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Original Article

Lactate profiles of pediatric shock patients in Cipto Mangunkusumo General Hospital 2015: a pilot study

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Abstract

Background The 2015 Surviving Sepsis Campaign (SSC) guidelines for management of shock recommend blood lactate to assess the success of resuscitation in shock. However, a study in adults found that 1/3 of septic shock patients had normal lactate levels (alactatemia) and lower mortality rates.

Objective To evaluate lactate profiles, possible factors affecting lactate levels, and mortality outcomes in pediatric shock patients in the emergency room (ER) and pediatric intensive care unit (PICU).

Methods This was a retrospective study on pediatric shock patients aged 1 month to 18 years in the ER or PICU from June 2014 to December 2015. Data were taken from subjects' medical records including lactate levels, examination data required to calculate a PELOD score, and mortality outcomes.

Results Of 223 shock patients evaluated, only 92 cases (41.2%) underwent lactate examinations. Of these, 59 (64.1%) had alactatemia and 33 (35.9%) had hyperlactatemia. A total of 23.7% of the alactatemia group and 36.4% of the hyperlactatemia group died, thus, the initial lactate level was not significantly associated with patient outcomes (P=0.197). The mortality rates of patients with <10% and ≥10% lactate clearance were 31.3% and 17.6%, respectively (P=0.362).

Conclusion In alactatemia patients, lactate level can not be used as a goal for resuscitation. Further study is needed to find a biomarker for assessing the success of pediatric shock resuscitation. Moreover, the clinical relevance of alactatemia is uncertain in pediatric shock patients. **[Paediatr Indones. 2017:57:12-7. doi: 10.14238/pi57.1.2017.12-7]**.

Keywords: *lactate; pediatric; shock; emergency room; pediatric intensive care unit*

Shock remains a problem in the field of pediatrics and is often found in the ER and PICU patients. In developed countries, such as the United States, a reported 37% of pediatric ER patients are in shock.[1] Shock can be classified by etiology, such as hypovolemic shock caused by decreased intravascular volume, cardiogenic shock caused by heart failure as the circulatory pump, distributive shock caused by excessive vasodilatation, endothelial dysfunction, and the loss of vascular tone, as well as obstructive shock caused by obstruction of blood flow to and from the heart.[2] The early management of shock is associated with a lower mortality rate (5.06%, compared to 16.37%of patients with delayed treatment).1 In developing countries, referral delays and limited facilities lead to mortality rates of 47-54.6%, but this number decreases to 11.4-21.8% with early and proper treatment.[3] This finding illustrates the importance of early detection and proper treatment of shock.

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Prior to 2015, physicians followed the 2012 *Surviving Sepsis Campaign* (SSC) guidelines for shock management. The treatments included initial resuscitation with fluid and vasopressor or inotropic drugs, infection control with antibiotics, and other supportive treatments. The 2012 SSC recommended that one of the targets of successful shock resuscitation was lactate clearance value higher than 10% in the first 6 hours of resuscitation.[4] In 2015, revised SSC guidelines added blood lactate examination as a required step in the first three hours.[5] This recommendation was based on the observation of hyperlactatemia often occurring in shock, caused by an increase in lactate production or disruption in lactate clearance.[6] Increased lactate production in shock can be caused by hypoperfusion, which leads to anaerobic metabolism with lactate as the end product.[5] Nevertheless, Hernandez *et al.* found that 1/3 of adult patients with septic shock had alactatemia, and a lower mortality rate.[7] The underlying condition that causes alactatemia is unknown, but it might be due to differences in metabolism in children and adults.[8]

The aim of this study was to evaluate lactate profiles, possible factors affecting lactate levels, and related outcomes in pediatric patients with shock in the ER or PICU.

Methods

This retrospective study was done using the medical records of all pediatric patients aged 1 month to 18 years with shock who were assessed in the ER or treated in the PICU from June 2014 to December 2015. Shock was defined as a clinical condition in which tissue perfusion was unable to meet the demand of tissue metabolism. Types of shock in the subjects' medical records included hypovolemic shock, septic shock, anaphylactic shock, cardiogenic shock, and dengue shock syndrome (DSS).

Patients with incomplete medical records, including data on mortality, blood lactate examination, renal function test, liver function test, and other examinations required to calculate the pediatric logistic organ dysfunction (PELOD), were excluded from the study. The study form was used to record the data from the medical records, which included initials, age, medical record number, dates of admission and discharge, blood lactate level, examination data required to calculate PELOD scores, and mortality outcome.

