"CORRELATION OF SERUM LDH LEVEL IN PERINATAL ASHYXIA AS A MARKER OF HYPOXIC ISCHEMIC ENCEPHALOPATHY"

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ABSTRACT

Introduction

Perinatal Asphyxia is common cause of multiorgan dysfunction in neonates. It leads to significant mortality and morbidity. Serum lactate dehydrogenase (LDH), if measured can differentiate asphyxiated neonates from non-asphyxiated neonates.

Objectives

To find whether serum LDH can distinguish an asphyxiated from a non-asphyxiated term neonate. To co-relate serum LDH level in perinatal asphyxia with various stages of HIE and to see whether it can predict mortality.

Methodology

This is a prospective study done from June 2018 to May 2019 in NICU of Nobel Medical College, on child with Perinatal Asphyxia. All neonates included in the study underwent thorough clinical and neurological examination. Severity of HIE was done by Sarnat & Sarnat staging criteria. Serum LDH level were measured in all the cases. Statistical analysis was done using SPSS 11.

Results

90 neonates with perinatal asphyxia were enrolled and 30 normal neonates were enrolled as controls. The number of neonates with LDH level > 600U/L was significantly more in cases with perinatal asphyxia group as compared to controls (non-asphyxiated) with 'p' < 0.001. Serum LDH level was progressively high in relation to stages of HIE and difference between mean LDH level between neonates expired and survived was statistically significant with 'p' <0.001.

Conclusion

Serum LDH level is a reliable indicator of perinatal asphyxia and helps to differentiate different stages of HIE.

INTRODUCTION

Despite advances in perinatal care, perinatal asphyxia is still one of the major causes of mortality and morbidity in newborns. Perinatal asphyxia is defined as a condition during the first and second stage of labor in which impaired gas exchange leads to fetal hypoxemia and hypercarbia as evidenced by fetal acidosis with umbilical arterial blood pH <7.0.[1] Perinatal asphyxia is an important cause of admission to neonatal intensive care units (NICU) with multi organ dysfunction.[1] Globally hypoxia of newborn or fetus is estimated to account for 23% of 4 million neonatal deaths and 26% of 3.2 million stillbirth each year.[2] In Nepal, incidence of perinatal asphyxia is 9.7/1000 live births.[3] In a survey done in Nepal by multiple indicator cluster survey 2014, neonatal mortality rate was 23 per 1000 live births and birth asphyxia accounted for 16% of neonatal mortality.

When an asphyxia event occurs, it leads to a series of physiological mechanisms in order to preserve the function of vital organs (Brain, heart and adrenals), whereas other organs such as the kidneys, gastrointestinal tract, and skin are affected to a varying degree based on the duration of the asphyxia episode.[4,5,6] In a term infant with perinatal asphyxia, renal, neurological, cardiac and lung dysfunction occurs in 50%,28%,25% and 23% cases respectively.[7] HIE is the foremost concern in an asphyxiated neonate because, contrary to other system derangements, this has the potential to cause serious long term neuro developmental sequel. As specific methods for diagnosis and prediction of HIE are still lacking, a variety of markers have been examined to identify perinatal hypoxia including electronic fetal heart monitoring, low Apgar score, cord pH, EEG,CT scan, MRI scan and Doppler flow studies, still there is need of sensitive and specific test for early diagnosis of HIE.

In these asphyxiated neonates, despite preferential myocardial perfusion, hypoxia leads to lactic acidosis. If hypoxia is severe and persistent, it leads to lactic acidosis, due to anaerobic glycolysis resulting in myocardial suppression. As ischemia progresses, Creatine phosphate reserves are used up, adenosine triphosphate levels fall, and cardiac tissue becomes more acidic as lactate and other acidic intermediates of glycolysis accumulate.[8] Once all the glycogen and Creatine phosphate reserves have been used, dramatic structural changes occur, as evidenced by damage to cell membrane and cytosolic enzymes (CK-MB and LDH) are released into blood stream indicating irreversible cell damage. Hence in this study, we will try to correlate the occurrence of Perinatal asphyxia and assessment of severity of HIE by measuring serum LDH level.

