

## The Role of Blood Lactate Levels as Outcome Predictor of Isolated Traumatic Brain Injury Patients

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**Objectives:** Traumatic brain injury (TBI) is accompanied by regional alterations of brain metabolism, reduction in metabolic rates and possible energy crisis. This metabolic disturbance reflected by increase and accumulation of the brain lactate levels. Objective of this study was to determine the correlation between abnormalities in lactate metabolism for predicting neurologic outcome after moderate or severe traumatic brain injury.

**Methods:** An observational prospective study in 60 patients with isolated TBI. Blood sample taken from vein of the limbs after underwent initial resuscitation. Serial assessment of the blood lactate level was measured in 1<sup>st</sup>, 2<sup>nd</sup> and 7<sup>th</sup> day with Lact2 Roche Cobas® C-System. Neurologic outcome assessed on 7<sup>th</sup> days using Modified GCS.

**Results:** On initial assessment, 38.3% of patients with normal lactate ( $\leq 2$  mMol/L), 61.7% of patients was hyperlactatemia ( $> 2$  mMol/L). In this study, it was obtained that the lower of GCS level, the higher of blood lactate level, and vice versa ( $p = 0.033$ ). In both treatment, there was a significant lactate clearance 24-hour as  $37.96\% \pm 32.76$  ( $p = 0.001$ ) and  $13.49\% \pm 40.32$  ( $p = 0.011$ ), respectively. No significant changes between blood lactate level on the 2<sup>nd</sup> and 7<sup>th</sup> day, both operative ( $p = 0.938$ ;  $p > 0.05$ ) neither conservative ( $p = 0.280$ ;  $p > 0.05$ ) patient. While, there was no correlation between neurologic outcome with 24-hour lactate clearance ( $p = 0.349$ ). The higher of the initial blood lactate level, the patient's outcome was worsen ( $p = 0.029$ ).

**Conclusion:** There is a significant correlation between blood lactate level and severity TBI according to GCS level. The lower GCS level, the higher blood lactate level and vice versa. This study also demonstrates that 24-hour lactate clearance did not affect patient's outcome, but more influence by initial blood lactate level. Therefore, initial blood lactate level can used as an outcome predictor in TBI patients.

**Keywords:** traumatic, brain injury, lactate level, outcome

### INTRODUCTION

TBI is a public health problem, that can lead to disability and death. Even for the high incidence, there is mention as a silent global epidemic.<sup>1,2</sup> In the United States reported about 1.6 million people a year suffered of TBI, where about 270,000 people receiving treatment in hospital, with mortality rates reaching of 52,000 cases per years.<sup>2</sup> In Indonesia, there is no incidence national data reported. However, brain injury cases reported from Dr. Wahidin Sudirohusodo General Hospital Makassar was about 861 cases in the year of 2005. The cases were increase in the year of 2006 become 817 cases and 1,078 cases in 2007. About 24% are brain injuries and 17% are strong brain injuries.<sup>3</sup>

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In a study reported that the mortality rate reached 23.9% in patients with diffuse injuries and 40.4% in patients with focal injuries.<sup>2</sup> TBI most often occur due to traffic accidents, industrial/work accidents, falls, or violence, and generally in the form of "multiple system disorders", so the handling should be holistic. Mortality and morbidity due to brain injury is certainly going to bring great impact on overall public health programs. Understanding of the variability of outcomes of brain injury requires a careful and in-depth study to reveal the relationship between initial injury severity and outcome, as well as the understanding of brain injury.<sup>1,3</sup> Some researchers proved that the primary brain damage due to trauma is considered irreversible and strongly influence patient outcomes. However, the pathophysiological changes that accompany such changes in the ultrastructure of the blood brain barrier, neuronal function, metabolism, inflammation and others who may contribute to secondary brain injury that lasts over time. It is

still possible to be prevented and treated. Therefore, although the severity of primary brain injury greatly affects patient outcomes, but these secondary factors involved responsible for the diverse outcome, still can be manipulated to protect and limit damage of brain tissue and functionally, so that patient outcomes could be better and cure rates of brain injury patients will increasingly tinggi.<sup>1,2,4,5</sup>

