

Research Article

Urinary Lactate as a Predictor of Early Onset Sepsis in Neonates

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A B S T R A C T

Objectives: Diagnosing Early-Onset Sepsis (EOS) requires a sensitive, specific, and easily available marker. This study was conducted for the estimation of the cut-off level of urinary and plasma lactate for the diagnosis of EOS.

Study Design: Hundred neonates at risk of early onset sepsis were included. Sepsis screen, blood culture, and plasma lactate within 2 hours and urinary lactate in the first urine sample were done. CRP, plasma and urinary lactate were repeated at 24 ± 2 hours. Receiver-operating characteristic curve was drawn to find the optimal cut-off point of urinary and plasma lactate levels.

Results: Median urinary lactate in the sepsis group were 0.6 mMol/L and 0.40 mMol/L and in the non-sepsis group, they were 0.41 mMol/L and 0.38 mMol/L in the 1st passed sample and at 24 hours respectively. Both urinary and plasma lactate were not able to diagnose early onset sepsis. However, urinary lactate proved to be a useful marker for diagnosing sepsis with shock and mortality.

Conclusion: Our study concludes that although urinary and plasma lactate do not predict EOS, urinary lactate can predict shock and mortality in babies with EOS at 24 hours of life.

Keywords: Early Onset Sepsis, Lactate, Neonates

Introduction

Bacterial pathogens that are transmitted from the mother to the infant before/ during the delivery cause Early-Onset neonatal Sepsis (EOS). It occurs before 72 hours of birth. A timely diagnosis of EOS has been challenging. Management

of neonates who are born at risk of EOS depends on the risk factors present in mother as well as baby, positivity of sepsis screen parameters performed after birth, and clinical symptoms.^{1,2} The gold standard for diagnosing neonatal sepsis is blood culture,² but as the report takes at least 48 hours, many of these babies end up getting

intravenous antibiotics, even when they are not infected. To avoid unnecessary treatment of uninfected babies, an early, sensitive, specific and easily available laboratory test is required that can predict EOS in at-risk neonates. Until now, no single ideal biomarker has been identified, that can accurately diagnose septicaemia and could guide efficacious antibiotic treatment. Lactate has been used as a marker of hypoxia and poor perfusion in various conditions in paediatric and neonatal populations.^{3,4} Urinary lactate has been studied in conditions like hypoxic-ischemic encephalopathy and bronchopulmonary dysplasia and has proven useful,^{5,6} but has not been studied in sepsis. The parameter carries the additional advantage of being a non-invasive test. No cut-off level of urinary lactate is known that can determine sepsis in neonates. Thus, we planned this study with the primary objective of determining the cut-off level of urinary lactate for diagnosis of EOS in neonates at risk in first-passed urine and at 24 ± 2 hours after birth. Our secondary objective was to determine the cut-off for plasma lactate level for diagnosing EOS at 2 hours and at 24 ± 2 hours after birth.

Material and Method

This cross-sectional study was conducted from March 2017 to April 2018 in the Department of Paediatrics in a tertiary care hospital after approval from the Institute Ethics Committee. Neonates with two or more risk factors for EOS were included in the study² after taking written informed consent from parents/ guardians of the neonates. Babies with birth asphyxia (low Apgar score < 7 at 1 min), those who were born through meconium-stained liquor or with congenital anomalies/ multiple pregnancies/ Infants of Diabetic Mothers (IDM) and babies born to mothers with known metabolic abnormalities and other morbidities were excluded. Sepsis screen [ANC, TLC, micro ESR, CRP, I/T ratio], blood culture and plasma lactate were done within two hours of birth in all these babies. CRP and plasma lactate were repeated at 24 ± 2 hours. Two urine samples were collected for lactate estimation, the first passed urine and then at 24 ± 2 hours. Babies were monitored for the development of sepsis and blood culture positivity. All the neonates were managed according to the Standard Operating Protocols in NICU.^{2,7}

Antibiotics were started if foul-smelling liquor or more than two risk factors for EOS or more than one antenatal risk factor and positive sepsis screen was found.

Neonates were further classified as proven (clinical signs/ symptoms present), probable (clinical signs/ symptoms present with a minimum of two abnormal laboratory results), and no sepsis (presence/ absence of clinical signs, negative sepsis screen and culture).⁸ A pre-designed case record form was used to record the details.

