Original Article

Can Lactate be Valuable in Early Diagnosis and Prognosis of Neonatal Sepsis?

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Abstract

Background: Sepsis monitoring tissue perfusion is crucial for detecting circulatory failure early, implementing the right treatments, and assessing response. Insufficient oxygenation leads to a rise in lactate level and has been shown to be useful in predicting mortality and morbidity in newborns. There have not been many studies on how lactate measurement affects neonatal sepsis diagnosis and prognosis. **Aim:** The aim of our study was to determine the impact of lactate on early diagnosis and prognosis in neonatal sepsis. **Materials and Methods:** Eighty-seven newborns diagnosed with neonatal sepsis at a neonatal intensive care unit between January 2010 and July 2021 were included in the study. Venous blood gas, lactate, and C-reactive protein (CRP) levels and complete blood count on the first, second, and third day of hospitalization were noted. Lactate values were correlated with other variables to determine the impact of hyperlactatemia on morbidity and to determine factors affecting the length of stay. IBM SPSS Statistics version 22.0 for Windows was used to analyze the data (SPSS Inc., Chicago, IL, United States). **Results:** A strong negative correlation between lactate and oxygenation and perfusion indicators (HCO_3, BE, PaO_2) during the therapeutic process was observed. With treatment, the initial measured lactate value decreased, and a significant increase in CRP and oxygen saturation was observed, which was interpreted as the observation of an early lactate response to infection before a CRP response. The initial lactate level, as well as the change in lactate levels, was not, however, significantly correlated with the length of stay. **Conclusion:** Lactate can be used in the early diagnosis of neonatal sepsis and for determining prognosis.

Keywords: *Early diagnosis, lactate, neonatal sepsis, prognosis*

Introduction

Hypoxia and impaired perfusion cause tissue damage; even in the absence of tissue perfusion and hypoxia, the lactate level can increase. Elevated lactate levels primarily result from an imbalance between the cascade of carbohydrates involved in aerobic and anaerobic metabolism. It has been suggested that there may be other causes of hyperlactatemia besides hypoxia as lactate metabolism is more fully understood over time.[1,2] In critically ill newborns with sepsis, monitoring tissue perfusion is crucial for detecting circulatory failure early, implementing the right treatments, and for assessing response. Changes in heart blood pressure, A1. hearth rate, urine output, and skin perfusion, which are typically used to detect tissue malperfusion in this age group, are insensitive markers because clinically relevant cellular hypoxia and malperfusion may be present long before changes in cardiovascular responses become clinically apparent. Another method for evaluating tissue perfusion in critically ill adults is the measurement of blood lactate concentrations. Tissues increasingly rely

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on anaerobic metabolism for the energy they require because aerobic metabolism through the Krebs cycle cannot be sustained when oxygen and substrate delivery are critically reduced. Blood lactate is then produced more frequently and builds up as a result. Adult patients who are critically ill or injured can use blood lactate concentrations to assess illness severity, predict outcome, and identify tissue hypoxia at an early stage. Although there is a wealth of information on the importance of blood lactate measurement in sick adults, there is little data on its significance in critically ill neonates. Increased mortality is linked to hyperlactatemia.[3] In term infants with serious respiratory failure as well as in premature newborns with respiratory distress syndrome, hyperlactatemia is linked to an increased mortality rate. Studies have demonstrated that lactate in scalp blood has predictive and preventive properties superior or equivalent to pH in the detection of metabolic acidemia, low Apgar scores, and short-term neonatal morbidity with no appreciable difference in the rate of operative deliveries.[4] An association between the blood lactate level and cerebral oxygenation has been described in extremely pre-term neonates during the first few days after birth.[5] It has also been noted that elevated lactate concentrations in pre-term infants can serve as a warning sign for sepsis.[3] Insufficient oxygenation resulting in the rise of lactate level has been shown to be useful in predicting mortality and morbidity in critically ill newborns.[3-5]

High observed mortality and high severity of illness scores were observed in children with hyperlactatemia. Hyperlactatemia at admission seems to be a strong diagnostic indicator of intensive care mortality.[6] Peak lactate or the presence of persistent hyperlactatemia after 24 hours of treatment can be used to identify non-survivors.[6] It has been discovered that sepsis and its prognosis in children are particularly negatively correlated to persistently high lactate levels.[7,8] On the first day of life, lactate levels and base deficit have a significant correlation. Serial lactate measurements greater than 5.6 mmol/L can aid the clinician in making decisions at the bedside by predicting negative outcomes.[9]

Plasma lactate level can be a useful diagnostic tool because it is simple to check at the bedside in routine applications in intensive care diagnostic methods. There have not been many studies on how lactate measurement affects neonatal sepsis diagnosis and prognosis.