Inflammation, for example, as well as other organs, is also an important part of the pathophysiology of TBI. In an event of brain injury a proper balance between cytokines that cause inflammatory reactions (pro-inflammatory) need to be concerned. In order to limit and recover damages, as well as anti-inflammatory cytokine (IL-10) which restrict to limit the work of pro-inflammatory cytokines, that the event would likely cause adverse effects. If the regulation is controlled by less excessive IL-10, producing TNF- $\alpha$  leads to tissue damage, clearance tissue debris and imperfect journey toward chronic disease. The study of Islam (2006), found that although TNF $\alpha$  in a high rate, when IL-10 levels still high, then the outcome will be better.<sup>7</sup>

Meanwhile metabolic changes also occur in brain injury. These metabolic changes thought to reflect changes in brain energy metabolism in response to trauma. In addition, due to release of stress hormones such as catecholamines and adrenaline that will affect of increased 'metabolic rate'. The existence of these metabolic changes is a common condition found in any great trauma. One effect is the occurrence of hyperglycemic and increased lactate production network that lasts a while. Hyperglycemia showed mobilization of glycogen reserves to meet energy needs, while the high lactate production reflects the depletion of energy supply and demand.

Based on the above facts, this study tries to reveal the relationship between changes in blood lactate levels in patients with closed brain injury and its role in influencing patient outcomes.

## METHODS

This is an observational study with a prospective approach to evaluate the performance of patients at Sub-Section of Neurosurgery Department of Surgery Faculty of Medicine, University of Hasanuddin/Dr. Wahidin Sudirohusodo Hospital Makassar. The study took place between March and October 2010. A number of 60 patients who met the criteria of the sample. were recruited in this study. Venous blood samples

were taken from the extremities of patients, then transmitted and checked on the Clinical Pathology Laboratory Section at Hasanuddin University School of Medicine. Blood lactate levels were measured using the Roche Cobas ® technology Lact2 C-System.

## Statistical Analysis

All data analyses were performed using the SPSS software V.15.0. Values of  $p < 0.05$  were considered to be indicative of statistically significant differences. Pearson Correlation Coefficient was employed to determine the correlation and Paired-Samples T-Test for evaluating the different.

## RESULTS

### Characteristics of Samples

During the study period from March to October 2010, a number of 60 patients were recruited and met the inclusion criteria (Table 1).

Table 1  
Distribution of Study Sample (N = 60)

Parameter	N	Percent
Sex		
male	46	76.7
female	14	23.3
Age (years)		
15-20	21	35
21-30	18	30
31-40	10	16.7
41-50	3	5
51-60	8	13.3
GCS		
GCS 6	4	6.7
GCS 7	5	8.3
GCS 8	5	8.3
GCS 9	3	5
GCS10	7	11.7
GCS11	11	18.3
GCS12	11	18.3
GCS13	14	23.3
Injury criteria		
stornj capity trauma	14	23.3
mild capity trauma	46	76.7
Treatment		
operative	34	56.7
conserfative	26	43.3

### Blood Lactate Levels

In this study, blood lactate levels for each patient was measured 3 times, i.e. on the first day of admission (referred to lactate-1), on the second

day after the action (operative/conservative) identified as lactate-2, and the seventh day after treatment referred as lactate-7, at the same time the patient outcome was assessed using Modified GOS scale. Lactate-2 was identified as a 24-hour lactate clearance. On examination, it was found that 61.7% (37/60) patients were hyperlactatemia with lactate-1 levels  $> 2$  mmol/L and 38.3% (23/60) patients were normolactatemia (lactate  $\leq 2$  mmol/L) as can be seen on Figure 1. The average lactate-1 levels was  $2.84 \pm 1.44$  mmol /L or in the range of 0.9 – 7.2 mmol/L.

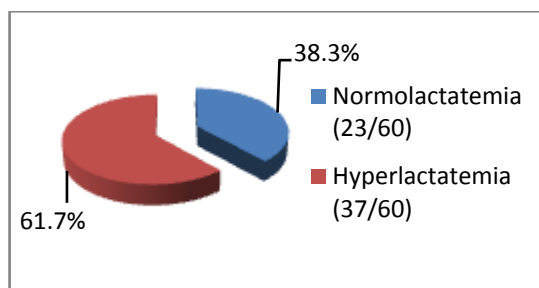


Figure 1  
Lactate-1 Levels Based on Hyperlactatemia

Examination of lactate-2 levels indicates that the highest value was 3.6 mmol/L and the lowest was 0.9 mmol/L on average of  $1.69 \pm 0.64$  mmol/L. There were 14 patients with lactate  $> 2$  mmol/L, in which 2 patients on examination lactate-1 were a normolactatemia and the rest 12 patients were hyperlactatemia.

