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Lactate Clearance in Neonates withSeptic Shock as a Predictor of Outcome

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ABSTRACT: Background: Neonatal sepsis is one of the leading cause of neonatal deaths.According to the World Health Organization (WHO), five million neonatal deaths occur each year with a neonatal mortality rate of 34 per 1,000 live births. Neonatal sepsis and septic shock are the frequently encountered causes in the NICU; neonatal sepsis causes septic shock in about 1% to 5% of the cases, with the mortality rate being around 71%.

Objective: To assess the blood lactate levels &use lactate clearance to predict outcome in terms of survival or mortality in neonates with septic shock .

Methods: We conducted a prospective cohort study in the neonatal care unit, Department of Paediatrics, Hi-Tech Medical College, from November2018 to October 2019. We enrolled 117 neonatal sepsis patients, who were divided into either the high or low lactate clearance groups. All neonates were followed up until they were discharged from the hospital, as to whether they survived or died. We performed blood lactate measurements early on following their diagnosis of septic shock, and after the subsequent six hours following the first antibiotic administration and resuscitative measures. Logistic regression for the multivariate analysis and ROC curves for the accurate analysis of predictive outcome factors were performed.

Results: More deaths occurred in neonates with low lactate clearance at six hours (43%) than in those in the high lactate clearance group (5%). Low lactate clearance at six hours was a significant predictor of mortality (RR14.6, 95%CI 1.5 to 122), whereas the ROC analysis showed good accuracy.

Conclusion: Lactate clearance at six hours can be used as a predictor of mortality in neonates with septic shock.

Keywords: lactate clearance; predictor; mortality; neonatal sepsis, septic shock.

I. INTRODUCTION

Neonatal sepsis is a major health problem in neonatal care. According to the World Health Organization (WHO), five million neonatal deaths occur each year, [1] of which neonatal sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries. [2]

The incidence of neonatal sepsis according to National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The NNPD network in India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths .[3]

While the incidence of sepsis is known, the true incidence of septic shock in neonates has not been well documented. It is estimated to be around 1–5% of all infants with proven severe sepsis (Haque 2004).[4] Kermorvant-Duchemin E. et al. (2008)[5] reported septic shock in 1.3% of extremely low birth weight newborns with an associated mortality peaking at 71%.

Sepsis or serious infection within the first 4 weeks of life kills > 1 million neonates globally every year. Neonates with sepsis may present in or progress to septic shock, exemplified initially by cardiovascular dysfunction requiring fluid resuscitation or inotropic support.The clinical presentation of early onset sepsis in the newborn is variable. Typically, cold shock is characterized by peripheral vasoconstriction, cool peripheries, and tachycardia; hypotension is often a pre-terminal event. Warm shock is characterized by peripheral vasodilation and hypotension secondary to endotoxin release. These clinically different presentations may benefit from different therapeutic interventions.

The main cause of death in septic shock is organ system failure initiated by cellular hypoperfusion resulting in cellular hypoxia.[6] This condition is caused by the formation of microthrombi in small blood vessels which impair the blood flow.[7] Disruption of tissue perfusion and cellular hypoxia can occur before cardiovascular responses emerge. Some clinical signs such as changes in heart rate, blood pressure and urine output, cannot be used as sensitive markers for hypoxia and perfusion disorders, therefore, we need

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another parameter for monitoring tissue perfusion as an early assessment tool for microcirculation disorders.

Some studies have suggested that blood lactate levels may be used to assess tissue perfusion and be a marker for the onset of tissue hypoxia.[8,9] There is a proportional increase between blood lactate level and severity of tissue hypoxia.[10,11]Under normal conditions, serum lactate level is 2 mEq/L or lower. However, exercise can elevate it up to 4 mEq/L. Most lactate formed is efficiently eliminated by the liver and is utilized in gluconeogenesis or in the production of energy. Lactic acid is increased in situations of tissue hypoxia–ischemia. Lactic acidosis or hyperlactatemia occurs when production exceeds clearance, which has been confirmed to be associated with worse clinical outcomes in critically ill patients.[9,12] Such association has been replicated in several patient populations, including trauma, severe sepsis and septic shock. [13,14]

Lactate clearance is the reduction of lactate concentrations with interventional strategies, therapeutic strategies that can potentially decrease arterial lactate may be associated with improved clinical outcomes. [15]The aim of such a strategy is to reverse the global tissue hypoxia. The idea of lactate clearance(LC) is to accommodate this concept. Many clinical studies have demonstrated that patients with LC showed better clinical outcomes as compared with those without LC ;[16] furthermore, patients with rapid LC were more likely to survive than those with slow LC. [17]

II. METHODOLOGY

This study was a Prospective Cohort Study conducted on neonates in level 2 and 3 neonatal care units of Hi-Tech Medical College & Hospital, Bhubaneswar from November 2018 To October 2020.

