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ORIGINAL ARTICLE

Diagnostic Accuracy of Lactate Dehydrogenase for Diagnosis of Birth Asphyxia in Preterm Neonates

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ABSTRACT

Background: Birth asphyxia remains a major cause of neonatal morbidity and mortality, particularly in preterm infants. Serum lactate dehydrogenase (LDH) has been identified as a potential biochemical marker for early detection of hypoxic-ischemic injury. Elevated LDH levels within the first six hours of life have been shown to predict the development of hypoxic-ischemic encephalopathy (HIE) within 6–72 hours after birth.

Objective: To determine the diagnostic accuracy of serum LDH for the diagnosis of birth asphyxia in preterm neonates, using arterial blood gas (ABG) acidosis as the gold standard.

Methods: The study protocol was approved after which the cross-sectional validation study was carried out in the Department of Pediatrics, Jinnah Hospital, Lahore, in a duration of six months from June 2017 to November 2017. Immediately after delivery of the placenta blood samples were taken under aseptic conditions to determine the level of serum LDH. Afterwards, blood samples taken in the arteries were measured to assess pH and base excess. Neonates were identified as positive or negative birth asphyxia according to pre-determined LDH and ABG results. Parameters of diagnostic accuracy such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were computed.

Results: Among 320 preterm neonates, the diagnostic accuracy of LDH for identifying birth asphyxia was 76.56%, with a sensitivity of 80%, specificity of 70.83%, PPV of 82.05%, and NPV of 68%.

Conclusion: Serum LDH demonstrates good diagnostic performance for early detection of birth asphyxia in preterm neonates. It can serve as a reliable, cost-effective, and less invasive complement to conventional diagnostic tools such as ABG analysis.

Keywords: Lactate dehydrogenase, Birth asphyxia, Preterm neonates, Arterial blood gases, Acidosis

INTRODUCTION

In the world, birth asphyxia is one of the primary contributors to neonatal morbidity and mortality, especially in developing nations, where the lack of perinatal surveillance and insufficient care provided to children are significant issues.[1] It is approximated that approximately one million annual birth-related hypoxia-related neonatal deaths are caused by intrapartum factors, and most survivors experience long-term neurological consequences, such as cerebral palsy, epilepsy, and developmental delay (World Health Organization [WHO].[2] The disorder is caused by deficient gas exchange that causes hypoxemia, hypercapnia and metabolic acidosis that collectively cause malfunctioning of various organs and hypoxic-ischemic encephalopathy (HIE).[3] It is thus essential that the asphyxia is diagnosed earlier and precisely to provide the timely interventions that are likely to minimize the irrelevant neurological damage and enhance the survival rates.

Historically, the clinical determinants of the diagnosis of birth asphyxia included low Apgar levels, abnormal fetal heart rate monitoring, the presence of meconium in the amniotic fluid, and requirement of a prolonged resuscitation of the newborn.[4] These parameters, however, are not sensitive and specific enough especially in preterm babies who can have low Apgar scores not because of hypoxia but because of immaturity.[5] The analysis of arterial blood gases (ABG) analysis is the gold standard of determining the presence of metabolic acidosis (pH < 7.0, base deficit > 12 mmol/L) (American Academy of Pediatrics [AAP].[6] However, ABG sampling is invasive, technically demanding and might not be available in all resources-restricted or emergency environments. This has elicited growing interest in the possibility of identifying biochemical indicators that are least invasive, cost-effective and can accurately indicate the extent of hypoxic injury.

Serum lactate dehydrogenase (LDH) is one of the suggested biomarkers that have attracted a lot of interest because it is highly correlated with cellular damage and tissue hypoxia.[7] LDH is a cellular protein found in almost all tissues, which supports the transformation of pyruvate into lactate in the process of anaerobic glycolysis.[8] Hypoxic or ischemic conditions result in cell membrane breakdown that causes LDH to be released into the blood. High LDH levels are thus used as an indirect measure of cellular injury in vital organs including the brain, heart, and liver.[9] Previous studies have demonstrated that high serum LDH levels in the first six hours of life correlate with subsequent development of HIE at 6-72 hours of life.[10, 11]

Despite the fact that earlier researchers have primarily focused on infants in the term period, minimal evidence has been discovered to assess the accuracy of LDH in diagnosing preterm babies. Premature babies are a more susceptible group since they are more susceptible to hypoxic injuries due to their underdeveloped compensatory and metabolic systems.[12] Moreover, even the old modes of diagnosing such as ABG or neuroimaging may not be practical or fast in such delicate patients. A good biochemical surrogate such as LDH can thus be an efficient way of identifying at-risk neonates early enough, and taking up neuroprotective measures such as therapeutic hypothermia.[13]

