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Original Research Article

Comparative Study of Serum Creatine Kinase Muscle-Brain Fraction (CK-MB) and Lactate Dehydrogenase (LDH) Levels Among Asphyxiated and Non-Asphyxiated Term Neonates

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Abstract:

Background: For differentiating an asphyxiated from a non-asphyxiated neonate with reasonable degree of precision, estimation of serum levels of CK-MB and LDH can play a crucial role.

Methods: This hospital based study was conducted for a period of one year at tertiary care teaching hospital of Jaipur, Rajasthan in asphyxiated (Cases) and non-asphyxiated (Controls) term neonates. Creatine Kinase Muscle-Brain fraction (CK-MB) levels at 8 hours and 24 hours and Lactate Dehydrogenase (LDH) levels were measured. Sensitivity, specificity and positive predictive value and negative predictive value of the test were performed. ROC Curve analysis has been performed to find the diagnostic performance of CK-MB and LDH.

Results: Statistically significant difference was found with elevated CK-MB levels at 8 hours and at 24 hours respectively among cases as compared to control ($p<0.05$). The number of neonates with LDH > 580 U/L (cut off value) was significantly more in cases when compared to controls ($p<0.05$). The correlation of Low Apgar score at 1 minute and 5 minute, CK-Mb at 8 hours, 24 hours and LDH with stages of Hypoxic ischemic encephalopathy (HIE) was found to be statistically significant ($p<0.05$).

Conclusion: This study concluded that all these markers can be very advantageous in differentiating neonates with asphyxia and without asphyxia which will further help in appropriate management and better outcome of these newborns.

Keywords: Creatine Kinase Muscle-Brain Fraction (CK-MB), Lactate Dehydrogenase (LDH), asphyxia, neonate.

Introduction

In developing as well as developed countries, perintatal asphyxia is one of the major causes of mortality and morbidity. According to WHO definition, birth asphyxia defined as “the failure to initiate and sustain breathing at birth a common neonatal problem, perinatal asphyxia contributes to marked morbidity and mortality [1].

Due to dearth of perfusion of vital organs of the human body, it is an insult to the neonate. In India, birth asphyxia contributes approximately 28.8% of neonatal death, a study conducted by NNPD (National Neonatal Perinatal Database for the year 2002-2003 [2]. Asphyxia should be diagnosed when newborn has choking at birth and inadequate respiration or no respiration at 1 minute after birth [3]. Each normal fetus undergoes an episode of hypoxemia, hypercapnea and mixed acidosis during intrapartum period. This occurs because of impaired blood flow in the uterus during labour. In this mild asphyxia episode, there is no signs of neurological dysfunction [4,5]. Perinatal asphyxia is associated with vast etiology and the clinical manifestations may vary from person to person. There is no sign of neurological injury in infants with mild asphyxia; while newborns with severe perinatal asphyxia can be fatal in utero or immediately after birth. Those who are survivors of birth asphyxia show considerable neurological consequences, with or without cognitive defects [6].

The clinical presentation of asphyxiated newborn with multi organ involvement includes seizures, renal failure, encephalopathy, cyanosis, respiratory distress, feeding intolerance etc. Along with these, other illnesses like sepsis, intraventricular hemorrhage, pneumonia and hyaline membrane

disease can also be observed. All these clinical presentation can occur as a single system disorder or in combination [7,8]. The consequences of asphyxia depend on the extent of multi organ damage. The outcome of asphyxiated neonate is determined by extent of multiorgan damage. Eventually, the newborn perishes as a consequence of organ damage or recovers completely [9]. The need for correct diagnosis of perinatal asphyxia is of great value as the long term prognosis of perinatal asphyxiated and non-asphyxiated newborns is totally different [7]. The most crucial part of perinatal asphyxia is prediction of its outcome. For identifying the neonates with perinatal asphyxia, several markers have been used including apgar score at 1 and 5 minutes, fetal heart rate monitoring, pH of umbilical cord blood at birth, electroencephalograms (EEG), magnetic resonance imaging (MRI), computed tomography (CT) and Doppler flow [10,11], but they all have limited role in predicting outcome.

