

Cord Blood Lactate Levels as Marker for Perinatal Hypoxia and Predictor for Hypoxic Ischemic Encephalopathy

Ashish Kumar Simalti, Vandana Negi¹, Anil Kumar², Suman Kumar Pramanik³

Department of Pediatrics, Army Hospital Research and Referral, New Delhi, ^{1,2}Department of Pediatrics Base Hospital, Delhi, ³Department of Hematology, Army Hospital Research and Referral, New Delhi, India

Abstract

Introduction: This study was conducted to find if cord blood lactate correlates well with Apgar score and umbilical cord blood pH and subsequent development of hypoxic ischemic encephalopathy (HIE). **Materials and Methods:** It was a cross sectional, observational study which was conducted at a tertiary care referral center of North India from June 2018 to June 2019. Monitoring of cord blood lactate levels along with Apgar and cord blood pH was done for correlation of cord blood lactate with Apgar, cord blood pH, and subsequently development of HIE. **Results:** During the study period, 115 term neonates got enrolled based on inclusion criteria. Out of these, 83 babies had some degree of HIE based on Sarnat staging. Among these 83 neonates with encephalopathy, 36 had Stage III HIE while, 28 and 19 babies had Stage II and Stage I encephalopathy, respectively. Lactate levels correlated negatively with Apgar score and umbilical cord blood pH and higher levels of lactate correlated well with lower Apgar and cord blood pH. The mean lactate level was significantly higher in cases with HIE (5.18 mmol/L) as compared to cases without HIE (2.91 mmol/L). **Conclusion:** Our study shows that cord blood lactate can be used as a predictor for perinatal hypoxia. With the availability of cheaper handheld lactate monitors, lactate monitoring may become more practical option and need to be explored.

Keywords: Cord blood lactate levels, Apgar score, Cord blood pH, perinatal asphyxia, Hypoxic Ischemic Encephalopathy

INTRODUCTION

Cerebral injury during the perinatal period is a preventable cause of long-term neurological morbidity. The incidence of hypoxic ischemic encephalopathy (HIE) is estimated to be 1–4/1000 live births.^[1] Significant proportion of neonates with HIE Stage III does not survive neonatal period, while 25%–60% of babies develop permanent disabilities such as cerebral palsy (CP), learning disabilities, mental retardation, and seizures.^[2] National Neonatal Perinatal Database reported that perinatal asphyxia was the most common cause of stillbirth in India, accounting for 45.1% of all such cases.^[3] It is important to be able to identify these neonates as soon as possible during or after birth as early assessment of the severity secondary to hypoxic ischemic injury may assist in making objective preventive or therapeutic decisions. Five-minutes Apgar scoring and cord blood pH are well-established markers for perinatal asphyxia. In view of their nonspecificity, biochemical indicators may be better than the clinical scoring system such as Apgar and cord blood pH.^[4] Serum lactate levels have been

one of the earliest biochemical markers correlating with brain hypoxia as lactate accumulates in hypoxic cell because of anaerobic metabolism.^[5] There are not many Indian studies correlating cord blood lactate levels with these two markers and this study was conducted to find the correlation between cord blood lactate levels, umbilical cord blood pH, Apgar score, and subsequent development of HIE.

MATERIALS AND METHODS

It was an observational, cross-sectional study conducted during one calendar year (June 2018–June 2019) including term neonates with suspicion of perinatal hypoxia. Apgar score <7 at 1 min of life, term newborns with normal respiration not established at 1 min after birth, and term newborn requiring resuscitative measures were included in

Address for correspondence: Dr. Vandana Negi,
Department of Pediatrics, Army Hospital (Research and Referral),
New Delhi - 110 010, India.
E-mail: vandipgi@gmail.com