It has been inconsistent among studies regarding the diagnostic effectiveness of LDH to detect cases of birth asphyxia. A study conducted by Bose et al. (2018) reported the sensitivity of 62.5% and specificity of 94.1% as examples, and another study reported the sensitivity of 100% and the specificity of 97%.[14, 15] It is possible to attribute these differences to the difference in study design, population and the threshold values used to define LDH positivity. Also, no large-scale validation study involving Pakistan was reported to validate LDH as a diagnostic bio-marker of birth asphyxia in pre-term babies. This is a severe gap in knowledge, because the local epidemiological features, such as a high rate of preterm births, maternal anemia, and inadequate intrapartum care may define the prevalence of the disease and the biomarker activity.[16]

In this respect, the present study was conducted to ascertain the diagnostic usefulness of serum LDH to diagnose birth asphyxia in preterm infants by using acidosis of the arterial blood gas to be used as a gold standard. The purpose of the study by determining sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was to answer the question whether LDH would be a good alternative as a non-invasive, reliable, and cost effective diagnosis compared to its traditional forms. It is suggested that the findings of the current research would be of invaluable contribution to the body of neonatal care in low-resource settings and would allow integrating LDH testing into the clinical

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guidelines to make sure that the perinatal asphyxia is diagnosed and treated accordingly.

MATERIALS AND METHODS

It was a cross-sectional validation study, done in the Department of Pediatrics, Jinnah Hospital, Lahore, and over a six months period (June 2017 to November 2017) after the study protocol was approved. The purpose of the study was to determine the diagnostic accuracy of serum lactate dehydrogenase (LDH) in the detection of asphyxia at birth in preterm infants associated with arterial blood gas (ABG) acidosis as the gold standard. With the frequency of birth asphyxia of 47.7, the LDH sensitivity of 62.5% (margin of error of 8%), and specificity of 94.1% (margin of error of 3%), a sample of 320 neonates was calculated at the 95% confidence level. The sampling method used was non-probability consecutive sampling.

The study was limited to non-premature babies of all genders that had a gestational age of 32 to 37 weeks (documented on the antenatal record of the mother) and a birth weight of less than 2000 grams. Infants who were determined to be at risk of birth asphyxia were included only. Neonates were not included in the case when they had some congenital malformations, maternal diabetes (defined as blood sugar random >186 mg/dL), blood group incompatibility, or very low birth weight (<1500 grams), as reported in the medical record.

The Emergency Department of Pediatrics, Jinnah Hospital, Lahore recruited 320 neonates who fit the inclusion criteria. Demographic data such as name, gender, gestational age, and weight at birth were documented after informed consent of parents or guardians were obtained. A 3cc of blood under aseptic conditions was drawn out of a trained staff nurse immediately after placental delivery using a BD syringe. The samples were properly stored and carried to the Pathology Laboratory of the hospital to examine serum LDH. The neonates were categorized as LDH positive and negative based on the operational definitions used in the study depending on the results of the lab. This was then succeeded by an arterial blood sample cooked with a 3cc BD syringe under aseptic conditions in order to establish the values of pH and base excess. These samples were also investigated by the Pathology Laboratory and classified the neonates as positive or negative to birth asphyxia based on the ABG acidosis criteria. All the data were captured in a well structured proforma, which was designed to carry out the study.

Data was analyzed with the use of SPSS 20. Quantitative variables (gestational age, birth weight, LDH levels, and qualitative variables (gender and asphyxia, according to LDH and ABG) were presented in the form of the mean and standard deviation (SD) and frequencies and percentages, respectively. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the overall diagnostic performance of the LDH were computed through a 2x2 contingency table using the ABG acidosis as the gold standard. Gender, gestational age and birth weight were also used to stratify data to adjust potential confounders. After stratification, 2x2 tables were created again to evaluate the diagnostic performance of LDH in each of the subgroups.

RESULTS

This study involved 320 preterm babies to examine diagnostic validity of serum lactate dehydrogenase (LDH) in initial diagnosis of birth asphyxia, considered to be arterial blood gas (ABG) acidosis as gold standard. The average weight of the infants at birth was 1490.62/264.04g; minimum weight of the newborn was 1003g and maximum weight was 1950g (Table 1).

The sample size used in this study was an equal mixture of male and female neonates where 50% were males and 50% were females (Figure 1). The average gestational age was 34.42, with the spread of 32-37 weeks (Table 2).

The mean LDH level among neonates was 4.92 ± 2.25 mmol/L, with a range of 2–9 mmol/L. Based on LDH findings, birth asphyxia was diagnosed in 195 neonates (60.9%) (Table 3).