Myocardial dysfunctioning along with transient myocardial ischemia can occur in any neonate with perinatal asphyxia. For determining the presence of myocardial damage, factors like elevated levels of serum creatine kinase muscle-brain fraction (CK-MB) or serum cardiac enzymes like troponin T (cTnT) level are of much importance. An elevation of serum CK-MB fraction of >5% to 10% may represent myocardial injury. Creatine phosphokinase is an enzyme expressed by various cell types and tissues.

Creatine kinase is an enzyme which catalyzes the conversion of creatine to phosphocreatine [12,13]. For differentiating an asphyxiated from a non-asphyxiated neonate with reasonable degree of precision, estimation of serum levels of CK-MB and LDH can play a crucial role. It can also correlate with severity of birth asphyxia.

In signalling multi organ damage, leakage of intracellular enzymes, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) are useful [14,15]. But, still there is lack of precise identifying markers for distinguishing asphyxiated from non-asphyxiated neonates.

The study was conducted to compare the serum level of CK-MB and LDH among asphyxiated and non-asphyxiated term neonate.

Materials and Methods

This hospital based study was conducted for a period of one year at tertiary care teaching hospital of Jaipur, Rajasthan in asphyxiated and non-asphyxiated term neonates recruited from Special newborn Care Unit and Post Natal Wards. Institutional ethics committee permission was taken before starting the study.

The study included cases and control two groups.

Inclusion Criteria for cases:

1. Gestational age ≥ 37 weeks.
2. Appropriate for gestational age.
3. The neonates were identified to have experienced perinatal asphyxia when at least 3 of the following are present:

a) Intrapartum signs of fetal distress, as indicated by late decelerations on fetal monitoring or by thick meconium staining of the amniotic fluid.
b) Apgar score of <7 at one minute of life.
c) Resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration.
d) Profound metabolic or mixed acidemia (pH<7.00) in an umbilical artery blood sample, if obtained.
e) Mild, moderate or severe hypoxic ischemic encephalopathy (HIE)

Exclusion Criteria for cases:

1. Congenital malformations.
2. Maternal drug addiction.
3. Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opioids (pharmacological depression).
4. Congenital or acquired infections.
5. Hemolytic disease of the newborn.

The control group: It included full term apparently healthy neonates appropriate for gestational age without signs of perinatal asphyxia as evidenced by normal fetal heart rate patterns, clear liquor and one minute Apgar score ≥7.

Sample size: Sample size was calculated at alpha error 0.05 and study power 90% using the formula $n = 2\times(Z_1-\alpha/2+ Z_1-\beta)^2\times\sigma^2(\mu_1-\mu_2)^2$, Where n = Sample size, $(Z_1-\alpha/2)$ = taken as 1.96 for alpha error 0.05, $(Z_1-\beta)$ = taken as 1.28 for 90% study power, σ variance was taken as 141.45 for CK-MB as calculated from findings of Shylaja et al [16]' , $\mu1-\mu2$= The difference in CK-MB level between the two population was taken as 97 as reported by Shylaja et al [16].

Sample size was calculated to be a minimum of 44.69 subjects in each group, considering 10% dropout, 50 subjects in each group were included.

Procedure: Detailed maternal history, assessment of intrauterine fetal wellbeing by continuous electronic foetal monitoring, meconium staining of amniotic fluid, birth events, Apgar score, sex of the baby and weight of the entire baby were recorded on the precoded proforma. Gestational age was assessed by New Ballard scoring system. Arterial blood gas analysis (ABG) was done if umbilical arterial blood was obtained and also depending on the availability of the facility for analysis.

Thorough clinical and neurological examination was done for all the neonates included in the study. The asphyxiated neonates (case group) were monitored for seizures, hypotonia and HIE in the immediate neonatal period in the NICU. A clinical grading system by Levene et al study was used to grade the severity of HIE [17]. The cases were also observed for other systemic effects of asphyxia.

