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ORIGINAL ARTICLE

Serum lactate in asphyxic and non-asphyxic newborns: a historical cohort

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Abstract

Introduction: Perinatal asphyxia (AP) is the leading cause of death in the neonatal period and there is no consensus in the literature on its adequate diagnosis. Serum lactate is a promising laboratory marker and has been scarcely studied in the literature. **Objective:** To associate serum lactate level with the diagnosis of perinatal asphyxia. Methods: This is a descriptive study of a historical cohort performed through the analysis of medical records of newborns with gestational age greater than or equal to 34 weeks, who had lactate levels in the first 24 hours of life and were admitted to the neonatal intensive care unit of the Clinics Hospital of the Federal University of Goiás, from 2015 to 2018. We analyzed the serum lactate level with one hour of life and 24 hours of life. Statistical analysis was performed using SPSS v.20 software (SPSS Inc.; Chicago, IL). **Results:** The final sample consisted of 92 children, with a mean gestational age of 36.5 weeks, weight average of 2,746.7 grams, 52.2% male and 47.8% female. In children diagnosed with perinatal asphyxia, the serum lactate value in the first hour of life was significantly higher (p=0.003) compared to the non-asphyxiated group. At 24 hours of life there was a relative decrease in lactate value, but still remained higher in newborns with perinatal asphyxia. **Conclusion:** There was a strong association between increased serum lactate in the first hours of life and the diagnosis of perinatal asphyxia.

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INTRODUCTION

Perinatal asphyxia (PA) is the leading cause of death in term newborns, especially in developing countries, excluding congenital malformations[1,2]. Data from the World Health Organization (WHO) estimate that about four million children die per year before completing one year of life, with 90% of these deaths occurring in developing countries and, about 25% of these are caused by perinatal asphyxia[3,4].

In Brazil, there is little population data on perinatal asphyxia. Almeida et al. (2017)[2] evaluated causes of death in newborns (NBs) with birth weight ≥ 2500 grams in the first six days of life, and found 10,675 deaths from perinatal asphyxia, representing 40% of all Brazilian neonatal deaths among low-risk. Perinatal asphyxia is a sensitive measure of the quality of care provided in the perinatal period, both in the care of pregnant women and newborns, capable of preventing death and sequelae, through early diagnosis and treatment[5,6]. However, the lack of standardization for the diagnosis of PA makes it difficult to intervene in a timely manner, in addition to making methodological comparisons between different studies difficult[7].

The diagnosis of PA is currently based on the recognition of the hypoxic-ischemic event and the demonstration of the provoked injury, through clinical evaluation and complementary exams[8,9]. Clinical evaluation, in addition to being subjective, is not always early, delaying the diagnosis of PA. Workup can be hampered by methods such as electroencephalographic recordings[10], which are not always accessible to all neonatal care units, so that biochemical markers could help, in a simpler way, in the early recognition of PA.

Progressive hypoxia is detected by the carotid artery chemoreceptors, leading to direct blood flow to vital organs such as the brain, heart and adrenals[11-14]. With the persistence of hypoxia, the organs are forced to use their reserves of glycogen to generate energy. This reserve is limited and as the hypoxic-ischemic event progresses, energy production is maintained through the anaerobic pathway, increasing lactate release, reducing systemic pH, closing the feedback loop of tissue asphyxia[15-17].

As there is no consensus in the literature on the diagnosis of PA, it is speculated that biochemical markers may be useful. Among the possible biochemical markers, lactate, due to its association with metabolic acidosis and increased production in situations of low tissue perfusion, can help in screening for recognition of NBs with PA and tissue injury. Although the use of lactate in hypoxia is already well established in pediatric patients, few studies demonstrate its use in Neonatology[18,19].

In this context, the authors evaluated the level of serum lactate in asphyxiating and non-asphyxiating newborns in the first 24 hours of life at the Neonatology Service of the Federal University of Goiás University Hospital.

