

## Original Article

## Comparison of serial blood lactate level between dengue shock syndrome and dengue hemorrhagic fever (evaluation of prognostic value)

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### Abstract

**Background** Dengue shock syndrome (DSS) mortality is still high. Monitoring of blood lactate level is important to evaluate shock.

**Objectives** The study were to review the difference between blood lactate level of DSS and that of dengue hemorrhagic fever (DHF), to correlate blood lactate level with hypoxia state as shock risk factors (PaO<sub>2</sub>, oxygen saturation, and anion gap) and to determine the cut-off point of blood lactate level to predict shock.

**Methods** The study was carried out at the Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, from January until July 2006. Three mL venous blood specimen was collected from all subjects for peripheral blood, blood gasses, serology, and blood lactate examinations. This study consisted of a retrospective cohort and a cross sectional method. Data were analyzed with Chi-square test. Continous data tested using Mann-Whitney method. To know the correlation between blood lactate level and shock risk factors we use logistic regression test.

**Results** In DSS group, 73% shows hyperlactatemia (lactate = 2 mmol/L). Conversion of lactate means between two groups is significantly different from day one to day two and three. There was a negative correlation between lactate level and pO<sub>2</sub> and oxygen saturation. Oxygen saturation is the only value that has clinical correlation. Regressions analysis can be applied using  $Y = 7.05 - 0.05 X$  equation. The cut-off point of lactate level as marker for shock by using ROC curve is  $32.015$  mmol/L with 70% sensitivity and 83.3% specificity.

**Conclusions** Hyperlactatemia in DSS can be considered as a sign for unappropriate treatment of shock. Blood lactate level can be used as a biochemical marker for tissue hypoxia, to assess severity of the disease, as monitoring of treatment, and has prognostic value of DHF cases. [Paediatr Indones 2007;47:150-155].

**Keywords:** serial blood lactate, dengue shock syndrome, prognostic

Dengue shock syndrome (DSS) mortality rate in hospital is still high.<sup>1,2</sup> Blood lactate level has been studied to be used as a biochemical marker for tissue hypoxia.<sup>3-10</sup> Serial blood lactate levels can predict shock, multiple organ failure and survival better than cardiac output, oxygen delivery and *interleukin-6* (IL-6).<sup>7,8,10</sup> Bed side monitoring of blood lactate level is important to evaluate shock therapy.<sup>7,8,10</sup>

Setiati *et al*<sup>11</sup> reported blood lactate level as a predictor for severe DHF mortality. The study found increased blood lactate levels in patients with positive serologic dengue blot test.<sup>11</sup> The aims of the study were to review the difference of blood lactate level between DSS and Dengue hemorrhagic fever (DHF), to know the correlation between lactate level and shock risk factors and to calculate the cut-off point of lactate to predict shock.

### Methods

The study was carried out prospectively in the Department of Child Health, Medical School, Univer-

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sity of Indonesia, Cipto Mangunkusumo Hospital, Jakarta from January to July 2006. Serial data about the results of peripheral blood, blood gas analysis, anion gap and blood lactate level examinations and parameters of clinical stage of DHF and DSS were recorded. Inclusion criteria were age of patients 0–18 years and proved to suffer from DHF. Patients suffered from bacterial infection, liver disease, and those with incomplete data were excluded. Thirty subjects with DHF without shock and 30 with DSS were eligible.

All data obtained from history, physical examination, and routine laboratory test were recorded. From all subjects were collected three mL venous blood sample for peripheral blood, and serological (IgM/IgG) examination on day-five. If the result approved for DHF (thrombocytopenia and hemoconcentration) in acute phase (day of illness three until seven), then other examinations would be performed such as blood gas analysis, anion gap, serial blood lactate level, hemoglobin, hematocrite, and platelet during hospitalization.<sup>12-25</sup>

Descriptive data were presented in text and tables. Data were analyzed with Chi-square test or Fischer exact method. Continuous data were tested by Mann-Whitney method. To determine the correlation between blood lactate level and the risk for shock we used logistic regression analysis.<sup>25</sup>

## Results

There were 93 cases of dengue fever and DHF from 1 March until 15 June 2006. Only 62 subjects fulfilled

the criteria, but two subjects dropped out. They were divided into two groups, 30 cases with DHF without shock (grade II DHF) and 30 cases with DSS (26 cases of grade III DHF and four cases of grade IV DHF). There was one case with grade IV DHF who died.

