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RESEARCH ARTICLE

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Can lactate levels be used as a marker of patent ductus arteriosus in preterm babies?

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Objective: Serum lactate levels provide information on metabolic capacity at the cellular level. In addition, lactate reflects tissue perfusion and oxygenation status. The aim of this study was to determine the usefulness of high lactate levels as a marker in hemodynamically significant patent ductus arteriosus (hsPDA), which may lead to tissue perfusion defects.

Methods: Preterm infants with gestational age ≤32 weeks and birthweight ≤1500 g were included. Lactate levels were determined at postnatal 48-72 hours before echocardiographic evaluation. Eligible infants were divided into two groups as infants with and without hsPDA. Cut-off values for lactate were taken as lactate >4 mmol/L, identified as a high lactate level. Infants were also divided into two groups according to lactate levels as group I: lactate levels >4 mmol/L and group II: lactate levels ≤4 mmol/L. Haemodynamic PDA and lactate levels were compared.

Results: A total of 119 patients with gestational age ≤32 weeks and birthweight ≤1500 g were included in the study. Fifty patients had echocardiographic hsPDA and 69 patients had no PDA. Twelve (24%) of the patients with hsPDA and 22 (31.9%) of the non-hsPDA patients had a lactate level of 4 mmol/L ($P = 0.392$). There was no correlation between hsPDA presence and lactate levels ($P = 0.35$).

Conclusion: High lactate levels are multifactorial and usually indicate impairment of tissue perfusion. There are a number of factors that can lead to impaired tissue perfusion in preterm infants. For the first time in this study, it was shown that lactate levels did not significantly increase in the presence of hemodynamically significant PDA. This may be due to the fact that peripheral tissue perfusion in the presence of hemodynamic PDA does not deteriorate enough to cause an increase in anaerobic metabolism.

KEYWORDS
lactate, patent ductus arteriosus, preterm

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is a common problem in preterm infants. In studies performed in prematurity, the rates range from 29%-80%.[1] Three main definitions emerged when evaluating PDA studies, outcomes, and treatment options: clinical PDA, symptomatic PDA, and hemodynamically significant PDA (hsPDA). In symptomatic PDA, the PDA has begun to affect the baby's clinical condition. When symptoms such as hypotension appear, the PDA becomes symptomatic and pulmonary hyperperfusion and/or systemic hypoperfusion develops. Since the effects of PDA on respiration and circulation are more easily described, the findings of these systems are evaluated.

Symptomatic PDA is characterized by difficulty in separating from a mechanical ventilator, worsening of respiratory parameters and mechanical ventilator settings, persistent apnea attacks, pulmonary hemorrhage, and hypotension.[2] Of these characteristics, the most specific is the development of pulmonary hemorrhage in the first week. A hemodynamically significant PDA diagnosis is made by means of echocardiographic evaluation of the high-volume current in the PDA. The benefit of diagnosing a hemodynamically significant PDA is that the larger PDAs are associated with pulmonary hemorrhage, intraventricular hemorrhage, death, or severe morbidity in infants younger than 28 weeks, and clinicians should consider closing the PDA to prevent these complications.[2] Bleeding in the lungs (ductal stealing) can cause hypoperfusion in extreme organs such as the kidneys, intestines, and brain. These effects, which develop during the first week of life, can lead to problems such as bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis (NEC), which may persist for a long time.[3] Echocardiographic evaluation is the gold standard for hsPDA. However, studies have also indicated that some clinical and biochemical markers can predict hsPDA in addition to echocardiographic evaluation.[4,5] Lactate is produced in all body tissues, with the highest level in the muscles. Under normal conditions, cholestasis occurs in the liver and in the kidneys in small amounts.[6-9] Serum lactate levels provide information on metabolic capacity at the cellular level. In addition, lactate reflects tissue perfusion and oxygenation status.[9] Studies of readily measurable lactate in newborns indicate that arterial and venous lactate levels correlate.[10] The aim of this study was to determine the usefulness of high lactate levels as a marker in hemodynamic significant PDA, which may lead to objective tissue perfusion defects.

