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The correlation of blood thiamine concentrations with lactate acidosis in peritonitis patients with sepsis

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ABSTRACT

Background: Vitamin B1 (Thiamine) functions as a pyruvate dehydrogenase cofactor to produce acetyl Co-A and activate the Krebs cycle in cellular metabolism. The hypermetabolic state in septic condition requires excess thiamin to keep the Krebs cycle functioning well. The thiamin level in the blood decreases and causes mitochondrial dysfunction and vice versa results in an increase in lactate levels. This study aims to evaluate the correlation of blood thiamine concentrations with lactate acidosis in peritonitis patients with sepsis.
Methods: Prospective observational study in 65 adult septic patients who came to the hospital with peritonitis and underwent laparotomy. Thiamine concentration was assessed on days 1, 3, and 5 by liquid chromatography-mass spectrometry (LC-MS). The primary outcome was lactate levels. Data was analyzed using SPSS version 23 for Windows.
Results: The incidence of thiamine deficiency (TD) was 61.5% of patients. Specifically, 29 cases (44.6%) had absolute thiamine deficiency (TD) on presentation, 4 patients (6.1%) developed it on day 3, and another 7 patients (10.8%) on day 5. Thiamine was negatively correlated with lactate levels (r=-0.600; p=0.020). The relationship appeared after multivariable regression analysis controlling for sex, septic shock, and malnutrition. Overall, for the TD group, there was a significant association with septic shock, malnourishment, and Mortality ($p<0.05$).
Conclusion: Thiamine deficiency had significantly raised lactate levels, which might increase the risk of Mortality.

Keywords: Thiamine Deficiency, Sepsis, Lactic Acidosis, Mortality.
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INTRODUCTION

Clinicians and researchers have made various efforts to reduce the mortality rate of sepsis patients. Peritonitis is the most common cause of abdominal sepsis associated with significant morbidity and mortality rates up to 25-60%.[1,2] High mortality rate in sepsis is partially caused by inadequate function of aerobic metabolism due to mitochondrial and cellular dysfunction.[3]

Thiamine is an essential water-soluble vitamin for aerobic metabolism. It acts as a cofactor for pyruvate dehydrogenase, the enzyme to convert pyruvate from glucose to acetyl Co-A. As a result, acetyl Co-A will enter the Krebs cycle for the aerobic metabolic process.[4] In abdominal sepsis, the hypermetabolic state occurs due to an infectious process.[3] The store of thiamine in the body is rapidly depleted, particularly after the administration of large amounts of glucose. Because of the limited content in the human body and high utilization rate, thiamine stores may be depleted 18 days later in healthy individuals, and the day might be shorter in the case of systemic inflammation, hypermetabolism, or low intake of thiamine.[5,6] Moreover, thiamine deficiency might appear in surgical patients who keep consuming parenteral glucose.[7] The European Society for Clinical Nutrition and Metabolism guidelines for parenteral nutrition recommended thiamin supplementation of 100 to 300 mg/day during the first three days in intensive care units for all patients suspected of thiamine deficiency.[8] Because anaphylaxis has been reported in rare instances, guidelines have recommended that thiamine should be administered over a 15-to-30-minute interval in a mixture of saline solution or dextrose to decrease adverse reactions.[9]

Lack of thiamine results in the failure of pyruvate to enter the Krebs cycle. This state causes pyruvate to be converted to lactate (anaerobic metabolism). This biochemical lesion may lead to lactic acidosis, inability to use oxygen, cardiovascular collapse, and patients may die if untreated well.[4,10-12] The occurrence of lactic acidosis and organ dysfunction is considered related to thiamine deficiency. Based on those mentioned above, this study aims to investigate our hypothesis that low thiamine concentration is correlated with higher lactate levels in sepsis patients.

METHODS

Study Design

This prospective cohort study was conducted at Dr. Soetomo General Hospital referral teaching hospital in East

Indonesia between June until October 2020. The Research Ethics Committee of Dr. Soetomo General Hospital approved the study, and written consent was obtained from each patient.

Inclusion Criteria

Inclusion criteria were between the ages of 18 to 60, having clinical evidence of complicated intra-abdominal infection (cIAI), sepsis (presence of SOFA score ≥2 with documented or suspected generalized peritonitis at the time of informed consent with/without hypotension followed by vasopressor-dependence after fluid resuscitation according to Surviving Sepsis Campaign/SSC Guideline (30 ml/kg within the first 1 hour), require surgical intervention and the patients will immediately be operated within 8 hours after stabilization in the emergency room (ER).

Exclusion Criteria

Exclusion criteria included: (1) history of liver injury (increased ALT or AST or known cirrhosis), (2) history of chronic kidney disease, (3) history of congestive heart failure, (4) history of medications associated with elevated lactate (metformin, linezolid, anti-retroviral) (5) cardiac index <2,5 L/min/m^2 or >4 L/min/m^2. Patients who did not receive sepsis management as defined in the 1-hour bundle protocol by SSC Guideline will be excluded from this study.

Operational Variables

Absolute thiamine deficiency was defined as a level ≤70 nmol/L using established standard laboratory values from our institution. Septic shock was defined by hypotension (systolic pressure < 90 mmHg) and lactate level of > 2 mmol/L at the time of informed consent and randomization after initial fluid resuscitation (30 mL/kg within the first 1 hour) followed by vasopressor-dependence. Vasopressor-dependence was defined as the continuous infusion of norepinephrine, dopamine (≥5 mcg/kg/min), vasopressin (> 0.04 units/min) or epinephrine. For the classification of nutritional state, anthropometric indexes of weight and height were used. Patients were classified as malnourished if they had a body mass index (BMI) less than 18.5 kg/m^2 of the World Health Organization 2006 standards.