In our study, we looked into how well lactate could predict the severity of sepsis in infants and whether it could be used as a screening test.

Subjects and Methods

The records of 99 infants who received a diagnosis of sepsis and were treated in the neonatal intensive care unit between January 2010 and July 2021 were retrospectively reviewed for our study. After 12 patients were excluded for having missing data in their records, the remaining 87 patients were included in the study. The study excluded patients with congenital anomalies, those who had received resuscitation, those whose gestational age was less than 34 weeks, and those who had severe respiratory failure. Sepsis diagnostic criteria included both clinical and suspected sepsis. The demographic details of the study participants were noted, in addition to venous blood gas, lactate, and C-reactive protein (CRP) levels, complete blood count obtained on the first, second, and third day of hospitalization, and the length of hospitalization. The first, second, and third lactate values of patients were correlated with other variables using correlation analysis. Additionally, correlation analysis was performed between the first lactate value and the second lactate value variation (Lactate Var.-1), the first lactate value and the third lactate value variation (Lactate Var.-2), and other variables. Linear regression analysis was applied to determine the factors affecting the length of stay of patients. All factors were included in the analysis. Stepwise method was used, and the result of the analysis is given in step 4, which was the last step.

Statistical analysis

IBM SPSS Statistics version 22.0 for Windows was used to analyze data (SPSS Inc., Chicago, IL, United States). The Kolmogorov–Smirnov test was used to determine whether the distribution of continuous variables was normal. The homogeneity of variances was assessed using Levene's test. Continuous data were described—unless otherwise stated—as mean and standard deviation (SD) for normal distributions and median (minimum to maximum) for skewed distributions.

Table 1: Demographic and clinical characteristic of patients

	n	%
Age, days, median (min.–max.)	1 (1-24)	
Gender		
Male	60	69.0%
Female	27	31.0%
Gestational week		
Preterm	41	47.1%
Term	46	52.9%
Hospitalization length		
days, median (min.–max.)	8.50 (2.00-35.00)	

*Continuous variables are expressed as median (minimum to maximum) and categorical variables are expressed as frequency (percentage)

Categorical data were expressed as percentages. The student *t* test was used in statistical analysis to compare differences between the normally distributed variables of two independent groups. The Mann–Whitney *U* test was used to compare data that were not normally distributed. Pearson's Chi-squared test or Fisher's exact test was used to compare categorical variables. Univariate and multivariate linear regression analyses were performed to assess the association between the risk factors and lactat levels. Spearman's correlation analysis was used to gauge the levels of relationship between the variables. *P* values less than 0.05 were accepted as significant in all statistical analyses.

Results

The patients were divided into 60 males (69.0%), 27 females (31.0%), 41 preterm (47.1%), 46 term (52.9%), and 8.50 days (median: 2.00–35.00) of hospitalization [Table 1]. Table 2 provides the patients' first, second, and third laboratory measurement means. An examination with a normal lactate level of 2.5 is given in Table 2.

There is no significant difference between the lactate ratios measured during the treatment process [Table 3].

A negative, low-level, statistically significant correlation was found between the first lactate values and the first base excess and bicarbonate (HCO_3) ($r = -0.363$, $P = 0.001$; $r = -0.378$; $P = 0.001$, respectively) as a result of the correlation analysis between the patients' first, second, and third lactate values and other variables. Furthermore, there was a positive, low-level, statistically significant correlation between first lactate values and absolute lymphocyte levels (ALL; $r = 0.276$, $P = 0.010$). There was a negative, low-level, statistically significant correlation between the first lactate values and second HCO_3, second base excess (BE), and third HCO_3 ($r = -0.306$ and $P = 0.031$, $r = -0.340$ and $P = 0.016$, $r = -0.373$ and $P = 0.036$, respectively). There was a negative, low-level, statistically significant correlation between the second lactate values of the patients and the second oxygen saturation (SpO_2) and the second CRP ($r = -0.299$ and $P = 0.066$, $r = -0.369$ and $P = 0.045$, respectively). There was a positive, moderate, statistically significant correlation between the third lactate values of the patients and the first partial pressure of oxygen (PaO_2; $r = 0.400$ and $P = 0.026$). There was a negative, low-level, statistically significant correlation between the third lactate values and the second CRP, first SpO_2, and second HCO_3 values ($r = -0.369$ and $P = 0.045$, $r = -0.399$ and $P = 0.032$, $r = -0.396$ and $P = 0.027$, respectively). There was no statistically significant correlation between the first lactate value and the second lactate value variation (Lactate Var.-1),