2 | MATERIALS AND METHODS

Between March 2017 and November 2017, a prospective observational study was carried out and included preterms with gestational age ≤32 weeks and birthweight ≤1500 g in a tertiary neonatal intensive care unit. Patients' postnatal lactate levels at 48-72 hours were determined before echocardiographic evaluation hourly. All preterm infants whose gestational age was ≤32 weeks were examined by blinded pediatric cardiologists for hsPDA in the first 3 days of life. After echocardiography, patients were divided into two groups: those with and without hemodynamic PDA, according to hsPDA status. The following diagnostic criteria for hsPDA were applied: a diastolic turbinate flow in the pulmonary artery (left-to-right or bilateral shunt), a left atrium/aortic rate of >1.5, and a ductal diameter of >1.5 mm.[11] Babies with septic shock, shock, severe asphyxia, congenital heart disease, persistent pulmonary hypertension, major congenital malformation, hydrops fetalis, or congenital metabolic disease were excluded from the study. Infants who were discharged from the unit before control echocardiography were excluded from the study. Lactate values were assessed at 12 hours before echocardiographic evaluation (Radiometer ABL 700 automated blood gas analyzer, Copenhagen, Denmark). Cut-off values for lactate were set, with >4 mmol/L taken as a high lactate level. Patients were compared in two groups: those with lactate levels >4 mmol/L and those with lactate levels ≤4 mmol/L. Bronchopulmonary dysplasia was defined as persistent oxygen need at postmenstrual week 36 (BPD Jopee).[12] Clinical manifestations and abdominal radiographs were reviewed and categorized according to the NEC modified Bell classification.[13] Severe premature retinopathy (ROP) was diagnosed using a test performed by an ophthalmologist after 28 days of life and classified as stage 3, 4, or 5 according to the international classification.[14] IVH was diagnosed using cranial ultrasonography and classified according to the Papile-Burstein system,[15] which classifies IVH grades III and IV as severe. Demographic data, short- and medium-term morbidity rates, respiratory support, and hospital stay were recorded. Compliance with the ethical committee was confirmed by the Local Ethics Committee.

2.1 | Statistical analysis

Statistical analysis used SPSS for Windows v. 17.0 (SPSS Inc., Chicago, IL). Frequency and mean measures of descriptive statistics were used. Student's *t* test was used to compare normal variance variables, Mann-Whitney U test for nonparametric variables, and χ^2 test for categorical variables. Pearson correlation test was used for correlation statistics.

3 | RESULTS

A total of 119 patients with gestational age ≤32 weeks and birthweight ≤1500 g were included in the study. Mean gestational age was 28.5 ± 2 weeks, and birthweight was 1075 ± 294 g. Fifty patients had echocardiographic hsPDA, and 69 patients had no PDA. Birthweight, first minute, and fifth minute Apgar scores were lower in the hsPDA group ($P = 0.001$, 0.013, and 0.003, respectively). Twelve patients with hsPDA (24% of the total) and 22 non-hsPDA patients (31.9%) had lactate levels of 4 mmol/L ($P = 0.392$). The duration of noninvasive and mechanical ventilation was longer in the hemodynamic PDA group, and rates of ROP were higher ($P = 0.038$, 0.016 and 0.021, respectively) (Table 1). There were 34 patients (28.6%) with lactate levels >4 mmol/L and 85 patients (71.4%) with ≤4 mmol/L. The birthweight in the high lactate group was lower ($P = 0.026$), and mortality rates were higher ($P = 0.042$). There was no difference in the duration of noninvasive ventilation, mechanical ventilation, or stay ($P = 0.34$, 0.43, and 0.16, respectively) in patients with lactate levels >4 mmol/L and ≤4 mmol/L. Bronchopulmonary dysplasia, ROP, and intraventricular bleeding rates were similar between the two groups ($P = 0.81$, 0.56, and 0.13, respectively). There was no correlation between hsPDA presence and lactate levels ($P = 0.35$) (Table 2).

There was no significant correlation between ductal shunt diameter and lactate levels ($r = 0.07$ and $P = 0.45$).