OBJECTIVES

1. To ascertain whether this enzyme can distinguish an asphyxiated from a non-asphyxiated term neonate.
2. To co-relate the serum LDH level in perinatal asphyxia with various stages of HIE.
3. To ascertain whether serum LDH can predict mortality in cases of perinatal asphyxia.

METHODOLOGY

The study is a prospective case control study conducted on asphyxiated and non-asphyxiated term neonates admitted in Neonatal Intensive Care Unit and Post Natal Wards of Nobel Medical College during 12 months period from June 2018 to May 2018 after approval from Institutional review committee (IRC).

SAMPLE SIZE CALCULATIONS

Sample size was calculated by using following formula:

n = sample size in case group
r = ratio of controls to cases
p^- = measure of variability
Z_β = desired power
$p^1 - p^2$ = effect size
$Z\alpha/2$ = level of statistical significance

Total number of cases was calculated using this formula was 90, whereas controls were 30.

Method of Collection of Data
Inclusion criteria:

All appropriate for gestational age, term neonates with perinatal asphyxia were included, if at least 3 of the following are present:

A) Intrapartum signs of fetal distress, as indicated by Non stress test.
B) Apgar score of <7 at one minute of life.
C) Resuscitation with >1 minute of positive pressure ventilation.
D) Profound metabolic acidosis (pH<7.0), if obtained.
E) Mild, moderate or severe hypoxic ischemic encephalopathy, as defined by Sarnat & Sarnat criteria, 1976.

Exclusion Criteria

Neonates with Congenital malformations, maternal drug addiction, born to mothers who had received magnesium sulphate or opioids, baby received under general anaesthesia, baby with congenital infections and prematurity were excluded.

30 full term apparently healthy appropriate for gestational age neonate without signs of perinatal asphyxia were enrolled as control group from ward of Nobel Medical College.

All neonates included in the study underwent thorough clinical and neurological examination. Severity of HIE was done by Sarnat & Sarnat, 1976 scoring. Blood sample was collected for Lactate dehydrogenase level and Umbilical arterial blood for ABG Analysis (if available). Blood for Lactate Dehydrogenase (LDH) was drawn at 24 hours of life. Laboratory technicians performing the LDH tests were masked to the identity of the neonate. Normal serum level of LDH in Newborn is 240-600 U/L. All data was tabulated and statistically analysed using SPSS 11. Sensitivity, specificity, positive predictive value, negative predictive values were assessed and both the groups were compared using suitable statistical tests.

RESULT

One hundred twenty cases were collected during one year study period, which included 90 cases and 30 controls. Among 90 cases, 30 cases were of HIE I, 31 cases were of HIE stage II and 29 cases were of HIE stage III.

Table 1: Basic demographic characteristics of case and controls

Parameters	Control	HIE I	HIE II	HIE III	p value
Maternal age					
< 18 years	3(10%)	4(13.3%)	8(25.8%)	6(20.7%)	
18-35 years	27(90%)	24(80%)	22(71%)	20(69%)	0.299
>35 years	0(0%)	2(6.7%)	1(3.2%)	3(10.3%)	
Sex					
Male	22(73.3%)	15(50%)	19(61.3%)	19(65.5%)	0.304
Female	8(26.7%)	15(50%)	12(38.7%)	10(34.5%)	
Parity					
Primi	20(66.7%)	19(63.3%)	16(51.6%)	14(48.3%)	0.408
Multi	10(33.3%)	11(36.7%)	15(48.4%)	15(51.7%)	
Gestational Age					
Term	30(100%)	24(80%)	26(83.9%)	24(82.8%)	0.095
Post-term	0(0%)	6(21%)	5(16.1%)	5(17.2%)	
Birth weight (grams)	2780 ± 371	2923.33 ± 535.4	2871.29 ± 489.14	2813.79±543	0.669
Liquor					
Clear	24(80%)	16(53.3%)	16(51.6%)	18(62.1%)	0.091
MSAF	6(20%)	14(46.7%)	15(48.4%)	11(37.9%)	
Presentation					
Vertex	29 (96.7%)	26 (86.7%)	28 (90.3%)	28 (96.6%)	0.373
Non-vertex	1 (3.3%)	4 (13.3%)	3 (9.7%)	1 (3.4%)	

Basic demographic parameters were similar among study and control group.