Subjects of this study consisted of 24 girls and 36 boys. We found that in the DSS group, the biggest proportion were those with secondary infection with the age of 6-10 years, while in DHF group the age was 11-15 years. In DSS group, most subjects were over nourished.

The longest duration of fever at the day of admission was four days. In DSS group, the biggest proportion had temperature below 38°C with mean of 36.9°C. The highest hematocyte level proportion in both groups was 40-45%. Platelet level ranged between 51,000-100,000/ $\mu$ L. Abdominal tenderness, hepatomegaly, vomiting and spontaneous bleeding were found more frequently in DSS group compare to those in DHF with shock.

Blood for the first lactate sample (L1) was taken within first 24 hours since admission, L2 within 24-48 hours, L3 within 48-72 hours. The blood lactate level in most subjects of DHF was within the normal range (<2 mmol/L), i.e. 83.3% in L1, 93.3% in L2, and 100% in L3. In DSS group the majority of subjects (73%) had hyperlactatemia ( $\geq$ 2 mmol/L). Blood lactate level of L2 and L3 in most subjects (87%) returned to normal value (<2 mmol/L). (Table 1)

Most patients showed lactate level of L1. The increased blood lactate level in DHF group was up to 1.48 (SD 0.48) mmol/L, while in DSS group up to 2.61(SD 1.06 mmol/L (Figure 1).

**Table 1.** Distribution of blood lactate (L1, L2, and L3) in group DHF without shock and DSS

Blood lactate (mmol/L)	Groups		P
	DHF without shock	DSS	
Lactate 1			
<2	25 (83%)	8 (27%)	
$\geq$ 2	5 (17%)	22 (73%)	
Total	30 (100%)	30 (100%)	0.000
Lactate 2			
<2	28 (93%)	26 (86%)	
$\geq$ 2	2 (7%)	4 (13%)	
Total	30 (100%)	30 (100%)	0.671
Lactate 3			
<2	30 (100%)	26 (87%)	
$\geq$ 2	0	4 (13%)	
Total	30 (100%)	30 (100%)	0.112

Chi square test

Most patients in DHF group showed conversion of lactate level from L1 to L3, which was 0.46 (SD 0.62) mmol/L, while in DSS group from L1 to L2, which was 1.25 (SD 1.01) mmol/L. Mann-Whitney statistical test revealed a significant difference between conversion of L1 to L2 ( $P < 0.0001$ ) and L2 to L3 ( $P = 0.002$ ).

There was a significant difference in mean of hemoglobin and hematocrite level of DSS group compared with that of DHF group at the first 24 hours. The mean  $pO_2$  level of DSS group on the first 24 hours was 75 (SD 34.4) mmHg, differed significantly with that of DHF group ( $P = 0.007$ ). Mean  $O_2$  saturation level of DSS group at the first 24 hours was 92.3 (SD 10)%, differed significantly with that of DHF group ( $P = 0.001$ ).

The study showed no correlation between blood lactate level and hemoglobin ( $r = 0.01$ ), haematocrite ( $r = 0.04$ ), platelets ( $r = -0.03$ ) and anion gap level ( $r = 0.03$ ) in DSS group in the first 24 hours.