Table 2: First, second, and third laboratory measurements of patients

Variables	mean ± standard deviation (SD) median (minimum-maximum)
1. pH	7.35 (7.08-7.49)
$PaCO_2$ (mmHg)	41.97±9.85
PaO_2 (mmHg)	48.90 (30.90-94.10)
Lactate (mmol/L)	2.76 (1.10-7.95)
BE (mmol/L)	−3.52±3.78
SpO_2 (%)	86.55 (62.70-97.90)
HCO_3 (mmol/L)	21.05 (14.30-28.20)
2. pH	7.39 (7.21-7.48)
$PaCO_2$ (mmHg)	40.00±9.04
PaO_2 (mmHg)	49.60 (32.90-89.20)
Lactate (mmol/L)	2.65 (−4.70-9.10)
BE (mmol/L)	−2.00 (−9.00-5.10)
SpO_2 (%)	86.80 (8.10-97.80)
HCO_3 (mmol/L)	22.25 (2.40-28.90)
3. pH	7.39 (6.71-7.51)
$PaCO_2$ (mmHg)	41.60 (24.70-137.80)
PaO_2 (mmHg)	49.90 (18.80-90.70)
Lactate (mmol/L)	2.36 (0.75-8.45)
BE (mmol/L)	−1.70 (−22.70-6.70)
SpO_2 (%)	88.90 (47.00-98.40)
HCO_3 (mmol/L)	23.36±2.90
CRP-1 (mg/L)	1.00 (0.02-217.00)
CRP-2 (mg/L)	3.42 (0.18-108.00)
CRP-3 (mg/L)	2.18 (0.18-24.00)
Hemoglobin (g/dl)	16.43±3.07
Leukocytes (× 10^3 µl)	13.50 (4.50-1501.00)
ANS (× 10^3 µl)	6.96 (1.12-23.83)
ALS (× 10^3 µl)	4.54 (1.18-13.77)
Platelets (× 10^3 µl)	311.73±118.34

*Continuous variables are expressed as either mean±standard deviation (SD) or median (minimum to maximum). ** ANS: Absolute neutrophil count, ALS: Absolute lymphocyte count, BE: Base excess

Table 3: Lactate ratios of patients during the treatment process

	n	%	Mean±SD Median (min.–max.)	*P*
Lactate-1 (mmol/L)				
≤2.5	35	40.2%		
>2.5	52	59.8%	3.26±1.62	
			2.94 (1.10-13.43)	
Lactate-2 (mmol/L)				
≤2.5	21	41.2%		0.911
>2.5	30	58.8%	2.72±1.65	
			2.60 (−4.70-9.10)	
Lactate-3 (mmol/L)				
≤2.5	17	53.1%		
>2.5	15	46.9%	2.87±1.54	
			2.32 (0.75-8.45)	

Table 4: Correlation analysis between Lactate-1, Lactate-2, Lactate-3, Lactate Var.-1, and Lactate Var.-2 and other variables and their changes in patients with sepsis*

	Lactate-1	Lactate-2	Lactate-3	Lactate Var.-1	Lactate Var.-2
Day					
pH					
r	−0.129	−0.104	0.144	0.043	0.192
P	0.235	0.466	0.433	0.762	0.292
$PaCO_2$ (mmHg)					
r	−0.147	−0.067	−0.214	0.054	−0.256
P	0.176	0.643	0.248	0.711	0.164
PaO_2 (mmHg)					
r	−0.078	0.089	0.400*	0.062	0.314
P	0.477	0.537	0.026	0.668	0.086
BE (mmol/L)					
r	−0.363**	−0.114	0.028	0.199	0.211
P	0.001	0.430	0.882	0.166	0.255
SpO_2 (%)					
r	−0.170	−0.113	0.073	0.095	0.231
P	0.143	0.449	0.692	0.526	0.203
HCO_3 (mmol/L)					
r	−0.378**	−0.110	0.090	0.213	0.289
P	<0.001	0.447	0.629	0.138	0.115
2. Day					
pH					
r	−0.034	−0.132	0.143	0.133	0.139
P	0.814	0.355	0.436	0.351	0.448
$PaCO_2$ (mmHg)					
r	−0.233	0.000	−0.178	0.015	0.049
P	0.103	0.998	0.337	0.919	0.794
PaO_2 (mmHg)					
r	−0.129	−0.068	−0.030	0.123	0.244
P	0.371	0.639	0.871	0.396	0.186
BE (mmol/L)					
r	−0.306*	−0.196	0.100	0.164	0.312
P	0.031	0.172	0.592	0.256	0.088
SpO_2 (%)					
r	−0.156	−0.299*	−0.336	−0.034	0.004
P	0.305	0.046	0.075	0.824	0.985
HCO_3 (mmol/L)					
r	−0.340*	−0.260	0.022	0.145	0.222
P	0.016	0.069	0.907	0.315	0.229
3. day					
pH					
r	−0.027	0.167	−0.267	0.181	−0.272
P	0.884	0.361	0.140	0.322	0.132
$PaCO_2$ (mmHg)					
r	−0.178	−0.150	0.018	−0.023	0.278
P	0.330	0.413	0.922	0.899	0.124
PaO_2 (mmHg)					
r	0.088	−0.095	−0.063	−0.131	−0.210
P	0.632	0.604	0.732	0.474	0.249
BE (mmol/L)					
r	−0.322	0.044	−0.188	0.266	0.032
P	0.072	0.811	0.304	0.141	0.864
SpO_2 (%)					

