ORIGINAL ARTICLE

BLOOD LACTATE LEVELS AND LACTATE CLEARANCE AS PREDICTORS OF MORTALITY IN NEONATAL SEPSIS

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Background: Sepsis is life-threatening organ dysfunction caused by dysregulated host response to infection. Aim of the study is Neonatal sepsis refers to infection involving the blood stream in neonates. It is major health problem causing neonatal mortality and morbidity in developing countries. Our study aimed to assess the correlation between lactate clearance and blood lactate levels with outcome of neonatal sepsis. **Methods:** Seventy-three eligible neonates recruited with convenience sampling technique. Study was conducted at the Neonatology department, The Children's Hospital & the Institute of Child Health, Lahore. After approval from institutional review board, and informed consent of parents/guardians, neonates with sepsis were selected through a present inclusion and exclusion criteria. Data was collected with the predetermined demographics, inflammatory markers and lactate levels. **Results:** This research revealed 37% (n=27) mortality rate among septic neonates who were having higher blood lactate levels and low lactate clearance at 6 hours of admission in nursery. Hence higher serum lactate levels and low lactate clearance (<10%) at 6 hours were significant predictors of poor outcome in septic neonates (*p*-Value, <0.05). The lactate level of neonates who could not survive was 5.68±1.22 as compared to who were discharged 4.11±1.14 (*p*-Value, <0.05). **Conclusion:** Higher blood lactate levels and lactate clearance of less than 10% at 6 hours of admission in nursery are significant predictors of mortality in neonatal sepsis. Early lactate stabilization and sepsis management can improve the clinical outcomes.

Keywords: Sepsis; Lactate; Neonate; Correlation

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INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by dysregulated host response to infection.[1] This is a clinical syndrome defined as presence of both infection and systemic inflammatory response (SIRS) before first 28 days of life. SIRS is used to describe unique process of infection and subsequent systemic response. It is combination of certain symptoms, signs and laboratory test including hyperthermia/hypothermia, tachycardia, tachypnoea, abnormal white blood cell count, increased C.-reactive protein (CRP), raised IL-6, IL-8, positive PCR and recombinant RNA gene.

Neonatal sepsis is broadly categorized into two (i.e.) early onset sepsis (EOS) & late onset sepsis (LOS).[2] Early onset sepsis is defined as sepsis in first 72 hours of life. Neonate acquires early onset infection during antepartum or intrapartum period from maternal genital tract. LOS is defined as sepsis acquired after 72 hours till first 28 days of life. Bacteria responsible for LOS are mostly acquired through environment e.g., human contact, contaminated equipment, nosocomial infections.[3] Neonatal sepsis is major health problem in neonatal health care units worldwide. According to World Health Organization 2.4 million deaths occur due to neonatal sepsis.[4] Neonatal mortality rate in Pakistan is 41/1000 live births. Neonatal sepsis accounts total of 29.92% deaths.[5] Lactate is an organic compound and a metabolite of glucose produced through anaerobic glycolysis especially in muscles for provision of energy under stressful conditions where tissues suffer from hypoxia. It is actively cleared by liver and kidney hence its level in blood remains maintained under normal circumstances.[6]

The pathophysiology of sepsis includes cellular hypoxia, increased production of inflammatory mediators and increased lactic acidosis which in turn could result in subnormal tissue perfusion. Furthermore, activation of extrinsic coagulation cascade results in damage of small blood vessels which impairs blood flow by making small thrombi leading to multi organ failure.[7,8] In this scenario, oxygen demand outstrips the available oxygen supply, either systemically or regionally and lactic acidosis further reduces cardiac contractility contributing to shock, organ failure and death.[9,10] This ongoing tissue hypoxia and release of inflammatory mediators result in increased production of lactate in muscles, liver and the gut. Concurrent reduced tissue blood flow results in decreased lactate clearance from liver causing further hyperlactatemia in

sepsis. Research studies have suggested that blood lactate levels and its clearance as early as 6 hours have a direct relationship with severity of neonatal sepsis thus it can be used to assess tissue hypoxia, severity and prognosis of sepsis.[11,12] This study was carried out to determine relationship between blood lactate levels and lactate clearance at 6 hours with outcome of neonates admitted in nursery with sepsis.

MATERIAL AND METHODS

Descriptive prospective observational research design was adopted to conduct the research at the Department of Neonatology, The Children's Hospital & the Institute of Child Health, Lahore. Research was conducted over the period of six month extended from March to August, 2020. A sample size of 73 infants was calculated with 80% power of test and 5% level of significance by taking expected mortality rate from sepsis as 26% from a study.[13]

Formula applied for calculation of sample size was; $n = z^2 * p * (1 - p) / d^2$

Non-probability convenience sampling technique was used.

Neonates of all gestational ages from birth to 28 days of life were included. They were fulfilling the criteria set for sepsis i.e., two or more of the following (one must be abnormal temperature or leucocyte count) temperature instability range<36 or > 37.9^{0}C, heart rate more than 180 beats/min, respiratory rate of more than 60 breaths/min, WBC (<4000* 10^9 or 34000 *109/L), CRP more than 10g/dl, and/or positive blood culture or CSF or urine culture.

Neonates having congenital anomalies e.g., congenital heart disease, Inborn error of metabolism, suffered from birth asphyxia and who received pre-admission. Antibiotic treatment was excluded. Data collection was done after taking ethical approval (Ref. #: 59523) from Institutional review board of The Children's Hospital & the Institute of Child Health. Informed consent from the parents was taken whose neonates met inclusion criteria. Data included basic demographic variables, inflammatory markers and lactate levels. The blood lactate levels were taken at zero and 6th hour of admission in nursery. Lactate clearance was calculated as;

High lactate clearance labelled as >10% clearance at 6th hour of admission.