Data required to calculate PELOD scores included the pediatric Glasgow coma scale (GCS) and pupillary reaction to assess the neurological system, heart rate and blood pressure to assess the cardiovascular system, serum creatinine level to assess renal function, PaO2/FiO2, PaCO2, and the use of mechanical ventilation to assess the respiratory system, leukocyte and thrombocyte counts to assess the hematological system, as well as aspartate transaminase level and prothrombin time (PT) or international normalized ratio (INR) to assess liver function.[9] The values of organ function mentioned above were adjusted to the age of the patient. Patient management was held in accordance with standard procedure for therapy of shock and any medications administered were not recorded in this study.

Blood lactate examinations were not part of the standard protocol for pediatric shock patients in the ER or PICU at Cipto Mangunkusumo Hospital. Subjects' lactate levels were measured in the laboratory using a Nova lactate meter and expressed in mmol/L. Normal lactate level was defined as 0.8-2.5 mmol/L. Alactatemia was defined as lactate level $<$2.5 mmol/L, while hyperlactatemia was defined as $>$2.5 mmol/L. Lactate clearance was calculated as the result of the final lactate level (at 6, 12, 24, or 48 hours after a child was diagnosed with shock) minus the initial lactate level, divided by the initial lactate level and multiplied by 100%.

One visit was defined as the time from the day of admission to the day of discharge from the ER or PICU. If a patient had more than one visit during the study period, the second or next visit was counted as a new case. The mortality outcome was defined as died or survived (at the time of discharge). Patients who survived could have been transferred to the ward, or discharged against medical advice from the ER or PICU.

Data was analyzed descriptively and analytically using *SPSS for Windows version 17.0*. Bivariate analysis was used to assess for a correlation between lactate level and PELOD score, renal function test, as well as liver function test. Chi-square was used as the statistical test, unless the criteria for using the test

were not fulfilled, then Fisher's test was done. This study was approved by the Ethics Committee of the University of Indonesia Medical School.

Results

From June 2014 to December 2015, 223 pediatric patients with shock were treated in the ER or PICU of Cipto Mangunkusumo General Hospital. Of the 223 cases, 123 cases (55.4%) had distributive shock, 85 cases (38.1%) had hypovolemic shock, and 15 cases (6.5%) had cardiogenic shock. Of the 123 cases of distributive shock, 113 cases (51% of total shock patients) had septic shock, 9 cases (4%of total shock patients) had dengue shock syndrome (DSS), and 1 case (0.4%of total shock patients) had anaphylactic shock (**Figure 1**).

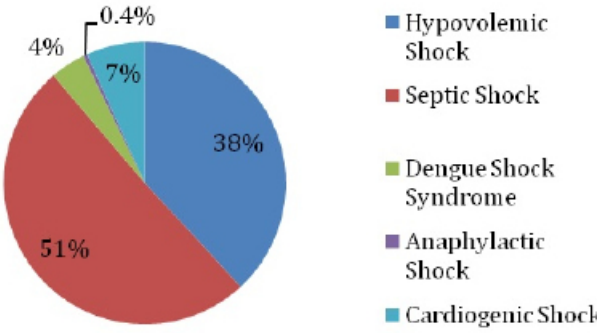

Figure 1. Distribution of types of shock among patients

Of the 92 patients with lactate level data, 23 cases (25%) were hypovolemic, 3 cases (3.3%) were cardiogenic, and 66 cases (71.7%) were distributive shock. Blood lactate was more frequently examined in patients with septic shock (62 cases, 67.4%). There were 59 cases (64.1%) with lactate level < 2.5 mmol/L (alactatemia group) and 33 cases (35.9%) with lactate level ≥ 2.5 mmol/L (hyperlactatemia group). Characteristics of the study subjects are presented in **Table 1**.

The time of lactate examinations varied as follows: 6 patients during the first 0-1 hour, 16 patients (17.4 %) during the next 1-6 hours, 31 patients (33.7%) during the first 6-24 hours, and 39 patients (42.4%) more than 24 hours after shock.

Table 1. Characteristics of subjects with lactate measurements

Characteristics	Total subjects (N=92)	Alactatemia (n=590	Hyperlactatemia (n=33)
Age classification, n(%)	38 (41.3)	24 (40.7)	14 (42.4)
1-12 monoths	37 (40.2)	24 (40.7)	13 (39.4)
13-60 months	5 (5.4)	3 (5.1)	2 (6.1)
60-144 months	12 (13)	8 (13.6)	4 (12.1)
> 144 months			
Gender, n(%)			
Male	51 (55.4)	33 (55.9)	18 (54.5)
Female	41 (44.6)	26 (44.1)	15 (45.5)
Type of shock			
Hypovolemic	23 (25)	15 (25.4)	8 (24.2)
Distributive			
Septic	62 (67.4)	41 (69.5)	21 (63.6)
DSS	4 (4.3)	2 (3.4)	2 (6.1)
Cardiogenic	3 (3.3)	1 (1.7)	2 (6.1)

Serial lactate examinations to ascertain lactate clearance were not routinely performed, as only 45 patients (48.9%) underwent lactate reexamination, 28 patients from the alactatemia group and 17 patients from the hyperlactatemia group. The time of lactate reexamination varied from 1 hour to 48 hours from the first lactate examination. Among 45 patients with lactate reexamination, most of them, 33 of 45 (73.3 %) had lactate reexamination in period of 48 hours. Only 5 of 33 patients (15 %) had lactate reexamination in first 6 hours. Lactate clearance in the first 48 hours is presented in **Table 2**.