Table 2: Comparison of cut-off value of LDH level in cases and controls

LDH (Cut-off value 240-600 U/L)	< 240-600 U/L	> 600 U/L	Mean LDH level ± SD (U/L)	p value	Odds ratio 95% CI
Control (n=30)	29 (96.66%)	1 (3.33%)	306.10±103.586	p < 0.001	4.93 (55.28 to 4396.50)
Cases (n=90)	5 (5.55%)	85 (94.44%)	1880.6±1658.81		

Among 30 neonates in control group, 29 (96.66%) had LDH level < 600 U/L and 1 (3.33%) had LDH level > 600 U/L. In perinatal asphyxia group 5 cases had serum LDH level < 600U/L, whereas all 85 case (94.44%) had serum LDH level > 600 U/L. Mean serum LDH level in asphyxiated group was 1880.68 ± 1658.81 U/L and in control group was 306.10 ± 103.586 U/L (p <0.001). The number of neonates with LDH level > 600U/L is significantly more in cases with perinatal asphyxia group as compared to controls (non-asphyxiated) with 'p' < 0.001.Table 3: shows sensitivity, specificity and predictive values of LDH level

Table 3: Shows sensitivity, specificity and predictive values of LDH level

	Cut-off	Sensitivity	Specificity	PPV	NPV	ACCURACY
LDH (U/L)	> 600 U/L	94.44% (95% CI- 87.51 -98.17)	96.67% (95% CI- 82.78-99.92)	98.84% (95% CI- 92.52-99.83)	85.29% (95% CI- 71.17-93.16)	95% (95% CI- 89.43-98.14)

The cut-off value of serum LDH level of > 600 U/L has sensitivity of 94.44%, specificity of 96.67%, and positive predictive value of 98.84%, negative predictive value of 85.29% and Accuracy of 95%. The diagnostic performance of test is excellent.
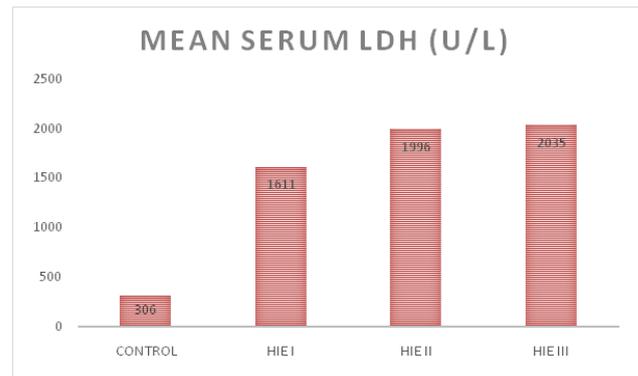

Figure 1: Comparison of mean LDH level between control and different stages of HIE

Among 30 neonates in control group mean serum LDH level was 306.10 ± 103.586 U/L, HIE I, HIE II and HIE III group of neonates had LDH level of 1611.93 ± 1522.547, 1996.39 ± 1608.56 and 2035.00 ± 1859.105 U/L respectively. Serum LDH level was progressively high in relation to stages of HIE, as evidenced by 'p' value < 0.001.Among 90 cases with Perinatal asphyxia studied, 67 (74.44%) neonates survived and were discharged once they were stable and fulfilled the criteria for discharge, 13 (14.44%) neonates expired during hospital stay, all of them were from HIE III stage and 10 (11.11%) went on LAMA.
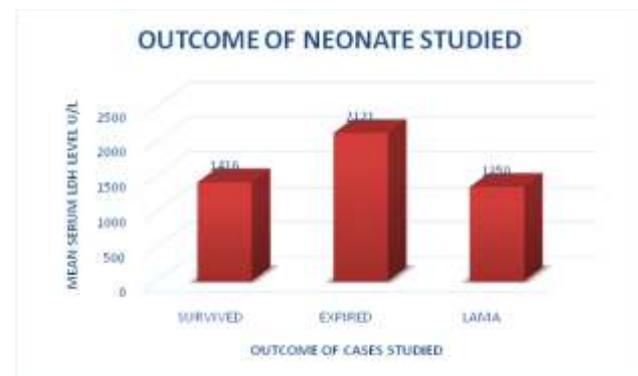
Mean serum LDH level in the neonates survived was 1416.08 ± 1602.16 U/L, whereas neonates expired during hospital stay had mean serum LDH level of 2121.23 ± 1985.12 U/L. Difference between mean LDH level between neonates expired and survived was statistically significant with 'p' <0.001. This difference suggests that high serum LDH level can predict neonatal mortality during hospital stay in neonates with perinatal asphyxia. Mean total days of hospital stay in neonates with HIE I was 6.97 ± 3.57 days, whereas it was higher in neonates with HIE II 9.97 ± 4.13 days. Neonates with HIE III had lower no. of days of hospital stay (7.66 ± 5.47 days).