In our study, the rate of hypotension (mean blood pressure <30 mm Hg) was 13.8%. There was no difference between the

TABLE 1 Comparison of demographic and clinical characteristics of patients with and without HsPDA

	Without HsPDA (n = 71)	With HsPDA (n = 48)	*P*
Birthweight, g[a]	1093.39 ± 289.05	1032 ± 282.9	0.261
Gestation week[a]	29.1 ± 1.78	27.9 ± 2.1	0.001
Male, n (%)	37 (53.5)	25 (50)	0.713
Cesarean section, n (%)	58 (81.7)	39 (81.3)	0.994
Crib II score[b]	2 (0-13)	2.5 (0-12)	0.092
Apgar, 1 min[b]	6 (3-7)	5 (1-8)	0.013
Apgar, 5 min[b]	8 (4-9)	7 (3-10)	0.003
Noninvasive ventilation time, d[a]	6.9 ± 11.2	11.3 ± 10.9	0.038
Mechanical ventilator duration, d[a]	4.5 ± 9.2	10.1 ± 15.9	0.016
Intra-periventricular hemorrhage, n (%)	5 (7.57)	6 (14.2)	0.305
Patent ductus arteriosus, n (%)	12 (35.3)	36 (42.3)	0.39
Preterm retinopathy, n (%)	3 (5)	8 (21.1)	0.021
Bronchopulmonary dysplasia, n (%)	7 (12.1)	12 (33.3)	0.039
Duration of stay, d[a]	45.5 ± 29.4	54.6 ± 35.8	0.133
Mortality, n (%)[a]	11 (15.5)	10 (20.8)	0.472

[a]Mean ± SD.
[b]Median (minimum-maximum)

TABLE 2 Comparison of demographic data and clinical characteristics of high and low lactate groups

	Lactate > 4 mmol/L (N = 34)	Lactate ≤ 4 mmol/L (N = 85)	*P*
Birthweight, g[a]	969 ± 318	1102 ± 261	0.026
Gestation week[a]	28.2 ± 2	28.7 ± 1.9	0.28
Male, n (%)	20 (59)	41 (48.2)	0.38
Cesarean section, n (%)	26 (76.5)	68 (80)	0.41
Crib II score[b]	3 (0-19)	2 (0-12)	0.203
Apgar, 1 min[b]	5 (2-7)	6 (1-8)	0.051
Apgar, 5 min[b]	7 (4-8)	7 (3-8)	1.00
Noninvasive ventilation time, d[a]	7.1 ± 1.6	9.3 ± 1.3	0.12
Mechanical ventilator duration, d[a]	5.1 ± 1.3	7.2 ± 1.5	0.71
Intra-periventricular hemorrhage, n (%)	5 (14.2)	5 (5.9)	0.13
Patent ductus arteriosus, n (%)	12 (35.3)	36 (42.3)	0.39
Preterm retinopathy, n (%)	2 (5.8)	9 (10.6)	0.56
Bronchopulmonary dysplasia, n (%)	4 (11.8)	15 (17.6)	0.81
Duration of stay, d[a]	42 ± 5.7	51 ± 3.5	0.14
Mortality, n (%)[a]	10 (29.4)	11 (12.9)	0.042

[a]Mean ± SD.
[b]Median (minimum-maximum).

groups ($P > 0.05$). Clinical and proven early neonatal sepsis rate was 28.5% and was similar among the groups.

4 | DISCUSSION

In our study, we found that venous lactate levels in hemodynamically significant preterm infants with PDA were not different from those of patients with hsPDA. However, we found that mortality rates were higher in preterm infants with lactate levels above 4 mmol/L. Lactate levels are often used in clinical practice to monitor the severity of the disease and the response to treatment. Lactate levels were first used for clinical prognostic purposes in 1964 by Broder and Weil, who observed that excess lactate (>4 mmol/L) over undifferentiated shock was associated with poor outcome in patients.[16] Lactate levels are often used following shock, but there are many reasons for high levels of lactate. Tissue perfusion disorder is the most common cause, but there are other contributory factors, including sepsis

and septic shock, cardiogenic, obstructive and hemorrhagic shock, cardiac arrest, trauma, seizures, burns and smoke inhalation, liver failure, inborn errors of metabolism, and drugs and toxins.[17]