For lactate-7, examination was carried out for 44 patients only, because 7 patients died before the day 7, and 9 patients went home before the examination. For the 9 patients who went home were all in good condition (GCS15) with minimal complaint or without complaint, therefore, all of them were included on outcomes evaluation. The average value of lactate-7 was  $1.69 \pm 0.69$  mmol/L, with the highest value of 3.7 mmol/L and the lowest 0.7 mmol/L. In this examination, we observed that there were 10 patients with lactate  $> 2$  mmol/L, 2 of them were normolactatemia since the examination of lactate-1, whereas 8 patients were those who from the beginning with hyperlactatemia. Meanwhile, for 14 patients who were on lactate-2 examination found hyperlactatemia, 4 of them on lactate-7 examination were found remained hyperlactatemia, 4 patients became normolactatemia, and 5 patients were not checked due to death (2 patients) and 3 patients went home before the examination. Average

examination results for serial blood lactate levels are shown in Table 2.

Table 2  
Average Examination of all Blood Lactate

Parameter	N	Lactate Levels (mmol/L)		
		Minimum	Maximum	Average
Lactate-1	60	0.9	7.2	$2.83 \pm 1.44$
Lactate-2	60	0.9	3.6	$1.69 \pm 0.65$
Lactate-7	44	0.7	3.7	$1.69 \pm 0.69$

### Twentyfour Hours Lactate clearance

Twentyfour hours lactate clearance is the decrease in percent of blood lactate levels from the initial lactate levels (lactate-1) to the second value of blood lactate levels (lactate-2).

### Patient Outcomes

Patients outcome on this study was evaluated based on GOS Modified scale. The results indicates that from 60 samples based on the seventh day examination, 65% (39/60) were favorable, 23.3% (14/60) were unfavorable, and the rest 11.7% (7/60) were died as can be seen on Figure 2.

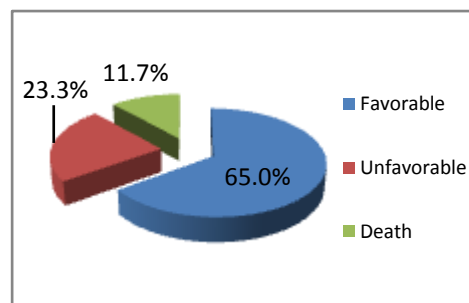


Figure 2  
Distribution of Outcome Patients

### Association between Initial Blood Lactate levels and the Degree of Brain Injury

To determine the relationship between initial blood lactate levels with the degree of brain injury (GCS) Pearson Correlation test was performed. In this study, it was obtained that there was a significant association between initial blood lactate levels with GCS with  $p = 0.033$  ( $p < 0.05$ ).

### Twentyfour Hours Lactate Clearance

Paired-Samples T-Test was applied to examine the association between the action with 24-hours lactate clearance. Results of analysis indicates that there was a significant association

between the action with 24 hour lactate clearance, as listed in Table 3 in both patients undergoing operative or conservative  $p = 0.001$  ( $p < 0.05$ ) and  $p = 0.011$  ( $p < 0.05$ ), respectively.

Table 3  
Association Between Action and 24-Hours  
Clearance

Variable pair	N	Mean	<i>p</i>
lactate-1 and lactate-2			
operative	34	1.51±1.52	0.001
conservative	26	0.65±1.21	0.010

In this study we obtained that the only association observed was between lactate-1 and lactate-2. On the other hand, no association between lactate-2 and lactate-7 observed, indicates by  $p = 0.938$  ( $p > 0.05$ ) for operative and  $p = 0.280$  ( $p > 0.05$ ) for conservative.

#### Correlation between 24-Hours Lactate Clearance and Patients Outcome

Pearson Correlation was employed to test correlation between 24-hours lactate clearance and patients outcome, the analysis used the Coefficient test is considered significant if  $p < 0.05$ . Statistinya the test results are  $p = 0.349$  ( $p > 0.05$ ), which means that there is no significant relationship between 24-hour lactate clearance with patient outcomes.

