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Original Article

Lactate clearance and mortality in pediatric sepsis

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Abstract

Background Sepsis is a life-threatening condition often encountered in the pediatric intensive care unit. In the last five decades, despite the use of aggressive antibiotics and advances in intensive care medicine, the mortality rate of sepsis remains high. In 2005, the *World Health Organization* (WHO) estimated that 11 million children die annually due to sepsis, of these, 30,000 children under five years of age die daily. Serum lactate concentration is useful to evaluate the progression of sepsis in children. Lactate clearance can be used to evaluate the outcomes in sepsis management in children.

Objective To evaluate the relationship between lactate clearance and patient mortality. We also attempted to assess the usefulness of lactate clearance as an early prognostic marker in pediatric sepsis.

Methods This prospective cohort study was conducted at the Pediatrics Department of Prof Kandou General Hospital from November 2013 to April 2014. Consecutive sampling was undertaken on 45 children aged 1 month to 15 years who were diagnosed with sepsis according to the inclusion criteria. First lactate serum was measured immediately following patient admission to the PICU. The next serum lactate measurement was six hours after initial treatment in the PICU.

Results The mean lactate clearance was higher in the survivors' than in the non-survivors' group (58.48%*vs.* 18.20%, respectively). Logistic regression analysis revealed a lactate clearance cutoff point of 34.7%, with sensitivity 87.50%, specificity 96.55%, positive predictive value 93.33%, and negative predictive value 93.33%. The formula used was y=1/{1+exp-(4.135-0.119 lactate clearance)}. Chi-square analysis of lactate clearance and mortality revealed an odds ratio (OR) of 196.0 (95%CI 16.34 to 2,351.53; P<0.001).

Conclusion Higher lactate clearances significantly associate with lower mortality in children with sepsis. **[Paediatr Indones. 2016;56:215-20. doi: 10.14238/pi56.4.2016.215-20]**.

Keywords*: sepsis; lactate clearance; mortality*

Septic shock is a life-threatening condition often encountered by physicians in pediatric intensive care units (PICU). Septic shock in pediatric patients is one of the leading causes of morbidity and mortality, despite advancements in the treatment of multiple organ failure. In the last five decades, despite the use of antibiotics and intensive care treatment, mortality–due to sepsis remains high. In 2005, the WHO reported that 11 million children die yearly from sepsis, of whom 30,000 ≤ 5 years of age die daily. Most of these deaths occur in developing countries, with infectious diseases as the most common cause (pneumonia, malaria, measles, neonatal sepsis and diarrhea).[1] In 2010, worldwide mortality due to sepsis was estimated to be 7.6 million children, with pneumonia as the primary disease in 68% of cases.[2]

Incidence of sepsis was 1-10 per 1000 life birth and mortality between 13-50%. Saez-Lorens[3] performed a retrospective study for 12 years in 815 children who was diagnosed as sepsis, it was found that 171 (21%) belonged to sepsis (21%), 497 severe sepsis (61%) and 147 developed septic shock (18%).[4]

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In Indonesia, mortality caused by sepsis still very high i.e. 50-70% and if septic shock and multiple organ dysfunction occur, mortality become 80%.[5,6] Serum lactate concentration can help clinicians predict the progression of sepsis in children. In sepsis, systemic inflammation can lead to multiple organ dysfunction, impairing tissue oxygenation and increasing the production of serum lactate. Increased serum lactate level is indicative of anaerobic metabolism caused by tissue hypoxia, and is a good marker to assess tissue perfusion in sepsis and septic shock. A state of hyperlactatemia (lactate serum >2 mmol/L) is a cardinal sign of sepsis and septic shock.[7] Unresolved global tissue hypoxia, as indicated by inadequate lactate clearance, is associated with multiorgan dysfunction and increased mortality during the early phase of resuscitation in patients with septic shock. However, the initial lactate level represents only a patient's initial status and, therefore, cannot reflect lactate level changes over time. Hence, lactate clearance can be used to demonstrate the severity of hyperlactatemia.[8] The purpose of this study was to evaluate the relationship between lactate clearance and patient mortality. We also attempted to assess the usefulness of lactate clearance as an early prognostic marker in pediatric sepsis.

Methods

This prospective cohort study was performed in the PICU of Prof. Dr. R. D. Kandou General Hospital, Manado, North Sulawesi Province, Indonesia. All data were prospectively reviewed for consecutive patients admitted to the PICU and diagnosed with sepsis from November 2013 until April 2014. The 2005 *International Pediatric Sepsis Consensus Conference* criteria (IPSCC) were used to diagnose sepsis.[6] The inclusion criteria were subjects diagnosed in accordance with the IPSCC whose ages ranged from 1 month to 15 years. The exclusion criteria were malnutrition, severe dehydration, malignancy, burns, trauma, congenital metabolic disorders (e.g., diabetes mellitus), severe malaria, or long term corticosteroid use.