Sample Collection

Three mL of venous blood was collected under aseptic precautions for plasma lactate using a heparinised syringe in a fluoride-oxalate vial and centrifuged at $400 \times g$ for 10 minutes within half an hour to separate the plasma. Plasma was then stored frozen at -20°C . Urine was preferably collected using a bag placed over the perineum and aspirated from the bag using a syringe. If could not be collected, urinary catheters were used.

Lactate Assay

Lactate levels were measured from stored plasma and urine samples, within 24 hours of sample collection, by colorimetric technique using Lactate Multipurpose liquid reagent on automated and semi-automated analysers.⁹

The primary outcome was to determine urinary lactate cut-off in the first-passed urine and at 24 ± 2 hours after birth in diagnosing sepsis in neonates at risk of developing EOS. The secondary outcome was to determine plasma lactate cut-off at 2 hours and 24 ± 2 hours after birth in diagnosing sepsis in these neonates.

Sample Size

No study was found that could give us a cut-off level of urinary lactate in neonates with EOS. We recruited 100 neonates as the convenience sample size.

Statistical Analysis

SPSS 20.0 statistical software was used. P value of < 0.05 was considered to be significant. Fischer's exact test was applied to find the association of blood culture positivity with categorical variables like gender, gestation at birth, Appropriate for Gestational Age (AGA): Small for Gestational Age (SGA) ratio, CRP positivity, outcome, and complications like shock and meningitis in neonates under study. Unpaired student t test was applied to compare mean gestational age, anthropometric parameters, vital parameters, ANC, TLC, micro ESR, and I/T ratio in blood culture positive and negative groups. Mann Whitney U test was applied for comparing median urinary and plasma lactate between blood culture positive and negative groups, survivor and non-survivors, and in babies with and without shock. Receiver-Operating Characteristic (ROC) curve was drawn for urinary and plasma lactate levels.

Results

Hundred neonates, born with two or more risk factors of EOS, were enrolled in the study. Neonates were categorised into group 1 if the blood culture was positive (sepsis) and group 2 if the blood culture was negative (non-sepsis). Out of 100 neonates, blood culture was found to be positive in 10 babies. Table 1 shows the baseline demographic profile of the neonates in both groups. EOS was found more in

preterm neonates compared to term neonates. Groups were comparable with respect to other parameters.

Heart rates and respiratory rates were comparable between the two groups. Respiratory distress was seen in 40% of culture-positive babies compared to 42% in culture-negative babies which was the most common clinical feature in both groups. Meningitis (10% vs 1.1%), shock (30% vs 6.6%), DIC (30% vs nil), lethargy (20% vs 7.7%), necrotising enterocolitis (10% vs 1.1%), pneumonia (30% vs 2.2%), hypoglycaemia (10% vs 1.1%), feed intolerance (20% vs 5.5%), and mottling (10% vs nil) were found more in sepsis babies than non-sepsis babies.

Mean I/T ratio, micro ESR, ANC, and TLC were comparable in the groups. CRP was positive in 10% of babies at 2 hours of life which increased to 40% at 24 hours in group 1 neonates. In group 2 neonates, 7.7% of neonates had positive CRP at 2 hours which increased to 14.4% at 24 hours. The positivity of CRP was more evident at 24 hours in sepsis group than non-sepsis, though the difference was not statistically significant (Table 1).

Table 1. Comparison of Baseline Demographic Profile and Sepsis Screen Parameters of Neonates between Sepsis and Non-Sepsis Groups

Variables	Group 1 (n = 10)	Group 2 (n = 90)	P-value
Male:female	5:5	53:37	0.738
Preterm:term	8:2	69:21	0.049*
SGA:AGA	3:7	41:49	0.519
Anthropometry Mean (SD)			
Gestational age (weeks)	33.40 (1.95)	34.45 (2.81)	0.253
Birth weight (gm)	1806.40 (692)	1942.87 (577)	0.491
Length (cm)	40.60 (5.44)	42.03 (3.5)	0.261
Head circumference (cm)	30 (2.44)	30.23 (2.14)	0.782
Sepsis Screen Parameters			
TLC /cu mm (mean ± SD)	17200 ± 10135.96	14715.33 ± 7171.82	0.322
ANC /cu mm (mean ± SD)	7604.3 ± 3808.98	7185.94 ± 3910.3	0.743
I/T ratio (mean ± SD)	0.06 ± 0.05	0.09 ± 0.13	0.433
Micro ESR (mm at 1st hr) (mean ± SD)	2 ± 1.05	1.57 ± 1.21	0.283