Contd...

Table 4: Contd...

	Lactate-1	Lactate-2	Lactate-3	Lactate Var.-1	Lactate Var.-2
r	−0.168	−0.046	0.010	0.154	0.051
P	0.385	0.813	0.957	0.425	0.795
HCO_3 (mmol/L)					
r	−0.373*	0.062	−0.184	0.316	0.059
P	0.036	0.735	0.312	0.078	0.747
CRP-1 (mg/L)					
r	−0.151	0.188	−0.234	−0.061	−0.347
P	0.166	0.190	0.204	0.674	0.056
CRP-2 (mg/L)					
r	0.099	0.214	−0.369*	−0.039	−0.266
P	0.419	0.139	0.045	0.788	0.155
CRP-3 (mg/L)					
r	−0.027	0.029	−0.289	0.056	−0.019
P	0.861	0.868	0.144	0.748	0.927
Hemoglobin (g/dl)					
r	0.175	0.026	0.122	−0.103	−0.071
P	0.106	0.858	0.512	0.478	0.706
Leukocytes (× 10^3 µl)					
r	0.180	0.219	0.316	0.050	0.128
P	0.097	0.126	0.083	0.731	0.492
ANS (× 10^3 µl)					
r	0.125	0.199	0.148	0.085	−0.006
P	0.253	0.166	0.428	0.558	0.973
ALS (× 10^3 µl)					
r	0.276**	0.058	0.215	−0.136	0.258
P	0.010	0.691	0.246	0.347	0.161
Platelets (× 10^3 µl)					
r	0.102	−0.217	−0.018	−0.296*	0.028
P	0.349	0.129	0.921	0.037	0.883

* Var.: Variation. ANS: Absolute neutrophil count, ALS: Absolute lymphocyte count

Table 5: The results of linear regression analysis to determine the factors affecting the length of stay in sepsis patients

Model	Unstandardized Coefficients		Standardized Coefficients Beta	*t*	*P*	95% Confidence Interval for B	
	B	Std. Error					
1							
(Constant)	431.305	170.773		2.526	0.020	75.078	787.531
2. pH	−56.574	23.216	−0.478	−2.437	0.024	−105.002	−8.145
2							
(Constant)	444.506	150.778		2.948	0.008	128.923	760.089
2. pH	−58.549	20.501	−0.495	−2.856	0.010	−101.458	−15.641
CRP	0.213	0.083	0.448	2.586	0.018	0.041	0.386
3							
(Constant)	398.932	122.151		3.266	0.004	142.302	655.562
2. pH	−55.201	16.536	−0.467	−3.338	0.004	−89.942	−20.461
CRP	0.231	0.067	0.485	3.463	0.003	0.091	0.371
$PaCO_2$	0.523	0.156	0.471	3.363	0.003	0.196	0.850
4							
(Constant)	352.144	100.301		3.511	0.003	140.527	563.761
2. pH	−49.266	13.560	−0.417	−3.633	0.002	−77.876	−20.656
CRP	0.231	0.054	0.485	4.266	0.001	0.117	0.345
$PaCO_2$	0.639	0.131	0.575	4.859	<0.001	0.361	0.916
Age	−0.114	0.036	−0.380	−3.205	0.005	−0.189	−0.039

the first lactate value and the third lactate value variation (Lactate Var.-2), and other variables in the correlation analysis [Table 4].