The relationship between increased blood lactate levels and mortality and morbidity has been demonstrated in a number of clinical scenarios.[18] It has been reported that the highest blood lactate level in the first 12 hours of life is associated with the hospital mortality risk of low birthweight neonates (1500 g, n = 381, median GA = 28 weeks).[19] In our study, mortality rates were higher in the group with lactate levels >4 mmol/L. PDA is an important complication in premature infants. Left-to-right shunting in PDA babies leads to systemic blood flow and concomitant reduction of blood flow to regional organs.[20] Studies have shown that the most frequent cause of death in PDA preterm neonates is multiple organ failure.[21] A patent research study investigated the impact on macrocirculation (the increased left ventricular output) but could not continue because the ductal steal phenomenon showed that blood was flowing to the peripheral organs. The blood flow in the celiac, upper mesenteric and renal arteries showed abnormal patterns compared to the closed DA group. These differences were lost after closure.[22] As left-to-right shunting may cause a large PDA, a significant retrograde diastolic flow in the abdominal aorta and diastolic flow may be greater than 50% of total aortic blood flow. This is reflected in the clinic as "ductal stealing"[23] and causes hypoperfusion in the end organs. Tuten et al evaluated the relationship between lactate levels and perfusion index values in the first 12 hours of life in preterm infants less than 1500 g at 32 weeks with preterm morbidities. Similarly, in our study, ROP rates were found to be high in preterms with lactate levels >4 mmol/L. However, there was no difference in terms of PDA.[24]

Ductusive blood may cause hypoperfusion in extreme organs such as the kidneys, intestines, and brain, rather than systemic circulation. These effects, which develop during the first week of life, can lead to problems such as BPD, intraventricular hemorrhage, and NEC, which may persist for a long time. Data are limited on the utilization of serum lactate values in the assessment of tissue perfusion in hypotensive newborns. Lactate values can give information on metabolism capacity at cellular level and reflect true perfusion and oxygenation status.

Numerous measurements have been tried to determine hemodynamic PDA by echocardiography. Recently, individualized treatment has been proposed, including clinical findings for PDA. It is controversial to suggest treatment planning if respiratory instability, separation from the ventilator, persistence of oxygen, pulmonary congestion, and haemodynamic effects indicate echocardiographic findings of significant shunt. Since our study was based on echocardiographic findings, there was no correlation between lactate levels and hemodynamic significance of PDA presence.[25]

Echocardiographic findings of hemodynamically significant PDA are associated with shunt size.[26,27] However, the effect of this shunt on oxygen consumption in pre-postdust tissues in preterm infants is not clear. The results of previous studies investigating the oxygen consumption of pre-postdust tissues of hsPDA using NIRS are uncertain. Van Der Laan et al observed postnatal changes in cerebral and renal blood flow in the presence of PDA during the first 2 weeks.[28] Postnatal lactate levels are measured in all preterm infants in our clinic from 48 to 72 hours. Since echocardiographic examination is performed hourly, patients are treated without deterioration of tissue perfusion. This limits the level of lactate that acts as a marker for hemodynamically significant PDA.

This study has some limitations. First, the number of patients may not be sufficient. Secondly, the threshold for the hemodynamic PDA of the lactate level may have been set lower than in other studies. There are also many confounding factors that can cause rapid deterioration of tissue perfusion in preterm infants. The observational nature of the study was another limiting factor. Lactate levels may not be sufficiently specific. In one study, lactate levels in 13 of 27 patients with superior mesenteric artery occlusion were within normal limits.[29] Dugas et al found that 45% of patients in the vasopressor-dependent septic shock group did not initially have a lactic acid level >2.4 mmol/L but had high mortality.[30] In this study, we have found that lactate levels, which are indicators of tissue perfusion impairment, do not reach levels at which tissue perfusion deteriorates hemodynamically in the presence of hsPDA. It may be that the preterm infants with hsPDA were diagnosed and treated in the first 72 hours, when the tissue perfusion had not yet deteriorated.

Conclusion: High lactate levels are multifactorial and usually indicate impairment in tissue perfusion. A number of factors can lead to impaired tissue perfusion in preterm infants. In this study, it is shown for the first time that lactate levels do not significantly increase in the presence of hemodynamically significant PDA. This may be due to the fact that peripheral tissue perfusion in the presence of hemodynamic PDA does not deteriorate enough to cause an increase in anaerobic metabolism.

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