CRP Positivity n (%)			
At 2 HOL	1 (10)	7 (7.7)	0.115
At 24 HOL	4 (40)	13 (14.4)	

HOL: Hours of life, * P-value < 0.05 significant

Median (IQR) of urinary lactate and plasma lactate in first-passed urine and at 24 hours in both groups did not show any statistically significant difference (Table 2) and were not able to diagnose culture-positive EOS.

Table 2. Comparison of Median (IQR) of Urinary and Plasma Lactate between Sepsis and Non-Sepsis Groups

	Group 1 (n = 10)	Group 2 (n = 90)	
Variables	Median (IQR)	Median (IQR)	P-value
Urinary lactate in first passed sample	0.6 (0.18-1.84)	0.41 (0.24-0.72)	0.349
Urinary lactate at 24 HOL	0.40 (0.27-1.87)	0.38 (0.16-0.78)	0.194
Plasma lactate at 2 HOL	3.05 (2.52-4.42)	3.1 (2.5-3.9)	0.577
Plasma lactate at 24 HOL	3.05 (3.05-3.8)	2.9 (1.9-3.62)	0.558

HOL: Hours of Life

Complication rates in the form of non-survival, shock and meningitis were also compared in the two groups. Three out of 10 babies (30%) in group 1 and 7/90 (7.7%) in group 2 did not survive. All the neonates who died in both groups were premature. Three out of 10 neonates (30%) in culture positive group developed shock and one baby developed meningitis (10%). In group 2, 7/90 babies developed shock (7.7%) and one baby developed meningitis (1.1%). Complication rates were comparable in both groups.

Urinary lactate and plasma lactate were also compared among survivors and non-survivors (Table 3). Median (IQR) urinary lactate in first-passed urine and at 24 hours was significantly higher in non-survivors than survivors ($p = 0.03$ and $p = 0.005$ respectively). A cut-off of 0.71 mMol/L had a sensitivity of 70% and specificity of 77.7% for urinary lactate for diagnosing mortality in first-passed urine. At 24 hours, urinary lactate had a sensitivity of 70% and specificity of 70% for diagnosing mortality at a cut-off of 0.54 mMol/L. Urinary and plasma lactate were also compared in babies who developed shock with those without shock (Table 3). A significant difference was found in median (IQR) urinary lactate at 24 hours of life in babies with and without shock.

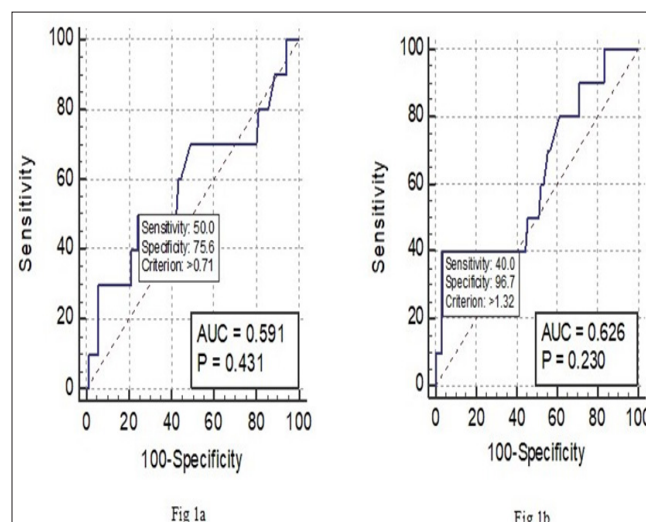
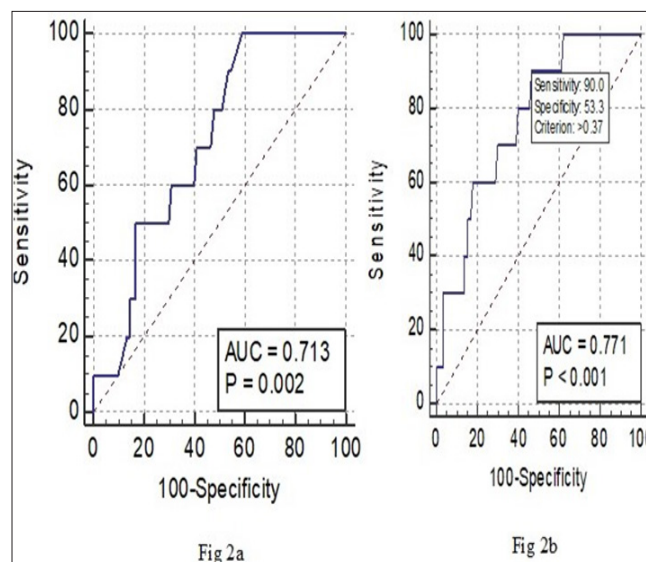
Table 3. Comparison of Urinary and Plasma Lactate in Survivors vs Non-Survivors and with Shock and Without Shock