**Figure 2** shows negative correlation ( $r = -0.40$ ;  $P = 0.030$ ) between blood lactate level and  $pO_2$  within the first 24 hours. Decrease in oxygen saturation was followed by an increase in blood lactate level. **Figure 3** shows negative correlation ( $r = -0.46$ ;  $P = 0.000$ ) between blood lactate level and oxygen saturation within the first 24 hours. Decrease in oxygen saturation was followed by increased blood lactate level. **Figure 4** shows weak positive correlation ( $r = 0.03$ ;  $P = 0.876$ ) between blood lactate level and anion gap within the first 24 hours. Increase in anion gap level was accompanied by an increase of blood lactate level. (**Table 2**)

Mean value of blood lactate level within the first 24 hours was between the lowest value of 0.89 mmol/L and the highest value of 5.18 mmol/L. A cut-off point of 2.015 mmol/L with 70% sensitivity and 83.3% specificity value was used.

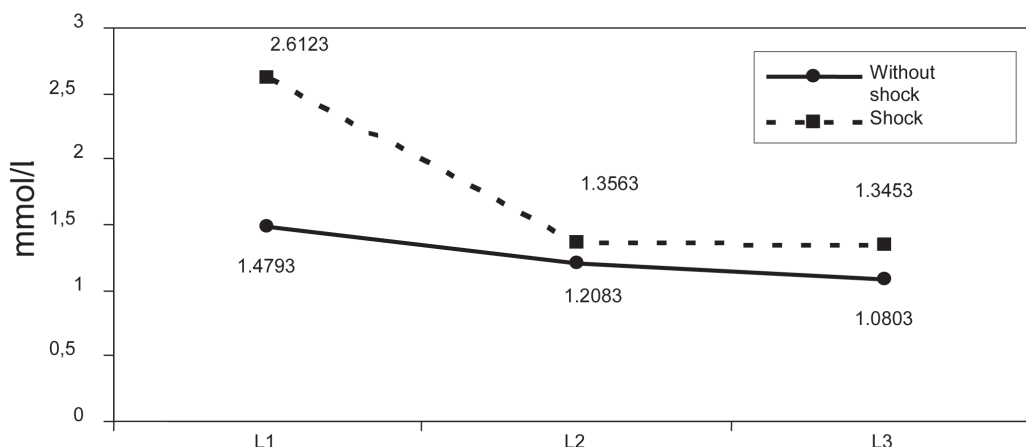
## Discussion

Blood lactate level has been studied as biochemical marker for hypoxia, severity of disease, shock therapy and prognosis in critical condition. Bedside serial blood lactate level was a sensitive indicator to evaluate severity of shock.<sup>16-24</sup>

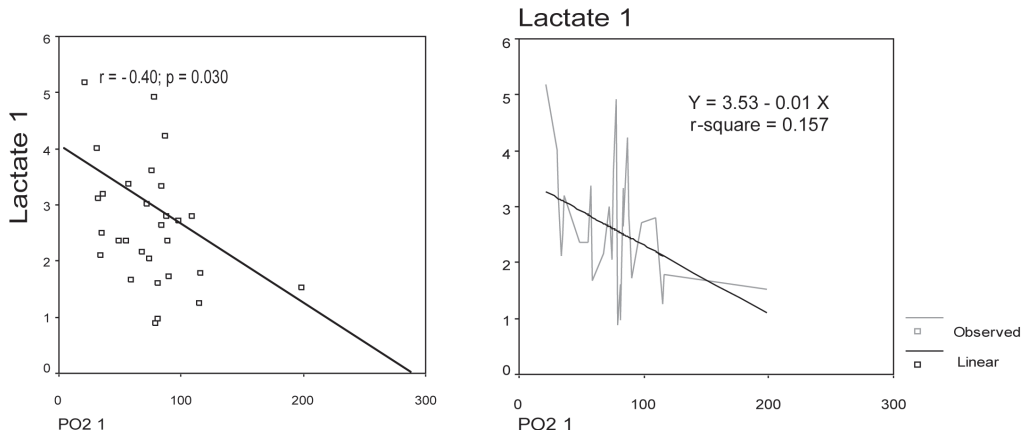
In DSS group, the biggest proportion was secondary infection, in accordance with that of Dewi<sup>2</sup> and Karyanti<sup>26</sup> study. Dewi<sup>2</sup> and Sumarmo<sup>14</sup> studies found that there was no difference concerning DHF patient gender. As a whole, most patients belonged to 6-10 age group. Proportion of well and over-nourished children in DSS group was higher than that of under-nourished cases and it was similar with the result of Setiati *et al*<sup>11</sup> study. The incidence of DSS was high on day three and four of fever with high haematocrite. The incidence was also high in those with hepatomegaly, it was similar with the result of Dewi<sup>2</sup> and Karyanti<sup>26</sup> study.