Approximately, 1 ml of blood was collected each time from the peripheral venous site from the neonates and sent for Creatine Kinase Muscle-Brain fraction (CK-MB) levels and Lactate Dehydrogenase (LDH) levels. Blood for CK-MB was drawn at 8±2 hours and 24±2 hours of age and LDH was drawn at 72±2 hours. CK-MB level analysis was done by Immuno-inhibition method. LDH level analysis was done by Deutsche Gesellschaft für klinische Chemie (DGKC) method. The upper limit of the normal range of CK-MB value >92.6 U/L at 8 hours, >60 U/L at 24 hours and LDH value >580 U/L at 72 hours was taken as the cut – off level. Laboratory technicians performing the CK-MB and LDH tests were masked to the identity and birth history of asphyxia of the neonate. Other relevant laboratory investigations like CBC, Blood urea, serum creatinine were also done. A 12-lead ECG was recorded. Infants with ECG changes of grade 1 or 2 were diagnosed to have mild, whereas those with changes of grades 3 or 4 were considered to have severe injuries. The grading was done as per criteria defined by Jedeikin et al [18].

The case group also had other investigations and imaging studies done as required for post-resuscitation management of asphyxiated neonates. The causes for hypotonia, seizures, lethargy, poor feeding other than HIE were ruled out with relevant investigations available. Peripheral smear for erythrocyte morphology and reticulocyte count was used to document haemolytic disease of the newborn.

Statistical Analysis: Data was analyses using Statistical Package for Social Sciences (SPSS) version 21, IBM Inc. Quantitative data was in Mean±SD and categorical data were presented in Number (%). Sensitivity, specificity and positive predictive value and negative predictive value of the test were performed. Student t test (two tailed, independent) was 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. ROC Curve analysis has been performed to find the diagnostic performance of CK-MB and LDH. P value less than 0.05 was considered significant. Diagnostic values based on ROC curve were 0.9-1.0 (for excellent test), 0.8-0.9 (for Good test), 0.7-0.8 (for Fair test), 0.6-0.7 (for Poor test) and 0.5-0.6 (for Fail test).

Results

Total 50 cases and 50 controls were included in the study. There was no statistically significant difference among cases and control regarding gender distribution, birth weight, maternal history and mode of delivery ($p>0.05$). Statistically significant difference was found in caesarean section and instrumental delivery among cases and controls ($p<0.05$).

Statistically significant difference was found in incidence of non-reassuring Non-stress test (NST) among both the groups ($p<0.05$). There was statistically significant difference among cases and controls for Meconium Stained Amniotic Fluid (MSAF) in Neonates ($p<0.05$). All neonates in control group had clear liquor. (Table 1)

All the neonates among case group had an Apgar score of <7 at 1 min. 32% cases had an Apgar score between 0-3 (severe birth asphyxia) and 68% cases had Apgar score between 4-6 (moderate birth asphyxia). All the neonates in control group had an Apgar score ≥ 7.

Statistically significant difference was found in Apgar score <7 among cases and controls. ($p<0.05$) Apgar at 5 minutes in cases, 56% neonates had score of ≥ 7 following resuscitation at birth. 44% had an Apgar score of 4 to 6 at 5 min even with resuscitation. All the 50 (100%) neonates in control group had an Apgar score >7 at both 1 and 5 min. Among cases, 42% neonates had had normal neurological examination while 58% had abnormal neurological examination.