Variables	Non-Survivors (n = 10)	Survivors (n = 90)	P-value
	Median (IQR)	Median (IQR)	
Urinary lactate at 2 HOL	0.8 (0.42-1.2)	0.41 (0.21-0.7)	0.03*
Urinary lactate at 24 HOL	0.91 (0.44-1.83)	0.35 (0.16-0.76)	0.005*
Plasma lactate at 2 HOL	3.2 (2.0-4.8)	3.1 (2.5-3.9)	0.80
Plasma lactate at 24 HOL	3.75 (2.7-5.6)	2.9 (1.9-3.5)	0.0594
Variables	Shock Present (n = 10)	Shock Absent (n = 90)	P-value
	Median (IQR)	Median (IQR)	
Urinary lactate at 2 HOL	0.69 (0.42-0.85)	0.69 (0.42-0.85)	0.130
Urinary lactate at 24 HOL	0.74 (0.38-0.98)	0.37 (0.16-0.77)	0.027*
Plasma lactate at 2 HOL	3.60 (2.0-4.8)	3.60 (2.0-4.8)	0.494
Plasma lactate at 24 HOL	3.35 (3.0-5.7)	3.35 (3.0-5.7)	0.066

HOL: Hours of Life, * P-value < 0.05 significant

At a cut-off of 0.42 mMol/L, urinary lactate at 24 hours of life was able to diagnose neonates with shock with a sensitivity of 70% and specificity of 58.9%. Further sub groups of the neonates under study were made as proven sepsis (n = 10), probable sepsis (n = 20), and no sepsis (n = 70). There was a significant difference between the groups in mean urinary lactate measured at 24 HOL. Mean (SD) was calculated to be 1.03 (1.001), 0.92 (0.78), and 0.43 (0.38) in proven sepsis, probable sepsis, and no sepsis respectively (p = 0.002).

Figure 1, shows the Receiver Operating Characteristic (ROC) curve for urinary lactate at 2 hours of life (1a) and 24 hours of life (1b). Figure 2, shows ROC curve for urinary lactate at 24 hours of life in shock (2a) and mortality (2b) groups. We could not determine a cut-off of urinary lactate and plasma lactate that could diagnose EOS with good sensitivity and specificity.

**Figure 1. ROC Curve for Urinary Lactate at 2 Hours of Life (1a) and 24 Hours of Life (1b) for Diagnosis of Culture-Positive Sepsis****Figure 2. ROC Curve for Urinary Lactate at 24 Hours of Life for Diagnosis of Shock (2a) and Non-Survivors (2b)**

Discussion

In the present study, we observed that urinary and plasma lactate were not able to diagnose EOS in neonates with risk factors at any cut-off with good sensitivity and specificity. Urinary lactate turned out to be a better marker to diagnose mortality and sepsis with shock than plasma lactate.