MATERIALS AND METHODS

This is a descriptive historical cohort study carried out at the Federal University of Goiás University Hospital (HC/UFG/EBSERH), between January 1, 2015, and December 31, 2018, in newborns admitted to our Neonatal Intensive Care Unit (NICU). For this study, a convenience sample was used in newborns who had a gestational age at birth ≥ 34 weeks. Gestational age was determined by first trimester obstetric ultrasound or, if unavailable, last menstrual period confirmed by the New Ballard score. From this population, two groups of neonates were defined: asphyxia and non-asphyxia.

The definition criterion for asphyxia adopted for this study was the presence of at least three of the following criteria: 1) five-minute Apgar score less than or equal to five and/or need for neonatal resuscitation in the delivery room; 2) presence of acidemia evidenced in cord blood gas analysis or arterial blood gas analysis performed until the end of the first hour of life with pH < 7.10 and/or base deficit ≥ 12 mmol/L; 3) signs of hypoxic-ischemic encephalopathy according to the modified Sarnat and Sarnat criteria; 4) multiple organ dysfunction screened in the following organs: liver, kidneys, bone marrow, heart and neuroendocrine system. Exclusion criteria were congenital malformations, chromosomal disorders, inborn errors of metabolism, congenital infections (syphilis, toxoplasmosis, herpes, cytomegalovirus, rubella and Zika virus infection) and lack of data in the medical records.

Serum lactate, at HC/UFG/EBSERH, is routinely collected for all newborns, together with an arterial blood gas sample in a volume of 0.5 ml of peripheral arterial blood, in a heparinized syringe, and the sample is immediately processed in the laboratory of hospital center by the COBAS B 221 ROCHE equipment.

To define system dysfunction, the serum dosage of the following enzymes is routinely used in the hospital: transaminases (aspartate aminotransferase/glutamic-oxaloacetic transaminase and alanine aminotransferase/glutamic-pyruvic transaminase), creatine kinase isoenzyme MB (CK-MB), total creatine kinase (CK), troponin, in addition to renal function (urea and creatinine), electrolytes, coagulogram, blood count, and isolated urine sodium sample to complement the diagnosis of syndrome of inappropriate antidiuretic hormone secretion.

The project was approved by the Research Ethics Committee (CEP) (CAAE: 98573018.0.0000.5078) of the UFG University, respecting the Regulatory Guidelines and Norms for Research in Human Beings established in Resolution 196/96 of the National Health Council/Ministry of health.

Continuous variables were expressed as absolute and relative frequencies, in addition to means and standard deviations. Means were compared using Student's t test, when symmetrically distributed, and Mann Whitney test. To assess the normality of data distribution, the Kolmogorov-Smirnov test was used. Pearson's Chi-Square test was used to compare independent categorical variables with each other and, when the criteria of this test were not met, we used the Fisher's exact test. The value of $p < 0.05$ was considered as the threshold value for statistical significance. After determining the incidence of lactate in each cohort, we calculated the relative risk (RR) between them. To process the data and analyze it, we used the Microsoft Excel software version 2015 and Statistical Package for the Social Sciences (SPSS®) 20.0 for MAC.

RESULTS

A total of 437 newborns were admitted to the NICU of HC/UFG/EBSERH during the study period, 92 of which met the inclusion criteria. Figure 1 represents the flow of patient choice.

Of the 92 patients selected, 19 were diagnosed with PA according to the institution's criteria. The cause of hospitalization of the other newborns was predominantly respiratory disorders specific to the neonatal period, mainly transient tachypnea of the newborn. The mean gestational age of newborns in this study was 36 weeks and 3 days of asphyxia was 38 weeks and of non-asphyxia 36 weeks and 1 day. The clinical and laboratory data of the two groups are shown in table 1.

Of the 19/92 (20.6%) asphyxia patients, 57.8% had altered lactate. Of the 73/92 (79.4%) of the non-asphyxiating patients, 17.8% had abnormal lactate (figure 2).

Serum lactate was significantly higher in the first hour of life (figure 3a) in newborns diagnosed with asphyxia in relation to non-asphyxiated patients ($p = 0.003$). The median lactate in asphyxiated neonates was 49 mg/dL and 25 mg/dL in non-asphyxia. The Relative Risk (RR) found was 3.25 (confidence interval: 1,259 – 8,393).