Patients' demographic data, laboratory results, and sources of infection were recorded. In our study, lactate clearance was defined to be the percent change in lactate level between the time of admission and six hours after initial treatment, with initital lactate as the denominator. Lactate clearance was measured by a handheld, portable lactate device (*Accutrend*®), using a drop of arterial blood (20-30 uL), followed by a 60-second analysis. The initial serum lactate (first lactate) was measured immediately following patient admission to the PICU. The next serum lactate measurement was six hours after initial treatment in the PICU.

Lactate clearance was calculated using the following equation:[9]

$$\text{Lactate clearance} = \frac{\text{(initial lactate level - six hour lactate level after initial treatment)}}{\text{initial lactate level}} \times 100\%$$

We evaluated mortality as the primary outcome and statistical analysis was performed using SPSS Windows software, version 22. Continuous variables were presented as means with differences between survivors and non-survivors. To evaluate the relationship between mortality and lactate clearance, logistic regression analysis was conducted. Logistic regression analysis was used to define a lactate clearance cutoff point. Chi-square analysis was used to find the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Results with P values <0.05 were considered to be statistically significant for all analyses.

Results

We identified 47 patients with sepsis from November 2013 to April 2014, but only 45 patients fulfilled the inclusion criteria. Two patients were excluded because they died before the 6 hours of treatment. Subjects' baseline characteristics are shown in **Table 1**. The mortality rate for this study was 35.6%. The mean ages of survivors and non-survivors were 21.38 (SD 28.56) months and 17.81 (SD 17.85) months, respectively. The

Table 1. Comparisions of the clinical characteristics of survivors and non-survivors.

Characteristics	Survivors (n=29)	Non-survivors (n=16)	Total (N=45)
Mean age (SD), months	21.38 (28.56)	17.81 (17.85)	
Gender, n			
Male	19	5	24
Female	10	11	21
Nutritional status, n			
Well-nourished	22	11	33
Undernourished	7	5	12
Focus of infection, n			
Respiratory system	19	6	25
Central nervous system (CNS)	5	1	6
Gastrointestinal	2	0	2
Respiratory system and CNS	2	9	11
Gastrointestinal and CNS	1	0	1
Microorganisms, n			
Gram positive bacteria	1	0	1
Gram negative bacteria	0	6	6
None (sterile culture)	26	12	38

Table 2. Serum lactate measurements at the time of hospital admission (initial) and six hours after treatment, as well as lactate clearance calculation

Variables	Survivors (n=29)	Non-survivors (n=16)
Mean initial lactate (SD), mmol/L,	2.67 (0.92)	6.77 (4.62)
Mean lactate after 6 hours (SD), mmol/L	1.56 (0.68)	5.68 (4.26)
Mean lactate clearance (SD), %	58.48 (13.47)	18.20 (16.46)

majority of subjects were male (24/45). Most patients had good nutritional status (33/45). The respiratory system was the most common focus of infection for sepsis (25/45). But only 7 cases had positive blood cultures; the remaining were sterile. The most common etiology of microorganisms was Gram negative bacteria. **Table 2** shows the results of initial serum lactate levels (at the time of admission and six hours after treatment) and lactate clearance.

The mean initial lactate level was relatively higher in non-survivors than in survivors (6.77 mmol/L *vs.* 2.67 mmol/L; P<0.001), as was the mean lactate level after 6 hours of treatment (5.68 mmol/L *vs.* 1.56 mmol/L; P<0.001). Logistic regression analysis revealed that lactate clearance was significantly higher in the survivor group (58.48%) than in the non-survivor group (18.20%); (OR 0.89; 95 CI 0.84 to 0.94; P<0.001).

Figure 1 shows a scatterplot of lactate clearance and the probability of mortality, which were negatively correlated, as reflected by the downward curve to right side. The following equation was used: [y=1/{1+exp-(4.135-0.119 lactate clearance)].