Inclusion criteria: Neonates with a clinical diagnosis of sepsis, that is, the presence of more than one symptom or sign, at least in four groups of symptoms from six groups of symptoms:1) common symptoms: ill-appearance, not eager to drink, increased or decreased body temperature (>37.5 or <36.5°C), sclerema/scleroderma; 2)Neurologic: convulsions, unconscious, decreased activity;2)Respiratory: respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis; 3)Cardiac: poor perfusion, rapid and weak pulse, hypotension,;4) Gastrointenstinal : jaundice, poor feeding, abdominal distension; 5) Hematological : bleeding, leukopenia, bands cell count, CRP. Further among the diagnosed neonates with sepsis, babies developing septic shock were included on basis of following criteria 1)Weak& fast pulse (HR>180/min); 2)Extremities cold to touch 3)Capillary Refill Time >3 sec ;4)With or without the following signs: a)Colour- very pale b)Lethargy not arousable on stimulation (due to cerebral hypo perfusion)

Exclusion criteria: 1)Neonates with gross congenital malformations or other life threatening conditions;2)Neonates less than 30 weeks gestation and Less than 1kg birth weight(ELBW);3)Neonates who received blood transfusion or infusion Ringer's lactate prior to examination, or those who suffered from shock and respiratory failure before examination.

Sepsis mortality predictors included sex, birth weight, gestational age, mode of delivery, asphyxia, and laboratory results, which were taken in the early diagnosis of sepsis including leukocytes, platelets, and venous blood sugar (recorded from medical records). Asphyxia was defined to be when the Apgar score was <7, or when the Apgar score was unknown, with the determination based on resuscitation requirement, or hypoxemia on blood gas analysis.

Using aseptic precautions 0.5 ml of arterial blood was withdrawn using 1ml pre-heparinised syringe from the radial or femoral artery and were immediately analysed using ABL 80 Flex Radiometer Blood Gas Analyser. Blood lactate levels recorded at diagnosis (0hr) and 6hrs interval from ABG. In interval period of 6hrs resuscitation measures to treat hypo perfusion, hypotension and antibiotic administration were undertaken as per the standard treatment protocol. LC has been incorporated into the initial resuscitation target in the 2016 Surviving Sepsis Campaign guideline. [14]Lactate clearance at six hours was calculated based on the following formula [13] :

$$\frac{\text{Initial lactate level} - \text{lactate level at 6 hours} \times 100}{\text{Initial lactate level}}$$

The subjects were classified into two groups based on lactate clearance: low lactate clearance or high lactate clearance. The clearance groups were based on the lactate level attenuation of more or less than 20% at six hours after administration of the first antibiotic. We evaluated the outcome of whether they survived or died during the hospitalization. We used first-line antibiotics to treat neonatal sepsis.

Data were analyzed by logistic regression analysis. Variables with P value <0.2 in the univariate analysis were included in the multivariate analysis

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to determine the effect of each predictor on outcomes of neonatal sepsis. The degree of correlated strength was expressed as RR with 95% confidence intervals (CI).Informed consent was obtained from patients' parents. This study was approved by the Medical and Health Research Ethics Committee of Hi-Tech Medical College & Hospital, Bhubaneswar,India.

III. RESULTS

A total of 117 cases were taken into study and serum lactate levels were measured at onset of septic shock, taken to be s.lactate at 0hrs then again at 6hrs interval following various resuscitative measures to improve outcome. The baseline characteristics of study subjects are presented in **Table 1**.

Table 1: Baseline characteristics of study subjects based on outcome of Neonatal sepsis.