At the end of the first 24 hours of life there was a drop in serum lactate in almost all newborns (figure 3b). The median lactate in asphyxiated newborns was 35 mg/dL, while in those not asphyxiated, 16 mg/dL ($p = 0.009$). There is also less variability in the lactate values of non-asphyxiated newborns.

Among the 92 study participants, nine (9.8%) died, with the highest incidence among babies with PDA, corresponding to seven (77.7%) of the nine deaths. Among the asphyxiated group, the death rate was 36.8% against 2.7% in the non-asphyxiated ($p < 0.001$).

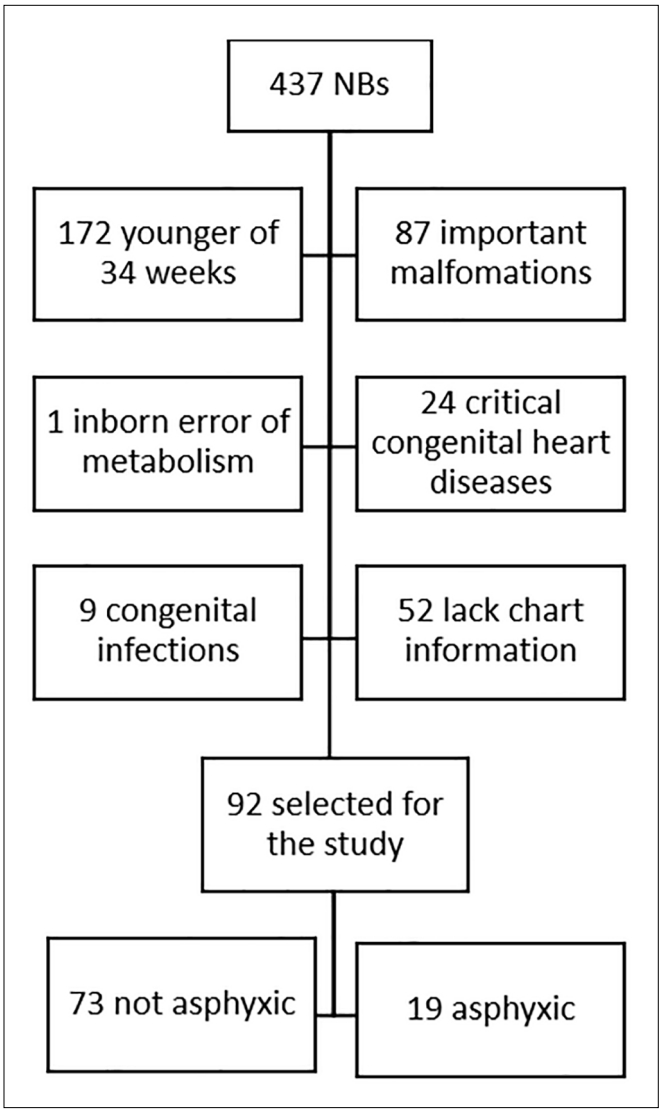


Figure 1. Patient selection flow diagram.

DISCUSSION

The present study showed a strong association between the increase in serum lactate and PA, especially in the first hour of life. Despite being a marker of hypoxia in other age groups, there are few current studies, like this one, evaluating the importance of lactate in aiding the diagnosis of PA[19,7].

Allanson et al. evaluated the measurement of lactate in umbilical cord blood to predict adverse events in NBs at risk for PA[19] and found high levels of lactate, similar to the present study, although with different methodologies.

Ericsen et al.[20] analyzed 16 newborns diagnosed with PA, who underwent therapeutic hypothermia (TH), and found mean lactate level of 102.6 mg/dL, mean levels even

Table 1. Clinical and laboratory data.