In control group, all the neonates had normal neurological examination. Out of total 50 cases, 38% had abnormal ECG findings, while 62% had normal in cases. (Table 1)

Table 1: Comparison between cases and controls

	Cases (n=50) N (%)	Controls (n=50) N (%)
Gender		
Male	22 (44)	27 (54)
Female	28 (56)	23 (46)
Birth weight (kg)		
2.5-3.0kg	32 (64)	28 (56)
3.1-3.5kg	13 (26)	19 (38)

>3.5kg	5 (10)	3 (6)
Maternal history		
Primigravida	39 (78)	32 (64)
Multigravida	11 (22)	18 (36)
Mode of delivery		
Normal	15 (30)	26 (52)
Instrumental	06 (12)	2 (4)
LSCS	29 (58)	22 (44)
Non-stress test		
Reassuring	21 (42)	50 (100)
Non-reassuring	29 (58)	0
Meconium Stained Amniotic Fluid (MSAF)		
Present	32 (64)	0
Absent	18 (36)	50 (100)
Apgar score at 1 minute		
0-3	16 (32)	0
4-6	34 (68)	0
≥7.0	0	50 (100)
Apgar score at 5 minute		
0-3	0	0
4-6	22 (44)	0
≥7.0	28 (56)	50 (100)
Neurological examination		
Normal	21 (42)	50 (100)
Abnormal	29 (58)	0
ECG changes		
Normal	19 (38)	50 (100)
Abnormal	31 (62)	0

Among the 50 neonates in the case group, 22% had CK-MB levels (at 8 hours) more than 92.6 U/L and 36% had CK-MB levels (at 24 hours) more than 60 U/L.

Among the 50 controls, all had CK-MB levels (at 8 hours) less than 92.6 U/L and 8% had CK-MB levels (at 24 hours) more than 60 U/L. Statistically significant difference was found with elevated CK-MB levels at 8 hours and at 24 hours respectively among cases as compared to control ($p<0.05$). Among the 50 neonates in the case group, 58% had LDH levels < 580 U/L and 42% had LDH levels >580 U/L.

Among the 50 neonates in the control group 96% had LDH levels < 580 U/L and 4% had LDH levels >580 U/L. The number of neonates with LDH > 580 U/L was significantly more in cases when compared to controls ($p<0.05$). (Table 2)

Table 2: Comparison of Cut-off Levels of CK-MB and LDH in Cases and Controls

	Cases N (%)	**Controls N (%)**	**P value**
CK-MB at 8 hours(Cut-off 92.6 U/L)			
<92.6U/L	39 (78)	50 (100)	0.041*
>92.6U/L	11 (22)	0	
CK-MB at 24 hours (Cut-off 60 U/L)			
<60U/L	32 (64)	46 (92)	0.03*
>60U/L	18 (36)	4 (8)	
LDH(Cut-off 580 U/L)			
<580U/L	29 (58)	48 (96)	<0.001*
>580U/L	21 (42)	2 (4)	

*significant

Among 50 neonate cases, 33.3% stage 1 HIE, 30.7% stage 2 HIE and 33.3 stage 3 HIE had Apgar score between 0 and 3 at 1 minute. While, 66.6% stages 1 HIE, 69.2% stage 2 HIE and 66.6% stage 3 HIE had Apgar score between 4 and 6 at 1 minute.

None of the case had Apgar score of 0-3 at 5 minutes. 38.9% stage 1 HIE, 42.3% stage 2 HIE and 66.6 stage 3 HIE had Apgar score between 4 and 6 at 5 minute.

While, 61.1% stage 1 HIE, 57.7% stage 2 HIE and 33.3% stage 3 HIE had Apgar score ≥7.0.

The correlation of Low Apgar score at 1 minute and 5 minute, CK-Mb at 8 hours, 24 hours and LDH with stages of HIE was found to be statistically significant ($p<0.05$). (Table 3)

Table 3: Correlation of Apgar score, CK-MB at 8 hours and 24 hours and LDH with HIE