We found abnormal blood lactate ( $\geq 2$  mmol/L) in the first 24 hours in DSS group was 73%. In the second and third day of examination, however, there were more patients with normal blood lactate level ( $< 2$  mmol/L) in both DHF and DSS group.

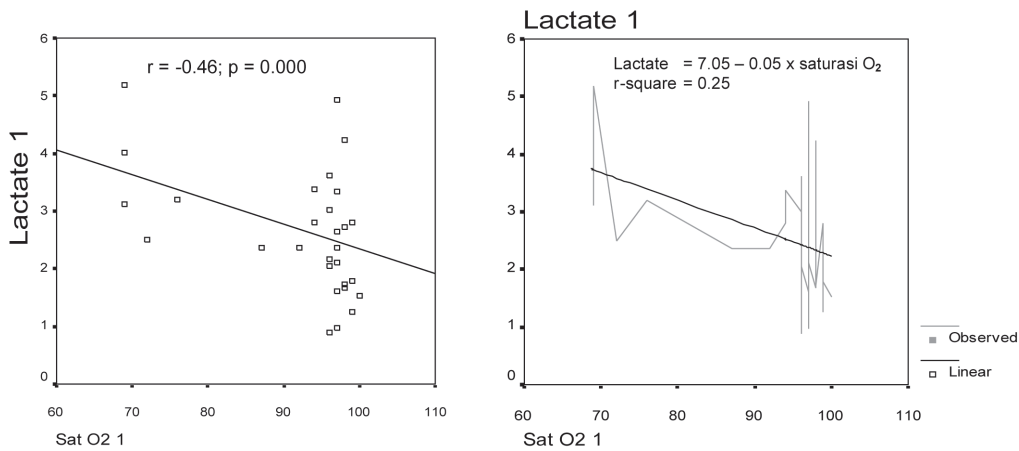
The increased blood lactate level shows the severity of shock in DHF. A study by Karyanti<sup>26</sup> has



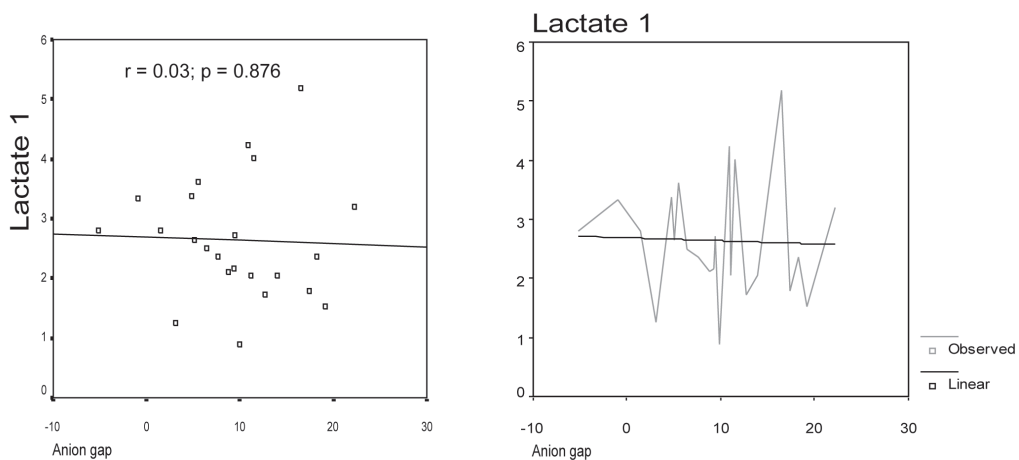
**Figure 1.** Graphics of mean blood lactate between group DHF without shock and DSS



