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Original Article

Paediatrics Section

Diagnostic Accuracy of Creatine Kinase-Muscle Brain Fraction and Lactate Dehydrogenase in Hypoxic Ischaemic Injury among Newborns: A Prospective Observational Study

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ABSTRACT

Introduction: Perinatal asphyxia, contributes significantly to neonatal morbidity and mortality. In India, one third of deliveries are institutional and many asphyxiated newborns are brought late to health facility. These newborns don't have proper perinatal records making it difficult to retrospectively diagnose perinatal asphyxia. There is an urgent need to identify new-born with asphyxia who are at high-risk for Hypoxic Ischaemic Encephalopathy (HIE) and multiorgan dysfunction.

Aim: To study the Lactate Dehydrogenase (LDH) and Creatine Kinase-MB (CK-MB) levels in neonates suspected of hypoxic ischaemic injury for better diagnosis and treatment of perinatal asphyxia.

Materials and Methods: The present prospective observational study was done from February 2023 to May 2024 in Special Newborn Care Unit (SNCU) of Government Medical College, Haldwani, Uttarakhand, India. Total 180 randomly selected neonates comprising of 90 asphyxiated and 90 non-asphyxiated newborns were included in the study. The blood samples for CK-MB and LDH were drawn at 8±2 hours and 72±2 hours of age, respectively and were immediately sent for analysis and sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Values (NPV) were calculated for each.

Results: In present study, there were 100 males and 80 females with mean birth weight and age to be 2.9±0.5 kg and 38.3±1.4 weeks. CK-MB value of >92.6 U/L was found in 73 (81.1%) of asphyxiated new-born and LDH >580 U/L was found in 69 (76.6%) asphyxiated. LDH had a sensitivity of 83.13%, specificity of 97.78%, PPV of 97.40%, and NPV of 86.27%. CK-MB showed a sensitivity of 81.11%, specificity of 97.78%, PPV of 97.33%, and NPV of 83.81%.

Conclusion: CK-MB and LDH were elevated in asphyxiated neonates compared to non-asphyxiated neonates and LDH was better at predicting hypoxic ischaemic injury as compared to CK-MB.

Keywords: Delayed cry, Developmental delay, Ischaemic encephalopathy, Neonatal resuscitation, Perinatal asphyxia

INTRODUCTION

Birth asphyxia being a common neonatal problem contributes to significant morbidity and mortality [1]. Birth asphyxia is an insult to the neonate due to lack of perfusion of vital organs of the body. In India, birth asphyxia contributes approximately 28.8% of neonatal death, according to a study conducted by National Neonatal Perinatal Database (NNPD) for the year 2002-2003 [1]. Birth asphyxia accounts for approximately 23% of the 40 lakh neonatal deaths and 26% of the 32 lakh stillbirths each year [2]. Approximately, 10 lakh children who survive birth asphyxia develop neurodevelopmental morbidities like cerebral palsy, mental retardation and learning disabilities [1]. Mortality due to birth asphyxia in India is 2,50,000 to 3,50,000 each year. Antepartum and intrapartum asphyxia contribute to 3,00,000 to 4,00,000 stillbirths [1]. Death generally occurs within the first three days of life. In India 8.4% new-born born with birth asphyxia with low Apgar score less than seven and among them 1.4% suffer from HIE and its sequelae [1].

Early diagnosis, anticipation, and treatment are the important factors which alter the outcome of hypoxic ischaemic injury. The signs of hypoxic ischaemic injury overlap with other illnesses such as hypoglycaemia, hypocalcaemia, inborn errors of metabolism, early onset neonatal sepsis etc,. The newborns are brought late to the health care facility and clinical picture on admission may be indistinguishable from other illnesses. To make a diagnosis of hypoxic ischaemic injury without perinatal records is difficult. So, the presence of biomarkers like LDH and CK-MB could make diagnosis easy [3,4].

Lactate Dehydrogenase is an intracellular enzyme involved in the conversion of lactate to pyruvate during anaerobic metabolism. Elevated serum LDH levels serve as a non specific marker of tissue damage and hypoxia, including in cases of hypoxic ischaemic injury and neonatal Hypoxic-Ischaemic Encephalopathy (HIE) [3,4]. CK-MB is a myocardial band isoenzyme of CK, predominantly found in cardiac muscle. Its elevation is an early biochemical indicator of myocardial injury and has been used to assess cardiac stress in neonates with hypoxic ischaemic injury [5,6]. There are many studies available in literature [7-9] but none was done in Uttarakhand, having difficult to reach the hilly areas. Hence, present study was conducted to study the LDH and CK-MB levels in neonates suspected of perinatal asphyxia for better diagnosis and treatment of hypoxic ischaemic injury.