#### Correlation Between Daily blood lactate levels with Patients Outcome

Pearson Correlation test was applied to determine correlation between daily lactate blood levels and patients outcome. The results was presented on Figure 3.

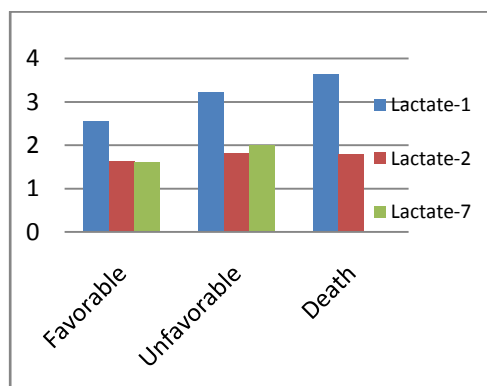


Figure 3  
Correlation between Daily Blood Lactate Levels  
with Patients Outcome

## DISCUSSION

### Correlation between Blood Lactate Levels with Degree of Brain Injury

In this study, it was obtained that the lowest the initial GCS value the higher blood lactate levels observed and vice versa. Therefore, initial blood lactate levels has a role on degree of brain injury. Supported by the data in this study that a number of 61.7% (37/60) of the samples tested were in hyperlactatemia.

Glenn, et. al. (2006)<sup>13</sup> on an observational study with 41 patients of traumatic severe brain injury found lower CMRO<sub>2</sub>, high blood-brain barrier destruction, high systematic blood lactate levels and worse outcome clinic. On the other hand, for mild brain injury, they found higher CMRO<sub>2</sub>, mild destruction of blood-brain barrier, lower systematic blood levels and followed by better clinical outcome.

Zoremba, et. al. (2007)<sup>14</sup> on an animal experimental study with a microdialysis found that the greater the neuronal damage the higher the extracellular brain lactate. Meanwhile, lower neuronal damage results in lower extracellular brain lactate. Even in normal physiologic stimulant leads to increase of brain lactate levels as reported by Simpson, et. al. (2007).<sup>15</sup>

Khosravani, et. al. (2009)<sup>16</sup> on an observational research of 13.932 critically ill patients, including 40% of them were traumatic brain injury who undergo intensive care, 40% of them were found hyperlactatemia. They also found that the greater the lactate levels the death risk were also high. Blomkalns, at. al. (2006)<sup>9</sup> based on Abramson and coworkers research reported that on a series of research with multi-traumatic patients, it was observed that only 27 from 76 patients (35.5%) have a normal lactate levels  $\leq 2$  mmol/L and the rest 49 patients (64.5%) experiencing hyperlactatemia.

In this study, it was obtained that in every patients who experience traumatic brain injury followed by brain energy metabolism destruction indicates by increase of blood lactate levels. This increase were primary due to impact of brain tissue damage as a results of trauma. Secondary, it was also due to a more complex pathophysiologic chain changes, such as increase of intra cranial pressure, perfusion disturbance, metabolism disruption, inflammation process, secretion of excite neurotransmittance, ionic balance disruption, and finally aggravate brain energy metabolism. From brain energy metabolism side, the condition will be presented through increase of brain lactate

production, then secreted to outside circulation and leads to hyperlactatemia. This also supported by Inao et al (1998),<sup>17</sup> they use animal model and found that an increase of brain lactate production was comparable to the proportion of injury severity.

### **Correlation Between Action with 24-Hours Lactate Clearance**

This research found that intervention on the first day in either operative or conservative are equally able to fix or reduce blood lactate levels. The study also obtained that impact of operation treatment decrease blood lactate levels greater than conservative treatment. Reinert, et. al. (2004),<sup>18</sup> stated that with a good resuscitation, including improve of hemodynamic and oxygenation can improve or lowering blood lactate levels. A good tissue oxygenation will return glycolysis aerobic metabolism, therefore, reduce conversion of pyruvate to lactate or lactate will be return to pyruvate. Oxygenation will also improved oxidative metabolism on mitochondria levels, in which pyruvate enter to TCA (Krebs) cycle, therefore, energy needed will be appropriate, instead there were permanent and wide damage on neuron. Furthermore, decrease of lactate also occurs due to recovery of ionic imbalance on cell membrane, decrease of ATP needed because of decrease potassium to sodium pumped, which was immediately took place after the event of trauma for some hours. This condition known as a sub-acute glycolysis.<sup>12,19</sup>