Characteristic	Died N=29	Survived N=88
Gender		
• Male	19	46
• Female	10	42
Mean Age At Diagnosis, Days (SD)	9.7 (5.2)	7.1 (5.0)
Birth Weight		
• <2500g	24	31
• ≥2500g	5	57
Mode Of Delivery		
• NVD	13	40
• LSCS	16	48
Gestational Age		
• <37 Weeks	21	33
• ≥37 Weeks	8	55
Asphyxia		
• Yes	6	20
• No	23	68

There were 29 deaths out of 117 cases with case fatality rate of 24.7%.Univariate analysis of predictive indicators of neonatal sepsis mortality (**Table 2**) revealed that sex, mode of delivery, birth weight, gestational age, presence of asphyxia, laboratory parameters of platelets, leukocytes, random blood sugar, and blood cultures, were not significant predictors of mortality in neonatal sepsis patients.

The mean six-hour lactate clearance in the group who died [-25.2 (SD ±25.4)%] was significantly lower than the group who survived[17.8(SD±22.3)%]. Univariate analysis indicated that only birth weight, gestational age and lactate clearance at 6 hrshad p value <0.2, therefore those variables were included in multivariate analysis. The multivariate analysis revealed that lactate clearance at 6hrs was a statistically significant outcome predictor of septic shock in neonates (RR14.6, 95%CI 1.5 to 122).A greater proportion of subjects in low lactate clearance group (43%) died than those in the high lactate clearance group (5%).

Table 2: Univariate and Multivariate analysis of the outcome predictors of neonatal sepsis.

Outcome predictors	Univariate			Multivariate	
	RR	95%CI	p value	RR	95%CI
Gender • Male • Female	0.9	0.4 to2.0	0.8		
Birth Weight • <2500g • ≥2500g	5.4	2.2 to 13.2	0.01	3.0	0.7 to 9.6
Mode Of Delivery					

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• NVD • LSCS	0.9	0.5 to 1.8	0.9		
Gestational Age • <37 Weeks • ≥37 Weeks	3.0	1.4 to 6.2	0.14	1.5	0.5 to 7.1
Asphyxia • Yes • No	0.9	0.4 to2.0	0.82		
Leucocyte count • >5000-30000 mm3 • <5000 and >30000mm3	0.6	0.3 to 1.5	0.3		
Platelet count • <50000/ mm3 • ≥50000/mm3	1.0	0.5 to 2.1	0.8		
Random blood sugar • <45 mg/dl • ≥45 mg/dl	1.2	0.3 to 3.2	0.4		
Blood culture • Positive • Negative	1.2	0.6 to 2.3	0.3		
Lactate clearance at six hours • Low lactate clearance • High lactate clearance	8.2	2.6 to 25	.01	14.6	1.5 to 122

ROC curve analysis for six hour lactate showed an area under curve (AUC) of 89% ($p<0.05$), suggesting that six hour lactate clearance measurement had good strength as a predictor of outcome in neonatal septic shock.

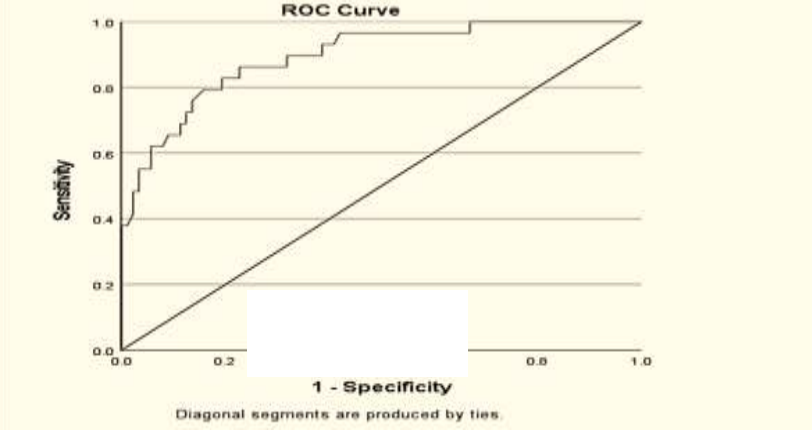

Figure1: ROC curve of six hours lactate clearance as a predictive indicator of neonatal sepsis.