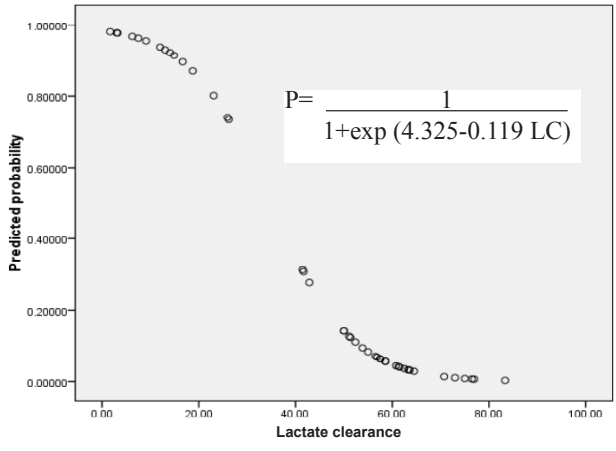

Figure 1. Scatterplot of lactate clearance and mortality in pediatric sepsis

Table 3 shows the Chi-square analysis of the relationship between lactate clearance and mortality in pediatric sepsis. In our study, the serum lactate clearance cutoff point was 34.7%, with sensitivity 87.50%, specificity 96.55%, positive predictive value (PPV) 93.33%, and negative predictive value (NPV) 93.33%. Mortality was significantly more likely in patients whose lactate clearance was ≤34.7% (OR 196.0; 95%CI 16.34 to 2,351.53; P<0.001).

Table 3. Lactate clearance and mortality in pediatric sepsis.

Lactate clearance	Outcomes		Total (N=45)
	Survivors (n=29)	Non-survivors (n=16)	
≤34.7%	1	14	15
>34.7%	28	2	30

X^2= 32.78; P<0.001

Discussion

Our study showed lactate clearance to be useful in predicting mortality in children with sepsis. Dharma *et al*. studied lactate levels in critically ill children. Their subjects' mean age was 45.7 months (range 2 to 156 months) and males predominated the study population (68.8%).[10] Similarly, our subjects' mean ages were 21.38 (SD 28.56) months in survivors and 17.81 (SD 17.85) months in non-survivors. Males were also predominant in our study (24 patients).

A local study reported that in Dr. Cipto Mangunkusumo Hospital in 2011 the primary causes of sepsis in children were etiologies from the respiratory system (16 patients, 76%), central nervous system (10 patients, 48%), urinary system (14 patients, 67%), and gastrointestinal system (21 patients, 54%). Among the 42 study subjects, 21 (50%) subjects had positive blood cultures. The most commonly isolated bacteria were *Klebsiella pneumonia* (24%), *Serratia marcescens* (14%) and *Burkholderia cepacia* (14%).[11] In our study, the most common focus of infection was the respiratory tract. We also noted that only seven subjects had positive blood cultures, possibly due to the timing of blood sampling for the culture. Some subjects were referral cases who had received antibiotics prior to the blood cultures thus affecting the blood culture results. Ideally, blood cultures must be taken from two separate puncture sites at the same time and include testing for aerobic, anaerobic, and fungal blood cultures. Our blood culture media was for aerobic bacteria only.

A previous study compared the initial values of lactate and lactate clearance in sepsis patients.[7] They found significant differences in the initial lactate levels and lactate clearance between sepsis groups who survived and died. In the sepsis group who died, the initial lactate levels were higher than than in the sepsis group who survived [6.16 (SD 4.87) mmol/L *vs.* 3.13 (SD 2.79) mmol/L, respectively], while lactate clearance in the group who died was lower than in the survivor group [-30.8 (SD 75.6) % *vs.* 32.8 (SD 63.4) %, respectively]. Similarly, the mean initial lactate level in our non-survivor group was higher than that of the survivor group, both at the time of admission (0 hours) (6.77 *vs.* 2.67 mmol/L, respectively) and after 6 hours of treatment (5.68 *vs.* 1.56 mmol/L, respectively). The initial lactate levels reflect the process of metabolism in children with sepsis. Higher lactate levels in the non-survivor group were likely due to anaerobic metabolism and tissue damage processes caused by lactate dehydrogenase (LDH) enzyme. The mean lactate clearance in the non-survivor group was significantly lower than that of the survivor group (18.20% *vs.* 58.48%, respectively).

Lactate clearance is more effective than initial lactate levels for predicting mortality outcomes in children with sepsis, because lactate clearance reflects changes in lactate metabolism. Sepsis patients who respond to treatment, have higher levels of lactate clearance, as the accumulated lactate is metabolized by pyruvate dehydrogenase to pyruvic acid, which in turn is converted to acetic acid and enters the Kreb's cycle. Sepsis patients who do not respond to treatment have decreased lactate clearance, with lactate accumulating in the body due to prolonged tissue hypoxia.[12]