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the study. While preterm, intrauterine growth restriction, or neonates with severe congenital malformations, chromosomal abnormalities and Rh incompatibility were excluded from this study. History of antenatal drug addiction or babies born to mothers who received magnesium sulfate 4 h before delivery was also excluded from the study. Ethical clearance was obtained from hospital ethical committee (IEC BHDC/26 of 2017) and informed consent was taken from mothers. One milliliter of blood was collected in heparinized syringe from doubly clamped segment of umbilical cord for arterial blood gas analysis (Autoanalyzer, Phox Ultra) to measure pH and lactate levels for all term babies born with asphyxia. All these newborns were then shifted to neonatal intensive care unit after resuscitation for further monitoring, screening, and staging of HIE as per Sarnat and Sarnat staging system. The quantitative data were expressed as mean \pm standard deviation categorical and nominal data were written in percentage. T for quantitative data *t*-test was used. Nonparametric data were analyzed by Mann–Whitney U-test and categorical data were analyzed using Chi-square test. Pearson correlation coefficient was used to compute correlation between lactate and cord blood pH, 1 min Apgar score with severity of HIE. The significance threshold of *P* value was set at <0.05 . All analyses were carried out using SPSS software version 21.

RESULTS

During the study period, 115 term neonates got enrolled based on inclusion criteria. Out of these, 83 babies had some degree of HIE based on Sarnat staging. Among these 83 neonates with encephalopathy, 36 had Stage III HIE while 28 and 19 babies had Stage II and Stage I encephalopathy, respectively. Lactate levels correlated negatively with Apgar scores and cord blood pH and higher lactate levels correlated well lower Apgar and cord blood pH [Table 1]. Mean lactate level was significantly higher in cases with HIE (5.18 mmol/L) as compared to cases without HIE (2.91 mmol/L). Lactate levels were also correlated with HIE and there was significant positive correlation between levels of lactate levels and presence of HIE [Figure 1]. HIE cases were classified based on Sarnat staging stages of HIE and levels of lactate correlated well with each other [Table 2].

DISCUSSION

Timely prediction of HIE is important because a brief therapeutic window exists for neuroprotective interventions.^[6] While discussing HIE, it is also important to consider that other antepartum causes besides perinatal hypoxia may also lead to neurodevelopmental handicaps. Himmelmann *et al.*^[7] in a study published in 2005 found that acidosis at birth suggesting perinatal asphyxia was present only in 35% of cases of CP on prolonged follow-up while remaining 65% did not have evidence of perinatal hypoxia. We aimed to assess cord blood lactate levels as indicator of perinatal hypoxia and risk of HIE. We found that lactate levels correlated well with Apgar score and cord blood pH which are well known parameters of perinatal hypoxia. In our study, lactate levels correlated well

Table 1: Correlation of lactate with Apgar, cord blood pH, and hypoxic ischemic encephalopathy

Parameter 1	Parameter 2	Correlation coefficient	<i>P</i>
Lactate	Apgar	-0.838133	<0.05
	pH	-0.203622	<0.05
	HIE	0.933311	<0.05

HIE: Hypoxic ischemic encephalopathy

Table 2: Mean lactate level comparison with severity of asphyxia

Variables	Group	<i>n</i>	Mean	SD	<i>P</i>
Lactate levels (mmol/L)	No HIE	32	2.91	1.33	<0.01
	Stage I	19	4.22	1.41	
	Stage II	28	5.06	0.98	
	Stage III	36	5.78	1.04	