**Figure 2.** Correlation between blood lactate level and  $pO_2$  on DSS group within first 24 hours



**Figure 3.** Correlation between blood lactate level and oxygen saturation on DSS group within first 24 hours



**Figure 4.** Correlation between blood lactate and anion gap level of DSS group in the first 24 hours

**Table 2.** Regression analysis of correlation between blood lactate level and pO<sub>2</sub> and oxygen saturation on DSS group within the first 24 hours

Indicator	Intercept	Coefficient of regression	Regression equation
pO <sub>2</sub> (P=0.379) & O <sub>2</sub> saturation (P=0.045)	6.40	-0.01 & -0.04	Y = 6.40-0.01 X1 - 0.04 X2
O <sub>2</sub> saturation	7.15	-0.05	Y = 7.15-0.05 X

proved that there was hepatocellular destruction from mild until severe in cases with dengue infection reflected by an increased level of transaminase. Harun<sup>1</sup>, Levraunt<sup>17</sup> and Douzinas<sup>19</sup> found a release of endotoxemia, TNF- $\alpha$  and IL-6 in cases with DSS. High endotoxin level was found in patients with gastrointestinal bleeding, recurrent shock, prolonged shock and when the patient died. These two factors were due to accumulation of increasing blood lactate level in DHF patients with shock.

Liver is the primary organ for metabolizing lactates. Almost 50% of lactate is extracted in liver. In several condition such as liver disease, blood flow and oxygen transport disorder, liver function on lactate homeostatis can be changed. This is due to a decrease of blood flow to the liver.<sup>5,27,28</sup>

Comparison of blood lactate level conversion between cases with and without shock are significantly different on L1-L2 (P=0.000) and L1-L3 (P=0.002). Increased lactate level can make some substrate used directly for oxidative process after a short period of hypoxia (when ATP of cytosol was low). Conversion of blood lactate level in this study is similar with that of Setiati *et al*<sup>11</sup> study. Baker *et al*<sup>6,7</sup>, Siswanto<sup>8</sup>, Levraunt *et al*<sup>17</sup> and Douzinas *et al*<sup>19</sup> showed an increase of blood lactate level in septic patients on first day of examination and followed by decreased blood lactate level on next day of examination. Khrisna *et al*<sup>27</sup> found that blood lactate level increased almost double in severe malaria cases, but soon decreased in patient who survived. Wang *et al*<sup>24</sup> study showed blood lactate level increased in cholera patients before rehydration phase and decreased after rehydration. Hendarto<sup>23</sup> had done a study to examine first lactate level in diabetic ketoacidosis, the result was 14 of 15 patients with lactate level <2 mmol/L were still alive until the end of the first 24 hour.

This study showed clinical negative correlation between blood lactate level and pO<sub>2</sub> and oxygen saturation in the first 24 hours in cases with DSS similar with Setiati *et al*<sup>11</sup>. This study also found weak corre-

lation between blood lactate level and anion gap level within first 24 hour in DSS group, it was similar with the result of Siswanto<sup>8</sup> study.

A cut-off point of 2.015 mmol/L of blood lactate level is used to predict the severity of shock in DHF cases. Setiati *et al*<sup>11</sup> study used 5.3 mmol/L blood lactate level cut-off point as a marker of poor prognosis in severe DHF. Meanwhile, Siswanto<sup>8</sup> study used 2.5 mmol/L of blood lactate level cut-off point as a marker to predict the prognosis. The study showed that blood lactate level increased in severe cases. On the contrary, the value of blood lactate level decreased in patients who achieved medical improvement or cured.

We concluded that hyperlactatemia in DSS can be considered as a sign for inappropriate treatment of shock. Blood lactate level can be used as a biochemical marker for tissue hypoxia, to assess severity of the disease, as monitoring of treatment, and has prognostic value of DHF cases.

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