Linear regression analysis was applied to determine the factors affecting the length of stay of patients. Stepwise method was used, and all factors were included in the analysis. Step 4 of the analysis revealed that the factors influencing the length of stay in sepsis patients were gestational age (prematurity), second pH, CRP, and the partial pressure of carbon dioxide ($PaCO_2$), according to the findings [Table 5].

Discussion

In severely stressed patients, increased glycolysis increases lactate production. Serum lactate levels are elevated in sepsis through multiple mechanisms, including anaerobic metabolism from tissue hypoperfusion, decreased clearance, and a bioenergetics response to sepsis that promotes lactate production. It is stated that it is appropriate to use the venous lactate level for screening purposes.[10] The use of lactate level to show treatment success has only been examined in a small number of observational studies.[3,7-9]

In adult septic patients, guidelines advise aiming for lactate normalization during resuscitation, but there is little evidence supporting this claim.[11] Blood lactate greater than 2 mmol/L is now considered an indicator of cellular/metabolic dysfunction in adults and is included within the operational definition of septic shock. There is a connection between elevated blood lactate levels and unfavorable septic shock outcomes in children, according to several observational studies.[12-14] Uncertainty still exists regarding the ideal cutoff point for hyperlactatemia. According to some studies, lactate concentrations greater than 4 mmol/L are consistently linked to mortality. Reduced risk of persistent organ dysfunction was associated with normalization of lactate within two to four hours of presentation.[14] However, no study has looked at whether the initial or subsequent measurements of blood lactate have any effect on how children are evaluated or treated. Lactate concentrations greater than 36 mg/dl were connected to mortality in children treated for sepsis in the emergency room, but the sensitivity of said concentrations was poor. The use of it as a screening marker for organ failure brought on by septic shock or septic shock itself is said to be supported by weak evidence.[14] In our study, patients with high lactate levels, above 2.5 mg/dl, were evaluated accordingly, in line with the literature.

Blood lactate levels indicate perfusion status but only become irregular in the presence of persistent anaerobic metabolism. Serial measurements are more useful for estimating outcomes than a single lactate concentration. According to reports, ventilated infants with high lactate concentrations that do not drop within 24 hours have higher mortality rates.[3] In our study, a significant correlation between lactate and oxygenation and perfusion indicators (HCO_3, BE, PaO_2) during the therapeutic process was discovered. HCO_3 and BE values increased while lactate values decreased. However, lactate levels measured at various times did not significantly differ from one another.

While the initial measured lactate value in our study decreased with treatment, a significant rise in CRP and oxygen saturation was seen. This finding was significant in the preliminary and early diagnosis of sepsis, which we interpreted as the observation of an early lactate response prior to a CRP response to infection. This finding is supported by similar studies in the literature.[8] It is reported that early blood lactate level can be used as a biochemical parameter to predict the prognosis of neonatal sepsis because of its high sensitivity.[15] Despite varying levels of lactat's spesivity can be a helpful clinical aid in the diagnosis of pediatric sepsis when used in the right clinical context.[16]

Whereas a high lactate level is linked to morbidity and mortality, a quick decline in lactate is a sign of good prognosis. Blood lactate measurements, whether initial or repeated, provide data for management of sepsis or direct evaluation.[7,17] In our study, the effects of lactate and additional variables were compared with the amount of time spent in the intensive care unit, and their effects were investigated. The initial lactate level, as well as the change in lactate levels, was not, however, significantly correlated to the length of stay. It was determined that the length of hospital stay was prolonged if the patient was premature, had low Second day blood gas pH is ph2, high CRP, and high $PaCO_2$.

The use of early lactate measurement in pediatric sepsis has not yet been included in pediatric sepsis guidelines.[18] However previous definitions of sepsis, such as the 2001 Consensus Conference[19] and the 2005 IPSCC[20] definitions, included markers of organ dysfunction such as lactate. We agree that it would be useful to use lactate values for risk stratification in newborns with suspected septic shock or other sepsis-related organ dysfunction.

The limitation of the study was that it was a retrospective study that included cases from only a single-center hospital, and the numbers of patients with sepsis were relatively small. Additional multicenter studies of larger cohorts are required.

Conclusion

In conclusion, our study showed a significant correlation between lactate and indicators of oxygenation and perfusion during the course of treatment, and therewithal early lactate response to the infection occurred before the CRP response. Our findings imply that lactate is a significant parameter and can be used as a useful tool in the early diagnosis and prognosis of neonatal sepsis.

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Conflicts of interest

There are no conflicts of interest.

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