HIE: Hypoxic ischemic encephalopathy, SD: Standard deviation

with the development of HIE. Similar findings were reported by Wiberg *et al.*^[8] who demonstrated that cord blood lactate was similar to pH and base excess (BE) for predicting perinatal hypoxia in a large cohort study. They found lactate to be more specific as compared to umbilical cord blood pH, but it was also less sensitive marker for short-term outcome. To predict low Apgar score at 5 min, they found lactate levels to have low sensitivity with low positive predictive value but good specificity along with good negative predictive value. Allanson *et al.*^[9] in a retrospective data analysis of 38, 284 measurements found lactate more than 3.21 mmol/l, had 69.7% sensitivity and 93% specificity for neonatal morbidity. Tuuli *et al.*^[10] investigated if lactate could be used to predict pH value and found that lactate levels of 3.9 mmol/l were associated with pH of 7.25. Labrecque *et al.*^[11] in a similar study have found lactate levels of 4.9 mmol/l to be associated with cord blood pH of 7.20 with reasonable sensitivity of 82% and a good specificity of 90%. Instead of cord blood, Ramanah *et al.*^[12] used fetal scalp lactate to correlate with cord blood pH and Apgar scores. In their study, fetal scalp lactate level above 6.35 mmol/L was suitable for predicting hypoxia. Gjerris *et al.*^[13] in a large study involving 2554 singleton deliveries demonstrated that cord arterial lactate was better marker for fetal asphyxia compared to pH, but cutoff of lactate value in their study was significantly higher 8.2 mmol/L. On the other hand, Kruger *et al.*^[14] recommended lactate more than 4.8 mmol/l should be used as measure of fetal hypoxia. In our study, mean lactate level in cases with HIE was 5.18 mmol/L which is similar to the levels reported by Labrecque *et al.*^[11] Apgar is a well-established clinical scoring system for perinatal hypoxia and a low Apgar score persisting for 5 min implies high risk of HIE.^[15] Some studies have recorded Apgar score till 20 min after birth and found it to correlate with poor neurodevelopmental outcome.^[16] However, the American Academy of Pediatrics as well as American College of Obstetricians and Gynecologists have raised concerns against using Apgar score alone for defining birth asphyxia.^[17] Apgar is a semi-quantitative score