Table 2. Lactate clearance from 33 patients with lactate reexamination in 48 hours

Lactate clearance	Alactatemia	Hyperlactatemia	P value
< 10%	12	4	0.049
≥ 10%	7	10	

Most alactatemia cases had lactate clearance of <10% (12/14). In the hyperlactatemia group, more than half (10/14) had a lactate clearance >10%. Significantly more hyperlactatemia subjects had >10% lactate clearance than alactatemia subjects (P=0.049) (**Table 2**).

The initial lactate level was not associated with patient mortality outcomes. Mortality rate was 23.7% in the alactatemia group and 36.4% in the hyperlactatemia group (P = 0.197) (**Table 3**).

Lactate clearance was not significantly associated with mortality outcomes. The group with lactate

clearance <10% had a mortality rate of 31.3%, and the group with lactate clearance >10% had a mortality rate of 17.6% (P=0.362).

Table 3. Initial lactate values and mortality

Lactate clearance			P value
	Survived	Died	
Alactatemia	45	14	0.197
Hyperlactatemia	21	12	

We also calculated PELOD scores and analyzed their relationship to lactate level. Of the 92 shock cases with lactate level data, only 58 patients had thorough organ examinations required to calculate PELOD score. There was no significant correlation between total PELOD score and lactate level in the 58 patients (**Table 4**).

Table 4. PELOD score and lactate level

PELOD score, n(%)	Lactate level		P value
	Alactatemia (n=37)	Hyperlactatemia (n=21)	
< 20	20	10	0.637
≥ 20	17	11	

Lactate is excreted on the liver and kidney. Therefore, we further analyzed for correlations between lactate level to liver and kidney function. Liver function tests were performed on 88 out of 92 shock patients underwent lactate examinations. We found no significant correlation between the liver function and lactate level (P=0.111) (**Table 5**). Furthermore, renal function tests were performed on 85 out of 92 shock patients underwent lactate examinations with no significant correlation between lactate level to kidney function (P=0.067) (**Table 6**).

Table 5. Liver function and lactate level

Liver function, n	Lactate level		P value
	Alactatemia (n=55)	Hyperlactatemia (n=32)	
Normal	37	16	0.111
Reduced	18	16	

Table 6. Kidney function and lactate level

Kidney function, n	Lactate level		P value
	Alactatemia (n=37)	Hyperlactatemia (n=21)	
Normal	43	19	0.067
Reduced	11	12	

Discussion

To date, shock remains to be one of the most frequent problems faced by ER and PICU doctors. In developed countries, sepsis is the most common cause of shock in pediatric patients (49-65%), followed by hypovolemic causes (17 - 31%).[10] During the period of study, septic shock occurred in 51% of our cases, followed by hypovolemic shock in 38.1% cases.

Management of patients with septic shock is generally done according to the 2015 SSC guidelines,[5] which recommend blood lactate examination in the first 3 hours after presentation to assess the success of shock resuscitation. Serum lactate level is used to evaluate tissue oxygenation, since tissue hypoxia in shock patients causes anaerobic metabolism, with lactate as the end product.[11]

This pilot study was done to evaluate lactate profiles of pediatric patients with shock in Cipto Mangkunkusumo General Hospital. To date, blood lactate examination has not been incorporated into the treatment guidelines. However, we found that blood lactate examinations were performed in 92 out of 223 (41.2%) shock cases. Among these 92 patients, 63% had lactate levels < 2.5 mmol/L (alactatemia), and 37% had lactate levels ≥ 2.5 mmol/L (hyperlactatemia). In contrast, in adult sepsis study by Hernandez *et al.* reported that only 1/3 of patients with septic shock had alactatemia, and those alactatemia shock patients had lower mortality rates.7 Moreover, Na S e*t al.* found that as few as 9.1%of 512 adult septic patients had alactatatemia.[12] In addition, a multi-center study of 2,424 septic shock patients by Cannonet al. found that 37.6% patients had alactatemia.[13]