Walker *et al*. reported that lactate clearance within the first 6 hours of treatment was a good indicator of mortality outcomes in children with sepsis. In their study, lactate clearance at the first 6 hours with a cutoff point of 36% had a sensitivity of 88%, specificity 64.1%, PPV 61.1%, and NPV 89.3%. Patients with lactate clearance <36% after 6 hours of treatment had higher risk of mortality (HR 7.33; 95%CI 2.17 to 24.73; P<0.001). Survivors had significantly higher lactate clearance compared to the group who died (61.1% vs. 10.7%, respectively; P<0.001).[13] In our study, the lactate clearance cutoff point at 6 hours of treatment was 34.7%, with sensitivity 87.50%, specificity 96.55%, PPV 93.33%, and NPV 93.33%. Chi-square analysis between lactate clearance and mortality revealed an odds ratio of 196.0 (95%CI 16.34 to 2,351.53; P<0.001). Hence, lower lactate clearance significantly increased the risk of mortality. Decreased lactate clearance may reflect disruptions in the body's metabolism due to anaerobic metabolism during sepsis.

A previous study used a lactate clearance cutoff point of 20% every 2 hours in patients treated in intensive care and found no significant difference in the incidence of mortality outcomes.[14] However, another study used a lactate clearance cutoff point of 30% and showed significant differences in mortality between survivors and non-survivors (63.2% *vs.* 28.6%, respectively; P<0.05).[15] To date, no lactate clearance cutoff value has been agreed upon. A study used a cut off point of > 10% within the first 6 hours of treatment, and reported that any increase in lactate clearance by 10% reduced mortality in children with sepsis.[16] Another study reported that of 187 sepsis patients, 68 patients' (36%) lactate levels fell to normal after treatment and 143 patients survived (76.5%). Patient with lactate clearance ≥ 50% had a greater chance of surviving (OR 4.0; 95%CI 1.6 to 10.0). At lactate clearance ≥ 10%, the ability to predict survival rate was lower than if lactate clearance was ≥ 50% (OR 1.6; 95%CI 0.6 to 4.4). Using an initial normal lactate concentration range of 2-4 mmol/L, was less accurate for predicting survival rates than lactate clearance of ≥ 10% (OR 1.5; 95%CI 0.8 to 3.3). Lactate clearance cutoff point of 50% was significant for predicting mortality in patients with sepsis (P=0.005). Similarly, the normalization of lactate levels (<2 mmol/L) in the first 6 hours of treatment was a good indicator of prognosis in sepsis patients (P=0.0045). As such, lactate clearance was more accurate than initial lactate examination for predicting mortality in sepsis patients.[17]

A study reported that initial lactate levels at the time of admission of >4 mmol/L had a low predictive value (AUC 0.56). Initials lactate measurements do not reflect the course of disease in sepsis, thus the need for serial lactate examinations. Lactate clearance had a better predictive value than initial lactate (AUC 0.619), with sensitivity of 63.46% (95%CI 49 to 76.4%) and specificity of 56.1% (95%CI 39.8 to 71, 5%). Lactate clearance values significantly differed between the two groups (P=0.021), similar to our study (P<0.001). Logistic regression analysis showed that lactate clearance was associated with mortality in sepsis patients (OR 0.35; 95%CI 0.01 to 0.76; P=0.047).[18] In our study, low lactate clearance was significantly associated with greater risk of mortality in children with sepsis (OR 196.0; 95%CI 16.34 to 2,351.53; P<0.001). Using logistic regression analysis, we calculated a regression coefficient (ß) of -0.119 and generated a logistic regression equation [P=1/1+exp-(4.135-0.119 LC)].

A previous study used lactate clearance as a benchmark of the success of early goal-directed therapy (EGDT) in patients with sepsis. In the study, lactate clearance was a good indicator for assessing the success of the first 6 hours of EGDT in septic patients. Increased lactate clearance was significantly associated with reduced mortality of patients with sepsis (OR 0.49; 95%CI 0.31 to 0.78; P<0.01). Lactate clearance examinations proved to be helpful for clinician in assessing the success of treatment and as a means of predicting mortality in patients with sepsis.[19] Arnold *et al*. compared mortality rates by comparing different categories of lactate clearance during treatment. They divided subjects into 2 groups: those with elevated lactate clearance of ≥ 10% and those with elevated lactate clearance of <10%. Significantly higher mortality rate was observed in the group with lactate clearance elevation of <10% than in the other group (60% *vs.* 19%, respectively; P<0.001); (OR 4.9; 95%CI 1.5 to 15.9).[20] In our study, the mortality rate increased significantly in the non-survivor group for a lactate clearance cutoff point of ≤34.7% (31.1%) *vs.* >34.7% (4.4%) (P<0.001). High lactate clearance indicates improved tissue

oxygenation and perfusion, as lactate in tissues and organs is converted to pyruvate then to metabolites by the Kreb's cycle. In conclusion, higher lactate clearance significantly associates with lower mortality rate in children with sepsis.

Conflict of interest

None declared.

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