DISCUSSION

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal mortality and morbidity. Factors like poverty, ignorance and lack of

medical facilities and obstetric care contributes significantly to the magnitude to problems in our country. The signs of asphyxia are non-specific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia. In the present study an attempt has been made to ascertain whether LDH level can distinguish asphyxiated neonate from non-asphyxiated neonates.

This study showed serum LDH level can differentiate asphyxiated and non-asphyxiated neonate. Mean serum LDH level in asphyxiated group was 1880.68 ± 1658.81 U/L and in control group was 306.10 ± 103.586 U/L (p <0.001). This finding is comparable to Reddy S et al.[9] and Rajakumar PS et al.[10] Karunatilaka D.H. et al.[11] also reported higher mean LDH level in perinatal asphyxia (2948 U/L), compared to controls (1671 U/L) and p value was <0.001. In the present study, the sensitivity, specificity, PPV and NPV of LDH were 94.44%, 96.67%, 98.84% and 85.29%. The accuracy for LDH level is 95% (excellent test). As the accuracy level is 95%, this test can be effectively used to differentiate asphyxiated neonate from non-asphyxiated term neonates even when antenatal birth records are not available, if they present within 24 hours of delivery. Serum LDH level was progressively high in relation to stages of HIE, as evidenced by 'p' value < 0.001. This result is similar to a study done by Karunatilaka D.H. et al.[11] who showed serum LDH increases with increasing severity of Encephalopathy.

Among 90 cases with perinatal asphyxia, 13 (14.44%) neonates expired during hospital stay, all of them were from HIE III which accounted for 44.8% cases of HIE III. 10 (11.11%)cases of perinatal asphyxia went on leave against medical advice. 67 (74.44%) neonates having asphyxia survived and were discharged. Mortality was lower in our study as compared to studies done by Kanik E et al.[12] (26.4%), Agarwal J et al.[13] (26.66%), and Simovic AM et al.[14] (23.63%). Difference in incidence of mortality is explained by the fact that their study group had higher percentage of cases with moderate to severe asphyxia (78.33%) as compared to present study (66.66%). Mean serum LDH

level in the neonates survived was statistically significant (1416.08 ±1602.16 U/L), as compared to expired (2121.23 ± 1985.12 U/L). This difference suggests that high serum LDH level can predict neonatal mortality during hospital stay in neonates with perinatal asphyxia.

CONCLUSION

Serum LDH level is a reliable indicator of perinatal asphyxia and helps to differentiate asphyxiated neonate from non asphyxiated neonate. It has prognostic role and can predict mortality and morbidity in neonates with perinatal asphyxia. The results could be of utility to pediatricians in referral hospitals, who receive sick neonates, without antenatal records. LDH could be used to diagnose asphyxia retrospectively in such cases.

LIMITATIONS OF THE STUDY

Utility of this study in preterm babies and small for gestational age is not known as they were excluded. Serum LDH level was collected within 24 hours of life in neonates with asphyxia, which could explain higher value of standard deviation from mean in our results. Other markers of myocardial dysfunction were not assessed, which would have strengthen our result. As this study was done in single center with a small sample size, a multicenter study with a larger population size is required for further validation.

CONFLICT OF INTEREST

None declared.

FINANCIAL DISCLOSURE

None

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