ORIGINAL RESEARCH

Early Onset Sepsis Prediction In Neonates Using Plasma And Urinary Lactate

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ABSTRACT

Aim: The purpose of this research was to determine the minimum threshold levels of plasma and urinary lactate that should be used to diagnose EOS. **Material and Method :**The study comprised of ninety neonates at risk for early-onset sepsis. The following tests were performed: sepsis screening, blood culture, plasma lactate within two hours, and urinary lactate in the initial urine sample. At 24 ± 2 hours, CRP, plasma, and urinary lactate measurements were repeated. **Results:** In the sepsis group, the median urinary lactate levels were 0.5 mMol/L and 0.45 mMol/L at the first passed sample, respectively, while in the non-sepsis group, they were 0.37 mMol/L and 0.43 mMol/L at 24 hours. Neither plasma nor urinary lactate could be utilized to diagnose sepsis with an early onset. In contrast, urinary lactate demonstrated utility as a diagnostic indicator for sepsis accompanied by mortality and shock. **Conclusion:** Our research concludes that plasma and urinary lactate do not predict EOS, urinary lactate can predict shock and mortality in infants with EOS at 24 hours of life

INTRODUCTION

Neonatal sepsis is a systemic condition caused by a bacterial, viral or fungal agent; it is characterized by clinical manifestations and hemodynamic changes; and it is extremely dangerous, with high rates of mortality and morbidity. Its incidence ranges from 1 to 5 per 1000 live births, contingent upon the population under study and the case definition.[1] The spectrum of clinical presentations extends from minor subclinical infections to major focal or systemic diseases. Although the infectious agent may originate from maternal or intrauterine flora, it could also be a product of the community or hospital. Early-onset, late-onset, and very late-onset neonatal sepsis are the three classifications based on the timing of the emergence of the symptoms. Although the term "early onset neonatal sepsis" refers to cases in which clinical manifestations occur within the initial three days of life (less than 72 hours), certain researchers expand this threshold to the first seven days. In this context, late-onset neonatal sepsis refers to cases that are identified between the 4th and 30th day of life, or after the initial seven days. Conversely, very late-onset neonatal sepsis pertains to instances of sepsis that are identified in infants who require hospitalization in the neonatal intensive care unit from the initial 30 days following birth until their discharge.[2,3] Infant sepsis caused by causative microorganisms is typically transmitted vertically from the mother. Chorioamnionitis can be caused by microorganisms present in the cervix, vagina, rectum, birth canal, or uterus that traverse intact or ruptured membranes prior to or during labor.[4] However, the presence of severe clinical manifestations and bacteremia indicators from the moment of birth, particularly in infants delivered via cesarean section without membrane rupture, indicate the possibility of placental transmission.[5] Promptly diagnosing EOS has proven to be difficult. The course of treatment for neonates at risk of EOS is determined by clinical symptoms, the presence of sepsis screen parameter positivity after birth, risk factors in both the mother and the infant, and the outcome of postnatal sepsis screening.[6,7] Blood culture is the gold standard for diagnosing neonatal sepsis; however, due to the minimum 48-hour turnaround time for the report, many of these infants receive intravenous antibiotics despite not being infected. To prevent unnecessary treatment of uninfected infants, a laboratory test that can predict EOS in at-risk neonates and is early, sensitive, specific, and readily available is necessary.[8] To date, there has been no identification of a singular

biomarker that possesses the capability to precisely diagnose septicaemia and direct the administration of effective antibiotics. As an indicator of hypoxia and inadequate perfusion in pediatric and neonatal populations, lactate has been utilized under a variety of conditions.[9] The utility of urinary lactate has been demonstrated in the treatment of hypoxic-ischemic encephalopathy and bronchopulmonary¸ dysplasia [10,11], but it has not been investigated in sepsis. Furthermore, the parameter exhibits the benefit of functioning as a noninvasive test. The absence of a known threshold for urinary lactate level that can diagnose sepsis in neonates. Therefore, we designed this research with the principal aim of ascertaining the threshold value of urinary lactate for identifying EOS in at-risk neonates in first-passed urine and 24 ± 2 hours after birth, as well as the threshold value for plasma lactate for diagnosing EOS at 2 hours and 24 ± 2 hours after birth.