The cause of alactatemia remains unclear. In our subjects, no well-defined differences in characteristics were observed between the alactatemia and hyperlactatemia groups (**Table 1**). We also noted no significant difference in mortality rates between the alactatemia and hyperlactatemia group (22.4% vs. 38.2%, respectively, P=0.104). Similarly, a study in pediatric patients aged 1 month – 13 years concluded that initial lactate levels could not be used as a prognostic tool for patient outcomes. Munde et al. found similar lactate levels between patients who died and survived.[14] Another study in children concluded that there was no significant difference between the

initial lactate and lactate levels at the first 6 hours; In addition, those two lactate values did not affect mortality rates.[15]

Lactate clearance above 10% is expected to reduce mortality from shock up to 11%.[16] However, in our study, lactate reexamination was not routinely performed. Lactate reexamination was only performed in 45 patients (48.9%), 28 patients from the alactatemia group and 17 patients from the hyperlactatemia group. Moreover, the time of lactate reexamination varied among patients. Only 5.4% of patients underwent lactate reexamination in the first 6 hours, as recommended by the SCC to evaluate the lactate clearance levels. Most patients (33/45 patients, 73.3%) had lactate reexamination in a period of 48 hours.

The SSC issued an update that lactate examination should be done in the first 3 and 6 hours to assess the success of resuscitation.[5] This statement raised the question as to the role of lactate examination in pediatric patients with shock who were alactatemic since the initial diagnosis. To date, the cause of alactatemia in children with shock remains unclear. Therefore, further study is needed to determine the usefulness of lactate to assess the success of fluid resuscitation.

Lactate clearance in the first 48 hours is shown in **Table 2**. Patients who had lactate clearance of >10% were mostly in the hyperlactatemia group (58.8%), while those with lactate clearance <10% were mostly in the alactatemia group (75%). We also found that lactate clearance was not significantly associated with patient mortality. Patients with lactate clearance <10% had a mortality rate of 31.2% and patients with lactate clearance >10% had a mortality rate of 17.6% (P=0.362). In contrast, Munde *et al.* reported that lactate examination in the sixth hour showed differences in patient outcomes, with a lactate clearance cut-off of 30%, between patients who survived and died (sensitivity 75%, specificity 97%, positive predictive value 90%, and negative predictive value 91.42%).[14] In addition, Keswari *et al.* found that increased initial and 24th hour lactate levels increased the risk of mortality [relative risk (RR) 2.9; 95%CI 1.09 to 7.66; (P=0.029) and RR 4.92; 95%CI 1.77 to 13.65; (P=0.002), respectively]. Lactate clearance <10% in 24 hours also increased the risk of mortality [RR 6.50; 95%CI 2.27 to 18.62; (P=0.001)].15

PELOD is a scoring system to determine the severity of organ damage in pediatric sepsis patients. Saraswati et al. showed that subjects with PELOD scores ≥ 20 had a 39.08 times higher mortality risk than subjects with PELOD score < 20.[17] In our study,of the 92 patients who underwent lactate examinations, only 58 had the complete examination data required to calculate PELOD scores. We found no association between PELOD score and lactate level in shock patients (**Table 4)**, similar to a study by Ismyet al.[18] Therefore, lactate level didn't affect the severity of sepsis marked by PELOD scores.

Lactate is an indirect indicator of sepsis severity in pediatric patients. The cause of alactatemia in children is not known and there may be metabolism differences between pediatric and adult patients.[8] Many factors can affect lactate level and lactate clearance in children. Alactatemia may happen despite an increase in lactate production, if the body has good hepatic and renal lactate clearance. If the liver and renal functions deteriorate, lactate level is predicted to increase.[19] We found that 66.2% of the alactatemia group had reduced kidney function based on serum creatinine level, whereas 52.2% of the hyperlactatemia group had normal kidney function. However, the difference was not significant (P=0.121). Assessment of liver function by alanine aminotransferase (ALT) enzyme revealed normal liver function in 69.0% of patients in the alactatemia group, and 50% of children in the hyperlactatemia group. Therefore, further study on liver and renal function in pediatric shock patients with alactatemia should be done with hypoxia biomarkers.

The use of lactate as a biomarker of the success of resuscitations recommended by the 2015 SSC should be examined further in children. Previous studies found that lactate did not increase in some adult with sepsis (alactatemia).[7,11,12] In this pilot study, we find similar results, as 63%of our pediatric shock patients have alactatemia. Hence we conclude that lactate clearance, particularly in alactatemic conditions, can not be used as a means of assessing the success of fluid resuscitation. Lactate level is not associated with mortality nor with severity of disease. Further study is needed to elucidate the causes of alactatemia in pediatric patients with shock.

Conflict of Interest

None declared.

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