Apgar score	Hypoxic ischemic encephalopathy (HIE)			P value
	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	
Apgar score at 1 minute				
0-3	6 (33.3)	8 (30.7)	2 (33.3)	0.047*
4-6	12 (66.6)	18 (69.2)	4 (66.6)	
≥7.0	0	0	0	
Apgar score at 5 minute				
0-3	0	0	0	0.021*
4-6	7 (38.9)	11 (42.3)	4 (66.6)	
≥7.0	11 (61.1)	15 (57.7)	2 (33.3)	
CK-MB at 8 hours (Cut-off 92.6 U/L)				
<92.6U/L	12 (66.6)	24 (92.3)	3 (50)	0.03*
>92.6U/L	6 (33.3)	2 (7.7)	3 (50)	
CK-MB at 24 hours (Cut-off 60 U/L)				
<60U/L	10 (55.5)	18 (69.2)	4 (66.6)	0.002*
>60U/L	8 (44.4)	8 (30.8)	2 (33.3)	
LDH(Cut-off 580U/L)				
<580U/L	12 (66.6)	14 (53.8)	3 (83.3)	0.01*
>580U/L	6 (33.3)	12 (46.2)	3(16.7)	

*significant.

The cut-off value of CK-MB at 8 hours has 76% sensitivity and 83% specificity. CK-MB has a positive predictive value of 92% while a negative predictive value of 100%. The cut-off value of CK-MB at 24 hours has 62% sensitivity and 92% specificity. CK-MB has a positive predictive value of 96% while a negative predictive value of 85%.The cut off value of LDH has 83% sensitivity with a specificity of 96%. LDH has a positive predictive value of 89% with a negative predictive value of 96%. (Table 4)

Table 4: Sensitivity, Specificity and Predictive Values of CK-MB and LDH

	Cut-off value	Sensitivity	Specificity	PPV	NPV
CK-MB (at 8hours)	>92.6	76%	83%	92%	100%
CK-MB (at 24hours)	>60U/L	62%	92%	96%	85%
LDH (at 72 hours)	>580	83%	96%	89%	96%

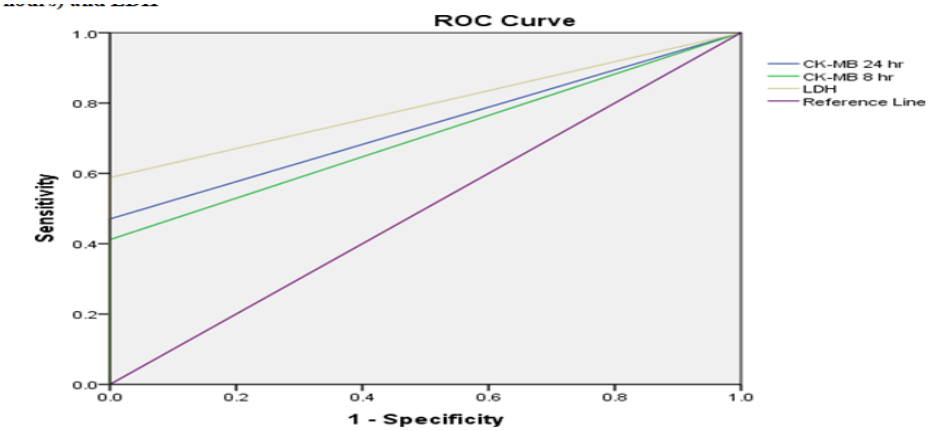

Figure 1: Comparison of Receiver Operator Characteristics (ROC) Curves of CK-MB (at 8 hours and at 24 hours) and LDH

Discussion

Birth asphyxia is a condition that occurs due to impairment in exchange of blood gas during, or after the birth resulting in neuronal cell death and brain damage of neonates due to ischemia. Perinatal asphyxia may result in adverse effects on all major body systems. Many of these complications are potentially fatal.

In the present study, there was no statistically significant difference among cases and control

regarding gender distribution, birth weight, parity and mode of delivery (p>0.05). These results were similar to the study conducted by Reddy et al [19]. There was also no significant association between birth asphyxia and parity of mothers (p>0.05) which was comparable to Reddy et al and Khreisat et al studies [19,20].

Incidence of Caesarean section and instrumental delivery were significantly more in cases as compared to controls with (p<0.05) in the present study. This was comparable to study conducted by Reddy et al in which significantly more cases were delivered by emergency caesarean sections as compared to controls [19]. Similar results were reported by Khreisat et al study.