MATERIAL AND METHOD

- This cross-sectional study was conducted in the Department of Paediatrics in a tertiary care hospital after approval from the Institute Ethics Committee.
- The study enrolled neonates who possessed two or more risk factors for EOS, subsequent to obtaining written informed consent from the neonates' parents or custodians.
- Infants who were born with birth asphyxia, defined as having a low Apgar score of less than seven at one minute, congenital anomalies, multiple pregnancies, meconium-stained liquor, infants of diabetic mothers (IDM) or mothers with known metabolic abnormalities and other morbidities were excluded from the study.
- All of these infants underwent a sepsis screen [ANC, TLC, micro ESR, CRP, I/T ratio], blood culture and plasma lactate analysis within two hours of birth. At 24.2 hours, CRP and plasma lactate measurements were repeated.
- In order to estimate lactate, two urine samples were obtained: one first pass urine and then sample was collected at 24 ± 2 hours. The development of sepsis and the presence of positive blood cultures in infants were monitored.
- Antibiotics were initiated in cases where a positive sepsis screen was identified or foul-smelling liquor, more than two risk factors for EOS or more than one antenatal risk factor were present.
- Neonates were additionally categorized as having no sepsis (presence or absence of clinical signs, negative sepsis screen and culture), probable (present clinical signs or symptoms with a minimum of two aberrant laboratory results), or proven (clinical signs or symptoms present).

Sample size: Ninety neonates were enrolled as the convenience sample size.

Sample Collection

Under aseptic conditions, three milliliters of venous blood were collected using a heparinized cannula into a fluoride-oxalate vial containing plasma lactate. The plasma was then separated by centrifugation at 400 x g for ten minutes within thirty minutes. Following that, plasma was frozen at -20 °C. Preferably, urine was obtained by placing a sack over the perineum and utilizing a syringe to aspirate from the bag. If collection was not possible, urinary catheters were utilized.

Lactate Assay

Within twenty-four hours of sample collection, lactate concentrations in stored plasma and urine were determined using a colorimetric method and Lactate Multipurpose liquid reagent in conjunction with automated and semi-automated analyzers. Determining the urinary lactate cut-off in the first-passed urine and at 24 ± 2 hours after birth was the primary outcome in order to diagnose sepsis in neonates at risk of developing EOS. The second objective was to ascertain the plasma lactate threshold for diagnosing sepsis in these neonates at 2 hours and 24 ± 2 hours after birth.

Statistical Analysis

The statistical software SSPS 20.0 was used. P values less than or equal to 0.05 were deemed significant. Utilizing Fischer's exact test, the relationship between positive blood culture results and categorical variables was determined. Mean gestational age, anthropometric parameters, vital parameters, ANC, TLC, micro ESR, and I/T ratio were compared between blood culture positive and negative groups using the unpaired student t test. The Mann Whitney Company In order to compare the median urinary and plasma lactate levels of blood culture-positive and negative groups, survivors and non-survivors, and infants with and without shock, the U test was utilized.

RESULTS

Ninety neonates who were born with two or more EOS risk factors were included in the study. Group 1 (sepsis) was assigned to neonates with a positive blood culture result; group 2 (non-sepsis) was assigned to those with a negative blood culture result.

