactate dehydrogenase also increased across all time periods. Upon admission HIE 3 group has 162 %, at 24 hrs 139% and 72 hrs 152% increase than HIE 1 patients at respective timelines.

SGOT

At 72 hours after admission, an increase in mean concentrations of SGOT is seen in HIE2 (23% increase) and HIE3 (40% increase) groups.Decrease in levels have been observed for HIE 1 group patients. And we can also see the increase in mean concentration levels of SGOT as the severity increases across all the time periods.Up on admission patients in HIE 3 group have 100% more increase in levels than HIE 1 group .Patients with severity of HIE 3 have more levels of mean concentrations of SGOT after 24 hrs (196%) and 72 hrs (304%) than HIE 1 and HIE 2 groups.

SGPT

Significant increase (77%) of SGPT is witnessed in HIE 3 category

patients after 72 hrs of admission. HIE 1 category patients witnessed 21%increase whereas HIE 2 witnessed decrease in mean concentration levels of SGPT by 11%. The levels were observed to be high as the severity increases from HIE 1 to HIE 3 across all time periods. During admission HIE3 category patients have 120% increase in levels than HIE 1. At 24 hrs HIE 3 patients have 121% in levels than HIE 1 and at 72 hrs increase of 61% for HIE 2 and 220% for HIE 3 have been noted.

aPTT

Mean concentration levels of APTT were increased in all the groups after 72 hrs of admission. A significant raise of 25% is seen in HIE 2 group patients than other two groups. Similarly APTT also show increase in concentrations as the severity of HIE increases across all time periods.

Pearson correlation

Pearson correlation was used to assess the strength of correlation between individual markers versus Lactate dehydrogenase and at baseline, there is a strong correlation observed with the 3 parameters.

Table 3: Pearson Correlation: Lactate dehydrogenase with other clinical variables

Pearson Correlation	R value	P value
Lactate dehydrogenase vs SGOT	0.549	<0.001**
Lactate dehydrogenase vs SGPT	0.082	0.458
Lactate dehydrogenase vs APTT	0.839	<0.001**
Lactate dehydrogenase vs PT1	0.558	<0.001**

It is observed that the significant elevations of Lactate dehydrogenase with the increase in severity of HIE and over a period of 72 hrs after admission positively correlates with the elevation of other biomarkers such as SGOT, APTT and PT than SGPT.

To observe these patients and to assess prognostic value of lactate dehydrogenase in predicting neurological sequelae, blood samples were again taken for neonates after 14 days and infants at 3 months of age, The mean serum concentrations (with standard deviation) of these this biomarker was studied in normal and abnormal subjects as assessed by MRI findings were recorded during final diagnosis. And also the biomarker (LDH) was measured in normal and abnormal patients as assessed by Hammersmith neurological examination to understand the possible correlation to predict neurological outcome

Table No.4 Lactate dehydrogenase in relation to MRI findings

Lactate d ehydrogenase	MRI Changes Normal	MRI Changes Abnormal	P value
Admission	249.57±57.98	394.58±210.22	<0.001**
24 hrs	346.89±89.76	548.20±173.61	<0.001**
72 hrs	380.07±115.7	678.83±133.11	<0.001**

Table No.5 Lactate dehydrogenase in relation to **Hammersmith neurological examination @ neonates** (at 14 days)

Lactate d ehydrogenase	Normal	Abnormal	P value
Admission	235.97±12.81	380.60±199.61	<0.001**
24 hrs	319.75±68.65	535.00±163.28	<0.001**
72 hrs	338.00±68.80	660.58±132.93	0.038*

Table No.6 Lactate dehydrogenase in relation to **Hammersmith neurological examination @ infants** (at 3 months)

Lactate dehydrogenase	Normal	Abnormal	P value
Admission	269.71±104.31	465.33±227.1	<0.001**
24 hrs	377.10±97.40	639.71±186.63	<0.001**
72 hrs	440.25±143.26	768.57±91.29	0.002**

As per the serum concentrations of lactate dehydrogenase recorded in abnormal patients as per MRI findings, there is an elevation of 58% - 78% of the enzyme in abnormal group as compared to normal. As per Hammersmith neurological examination of neonates and infants, the elevation of serum lactate dehydrogenase is 60% (at admission) to 95% (at 72 hrs after admission) in neonates and around 72% elevation at (admission) to 74% (at 72 hrs admission) in infants as compared to normal group.

Lactate dehydrogenase (72% higher levels of lactate dehydrogenase in abnormal groups over a period of 72 hrs as assessed by MRI findings and 73% and 65% elevation from Hammersmith neurological examination of neonates and infants respectively).

Up on observing the above values Lactate dehydrogenase showed significant difference in mean serum concentrations between normal and abnormal groups.

ROC curve analysis to predict advanced stage

ROC curve analysis was done to have sensitivity value, specificity value, the cut off value of the biomarker and the AUROC (Area under ROC curve) in predicting the neurological sequelae in patients with birth asphyxia. ROC curve analysis was shown in TableNo.7 .

Table 7: ROC curve analysis

Variables	ROC results to predict Advanced Stage				Cut off	AUROC	SE	P Value
	Sensitivity	Specificity	LR+	LR-				
Lactate dehydrogenase	52.00	100.00	0.0	0.48	>250	0.573	0.069	0.292

It was observed from ROC curve analysis that lactate dehydrogenase with AUROC value 0.573 and P value of 0.292 can not be served as a prognostic biomarker that can predict the possibility of neurological sequelae.

CONCLUSION:

The present study showed significant elevation of serum concentrations of hepatic enzymes (LDH,SGOT,SGPT, aPTT) from the time of admission to the 72 hrs after admission in patients among all grades of HIE. This clinically signifies the presence of hepatic dysfunction in Perinatal asphyxiated subjects and also signifies the extent of hepatic impairment in the patients. The increase in concentrations of serum liver biomarkers (LDH,SGOT,SGPT, aPTT) in correlation with different grades of HIE indicates that liver dysfunction is proportional to severity of HIE. Thus LDH along with SGOT,SGPT,aPTT can be used as clinically significant biomarker for the assessment of Liver Dysfunction in Birth ashyxia. LDH is further investigated for its prognostic ability as a biomarker in predicting neurological sequelae resulting from HIE by comparing the MRI findings and Hammersmith neurological examination of subjects having normal and abnormal changes. There is an evident increase in the serum concentrations of LDH in subjects having abnormal MRI changes than compared to normal. At 14 days and 3 months of age serum LDH levels show elevation in subjects having abnormal changes from Hammersmith neurological examination than to the normal.ROC curve analysis performed suggests that serum LDH with low AUROC value (0.573) and its non significant P value , it cannot be used a independent prognostic biomarker in predicting the neurological outcomes.

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