Lactate is known to be a marker of tissue hypoperfusion and is shown to be increased in patients with sepsis. Earlier studies hypothesised that sepsis is a condition causing tissue hypoperfusion due to macrocirculatory or microcirculatory dysfunction causing tissue hypoxia.^{10,12} Elevated lactate was classically believed to be due to

anaerobic metabolism associated with low oxygen delivery to the tissues.¹³ Different hypotheses for elevated lactate in septic conditions have been proposed by various researchers in recent years. Most patients with sepsis have hyperdynamic circulation with adequate delivery of oxygen to the tissues. Increased metabolic rate in septic patients leads to increased glycolytic flux, which enhances the ability of the pyruvate dehydrogenase enzyme to catalyse the process of change of pyruvate to lactate.¹⁴ Also, lactate is found to be a marker of endogenous catecholamine release. Enhanced concentrations of endogenous epinephrine and norepinephrine have been seen in septic shock animal models as well as septic humans. These concentrations have been linked to hyperlactataemia.^{15,18}

The cut-off of normal lactate levels in neonates is not well defined. Hawdon et al. have shown the variation of plasma lactate levels with gestation and postnatal day of life.¹⁹ A newborn's blood glucose level drops during the first two hours after birth and then rises to a constant level two to three hours later. The fall in glucose level is more in preterm neonates.²⁰ As majority of culture-positive neonates in our study were premature, this could have led to normal levels of urinary and plasma lactate at 2 hours of life in culture-positive babies.

In the case of patients with severe sepsis and septic shock, increased lactate is said to be present due to impaired clearance rather than excess production.^{21,22} Lactate clearance is lowered only when liver blood decreases to 25% of normal.²³ Absence of severe sepsis and septic shock on day one of life could be another reason for normal lactate levels in our septic neonates.

The renal cortex is a major lactate-consuming organ in the body after the liver. Lactate is handled by the kidneys through excretion, gluconeogenesis, and oxidation.²⁴ Renal excretion is only important with hyperlactataemia since the renal threshold is 6-10 mMol/mL.²³ We observed increased urinary lactate levels in first-passed urine and 24 hours of life in babies who developed shock later on. The difference was statistically significant. Patients having vigorous endogenous catecholamine release maintain blood pressure, thus presenting as an occult shock. Elevated lactate identifies these patients and aid in aggressive management.²⁵ All the babies in our study had normal renal function when lactate was measured. We hypothesise that excess lactate in blood could have been excreted in the urine giving a significant difference in urinary lactate in the diagnosis of EOS and not in plasma lactate. This also suggests that urinary lactate may be a marker of severe sepsis and septic shock in neonates at EOS risk.

For diagnosis of EOS, blood culture is considered to be the best test,² but the sensitivity of this test is only around

30-40%.⁸ As per the National Neonatology Forum, India, there is no rationale for performing a "sepsis screen" (i.e. CRP, haematological parameters, micro ESR) in suspected EOS due to very low Negative Predictive Value (NPV) of these parameters. Procalcitonin and IL-6 are found to be more promising for the diagnosis of EOS, but they are currently not easily available on the bedside and are not considered standards of care.⁷ Lactate is a bedside, easily available marker which can aid in the early diagnosis of EOS in suspected babies born with risk factors along with other markers.

The strength of our study is that most of our patients were haemodynamically stable septic patients whereas studies on lactate in adult and paediatric patients are in severe sepsis and septic shock conditions. To the best of our literature search, we could not find a study that has determined urinary lactate in neonatal sepsis. The major limitation of our study was inadequate sample size. The rate of culture positivity was too low and the time frame was limited. Post-hoc sample size considering AUROC of 0.625 for urinary lactate at 24 HOL and 10% culture positivity rate was calculated as 337 controls and 34 cases; making our study under powered to draw definite conclusions. Further studies with adequate sample size on urinary lactate may give us a non-invasive marker of diagnosis in early-onset sepsis. Serial measurements of urinary and plasma lactate beyond 24 hours of life are suggested to explore the role of lactate in early-onset sepsis.

Conclusion

A rapid, reliable and non-invasive biomarker is needed to diagnose babies with risk factors of early-onset sepsis. In our study, both urinary and plasma were not able to differentiate babies developing early onset sepsis from those who were not, at both 2 hours of life and 24 hours of life. However, urinary lactate turned out to be a better marker than plasma lactate for diagnosing mortality and sepsis with shock in babies at risk of EOS.

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