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 = 80)	P value
Male:female	5:5	48:32	0.634
Preterm:term	7:3	64:16	0.032
SGA:AGA	2:8	36:44	0.666
Anthropometry Mean (SD)			
Gestational age (weeks)	32.30	33.81	0.315
Birth weight (gm)	1744.34	1856.26	0.512
Length (cm)	40.41	43.34	0.234
Head circumference (cm)	31	31.20	0.653
Sepsis Screen Parameters			
TLC /cu mm (mean± SD)	16500 ±13435.96	13605.33± 6871.82	0.213
ANC /cu mm (mean± SD)	8609.3 ±3505.98	8105.94 ±3704.3	0.634
I/T ratio (mean ±SD)	0.04 ± 0.05	0.07 ±0.13	0.325
Micro ESR (mm at 1st hr) (mean ± SD)	1.66 ± 1.43	1.20 ±1.23	0.124
CRP Positivity n (%)			
At 2 HOL	1(10%)	6 (7.5%)	
At 24 HOL	4(40%)	12(15%)	0.123

The baseline demographic profile of the neonates in both groups is presented in Table 1. The incidence of EOS was greater in preterm neonates than in term neonates. The groups exhibited comparability in relation to additional parameters. In the groups, the mean I/T ratio, microESR, ANC, and TLC were comparable. Positive CRP levels were detected in 10% of infants at 2 hours of age, rising to 40% at 24 hours in group 1 neonates. At two hours, 7.5% of neonates in group 2 had positive CRP; by twenty-four hours, that number had increased to 15%. The sepsis group exhibited a more pronounced positivity for CRP at 24 hours compared to the non-sepsis group, although this distinction did not reach statistical significance. Respiratory and cardiac rates were comparable between the two cohorts. Respiratory distress was the most prevalent clinical feature in both groups, affecting 39% of culture-positive infants and 41% of culture-negative infants. More sepsis infants than non-sepsis infants were diagnosed with meningitis (8% vs 1.5%), shock (32% vs 6.4%), DIC (28% vs nil), lethargy (18% vs 6.4%), necrotizing enterocolitis (9% vs 1%), pneumonia (27% vs 3.1%), hypoglycemia (8% vs 1.5%), feed intolerance (21% vs 4.5%), and mottling (9% vs 1).

Table 2.Comparison of Median (IQR) of Urinary and Plasma Lactate between Sepsis and Non-Sepsis Groups Variables	Group 1 (n = 10) Median (IQR)	Group 2 (n = 80) Median (IQR)
Urinary lactate in first passed sample	0.5	0.45
Urinary lactate at 24 Hours Of Life	0.37	0.43
Plasma lactate at 2 HOL	2.89	2.71
Plasma lactate at 24 HOL	3.02	2.69

Median (IQR) of urinary lactate and plasma lactate in first passed urine and at 24 hours in both groups were not able to diagnose culture-positive EOS.

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

Variables	Non Survivors(n = 10) Median(IQR)	Survivors(n = 80) Median(IQR)	P value
Urinary lactateat 2 HOL	0.7	0.39	0.02
Urinary lactateat 24 HOL	0.83	0.31	0.003
Plasma lactate at2 HOL	2.9	2.8	0.87
Plasma lactate at24 HOL	3.5	2.6	0.0589
	Shock Present(n = 10)	**Shock Absent(n = 80)**	
Variables	**Median(IQR)**	**Median(IQR)**	**P value**
Urinary lactatat 2 HOL	0.57	0.57	0.134
Urinary lactateat 24 HOL	0.71	0.31	0.023
Plasma lactate at2 HOL	3.32	3.32	0.654
Plasma lactate at24 HOL	3.11	3.11	0.075

A comparison was also made between plasma lactate and urinary lactate levels in survivors and non-survivors. Non-survivors had substantially higher median (IQR) urinary lactate levels in first-passed urine and at 24 hours compared to survivors . In addition, plasma lactate and urinary output were compared between infants who developed shock and those who did not. At 24 hours of age, there was a notable disparity in the median (IQR) urinary lactate levels between infants who received shock and those who did not. With a specificity of 58.9% and a sensitivity of 70%, urinary lactate at 24 hours of life could diagnose neonates with shock using a cutoff of 0.42 mMol/L.