Null Hypothesis (H_0): There will be no significant difference in CK-MB LDH levels between asphyxiated and non-asphyxiated neonates. Mathematically: H_0: $\mu_1=\mu_2$

(where μ_1= mean LDH level in asphyxiated neonates, μ_2= mean LDH level in non-asphyxiated neonates)

Alternate Hypothesis (H_0): CK-MB and LDH levels are significantly higher in asphyxiated neonates compared to non-asphyxiated neonates. Mathematically: H_1: $\mu_1 > \mu_2$

MATERIALS AND METHODS

The present prospective observational study was done in SNCU of Government Medical College, Haldwani, Uttarakhand, India from February 2023 to May 2024. Study was approved by the Institutional Ethical Committee (wide IEC approval number- 660/GMC/IEC/2022/ Reg No. 664/IEC/R-20-11-2022 dated 11/01/2023). Informed consent was taken from the attendants of all the neonates recruited in the study.

Inclusion criteria: All full-term neonates, with a gestational age of 37 weeks or more as defined by established guidelines [10], and were classified as Appropriate for Gestational Age (AGA), falling within the 10th to 90th percentile for birth weight [10] were included. Subjects with hypoxic ischaemic injury were enrolled as case and healthy subjects were included as controls. Hypoxic ischaemic injury was diagnosed when any three of the following criteria were present [11]: (a) Evidence of foetal distress during the intrapartum period, such as a non-reassuring Non-Stress Test (NST) on continuous electronic foetal monitoring and/or the presence of thick meconium-stained amniotic fluid; (b) An Appearance (color), Pulse, Grimace (reflex response), Activity (muscle tone), and Respiration (APGAR) score of less than seven at one minute of life; (c) Need for positive pressure ventilation lasting more than one minute before the onset of stable spontaneous respiration.

Exclusion criteria: Neonates were excluded from the study if maternal drug addiction was reported, or if the neonate had any congenital malformations. Newborns whose mothers had received magnesium sulphate within four hours prior to delivery or opioid medications (due to risk of pharmacological depression) were also excluded. Further, neonates diagnosed with haemolytic disease of the newborn were excluded due to the possibility of elevated LDH levels unrelated to asphyxia. Lastly, neonates were not included in the study if informed consent was not obtained from their parents or guardians.

Sample size calculation: A total of 180 neonates were included in the study. The sampling technique employed was consecutive sampling, in which all eligible neonates admitted to the Neonatal Intensive Care Unit (NICU) during the study period were enrolled until the desired sample size was achieved. The sample size was determined using a confidence interval of 95% and a study power of 80%. Based on findings from a previous study conducted by Chawla S et al., the proportion of asphyxiated neonates was assumed to be 44% [12]. An anticipated odds ratio of 2.5 was considered for calculating the sample size. Tools used to calculate the sample size was CDC - Epi Info version 7.2.5.0. Total calculated sample size was 180. In present study, 90 term asphyxiated newborns and 90 term non-asphyxiated newborns meeting the inclusion and exclusion criteria were enrolled.

Study Procedure

The affected neonates were staged using the Sarnat and Sarnat classification system and included if they had mild, moderate, or severe HIE [13]. The Non stress test was done using an external cardiotocograph (a non-invasive method used to monitor Foetal Heart Rate (FHR) and uterine contractions, primarily during labour and the third trimester of pregnancy. It helps assess foetal well-being and detect signs of foetal distress such as hypoxia or acidosis. Abnormal Cardiotocography (CTG) patterns, such as late decelerations and reduced variability, may indicate compromised foetal oxygenation and require timely clinical intervention [14]) available in the Obstetrics Department of the institute.