According to ABG analysis, birth asphyxia was detected in 200 neonates (62.5%), while 120 neonates (37.5%) were classified as non-asphyxiated (Table 4).

Comparing LDH results to ABG acidosis (gold standard), sensors of LDH to detect birth asphyxia in preterm babies were 80 and 70.83, respectively. The positive predictive value (PPV) was 82.05 and the negative predictive value (NPV) was 68 and the overall diagnostic accuracy was 76.56 (Table 5).

Subgroup analyses revealed that there was a difference in LDH diagnostic performance based on birth weight, sex, and gestational age. The sensitivity and specificity of neonates with weights of 10001300 g were 71.43 and 73.33, respectively. The sensitivity and specificity of those with a weight between 1301 and 1600 g was 83.12% and 72.73% respectively, and with those with a weight between 1601 and 1950 g sensitivity and specificity were 82.43% and 67.92% respectively (Table 6).

Gender-based stratification showed that male neonates had slightly higher diagnostic accuracy, with sensitivity and specificity of 84.38% and 73.44%, compared to 75.96% and 67.86% among female neonates (Table 7).

Gestational age stratification revealed comparable accuracy: neonates aged 32–34 weeks demonstrated a sensitivity of 79.44% and specificity of 67.24%, whereas those aged 35–37 weeks showed sensitivity and specificity of 80.65% and 74.19%, respectively (Table 8).

These findings collectively suggest that serum LDH demonstrates good diagnostic potential for identifying birth asphyxia in preterm neonates, with particularly robust sensitivity across all subgroups.

Table 1. Birth Weight of Neonates (n = 320)

Variable	Mean (g)	SD	Min	Max
Birth weight (g)	1490.62	264.04	1003	1950

Table 2. Gender Distribution of Neonates

Gender	Frequency	Percentage
Male	160	50%
Female	160	50%

Table 2. Gestational Age of Neonates (n = 320)

Variable	Mean (weeks)	SD	Min	Max
Gestational Age	34.42	1.68	32	37

Table 3. LDH Levels and Birth Asphyxia by LDH Findings

Birth Asphyxia (by LDH)	Frequency	Percentage
Positive	195	60.9%
Negative	125	39.1%

Table 4. ABG Findings and Birth Asphyxia Diagnosis

Birth Asphyxia (by ABG)	Frequency	Percentage
Positive	200	62.5%
Negative	120	37.5%

Table 5. Diagnostic Accuracy of LDH for Birth Asphyxia (n = 320)

LDH (Birth Asphyxia)	ABG Positive	ABG Negative	Total
Positive	160 (80%)	35 (29.2%)	195
Negative	40 (20%)	85 (70.8%)	125
Total	200	120	320

Sensitivity: 80%, Specificity: 70.83%, PPV: 82.05%, NPV: 68%, Diagnostic Accuracy: 76.56%

Table 6. Diagnostic Accuracy Stratified by Birth Weight

Weight (g)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	DA (%)
1000–1300	71.4	73.3	74.5	70.2	72.3
1301–1600	83.1	72.7	91.4	55.2	80.8
1601–1950	82.4	67.9	78.2	73.5	76.4

Table 7. Diagnostic Accuracy Stratified by Gender

Gender	Sens (%)	Spec (%)	PPV (%)	NPV (%)	DA (%)
Male	84.4	73.4	82.7	75.8	80.0
Female	76.0	67.9	81.4	60.3	73.1

Table 8. Diagnostic Accuracy Stratified by Gestational Age

Gestational Age (weeks)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	DA (%)
32–34	79.4	67.2	81.7	63.9	75.2
35–37	80.7	74.2	82.4	71.9	78.1

Figure: 1

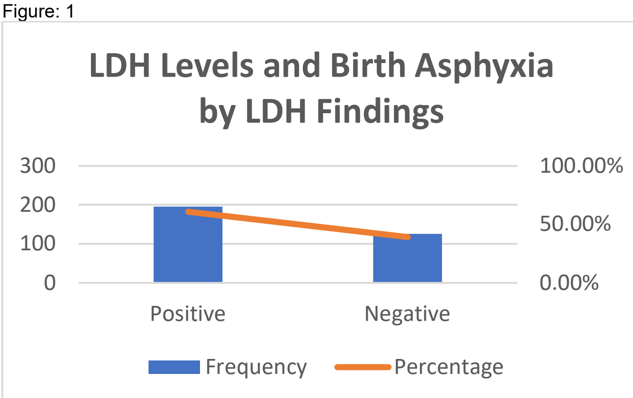
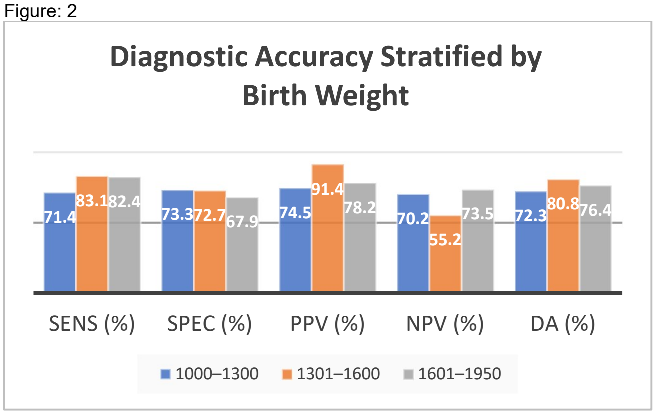