Low lactate clearance labelled as <10% clearance at 6th hour of admission.

We used the NOVA arterial blood gas machine to determine lactate levels in capillary blood obtained through heel prick sampling technique. Regular calibration of equipment was ensured for quality of results. All the information was recorded in predesigned data collection *proforma*.

The data was entered in SPSS 23.0. Frequency and percentage were calculated for the basic demographic variables while inferential statistics were applied to measure the association between dependent and independent variables. Chi-square test was applied and *p*-value of < 0.05 was considered as significant.

RESULTS

A total of seventy-three eligible septic neonates were recruited in this study. Male neonates were 39(53.4%) and female were 34 (46%). Most neonates 49 (67.1%) were born through caesarean section. Preterm neonates were 24 (32.9%) and weight of 21 (28.8%) neonates was <2.5 kilograms. During study period, 27 (37%) neonates died of sepsis. Table-1

Out of 46 neonates who were discharged from the hospital, 37(80.4%) neonates' lactate clearance was more than 10% in first 6hours of admission. Whereas, out of 27 neonates who died during study, 21(77.8%) neonates' lactate clearance was less than 10% (*p*-Value, <0.05). as depicted in Table-2.

The lactate level of neonates who died was 5.68±1.22 as compared to who were discharged 4.11±1.14 (*p*-value, <0.05) demonstrated in Table-3.

Table-1: Demographic variables of neonate (n=73)

Demographics		**Frequency (%)**
Gender	Male	39 (53.4)
	Female	34 (46.6)
Mode of delivery	SVD	24 (32.9)
	C- Section	49 (67.1)
Outcome	Discharged	46 (63)
	Died	27 (37)
Gestational Age	Preterm	24 (32.9)
	Term	49 (67.1)
Weight	<2.5 Kg	21 (28.8)
	>2.5 Kg	52 (71.2)

Table-2: Predictor of mortality associated with lactate clearance at 6th hour

	Lactate clearance at 6 hr.		**Total**	***p*-value**
	>10%	<10%		
Discharged	37 (80.4%)	9 (19.6%)	46 (100%)	0.0001
Died	6 (22.2%)	21 (77.8%)	27 (100%)	

Total	43 (58.9%)	30 (41.1%)	73 (100%)	

Table-3: Predictor of mortality associated with lactate levels

Outcome	N	Mean Lactate Levels	Std. Deviation	*p*-value
Discharged	46	4.11	1.14	0.003
Died	27	5.68	1.22	
Total	73	4.69	1.38	

DISCUSSION

Current study measured the association of blood lactate levels and lactate clearance among the neonates admitted with sepsis. Study revealed, 27 (37%) mortality among the neonates admitted in nursery with sepsis. This finding is considerably higher as compared to national and international studies. A national study done in Karachi[14] reported 16% mortality and 26.3% in international Taiwanese study[15]. Most neonates in the current study were born through caesarean section procedure. A meta-analysis highlighted the caesarean section as risk factor contributing to neonatal sepsis and report incidence of neonatal sepsis (n=3; OR 2.13; 95% CI [1.23, 3.70].[16] Therefore, higher caesarean sections could be the cause of neonatal sepsis in the current study.

Research studies have suggested that low lactate clearance and raised lactate levels were significantly correlated with prognosis of septic neonates as described in current study (*p*- value <0.003). Mortality was found higher among the neonates with <10% lactate clearance at 6th hour of admission in nursery in our study. This finding is aligned with the international studies[17,18] An Indonesian study[19] found significant correlation between increased lactic acid and neonatal sepsis which is comparable to findings in current research. However, in Indonesian study mortality rate was 48% in septic neonates with low lactate clearance and was found higher than the current study. Differences in patient management may have contributed to variations in the patient mortality rate.[20]

An East African study reported that hyperlactatemia as a risk factor for poor prognosis in children admitted with severe febrile illnesses and early lactate clearance within 8 hours of admission had an improved chance of survival.[20] Our study confirms this finding with higher survival rate 80.4% among those who were having high lactate clearance >10% within 6 hours of admission in nursery. Continual measurements of lactate and its clearance calculation provide trend and more accurate prognostic evaluation.[17] An Indonesian study found significant correlation between increased lactic acid and neonatal sepsis which is comparable to the findings in current research.[19]

The riddle of lactate management among the neonates is not easy as lactate can rise due to number of clinical pathologies and organ dysfunction in addition of sepsis. Therefore, careful analysis of patient condition and early response is imperative to the positive clinical outcomes.

Strengths & Limitations

Sample size is sufficient and greater as compared to number of studies with acceptable level of power. Moreover, robust measures and strict selection criteria was followed during the study. However, study from single clinical setting limits the generalizability.

CONCLUSION

Study yielded higher lactate levels and lactate clearance <10% within 6 hours of admission in nursery are significant predictors of mortality in neonatal sepsis. Therefore, early detection and meticulous management of neonatal sepsis is key for better outcome of septic neonates.

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AUTHORS' CONTRIBUTION

SC: Data collection, analysis, article write-up. FH: Analysis of results, article writeup and review of data. KAIW: Analysis of results, article writeup and review of data. GV: Statistical Analysis of data. MS: Data collection. BF: Data collection.

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