DISCUSSION

As an indicator of tissue hypoperfusion, lactate has been demonstrated to be elevated in septic patients. Previous research put forth the hypothesis that sepsis is a pathological state characterized by hypoxia in the tissues, which is caused by dysfunction in the macrocirculatory or microcirculatory systems.[12,13] Lactate elevation was traditionally attributed to anaerobic metabolism accompanied by inadequate oxygen delivery to the tissues.[14] Diverse hypotheses regarding the cause of elevated lactate levels in septic environments have been advanced by scientists in recent times. The majority of sepsis patients have hyperdynamic circulation, which ensures that oxygen reaches the tissues adequately. Septic patients with an elevated metabolic rate experience an increase in glycolytic flux, which facilitates the catalytic conversion of pyruvate to lactate by the pyruvate dehydrogenase enzyme.[15] Lactate has also been identified as an indicator of endogenous catecholamine release. Enhanced levels of endogenous epinephrine and norepinephrine have been observed in both septic humans and animal models of shock. Hyperlactatemic symptoms have been associated with these concentrations. The precise delineation of normal lactate levels in neonates remains ambiguous. The correlation between postnatal day of life and plasma lactate levels has been demonstrated by Hawdon et al[16]. After the initial two hours following delivery, the blood glucose level of a newborn decreases before stabilizing between two and three hours later. The magnitude of the glucose drop is greater in preterm neonates.[17] This may have resulted in culture-positive infants having normal levels of urinary and plasma lactate at two hours of age, given that the preponderance of culture-positive neonates in our study were premature.

According to Levraut J et al[18] and Bellomo R et al[19], elevated lactate levels in patients with severe sepsis and septic shock are the result of impaired clearance as opposed to excessive production. Lactate clearance is only reduced to 25% of normal when liver blood volume falls below that threshold.[20] The absence of severe sepsis and septic shock in our neonates who were born septic may also account for their normal lactate levels on day one of life. The renal cortex, following the liver, is the primary organ that consumes lactate in the body. According to Bellomo R et al[21], the kidneys are responsible for the metabolism of lactate via excretion, gluconeogenesis, and oxidation. In the case of hyperlactataemia, renal excretion is only significant due to the renal threshold of 6-10 mMol/mL. Urinary lactate levels were found to be elevated in first-passed urine and at 24 hours of life in infants who subsequently developed shock. Statistically, the difference was significant. Patients who maintain blood pressure through vigorous endogenous catecholamine release manifest an occult shock. Identifying these patients with elevated lactate levels facilitates aggressive management.[22] In our study, all infants exhibited normal renal function as determined by lactate measurement. We hypothesize that surplus lactate in the bloodstream may have been eliminated via urine, resulting in a notable distinction in urinary lactate rather than plasma lactate for the diagnosis of EOS. Additionally, this suggests that urinary lactate may serve as an indicator of septic shock and severe sepsis in neonates at risk for EOS. Although blood culture is considered the most accurate test for diagnosing EOS, its sensitivity is only 30–40%.Although procalcitonin and IL-6 have demonstrated greater potential in the diagnosis of EOS, their accessibility at the bedside is limited at present, and they are not regarded as benchmark diagnostic tools.[23] In addition to other indicators, lactate is a readily accessible bedside marker that can aid in the early diagnosis of EOS in infants who are suspected of having the condition. Our study's strength is that the majority of our patients were septic patients with stable hemodynamics, whereas studies on lactate in pediatric and adult patients have focused on patients with severe sepsis and septic shock. Our investigation was significantly limited by an insufficient sample size. The pace of cultural positivity was insufficient, and the available time was constrained. Additional research with a sufficient sample size on urinary lactate may provide a noninvasive diagnostic marker for sepsis with early onset. Serial urinary and plasma lactate measurements beyond 24 hours of life are recommended in order to investigate the potential involvement of lactate in early-onset sepsis.

CONCLUSION

There is a need for a non-invasive, swift, and dependable biomarker to diagnose infants with early-onset sepsis risk factors. Urinary and plasma samples failed to distinguish infants with early onset sepsis from those without the condition at two and twenty-four hours of age, respectively, in our study. In infants at risk of EOS, urinary lactate was found to be a more accurate indicator of mortality and sepsis with shock than plasma lactate.

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