Figure: 2



DISCUSSION

Birth asphyxia is a worldwide clinical issue with a considerable prevalence, especially among low- and middle-income groups, where it is the cause of a large fraction of neonatal mortality and neurodevelopmental disability.[17, 18] In spite of improvements in perinatal care, the diagnosis during the early stage is still difficult because of the limitation of clinical signs including Apgar scoring and invasiveness of arterial blood gas (ABG).[19] Therefore, the necessity of finding a quick, cost-effective, and reliable biochemical biomarker cannot be disregarded.

In this present study serum lactate dehydrogenase (LDH) has a diagnostic accuracy of 76.56, a sensitivity of 80 and a specificity of 70.83 which demonstrated that it has a massive potential in diagnosing birth asphyxia among preterm infants. These findings are similar to those reported by Patra et al. (2018) and Shylaja et al. (2019), who reported sensitivities and specificities of more than 88% with LDH in the identification of hypoxic-ischemic injury.[14, 15] Similarly, the usefulness of LDH as an initial biochemical indicator that is correlated with hypoxia severity and likelihood of hypoxia-ischemia encephalopathy (HIE) has been validated.[16, 17]

Such a relative lower specificity in our cohort may be explained by the differences in gestational age, time and cutoff levels used in other studies. Our study had an average gestational period of 34.4 weeks and birth weight of 1490 g, with this falling in the relatively vulnerable category of preterm infants. The metabolic processes are immature in these children, and the potential of tissue perfusion may be less developed, which may result in high LDH even under mild hypoxic stress and, consequently, a lack of specificity.[20] Nevertheless, other studies, such as Masaraddi et al. (2021) and Beken et al. (2015), reported variable predictive performance, which shows the need to use population-specific reference ranges and uniform assay protocols.[18, 19]

LDH is an intracellular enzyme that is ubiquitous and biochemically present in all tissues and is discharged in the bloodstream when the cell is injured or where there is a lack of oxygen. Its rise in the immediate postnatal period is a sign of multisystem cellular dysfunction of hypoxia and ischemia.[9] LDH levels have been associated with early detection, as well as predicting neurological and requiring neuroprotective treatment modalities, such as therapeutic hypothermia.[17] Furthermore, real-time monitoring of LDH may provide data on the frequency and severity of the hypoxic insult, which has great clinical and medicolegally significant importance.[8]

The results of the current experiment can be particularly applied to the resource-strained clinical setting where usage of the advanced neuroimaging and constant ABG are limited. In that, LDH testing is inexpensive, rapid and available and, therefore, renders it an appealing tool to carry out early screening of high-risk infants. The complex of LDH and other biochemical and clinical indicators can significantly contribute to the accuracy of the diagnosis and the possibility of early choosing neuroprotective measures.

Nevertheless, this paper admits some shortcomings. First, the study is a single-center study, and therefore the results might not be applicable to larger populations. Second, non-hypoxic factors, including prematurity, sepsis, or hemolysis, can affect LDH levels, which can affect diagnostic performance. Subsequent multicentric, longitudinal research using serial LDH levels and various biomarker sets (e.g., S100B, NSE, GFAP) should be justified to determine standardized cutoffs and enhance prognostic value.[7,10]

CONCLUSION

The current research showed that serum LDH is highly diagnostic in the detection of birth asphyxia among preterm babies relative to arterial blood gas acidosis as the gold standard. This high sensitivity and specificity of the enzyme underscores its possible use as a fast, cheap, and noninvasive biomarker of early hypoxic-ischemic damage detection. Since it is biochemically related to cellular hypoxia, LDH during the immediate postnatal period can serve as a supplement to standard diagnostic measures and initiate timely therapeutic measures including hypothermia. Neonatal screening LDH could improve the first-line diagnosis, decrease the morbidity and positively impact the long-term neurological outcomes, particularly in low-resource clinical institutions. The LDH thresholds should be standardized with further multicenter studies to confirm its predictive nature in different populations.

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