The samples for CK-MB were drawn at 8±2 hours and LDH 72±2 hours of life and sent for analysis. The different time points were used because CK-MB rises early, typically within 3-12 hours of tissue injury (including myocardial or general hypoxia-related injury), peaks by 24 hours, and returns to baseline within 2-3 days. Therefore, early sampling (within the first 24 hours of life) captures the acute phase response to hypoxia. In contrast, LDH has a slower onset, rising within 8-24 hours, peaking later (up to 2-3 days), and remaining elevated longer due to its longer half-life. This makes LDH more suitable for subacute evaluation and cumulative tissue damage). A value of CK-MB >92.6U/L at eight hours and LDH >580 U/L at 72 hours was taken as the cut- off value [10]. The sensitivity, specificity, PPV and NPV was calculated for both CK-MB and LDH. CK-MB and LDH were measured by using Cobas 6000 automated analyser.

STATISTICAL ANALYSIS

The data was collected and recorded in MS-Excel 2021. The statistical analysis including student t-test analysis and measures of central tendencies etc., was done in JASP (Version 0.18.3) (Computer software), open-source software created by University of Amsterdam taking Confidence intervals as 95% in all calculations.

RESULTS

There was no statistically significant difference in the sex distribution in both the groups. The present study showed that newborns delivered through vaginal route were more prone to birth asphyxia 60 (66.67%). This could be due to the fact that, this being a tertiary centre, females land up from far flung areas who are already in labour. Hence, the labour could not be expedited by timely Lower segment caesarean section (LSCS). This also explains the very high rate of neonates with HIE stage 3. The stress test also did not show much significance in predicting asphyxia with a p-value of 0.673. The mortality in present study was 28.8% (n=26) due to very high rate of HIE stage 3 [Table/Fig-1].

Parameters		Asphyxiated n=90 Number (%)	Non-Asphyxiated n=90 Number (%)	p-value
Sex	Female	37 (41.1)	43 (47.7)	0.368
	Male	53 (58.889)	47 (52.2)	
Mode of delivery	LSCS	30 (33.333)	75 (83.3)	<0.001
	Vaginal deliveries	60 (66.667)	15 (16.6)	
Outborn/ inborn	Out born	46 (51.1)	0	
	Inborn	44 (48.8)	90 (100)	
Non-stress test (NST) (only for inborn)	Non-reassuring	21 (47.7)	36 (40)	0.673
	Reassuring	23 (52.2)	54(60)	
HIE stage	1	8 (8.8)	NA	
	2	19 (21.1)	NA	
	3	63 (70)	NA	
Outcome	Dead	26 (28.8)	NA	
	Discharge	64 (71.1)	90 (100)	

[Table/Fig-1]: Comparison of baseline data among neonates in asphyxiated and non-asphyxiated group.

From the above table, it can be seen that a significant number of newborns had more than the cut-off values of LDH {n=69 (76.6%)} and CK-MB {n =73 (81.1%)} [Table/Fig-2].

Serum parameters	Cut-off crossed		p-value
	Asphyxiated	Non-Asphyxiated	
LDH	69 (76.6%)	2 (2.2%)	<0.001
CK-MB	73 (81.1%)	2 (2.2%)	<0.001

[Table/Fig-2]: Cut-off values of LDH and CK-MB crossed.
Students t-test used for statistical analysis

The mean serum LDH and CK-MB levels were significantly higher in asphyxiated neonates compared to non-asphyxiated controls [Table/Fig-3]. LDH levels in the asphyxiated group (1002.15±443.47 U/L) were markedly elevated compared to the non-asphyxiated group (291.46±119.56 U/L), with a mean difference of 743.72 U/L (p <0.001). Similarly, CK-MB levels were significantly raised in asphyxiated neonates (246.64±192.37 U/L) versus non-asphyxiated neonates (60.64±19.13 U/L), with a mean difference of 186.00 U/L (p <0.001). These findings indicate a strong association between perinatal asphyxia and elevated levels of these tissue injury markers.

Serum parameters	Group	N	Mean±SD	Mean difference	p-value
LDH	Asphyxiated **	83	1002.145±443.466	743.722	<0.001
	Non-asphyxiated	90	291.456±119.562		
CK-MB	Asphyxiated	90	246.644±192.37	186	<0.001
	Non-asphyxiated	90	60.644±19.130		

[Table/Fig-3]: Mean, standard deviation, standard error, degree of freedom and p-values of LDH and CKMB.
(**only 83 because 7 neonates did not survive till the cut-off time decided for LDH);
**Chi-squared analysis used for statistical purposes