Clinical-laboratory data	Asphyxiated	Not asphyxiated	*p* value
	19 (20.7)	73 (79.3)	
Gestational ages, mean (SD), weeks	38.0 (2.1)	36.1 (1.9)	*p= 0.001*
Weight at birth (g), mean (SD), grams	3068.7 (640.8)	2662.9 (717.6)	*p= 0.20*
Males, n(%)	10 (52.6)	38 (52.0)	*p= 0.585*
Females, n(%)	9 (47.4)	35(48.0)	*p= 0.585*
5-minute Apgar, median (IIQ)	5 (4-6)	8 (8-9)	*p< 0.001*
OTI in delivery room, n(%)	18 (94.7)	6 (8.2)	*p* < 0.001
Neonatal resuscitation without OTI, n (%)	1 (5.3)	22 (30.1)	*p* < 0.001
Vaginal delivery, n (%)	10 (52.6)	6 (8.2)	*p* < 0.001
C-section delivery, n (%)	9 (47.4)	67 (91.8)	*p* < 0.001
Meconial amniotic fluid, n (%)	11 (57.9)	9 (12.3)	*p* < 0.001
Clinical seizure, n (%)	12 (63.2)	5 (6.8)	*p* < 0.001
Death, n (%)	7 (36.8)	2 (2.7)	*p* < 0.001
Therapeutic hypothermia, n (%)	7 (36.8)	0 (0)	*p* < 0.001
pH, median (IIQ)	7.24 (7.09-7.35)	7.32 (7.26-7.38)	*p* = 0.015
Bicarbonate, median (IIQ)	15.7 (10.3-18.8)	18.7 (16.7-20.6)	*p* = 0.006
Base deficit, median (IIQ)	12.8 (7.4-18.6)	7.2 (5.35-10.6)	*p* = 0.001
Lactate (mg/dL) in the first hour of life, median (IIQ)	49 (30-99)	25 (18-38)	*p* = 0.003
Lactate (mg/dL) at 24h of life, median (IIQ)	35 (23.5-47.3)	16 (14.5-27.5)	*p* = 0.009
GOT/AST (UI/L), median (IIQ)	101 (66-292)	53 (40-83)	*p* = 0.355
PGT/ALT (UI/L), median (IIQ)	61 (17-92)	15 (10-163)	*p* = 0.407
CK (UI/L), median (IIQ)	1799 (636.5-3090)	439 (323.5-1167)	*p* = 0.311
CK-MB (UI/L), median (IIQ)	270 (129.5-757)	98.5 (46-98.5)	*p* = 0.130
Troponin T (µg/L), median (IIQ)	0.03 (0.015-0.136)	0.036 (0.008-0.086)	*p* = 0.598

SD, standard deviation; IIQ, interquartile range; OTI, orotracheal intubation; GOT, glutamic-oxaloacetic transaminase; AST, aspartate aminotransferase; PGT Glutamate-Pyruvate Transaminase; ALT, alanine aminotransferase; CK-MB, creatine kinase isoenzyme MB; CK, creatine kinase; mg, milligram; dL, deciliter; IU/L, units per liter; µg/L, micrograms per liter.