Evidence regarding foetal distress in the form of non-reassuring NST was found to be 58% of cases in the present study as compared to the 92% in study conducted by Reddy et al [19]. MSAF was found in 64% of the cases in the present study whereas only 8% was seen in Reddy et al study [19]. This difference could be seen due to the differences in the inclusion criteria for the cases. In the present study 38.2% had abnormal ECG findings, which were in consistent with Karnik et al study [21]. On the contrary, more cases had abnormal ECG changes in Agrawal et al (76.7%) and Rajakumar et al (73%) [22,23].

In the present study the number of neonates with CK-MB levels >92.6 U/L was significantly more in cases when compared to controls with (P<0.001). This was comparable to studies carried out by Reddy et al and Rajakumar et al [19,23].

In the present study, the mean CK-MB level at 8±2 hours and the mean LDH level at 24±2 hours were significantly higher in asphyxiated newborns compared to controls. Similar observations were also noticed by Primhak et al and Barberi et al studies [24,25].

In 2005, Boo et al study showed that at birth, asphyxiated infants had significantly higher concentrations of cTnT and CK-MB than controls. Unlike CK-MB, serum cTnT concentrations were significantly higher in asphyxiated infants who died or developed cardiac dysfunction [26].

The correlation of Apgar score at 1 minute, 5 minute, CK-Mb at 8 hours, 24 hours and LDH with stages of HIE found to be statistically significant (p<0.05). On the contrary, in a study conducted by Sanjay et al, there was no statistically significant difference [27]. In the present study, the sensitivity, specificity, PPV and NPV of CK-MB at 8hours were 76%, 83%, 92% and100% which was comparable to Reddy et al study [19].

The area under the ROC curve for CK-MB at 8 hours is 0.921 (excellent test) in the present study when compared to 0.82 (good test) in Reddy et al study [19]. 83% of the cases in the present study had LDH levels >580 U/L. This was lower when compared to Reddy et al study in which 100% of cases had LDH levels >580U/L [19]. The reason for the same could be due to inclusion of babies with haemolytic disease in the case group.

In the present study the mean LDH levels in cases were significantly higher in cases compared to controls with P<0.001 which was comparable to Reddy et al study [19]. LDH had 100% sensitivity, while CK-MB had 100% specificity for asphyxia in a study by Reddy et al [19]. Rajakumar et al study observed that the cardiac enzymes, cTnT and CK-MB, were significantly elevated in cases when compared with controls [23].

Karlsson et al in their clinical and experimental study done in 2008 on evaluation of organ damage in perinatal asphyxia concluded that in asphyxiated infants with differing degree of HIE and in infants where there had been signs of fetal distress during birth a cut off level of 1049 U/L for LDH was the most suitable predictor of mild, moderate, and severe HIE with a sensitivity of 100% and specificity of 97% [28].

In the present study, the sensitivity, specificity, PPV and NPV of LDH at 72 hours were 62%, 92%, 96% and 85%. The Specificity and PPV are comparable to Reddy et al and Karlsson et al studies [19,28]. The sensitivity and NPV of LDH in the present study was lower when compared to Reddy et al and Karlsson et al studies [19,28]. This could be attributed to exclusion of cases with hemolytic disease in the present study. The area under the ROC curve for LDH at 72 hours is 0.954 (excellent test) in the present study which was comparable to 0.998 (excellent test) in Reddy et al Study [19].

Limitations

Temporality could not be established in this study thus further longitudinal researches are required for follow-up. Further, the sample size was small in this study so the large sample size studies are needed in future.

Conclusion

This study concluded that CK-MB levels, LDH levels and ECG as a marker of severity of perinatal asphyxia has promising results which can aid in early diagnosis and prompt treatment and intervention. All these markers can be very advantageous in differentiating neonates with asphyxia and without asphyxia which will further help in appropriate management and better outcome of these newborns.

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