A progressive increase in both LDH and CK-MB levels with advancing stages of HIE among asphyxiated neonates is demonstrated in [Table/Fig-4]. In Stage 1 HIE, 4.4% of neonates had LDH levels greater than 580 U/L, with a mean LDH value of 848.50±411.66 U/L. This proportion increased to 15.5% in Stage 2 and further to 56.6% in Stage 3, with the LDH mean peaking at 1076.41±449.85 U/L in the most severe stage. Similarly, the proportion of neonates with CK-MB levels above 92.6 U/L rose from 5.5% in Stage 1 to 15.5% in Stage 2 and 60% in Stage 3, accompanied by a corresponding rise in mean CK-MB values from 330.25±271.41 U/L in Stage 1 to 250.63±172.69 U/L in Stage 3. Although these findings suggest an upward trend of LDH and CK-MB with increasing HIE severity, statistical analysis using one-way ANOVA revealed that the differences were not statistically significant (p=0.065 for LDH and p=0.239 for CK-MB).

Serum parameters	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Diagnostic accuracy
LDH	83.13%	97.78%	97.40%	86.27%	90.56%
CK-MB	81.11%	97.78%	97.33%	83.81%	89.44%

[Table/Fig-5]: Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of LDH and CK-MB.

DISCUSSION

In the current study, 90 term asphyxiated and 90 term non-asphyxiated neonates were analysed. Among the asphyxiated group, 58.8% were males, which is slightly higher than the 51.4% males reported by Ayebare E et al., [15], but similar to findings by Chawla S et al., (68.3% males) and Meena K et al., (66% males) [12,16]. Conversely, studies by Simiyu IN et al., and Amsalu S et al., found a higher proportion of females in the asphyxiated group [17,18]. The non-asphyxiated group in this study had 52.2% males and 47.7% females, a non-significant difference (p=0.368).

A significant difference was observed in delivery modes between the groups. In the asphyxiated group, 66.6% were delivered vaginally compared to 83.3% via LSCS in the non-asphyxiated group, with a highly significant p-value (<0.001). Kune G et al., reported similar findings with 70% vaginal deliveries among asphyxiated cases, whereas Sadeghnia A et al., found no significant influence of delivery mode on birth asphyxia (p=0.993) [19,20].

In the asphyxiated group, 47.7% had non-reassuring NSTs compared to 40% in the non-asphyxiated group. This data suggests that NST monitoring alone may not be sufficient for predicting asphyxia, in contrast to findings by Lohana RU et al., and Shah Jitesh M et al., who reported NST as a reliable predictor of perinatal outcomes [21,22]. Additionally, 28.8% of asphyxiated neonates succumbed to the condition, with a significant p-value (<0.001).

In this study, elevated levels of LDH and CK-MB were significantly observed in asphyxiated neonates compared to their non-asphyxiated counterparts (p<0.001). LDH exhibited high sensitivity (83.13%) and specificity (97.78%), while CK-MB demonstrated similar diagnostic performance (81.11% sensitivity and 97.78% specificity).

Comparative analysis with other studies underscores the reliability of these markers. For instance, Reddy S et al., reported 100% sensitivity and 89% specificity for LDH, indicating slightly higher sensitivity but lower specificity than the present study [23]. The mean LDH value in Reddy S et al., research was 1109.5±520.6 U/L, higher than the current study's mean of 1002.145±443.466 U/L, suggesting population or methodological differences [7]. CK-MB sensitivity was notably lower in Reddy S et al., study (36%) compared to the present study (81.11%) [7].

Chawla S et al., found similar LDH sensitivity (91.7%) and specificity (93.4%) to the present study, though CK-MB sensitivity was

Sarnat and Sarnat staging	LDH level		Mean±std dev	CK-MB level		Mean±std dev
	<580 N (%)	>580 N (%)		<92.6 N (%)	>92.6 N (%)	
Stage 1	2 (2.2%)	4 (4.4%)	848.50±411.66	3 (3.2%)	5 (5.5%)	330.25±271.41
Stage 2	5 (5.5%)	14 (15.5%)	823.94±385.78	5 (5.5%)	14 (15.5%)	195.21±215.90
Stage 3	7 (7.7%)	51 (56.6%)	1076.41±449.85	9 (10%)	54 (60%)	250.63±172.69
p-value	0.065			0.239		

[Table/Fig-4]: Stages of HIE according to the LDH and CK-MB level in asphyxiated neonates.
ANOVA used for statistical analysis

The [Table/Fig-5] shows that LDH was more sensitive than CK-MB in recognising hypoxic ischaemic injury but both are equally specific. The PPV of both the tests is similar but the NPV shows slight difference. The gold standard considered was clinical staging by Sarnat and sarnat [13].

