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Original Article

Lactate clearance as a predictor of mortality in neonatal sepsis

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Abstract

Background Neonatal sepsis remains the leading cause of neonatal deaths. Therefore, efforts should be made to reduce its mortality. Lactate clearance can be used as a marker of onset of hypoxia and microcirculation disorders, as well as to predict patient outcomes.

Objective To assess the use of lactate clearance to predict mortality from neonatal sepsis.

Methods We conducted a prospective cohort study in the levels 2 and 3 of neonatal care unit, Department of Child Health, Dr. Sardjito General Hospital, Yogyakarta, from October to November 2011. We enrolled 40 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 sepsis, and after the subsequent six hours following the first antibiotic administration. 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 (48%) than in those in the high lactate clearance group (7%). Low lactate clearance at six hours was a significant predictor of mortality (RR 15.1; 95%CI 1.7 to 133), whereas the ROC analysis showed moderate accuracy.

Conclusion Lactate clearance at six hours may be used as a predictor of mortality in infants with neonatal sepsis. **[Paediatr Indones. 2016;56:193-8. doi: 10.14238/pi56.4.2016.193-8]**.

Keywords*: lactate clearance; predictor; mortality; neonatal sepsis*

Neonatal sepsis is a major health problem in neonatal care. 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, 98% of whom originate from developing countries. Efforts are, therefore, needed to reduce mortality due to neonatal sepsis.[1]

The main cause of death in sepsis is organ system failure initiated by cellular hypoxia.[2] This condition is caused by the formation of microthrombi in small blood vessels which impair the blood flow.[3] 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 another parameter for monitoring tissue perfusion as an early assessment tool for microcirculation disorders.

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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.[4-6] There is a proportional increase between blood lactate level and severity of tissue hypoxia. [7-8] Several other studies showed that serial lactate measurements have advantages over a single lactate measurement, and can be used as a predictor of mortality.[9-11] Lactate clearance rates can be calculated by serial lactate measurements.[12] Other studies showed that lactate clearance can be used as an indicator of tissue perfusion recovery in septic shock, sepsis after resuscitation and therapy,[13] and as a predictive indicator of mortality in adult sepsis patients.[12,14]

Lactate clearance studies to predict mortality and prognosis in neonatal sepsis patients have never been done. Six-hour lactate clearance may be useful as a predictive indicator of mortality in critically ill neonates[15] and those who suffer from severe asphyxia.[16] Our study was conducted to determine the usefulness of lactate clearance as a predictor of mortality in neonatal sepsis patients.

Methods

We conducted a prospective cohort study at levels 2 and 3 of the Neonatal Care Unit of Dr. Sardjito General Hospital, Yogyakarta from October to November 2011. The inclusion criteria were neonates with a clinical diagnosis of sepsis,[17] 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) gastrointestinal symptoms including vomiting or existence of residual gastric contents, diarrhea, abdominal distension, and hepatomegaly; 3) respiratory symptoms including dyspnea, tachypnea (respiratory rate >60 times per minute), cyanosis; 4) cardiovascular symptoms including tachycardia (heart rate >180 beats per minute), edema, dehydration; 5) central nervous system symptoms including lethargy, irritability, and seizures; and 6) hematological symptoms including jaundice, splenomegaly, bleeding, leukopenia, and bands to segments ratio >0.2. The exclusion criteria were neonates with severe congenital abnormalities, those 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.

We measured capillary blood lactate levels using a portable hand analyzer (*Accutrend Lactate*®). Specimens were collected by taking 50 μL of capillary blood from the patient's heel, which was punctured aseptically with a lancet. Serial blood lactate levels were initially done when neonatal sepsis was diagnosed and repeated six hours after the first antibiotic administration. Lactate levels were expressed in mmol/L. Lactate clearance at six hours was calculated based on the following formula:[12]

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

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 10%[12] at six hours after administration of the first antibiotic. We evaluated the outcome of whether they survived or died during the hospitalization. All subjects received intervention according to the Medical Care Standard and Standard Operating Procedure of the NICU at Dr. Sardjito General Hospital. 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 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 Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

Results

A total of 45 neonates were included in the study. During the course of study, five parents withdrew their children from the study prior to the lactate level sampling, therefore, we analyzed 40 neonates. The baseline characteristics of study subjects are presented in **Table 1**.

Table 1. Baseline characteristics of subjects based on outcome of neonatal sepsis

Characteristics	Died (n = 13)	Survived (n = 27)
Gender, n		
Male	9	14
Female	4	13
Mean age at diagnosis, days (SD)	7.6 (5.4)	5.8 (5.3)
Birth weight, n		
< 2,500 g	9	15
≥ 2,500 g	4	12
Mode of delivery, n		
Vaginal birth	7	14
Caesarian section	6	13
Gestational age, n		
< 37 weeks	9	12
≥ 37 weeks	4	15
Asphyxia, n		
Yes	4	16
No	9	11

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 [-37.4 (SD 33)%] was significantly lower than that in group who survived [5.3 (SD 33)%; (P=0.001)]. Univariate analysis indicated that only gestational age and lactate clearance at 6 hours had P values <0.2, therefore, those variables were included in the multivariate analysis. The multivariate analysis revealed that lactate clearance at 6 hours was a statistically significant outcome predictor of neonatal sepsis (RR 15.1; 95%CI 1.7

Table 2. Univariate and multivariate analyses of the outcome predictors of neonatal sepsis

