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The correlation between plasma lactate concentrations and early neonatal mortality

Correlação entre a concentração de lactato plasmático e a mortalidade neonatal precoce

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ABSTRACT

Objective: To assess the correlation between plasma lactate concentrations in the first 6 hours of life and early neonatal mortality.

Methods: The patients were divided in 2 groups based on the cutoff point, obtained from a receiver operating characteristic (ROC) curve, of the plasma lactate concentration that best predicted neonatal mortality during the first 3 days of life. The differences between groups and the correlations between the investigated variables and the plasma lactate concentrations measured in the first 6 hours of life were analyzed using the Chi-square, Student's t, or Mann-Whitney tests and logistic regression.

Results: The best cutoff point of the plasma lactate concentration as determined by the ROC curve for death during the first 3 days of life was 4.2 mmol/L. The investigated groups differed with regards to the average birth weight, which was lower in the group with serum lactate levels > 4.2 mmol/L, and the match between birth weight and gestational age, where the group with serum lactate levels > 4.2 mmol/L exhibited a higher number of newborns small for their gestational age. Seizures, intracranial hemorrhage, and death during the first 3 days of life occurred more frequently in the group with serum lactate levels > 4.2 mmol/L.

Conclusion: In the investigated samples, the presence of plasma lactate concentrations > 4.2 mmol/L in the first 6 hours of life correlated with neonatal death during the first 3 days of life, a higher frequency of neurologic morbidity, and newborns that were small for their gestational age.

Keywords: Lactic acid; Asphyxia neonatorum; Neonatal mortality (Public Health)

INTRODUCTION

Due to the difficulty in establishing a simple, sensitive, and specific marker to predict the occurrence of neonatal death, researchers have developed scores such as Apgar,[1] Clinical Risk Index for Babies (CRIB),[2] Score for Neonatal Acute Physiology (SNAP), and Score for Neonatal Acute Physiology Perinatal Extension (SNAP-PE).[3,4] However, these scores do not fully accomplish their intended purposes.

Historically, plasma lactate measurements are used to assess early tissue injury before the appearance of specific clinical signs.[5-9] Although reports in the medical literature have attempted to correlate plasma lactate concentrations with the progression of newborns (NBs) to death,[10-12] the results were poor when the plasma lactate levels (PLLs) were measured during the first hours of life.

Therefore, the aim of the present study was to assess the correlation between plasma lactate concentrations measured in the arterial blood during the first 6 hours of life and neonatal mortality during the first 3 days of life.

METHODS

In this observational study using a historical cohort, the data were collected from the clinical records of all NBs admitted to a neonatal intensive care unit at Niterói County (RJ) (NICU) between June 2005 and February 2007. The patients transferred to other hospital units were excluded, as well as the NBs admitted after the age of 6 hours, those from whom arterial blood could not be harvested during the period of interest, and those with congenital malformations. The present study was approved by the Research Ethics Committee of the Faculty of Medicine of Fluminense Federal University/ Antônio Pedro University Hospital, number 026/07, Certification of Presentation of Ethical Assessment nº 0648.0.000.258-07. Informed consent was waived as blood sampling was a routine practice in the institution.

One milliliter of arterial blood was harvested by puncture or umbilical catheter within the first 6 hours of life at the time of admission to the neonatal intensive care unit (NICU). The samples were placed in vials with sodium fluoride and potassium oxalate, preserved in a cooled environment, and sent immediately for processing with the kit Lactate/Rolf Greiner BioChemica using the automatized device Selecta 1 (spectrophotometric method).[13,14]

The following antenatal and neonatal data described in the clinical records were investigated: prenatal alterations (centralization on obstetric ultrasound, oligohydramnios, pregnancy-induced hypertension), type of delivery, need for resuscitation, Apgar at 5 minutes,[1] gender, birth weight (BW), gestational age (GA; based on the Ballard score),[15] adequacy of fetal intrauterine growth according to Alexander,[16] CRIB score,[2] presence of intracranial hemorrhage (ICH),[17] seizures after blood sample collection to measure lactate,[18] persistent pulmonary hypertension (PPHNB),[19] and death during the first 3 days of life.

The NB were divided in 2 groups according to the plasma lactate concentration established as the cutoff point to predict death during the first 3 days of life using an ROC curve.

The qualitative variables were described as frequencies and analyzed using a Chi-square test with the Yates correction when needed. The quantitative variables were described as measures of central tendency and analyzed using a Student's t-test (variables with normal distribution) and Mann-Whitney test (variables without criteria of normality). Logistic regression analysis was performed with all the variables that exhibited a significant difference between the investigated groups. The level of significance was established at 5%, and the data were analyzed using the MedCalc 9.0.1 and Statistical Package for Social Science (SPSS) 16.0 software packages.

RESULTS

During the investigational period, 338 NBs were hospitalized, of whom 182 NBs were excluded (5 were transferred to other hospital units, 165 were admitted after the age of 6 hours, and 12 exhibited malformations). No NB in the excluded group died during hospitalization. A total of 156 NBs were therefore included, of whom 17 (10.9%) died, 9 (5.8%) died over the first 3 days, 3 (1.9%) died between the third and sixth days, and 5 (3.2%) died after the seventh day.