Better decrease of average blood lactate levels of operative treated patients was due to improvement of brain oxygenation as a result of intra-cranial pressure decrease post operation, improve of blood brain circulation, faster improvement of cerebral perfusion levels compare to patients treated conservatively. There was still high blood lactate levels on the second and seventh days indicates that increase of lactate was not due to hypoxia factor only, however, was also due to disruption of oxidative phosphorylation because of cell or tissue damage cause by trauma.<sup>20,21</sup> In addition it was also due to effect of inflammation, catecholamine or adrenaline responses.<sup>12</sup>

### **Correlation of 24-Hours Lactate Clearance and Daily Lactate Levels and Patient Outcomes**

Unlike the initial hypothesized, that there was a significant correlation between 24-hours lactate clearance and patients outcome. In the hope that the greater rate of the clearance the better the

patients outcomes. However, the results of this research was in contrast with that hypothesized in which we observed that the greater the clearance the worse the patients outcomes. Meanwhile, for dynamic daily lactate levels, it was obtained that there was the only significant correlation between lactate-1 and patients outcomes. For the other lactate levels, i.e. lactate-2 and lactate-7 there were no significant correlation observed.

Blomkalns, et. al. (2006)<sup>9</sup> reported that in either trauma and sepsis patients their lactate clearance was not significantly correlated to patients outcomes. On an observational study by Tim, et. al. (2009),<sup>22</sup> from 394 sepsis patients and hemorrhage/trauma that underwent intensive treatment, it was obtained that for sepsis patients their lactate clearance was correlated to outcomes, in which the greater the clearance the better the outcomes. Meanwhile, for hemorrhage/trauma patients, it was observed that there was no significant correlation between lactate clearance and outcomes. This was probably due to the occurrence of irreversible organ or tissue damage.

In an observational study by Michael, et al (2007),<sup>23</sup> with 63 patients who underwent post-surgical intensive care at Cipto Mangunkusumo found that the clearance of early lactate (6 hours) can not be used as a predictor of mortality in post-surgical patients with hyperlactatemia.

The results of this study indicates that patients that have a greater lactate clearance was probably due to greater initial blood lactate levels. Therefore, outcomes of the traumatic brain injury patients were depend on the initial blood lactate levels, not the 24-hours lactate clearance as also stated by Inao, et. al.<sup>17</sup>

### **Blood Lactate Levels as Outcome Predictors**

In line with Glenn, et. al. (2006)<sup>13</sup> and Khosravani, et. al. (2009),<sup>16</sup> this study found that blood lactate levels can be used as an outcome predictor of patients with isolated traumatic brain injury. Blood lactate levels predictor value towards outcomes were not rested on dynamic changes, but its rely on initial blood lactate levels during patients treated. Based on entrance GCS value and blood lactate levels, therefore, there was a reciprocity correlation between them to affect the outcomes.

### **Research Limitations**

There is a potential methodological limitation in this study, in which blood samples taken from the extremities performed can not be fully used as



a mirror of brain lactate metabolism. Creteur (2005),<sup>24</sup> states that blood lactate better reflect the state of global tissue oxygenation of the body, not lokoregional. The better way to understand of lokoregional lactate metabolism was measured the difference in arterial-venous lactate levels on both sides of the organ. Therefore, in this study brain lactate levels should be evaluated based on the difference between lactate levels and carotid artery jugular vein. Zaaror et al (2007),<sup>11</sup> says that the brain lactate levels are best measured through a liquor or directly on brain tissue with mikrodialisis techniques.

### CONCLUSION

In general, blood lactate levels can still be applied as one of outcome predictor on patients with isolated traumatic brain injury. The predictor value, was not rested on 24-hours lactate clearance, however, based on initial blood levels when the patients come to hospitals. Therefore, initial blood levels can be used as one of observation for every traumatic brain injury patients or other surgery patients. Blood lactate levels more than 3.3 mMol/L was the cut point for worse outcome predictor.

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