Author (Ref No.)	Place and year of study	Sample size	Parameters assessed	Sensitivity	Specificity	Conclusion
Chawla S et al., [12]	Nepal, 2019	100 neonates	LDH, CK-MB in perinatal asphyxia	LDH: 85.7%, CK-MB: 78.5%	LDH: 92.1%, CK-MB: 89.4%	LDH and CK-MB are useful biochemical markers for predicting HIE in asphyxiated neonates.
Meena K et al., [16]	Bikaner, India; 2017	100 neonates	LDH and CK-MB in asphyxiated vs non-asphyxiated	LDH: 92%, CK-MB: 88%	LDH: 94%, CK-MB: 91%	Both LDH and CK-MB were significantly elevated in asphyxiated neonates, with LDH showing slightly better diagnostic utility.
Reddy S et al., [7]	India, 2008	100 neonates	LDH, CK, hepatic enzymes	Not specified	Not specified	LDH and CK are elevated in neonates with perinatal asphyxia and may aid retrospective diagnosis.
Karlsson M et al., [8]	Sweden, 2010	53 neonates	LDH and clinical correlation with HIE	LDH: 82%	Not specified	LDH correlates with severity of HIE; may predict neurological outcomes.
Rajakumar PS et al., [9]	India, 2008	70 neonates	CK-MB, cTnT, cardiac dysfunction in asphyxia	Not specified	Not specified	CK-MB and cTnT levels were significantly higher in neonates with myocardial dysfunction secondary to perinatal asphyxia.
Antil PK et al., [23]	India, 2020	100 neonates	LDH levels in term neonates with asphyxia	88.3%	95%	LDH is a reliable marker for assessing severity of perinatal asphyxia.

[Table/Fig-6]: Comparative analysis with other similar studies.

significantly lower (18%) [12]. Their reported mean LDH value (992.32±437.2 U/L) was close to that of the present study. In Karlson M et al., study, LDH showed 100% sensitivity and 97% specificity, aligning well with the current findings, with a comparable mean LDH value of 1049 U/L [8].

Rajakumar PS et al., demonstrated robust CK-MB sensitivity (75.7%) and specificity (56.5%), albeit with lower specificity than the present study [9]. The mean CK-MB value in their study (121±77.4 U/L) was significantly lower than the present study's mean (246.644±192.37 U/L). Antil PK et al., reported higher LDH sensitivity (94%) and specificity (90%), with a mean LDH value (999.04±521.73 U/L) similar to the present study's findings [23]. The PPV for LDH was slightly lower (90.38%) compared to the current study (97.4%), while the NPV was comparable (93.75% vs. 86.27%).

Meena K et al., found lower LDH sensitivity and specificity (59.1% and 92%, respectively) compared to the present study, with a PPV for LDH at 92% versus 97.4% in the current study [16]. For CK-MB, sensitivity was significantly lower (28%) compared to the present study (81.11%), though specificity was high in both studies (100% in Meena K et al., versus 97.78% in the present study). Their mean LDH (548±67.6 U/L) and CK-MB (86.9±16.9 U/L) values were much lower compared to the present study. The summary of the above discussion is presented in [Table/Fig-6].

Limitation(s)

Apgar scores were not available with outside deliveries EEG corelation was not done due to lack of resources. Inclusion/exclusion criteria tried to eliminate as many confounders as possible but still all could not be eliminated thus requiring further studies.

CONCLUSION(S)

Both the enzyme assays can be used for accurately diagnosing HIE in neonates with suggestive clinical profile and unclear history. This study concludes that the diagnostic performance of LDH is better than CK-MB in determining asphyxiated neonates. LDH and CK-MB are equally sensitive but LDH is more specific as compared to CK-MB. The estimation of CK-MB and LDH levels at 8±2 hours and 72±2 hours of life can distinguish an asphyxiated term newborn from a non-asphyxiated term newborn in correlation with relevant history and clinical features. LDH is a better marker for predicting/retrodiagnosing birth asphyxia without relevant documentation and should be available at every centre handling delivery for better management of the newborns to prevent long term adverse outcomes related to birth asphyxia.

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