Analysis of the ROC curve showed that the PLL with the highest indexes of sensitivity and specificity for neonatal death during the first 3 days of life were > 4.2 mmol/L (sensitivity, 88.9%; specificity, 64.6%; positive predictive value, 13.3%; negative predictive value, 99%), whereas the area under the curve was 0.802 (confidence interval, CI: 0.731-0.862; Figure 1).
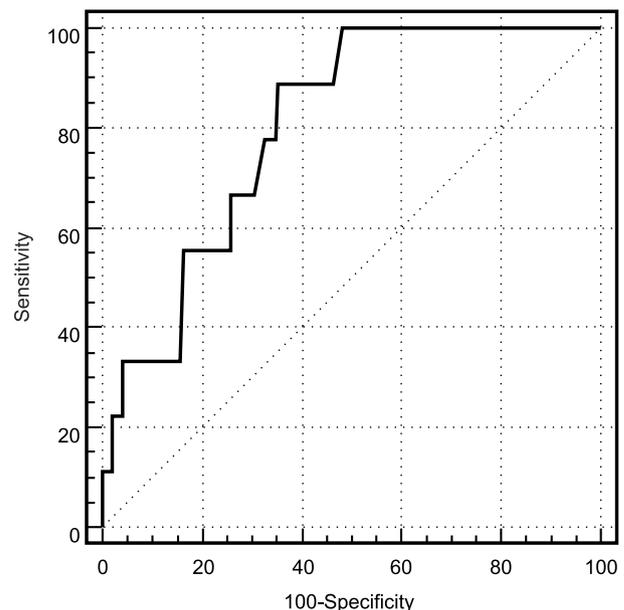

Figure 1 - The ROC curve for the correlation of blood lactate and neonatal death during the first 3 days of life.

Transfontanellar ultrasound (TFUS) was performed in 147 of the 156 NBs. Of the 9 patients in whom TFUS was not performed, 5 died (all during the first 3 days of life; 4 of these had PLL > 4.2 mmol/L), and 4 survived (one had PLL > 4.2 mmol/L).

An echocardiogram to diagnose PPHNB was performed in 154 out of the 156 NBs. Both NBs in whom echocardiogram was not performed had PLL ≤ 4.2 mmol/L; 1 died, and the other survived.

The number of NBs who died in the first 3 days of life was higher in the group with PLL > 4.2 mmol/L (Table 1).

The investigated groups exhibited significant differences with regards to the occurrence of seizures, ICH, and number

Table 1 - The characteristics of the newborns, prenatal period, and labor

	PLL > 4.2 mmol/L (N=60)	PLL ≤ 4.2 mmol/L (N=96)	p value	OR (CI)
NB data				
Gender				
Male	33 (55.0)	57 (59.4)	0.591	-
Female	27 (45.0)	39 (40.6)		
BW	1.835.92 ± 884.71 (1505.0)	2324.37 ± 914.58 (2.400.0)	0.001	-
GA	33.11 ± 4.06 (34.0)	34.32 ± 3.74 (35.0)	0.59	-
CRIB	5.60 ± 4.81 (5.5)	5.80 ± 4.88 (5.5)	0.858	-
BW matched to GA				
SGA	23 (38.3)	16 (16.7)	0.003	3.108 (1.472-6.564)
AGA	37 (61.7)	80 (83.3)		
Seizures				
Yes	7 (11.7)	1 (1.0)	0.019	12.530 (1.503-104.497)
No	53 (88.3)	95 (99.0)		
Death up to day 3				
Yes	8 (13.3)	1 (1.0)	0.013	14.576 (1.778-119.508)
No	52 (86.7)	95 (99.0)		
PPHNB	(N=60)*	(N=94)*		
Yes	11 (18.3)	11 (11.7)	0.255	
No	49 (81.7)	83 (88.3)		
ICH	(N=56)*	(N=91)*		
Yes	10 (17.9)	5 (5.5)	0.022	3.739 (1.206-11.592)
No	46 (82.1)	86 (94.5)		
Prenatal data				
Centralization				
Yes	10 (16.7)	7 (7.3)	0.075	-
No	50 (83.3)	89 (92.7)		
Oligohydramnios				
Yes	12 (20.0)	10 (10.4)	0.099	-
No	48 (80.0)	86 (89.6)		
PIH				
Yes	18 (30.0)	18 (18.8)	0.107	-
No	42 (70.0)	78 (81.2)		
Labor data				
Type of delivery				
Vaginal	5 (8.3)	8 (8.3)	1.000	-
Cesarean	55 (91.7)	88 (91.7)		
Resuscitation				
Yes	28 (46.7)	40 (41.7)	0.540	-
No	32 (53.3)	56 (58.3)		
Apgar < 5				
Yes	9 (15.0)	9 (9.4)	0.289	-
No	51 (85.0)	87 (90.6)		