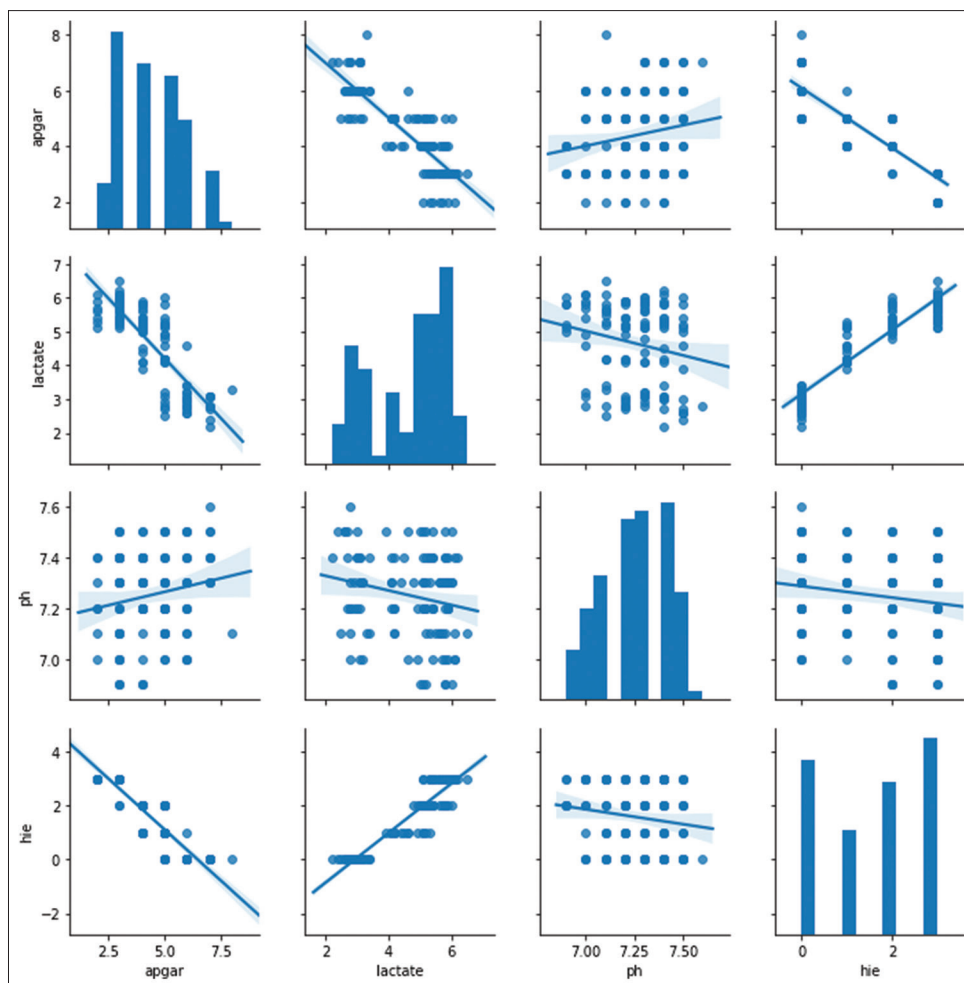


Figure 1: Correlation of lactate with Apgar, cord blood pH, and hypoxic ischemic encephalopathy

and involves subjectivity hence potential for intraobserver variability.^[18] Low Apgar score has been reported to have low specificity for intrapartum hypoxia and it is not considered a good predictor for subsequent neurological injury.^[19] Incidence of low Apgar score is much higher than the incidence of perinatal hypoxia.^[20] Apgar score does not add to decision-making regarding resuscitation and value of 5 min Apgar is more in retrospective in nature. Besides Apgar, monitoring cord blood pH at birth is another well-established parameter which is used for measuring perinatal acidosis.^[21] In a meta-analysis, acidic cord arterial pH has been consistently associated with a poor outcome. Malin *et al.* found^[22] strong correlation between a low arterial cord pH and neonatal morbidity in short term as well as long term in their systemic review. However, some researchers have raised concern about using cord blood pH as it cannot differentiate between prolonged or short-term insults to fetus. Ross and Gala^[23] and Goldaber *et al.*^[24] have sought to differentiate metabolic acidosis from respiratory acidosis and found that neonatal complications were common with metabolic acidosis. Since during early stages of inadequate perfusion, fetus develops hypoxemia along with hypercapnia, leading to respiratory acidosis where pH is low but BE remains unaltered. Metabolic acidosis develops later when metabolic

products of anaerobic metabolism accumulate. Using BE as indicator of metabolic acidosis can be inaccurate as it is not measured directly but calculated based on the pH, bicarbonate levels, PCO_2 value, and the hemoglobin levels. In view of this, it makes sense to directly measure lactate which is the product of anaerobic metabolism. Another benefit of using lactate as predictor for perinatal hypoxia is that now lactate levels can also be measured by a handheld meter which is cheaper, easier to maintain, and requires less amount of blood.^[25] We did not use this equipment in our study as the autoanalyzer we used could monitor pH as well as lactate simultaneously but in view of resource allocation in a developing country setup, it may be more practical to use handheld lactate monitors in place of more expensive autoanalyzers which require technical expertise and require high maintenance.^[26] Our study correlating lactate with cord blood pH, Apgar score, and later development of HIE in Indian setting is important from community health-care point of view. Theoretically, fetal lactate levels can be influenced by the maternal blood lactate but it has been shown that these account for insignificant component of fetal lactate measured at birth. Suidan *et al.*^[27] have demonstrated that maternal acid base balance does not influence cord blood lactate levels significantly.