Outcome predictors	Univariate			Multivariate	
	RR	95%CI	P value	RR	95%CI
Gender					
Male	1.6	0.6 to 4.5	0.29		
Female					
Birth weight					
<2,500 g	1.5	0.5 to 4.0	0.4		
≥2,500 g					
Mode of delivery					
Vaginal birth	1.0	0.4 to 2.5	0.9		
Caesarian section					
Gestational age					
<37 weeks	2.0	0.7 to 5.5	0.14	1.5	0.5 to 7.1
≥37 weeks					
Asphyxia					
Yes	0.4	0.1 to 1.2	0.9		
No					
Leukocyte count					
<5,000 – 34,000 mm3	0.5	0.1 to 1.6	0.3		
>34,000 mm3					
Platelet count (mm^3)					
< 100,000 mm3					
≥100,000 mm3	1.2	0.5 to 3.1	1.2		
Random blood sugar					
<45 mg/dl					
≥45 mg/dl	0.9	0.3 to 2.3	0.3		
Blood culture					
Positive	0.5	0.2 to 1.2	0.4		
Negative					
Lactate clearance at six hours					
Low lactate clearance	7.2	1.03 to 49	0.01	15.1	1.7 - 133
High lactate clearance					

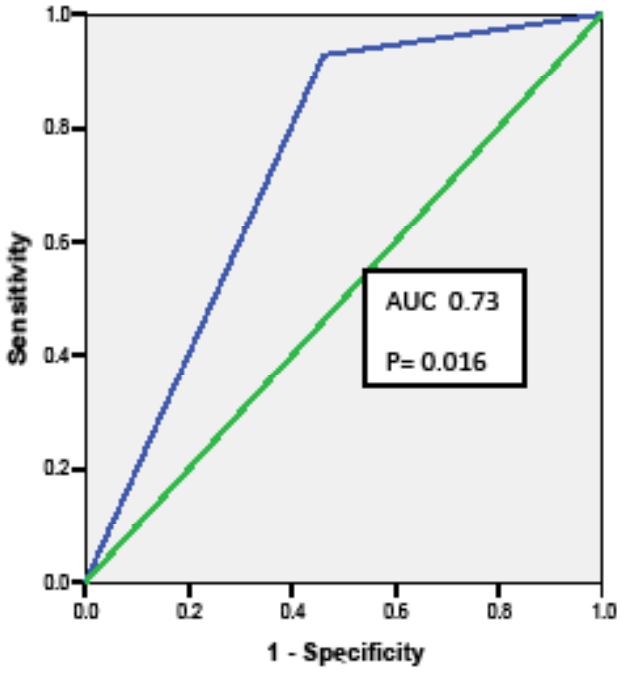

Figure 1. ROC curve of six hours lactate clearance as a predictive indicator of neonatal sepsis.

to 133). A greater proportion of subjects in the low lactate clearance (48%) group died than those in the high lactate clearance group (7%).

ROC curve analysis for the six-hour lactate clearance showed an area under the curve (AUC) of 73% (P<0.05), suggesting that the six-hour lactate clearance measurement had moderate strength as a predictor of outcomes.

Discussion

Our study demonstrated that a greater proportion of deaths occurred in the group of neonates with low lactate clearance at six hours (48%) than in those with high lactate clearance at six hours (7%). Logistic regression analysis showed that lactate clearance at six hours was a significant predictor of mortality (RR 15.1; 95%CI 1.7 to 133). 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%,[15] 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.[15,16]

Infants who died due to neonatal sepsis showed a lower mean percentage of lactate clearance at six hours than those who survived [-37.4 (SD 33) % *vs.* 5.3 (SD33) %; (P=0.001)], similar to another study which involved critically ill neonates.[15] The characteristics of their study subjects were similar to ours.

The presence of bacterial lipopolysaccharide membrane and exotoxins encourages the production of proinflammatory cytokines, activates the coagulation pathways, induces the production of tissue factors, as well as changes prothrombin to thrombin and triggers fibrin production. The final results of the process are fibrin clot deposition on the endothelium, the release of proinflammatory cytokines activating the coagulation cascade, and fibrinolysis impairment. These conditions tend to increase the accumulation of fibrin clots which can lead to blood fibrin microthrombi in small blood vessels, thus causing interference with microcirculation. In areas of impaired microcirculation, hypoperfusion causes an increase in lactate levels, while areas with open microcirculation experience a state of hyperoxia.[18,19] The disturbance results in tissue hypoxemia and hypotension, causing dysfunction of various organs of the body. These manifestations of multiorgan dysfunction appear clinically as symptoms of respiratory distress syndrome, hypotension, and renal failure. If not resolved, these conditions can be fatal.[3]

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.[4] 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.[11] 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.[18]

The release of proinflammatory cytokines in neonatal sepsis can be inhibited by administration of

antibiotics which are appropriate for the bacteria causing sepsis. Antibiotics reduce the amount of bacteria, causing a decline in the production of endotoxins by gram-negative bacteria, and exotoxin by gram-positive bacteria. Endotoxins and exotoxins stimulate release of proinflammatory cytokines as the beginning of a cascade of sepsis that results in interference with microcirculation.[3] Increased lactate clearance levels were reported to have a significant correlation with improved microcirculation.[20] This condition is associated with better outcomes in patients with sepsis,[21] such as in our study, in which the high lactate clearance group had lower mortality.

Limitations of our study were that the number of study subjects was less than the calculated minimum required sample size due to the lack of lactate reagent strips. The corrected power of our study with such a sample size was 50%. Another weakness was that the diagnosis of neonatal sepsis in our study was based on clinical signs of sepsis, instead of positive blood cultures.

In conclusion, lactate clearance at six hours can be used as a predictor of mortality in patients with neonatal sepsis.

Conflict of interest

None declared.

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