NB - newborn; PLL - plasma lactate level; CI - confidence interval; BW - birth weight; GA - gestational age; CRIB - Clinical Risk Index for Babies; BW matched to GA - the birth weight matched to gestational age at birth; SGA - small for gestational age; AGA - adequate for gestational age; PPHNB - persistent pulmonary hypertension of the newborn; ICH - intracranial hemorrhage; PIH - pregnancy-induced hypertension. The data are expressed as the number (%) or the mean ± standard deviation (medians). Chi-square, Student's t-, or Mann-Whitney tests. *Different totals; see methods.

of NBs classified as small for GA (SGA). All of these variables exhibited a higher frequency in the group of NB with PLL > 4.2 mmol/L. The remainder of investigated variables did not exhibit differences (Table 1).

The group with PLL > 4.2 mmol/L exhibited a lower average BW (1,835 ± 885 g; median, 1,505 g; range, 490 - 3,760 g) compared to the group with PLL ≤ 4.2 mmol/L (2,324 ± 915 g; median, 2,400 g; range, 485 - 4,720 g; p=0.001). The CRIB score (which was measured in the 50 NB with a birth weight <1,500 g) and GA did not differ between the groups (Table 1).

The mortality during the first 3 days did not differ as a function of the BW matched to GA. Of the 9 NBs who died, 2 were SGA, and 7 were not. Of the 147 NBs who survived the first 3 days of life, 37 were SGA, and 110 were not (p=0.8428).

DISCUSSION

The present study used a ROC curve to define the PLL cutoff point with a better sensitivity and specificity to predict early neonatal death in the investigated population. In addition, these findings will allow other investigators to perform the same analyses as the ones described above because there is currently no consensus for "reference values" for blood lactate concentrations in NBs.[5,10,20] In contrast, for adult patients, the reference values of PLL have already been established, and levels up to 2 mmol/L are considered normal.[6,7]

The present study found that NBs with PLL > 4.2 mmol/L during the first 6 hours of life had higher odds of dying within the first 3 days of life. However, the fact that the half-life of lactate is not known might explain the reason why a single measurement of PLL performed during the first hours of life does not reflect the events that occur after the third day of life.[5,12,21] Due to anaerobic cell metabolism, the PLL values are related not only to the severity of the clinical condition but also to asphyxia.[10-12]

The group of NBs with PLL > 4.2 mmol/L exhibited a higher frequency of neurologic manifestations related with the hypoxic-ischemic syndrome including a higher number of seizure episodes (OR=12.53) and ICH (OR=3.74). These results may be due to tissue hypoperfusion and hypoxia, which induce a shift from aerobic to anaerobic metabolism. This metabolism shift results in such manifestations and might eventually culminate in patient death.[19,20,22,23]

The higher frequency of SGA NBs in the group with high lactate levels suggests that chronic intrauterine hypoxia might be one of the causes of low weight at birth.[24,25]

Although we did not correlate the CRIB scores of our groups with PLLs, Philips et al.,[26] upon performing a joint analysis of PLL and CRIB to predict mortality in extremely premature NBs, observed that the new, combined score had a good prognostic value.

CONCLUSIONS

In the investigated samples, a PLL > 4.2 mmol/L correlated with a higher frequency of SGA NBs, neurologic morbidity, and death during the first 3 days of life.

RESUMO

Objetivo: Avaliar a correlação entre a concentração do nível plasmático de lactato, nas primeiras 6 horas de vida, e a mortalidade neonatal precoce.

Métodos: Os pacientes foram separados em dois grupos, a partir do melhor ponto de corte do nível plasmático de lactato para predição da mortalidade neonatal nos 3 primeiros dias de vida, obtido por meio da construção de curva ROC. Os grupos foram separados e analisados quanto às diferenças e correlações entre as variáveis estudadas e nível plasmático de lactato dosado nas primeiras 6 horas de vida, por meio dos testes qui-quadrado, t de Student ou Mann-Whitney, e regressão logística.

Resultados: O melhor ponto de corte do nível plasmático de lactato determinado pela curva ROC para óbito nos 3 primeiros dias de vida foi 4,2mmol/L. Os grupos estudados foram diferentes em relação à média de peso de nascimento (menor no grupo com nível plasmático de lactato >4,2mmol/L), adequação entre peso de nascimento/idade gestacional, com maior número de recém-nascidos pequenos para idade gestacional nesse grupo. A ocorrência de convulsões, hemorragia intracraniana e óbito nos primeiros 3 dias de vida foi mais freqüente no grupo com nível plasmático de lactato >4,2mmol/L.

Conclusão: Para a amostragem estudada, a presença de nível plasmático de lactato > 4,2mmol/L, nas primeiras 6 horas de vida, foi correlacionada ao óbito neonatal nos 3 primeiros dias de vida, à maior frequência de morbidade neurológica e de recém-nascidos pequenos para idade gestacional.

Descritores: Ácido láctico; Asfixia neonatal; Mortalidade neonatal

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