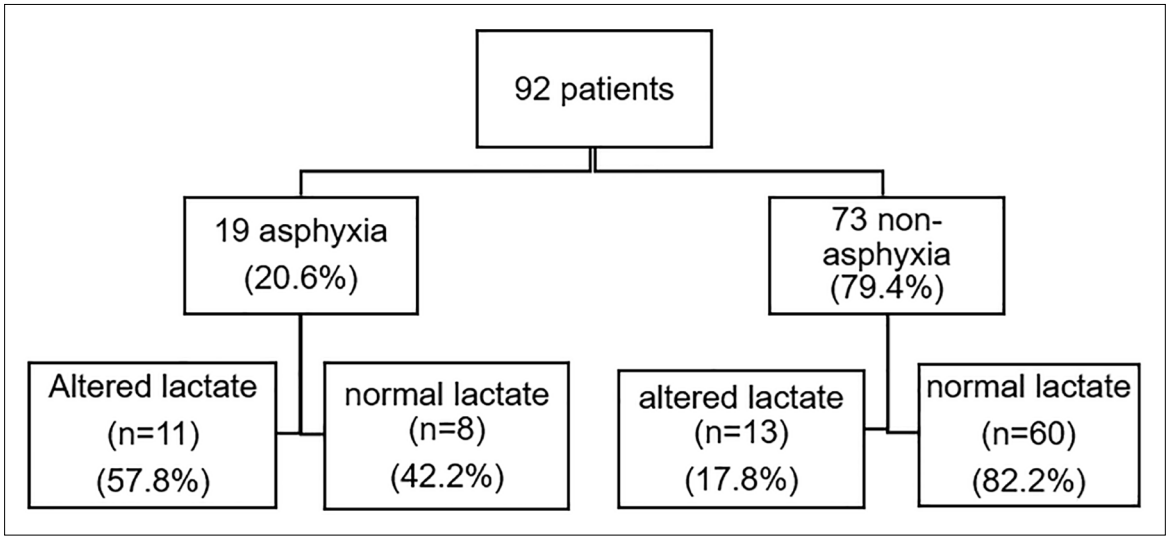


Figure 2. Flow diagram of participants selected for the study.

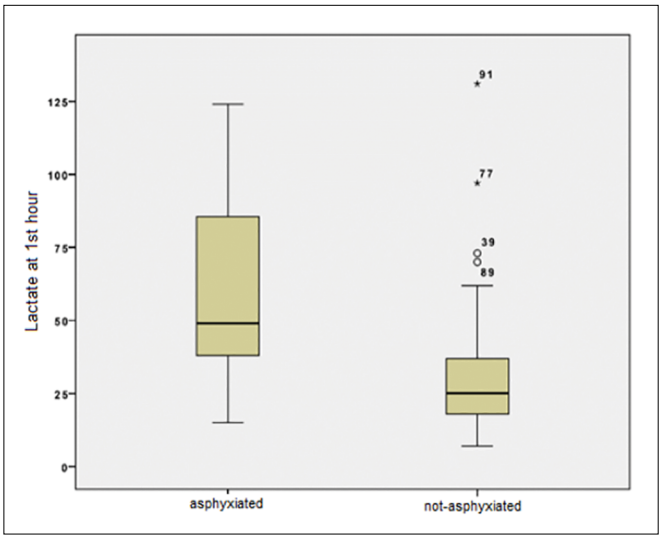


Figure 3a. Serum lactate level in the first hour of life.

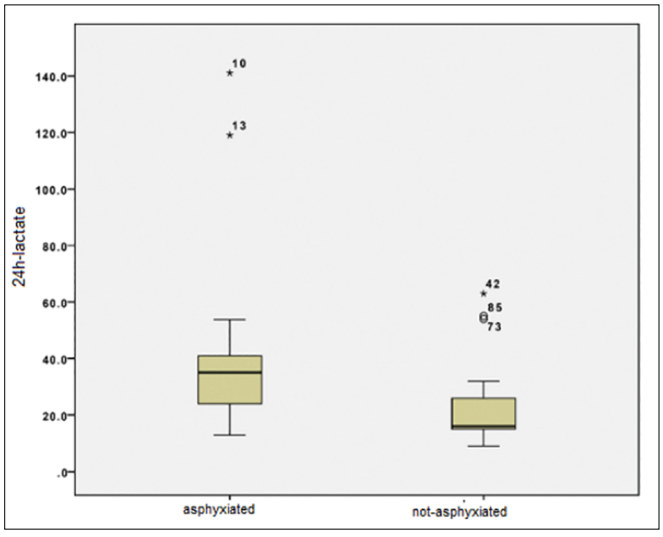


Figure 3b. Serum lactate level at 24 hours of life.

higher than that of the current study. However, Ericsen et al.[20] evaluated only newborns diagnosed with PA who underwent TH, that is, children with more severe asphyxia, who are already expected to have more metabolic acidosis and higher lactate values.