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Analysis of mortality: There were 29 deaths out of the total 117 cases, with the case fatality being 24.7%. The initial lactate concentration was not significantly different between those who died and those who survived [5.1(±1.7) vs. 5.7 (±1.6), p=0.18], but lactate clearance at 6hrs was significantly lower in those who died (-25.2%) than those who survived (17.8%) (p<0.001). When lactate clearance was compared between the survived and death cases there was a significant difference of 45% between the mean. The fatality rate was directly proportional to less percentage clearance of lactate as evident from the fact that the among the 60 neonates in low lactate clearance group, (14.3%) died who had clearance between 0 to20%, (25%) died where the clearance was between 0 to -20%, and (61.7%) died when the clearance was <-20%.(**Figure 2**)

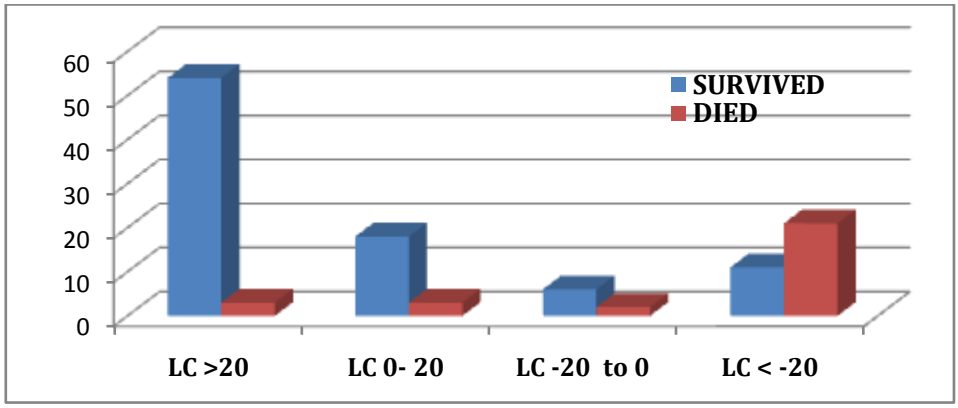

Figure 2: Bar Diagram Showing Outcome In Various Lactate Clearance Sub Groups.

IV. DISCUSSION

Our study demonstrated that a greater proportion of deaths occurred in the group of neonates with low lactate clearance at six hours (43%) than in those with high lactate clearance at six hours (5%). Logistic regression analysis showed that lactate clearance at six hours was a significant predictor of mortality (RR 14.6, 95%CI 1.5 to 122). Similarly, other studies, found that the mortality of critically ill neonates with low lactate clearance at six hours was significantly higher than that of the high lactate clearance group (50% vs. 9.4%)[17] respectively, and (68% vs. 13.1%)[16]respectively. A higher proportion of deaths in the low lactate clearance group in previous studies compared with our study were likely due to their subjects being recruited later in the course of their illness, compared to our subjects who were recruited at diagnosis.[17]

Infants who died due to neonatal sepsis showed a lower mean percentage of lactate clearance at six hours than those who survived [-25.2 (SD 25) % vs. 17.8 (SD21) %; (P=0.001)], similar to another study which involved critically ill neonates.[16]The characteristics of their study subjects were similar to ours.

Several studies have shown that lactate levels can be used as an early marker of tissue hypoxia, an assessment of disease severity, and a predictive indicator of outcomes in critically ill patients.[8]Low lactate clearance at six hours indicates a state of high blood lactate level that occurred within the preceding six hours. Such a condition accounts for hypoxia that persists in the tissues, causing organ dysfunction and death.[18]High lactate clearance indicates the return of lactate levels to normal values after treatment. High lactate clearance in septic patients was associated with lower's levels of proinflammatory cytokines (IL-1, IL-6, IL-8 and TNF-alpha) after 72 hours of treatment.

There was significant correlation between lactate clearance, outcome and prognosis. Hence, clearance directed therapy with respect to time is being investigated extensively among adults and pediatric population. There is no such studies in general neonatal ICU population to predict the outcome irrespective of type of illness. Less than 30 % clearance among pediatric population within first 24 hours of admission correlated significantly with mortality .[19]The non survivor group of the present study also had lactate clearance of less than 20% at 6 hours which was significantly different from mean value among survivors. The morbidity was high among the survived neonates with lactate clearance of less than 20% at 6 hours with significantly greater need of oxygen, fluid, inotrope, and mechanical ventilation.

V. CONCLUSION

Lactate clearance at six hours can be used as a predictor of mortality in neonates with septic shock.

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