CONCLUSION

Our study shows that cord blood lactate can be used as predictor for perinatal hypoxia and could be better marker for perinatal asphyxia than Apgar and cord blood pH. Former has limitation of subjectivity leading to interobserver bias and cord blood pH needs expensive autoanalyzer hence not suitable for universal monitoring in a developing country. With availability of cheaper handheld lactate monitors, lactate monitoring may become more practical option and need to be explored.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Vannucci RC. Hypoxic-ischemic encephalopathy. *Am J Perinatol* 2000;17:113-20.
- Naithani M, Simalti AK. Biochemical Markers in Perinatal Asphyxia. *J Nep Paedr Soc* 2011;31:151-6.
- Network NN. National Neonatal Perinatal Database–Report for the Year 2002–2003. New Delhi: NNF National Neonatal Perinatal Database Network; 2005. p. 1-58.
- Huang CC, Wang ST, Chang YC, Lin KP, Wu PL. Measurement of the urinary lactate: Creatinine ratio for the early identification of newborn infants at risk for hypoxic-ischemic encephalopathy. *N Engl J Med* 1999;341:328-35.
- Simalti AK, Joshi R, Aggarwal N, Agarwal M, Joshi RK. An unusual cause of persisting hyperlactatemia in a neonate undergoing open heart surgery. *World J Pediatr Congenit Heart Surg* 2015;6:130-4.
- Graham EM, Everett AD, Delpech JC, Northington FJ. Blood biomarkers for evaluation of perinatal encephalopathy: State of the art. *Curr Opin Pediatr* 2018;30:199-203.
- Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr* 2005;94:287-94.
- Wiberg N, Källén K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. *Acta Obstet Gynecol Scand* 2010;89:1263-9.
- Allanson ER, Waqar T, White C, Tunçalp Ö, Dickinson JE. Umbilical lactate as a measure of acidosis and predictor of neonatal risk: A systematic review. *BJOG* 2017;124:584-94.
- Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA, Cahill AG. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. *Obstet Gynecol* 2014;124:756-61.
- Labrecque L, Provençal M, Caqueret A, Wo BL, Bujold E, Larivière F, *et al.* Correlation of cord blood pH, base excess, and lactate concentration measured with a portable device for identifying fetal acidosis. *J Obstet Gynaecol Can* 2014;36:598-604.
- Ramanah R, Martin A, Riethmuller D, Maillet R, Schaal JP. Value of fetal scalp lactate sampling during labour: A comparative study with scalp pH. *Gynecol Obstet Fertil* 2005;33:107-12.
- Gjerris AC, Staer-Jensen J, Jørgensen JS, Bergholt T, Nickelsen C. Umbilical cord blood lactate: A valuable tool in the assessment of fetal metabolic acidosis. *Eur J Obstet Gynecol Reprod Biol* 2008;139:16-20.
- Kruger K, Hallberg B, Blennow M, Kublickas M, Westgren M. Predictive value of fetal scalp blood lactate concentration and pH as markers of neurologic disability. *Am J Obstet Gynecol* 1999;181:1072-8.
- Thorngren-Jerneck K, Herbst A. Low 5-minute Apgar score: A population-based register study of 1 million term births. *Obstet Gynecol* 2001;98:65-70.
- Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981;68:36-44.
- ACOG committee opinion. Use and abuse of the Apgar score. Number 174-July 1996 (replaces No. 49, November 1986). Committee on Obstetric Practice and American Academy of Pediatrics: Committee on Fetus and Newborn. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1996;54:303-5.
- O'Donnell CP, Kamlin CO, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute Apgar score. *J Pediatr* 2006;149:486-9.
- Buchmann EJ, Velaphi SC. Confidential enquiries into hypoxic ischaemic encephalopathy. *Best Pract Res Clin Obstet Gynaecol* 2009;23:357-68.
- Depp R. Perinatal asphyxia: Assessing its causal role and timing. *Semin Pediatr Neurol* 1995;2:3-6.
- Victory R, Penava D, da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. *Am J Obstet Gynecol* 2004;191:2021-8.
- Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: Systematic review and meta-analysis. *BMJ* 2010;340:c1471.
- Ross MG, Gala R. Use of umbilical artery base excess: Algorithm for the timing of hypoxic injury. *Am J Obstet Gynecol* 2002;187:1-9.
- Goldaber KG, Gilstrap LC 3rd, Leveno KJ, Dax JS, McIntire DD. Pathologic fetal acidemia. *Obstet Gynecol* 1991;78:1103-7.
- Karon BS, Scott R, Burritt MF, Santrach PJ. Comparison of lactate values between point-of-care and central laboratory analyzers. *Am J Clin Pathol* 2007;128:168-71.
- White CR, Doherty DA, Newnham JP, Pennell CE. The impact of introducing universal umbilical cord blood gas analysis and lactate measurement at delivery. *Aust N Z J Obstet Gynaecol* 2014;54:71-8.
- Suidan JS, Antoine C, Silverman F, Lustig ID, Wasserman JF, Young BK. Human maternal-fetal lactate relationships. *J Perinat Med* 1984;12:211-7.