Our study demonstrated higher serum lactate levels in asphyxiating neonates in the first hour of life; however, even in defervescence, at 24 hours of life, asphyxiated NBs still persisted with significantly higher serum lactate levels (p = 0.009). The drop in lactate values was already expected, even in asphyxiated NBs, since the hypoxic-ischemic insult had been reversed. However, one of the patients, who maintained high lactate at 24 hours of life, was on TH, which could partially explain the increase in lactate. The other patient who maintained high lactate at 24 hours of life was also in the asphyxia group and died, demonstrating that lactate elevation seems to be related to more severe conditions. In the first hour of the study, in the group of NBs without PA, we observed a baby, in particular, who had the highest lactate value of the entire study who, although he did not conclude the diagnosis of PA according to the unit's criteria, he presented Meconium Aspiration Syndrome in a major hypoxemic event, which reinforces the limitation of current PA diagnostic criteria[21,22].

Orotracheal intubation in the delivery room, in NBs diagnosed with PA, was necessary in most cases, which can be justified given the pathophysiology and severity of the disease. Similar to Simovic et al.[7], who evaluated the need for neonatal resuscitation in PA and found 72.7% of asphyxiated babies needed resuscitation, our study also found a higher prevalence of neonatal resuscitation in babies with PA, demonstrating that asphyxiating babies need, more often, neonatal resuscitation.

Another data from this study that should be considered is the mode of delivery. Among all the patients in the study, cesarean delivery occurred in 82.6% since the study was carried out in a high-risk maternity hospital. However, cesarean section was more frequent in the delivery of those who were not asphyxiated, which can be explained by the fact that most deliveries are performed by cesarean section due to the high risk of pregnancies in the unit and that those who evolved with vaginal delivery were more associated with high-risk pregnancies that arrived in fetal distress but were already in the expulsive period. These data are also conflicting in the literature, Chiang et al.[23] found a greater number of vaginal deliveries among asphyxiated children, with neurodevelopmental delay, and a greater number of cesarean sections in those asphyxiated children, but without delay in neurological development. Abiramalatha et al.[24] also evaluated NBs with perinatal asphyxia and vaginal delivery was the most frequent delivery method among them. However, in the study by Simovic et al.[7], 100% of babies without perinatal asphyxia were born vaginally, and Chilinda et al.[25] found that in babies with lower lactate levels, vaginal delivery corresponded to 61.9% of all deliveries.

It is already well established in the literature that meconium amniotic fluid is a risk factor for perinatal asphyxia. Likewise, as demonstrated in the results of the current study, we found the same ratio of PA and meconium amniotic fluid[13,26].

The values of metabolic acidosis markers, such as pH, bicarbonate and base deficit, markers of acidosis, were significantly lower in babies with perinatal asphyxia. Likewise, Gamboa et al.[27] carried out a study to evaluate the correlation between pH, base deficit and lactate with

morbidity in newborns with acidosis and found that these markers, in principle, would have a correlation in predicting NBs at high risk for adverse events.

In this study, lactate, a product of acidotic reactions in the body, has shown to be a promising early marker of PA, since patients with increased lactate had an approximately three-fold increased risk of perinatal asphyxia, emphasizing the need for more similar studies.

The authors recognize the limitation of a historical cohort, due to the difficulty in working with data from medical records recorded and observed by third parties, if not absent, generating bias in the analysis and collection of data. Furthermore, the fact that the study was monocentric, with a small and non-probabilistic population sample, limited to high-risk pregnant women and newborns, the results may undergo changes due to sampling bias.

On the other hand, we cite as a strong point of this study the fact that it was carried out in a Neonatology Service of a teaching hospital, a reference in the Center-West region of Brazil, with well-defined diagnostic and management protocols for perinatal asphyxia, which homogenizes the processing of data.

The discussion about PA, nowadays, assumes a significant importance, since the understanding of this pathology provides a better approach and, consequently, better short and long-term prognosis for asphyxiated children.

The data obtained and discussed in this study will serve as a basis for conducting more robust, multicenter studies with the aim of validating the use of lactate in the diagnosis and prognosis of neonatal asphyxia.

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