Table 1. Baseline characteristic of the study population

Variables	Values
Age (Years) (mean±SD)	54.00±14.00
Gender, n (%)	
Female	23 (35.40)
Male	42 (64.60)
Laboratory Parameters, median (minimum-maximum)	
Hemoglobin (g/dL)	10.30 (8.90-13.00)
Leukocytes (10^3/µL)	13.80 (6.20-21.50)
Platelet (10^6/µL)	199.00 (115.00-220.00)
Creatinine (mg/dL)	2.00 (1.30-4.90)
AST (IU/L)	21.00 (9.00-31.00)
ALT (IU/L)	25.00 (11.00-26.00)
Albumin (g/dL)	3.10 (2.40-3.70)
Lactate (nmol/L), median (minimum-maximum)	2.10 (1.10-6.40)
SOFA Score, median (minimum-maximum)	4.00 (1.00-10.00)
APACHE II Score (mean±SD)	25.80±9.30
Cardiac Index (L/min/m^2) (mean±SD)	3.10±0.80
Thiamine Deficiency (TD), n (%)	38 (58.50)
Septic Shock, n (%)	29 (44.60)
Malnourished, n (%)	20 (30.80)
Mortality, n (%)	23 (35.40)
Source of Perforation, n (%)	
Gastric	51 (78.50)
Intestinal	13 (20.00)
Appendix	1 (1.50)
Thiamine Concentrations (nmol/L) (mean±SD)	
0-hour	66.00±7.43
72-hours	69.00±10.70
120-hours	71.00±14.33
Lactate Levels (mmol/L) (mean±SD)	
0-hour	2.20±1.68
72-hours	1.80±0.66
120-hours	1.20±0.77

SD: Standard Deviations; AST: Aspartate Transaminase; ALT: Alanine Transaminase; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation

Blood Samples and Data Collection

Blood was collected at 0, 72, and 120 hours to assess thiamine concentrations. Within 1-hour after admission to ER, venous blood (10 mL) was taken and collected into EDTA tubes, while the addition of arterial blood (6 mL) was collected into the heparin tubes. Samples of venous blood (2 mL) were centrifuged, aliquoted into light-protected amber vials, and frozen at -80^{0}C. Based on a previous study, thiamine depletion has been reported within 3-25 days in patients with sepsis.[6] Therefore, we evaluated thiamine concentrations on those three-time measurements regarding those considerations.

Thiamine concentration in plasma was measured using Liquid Chromatography-Mass Spectrometry. Thiamine deficiency (≤70 nmol/L) was determined using a previously established standard laboratory reference range in our institution.

The primary outcome was thiamine and lactate level at 0 hours, 72 hours, and 120 hours. Additional outcomes included sex, septic shock, Mortality, and nutritional status.

Statistical Analyses

Data is analyzed using the IBM SPSS version 23 for Microsoft Windows. Baseline characteristics of the population overall were analyzed with descriptive statistics. Spearman correlation coefficient was used to determine the association between thiamine and lactate. We further performed a multivariable regression analysis to evaluate for confounders in the association between thiamine and lactate.

RESULTS

Sixty-five patients were recruited from June to October 2020. The baseline characteristics and laboratory values of the study population are summarized in Table 1. Mean thiamine concentrations at 0-hour, 72-hours, and 120-hours were 66.00±7.43 nmol/L, 69.00±10.70 nmol/L, and 72.00±14.33 nmol/L, respectively. In this study, 38 out of 65 (58.50%) had absolute thiamine deficiency (Table 1). Thiamine concentrations tended to increase during the first 5 days of hospital stay; meanwhile, lactate levels showed the opposite tendency.

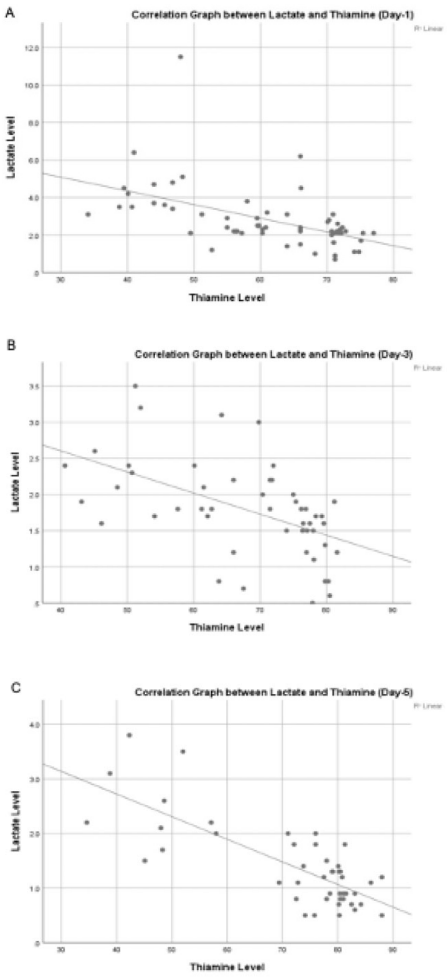

Figure 1. The negative correlation between thiamine and lactate levels (A) on 0-hour, (B) 72-hour, and (C) 120-hour.

The primary outcome of lactate levels at 0, 72, and 120 hours showed median of 2.20±1.68 mmol/L (95% CI: 2.04-3.05), 1.80±0.66 mmol/L (95% CI: 1.60-2.00), and 1.20±0.77 mmol/L (95%CI: 1.17-1.63), respectively. For the overall study group, there was a significantly negative correlation ($p<0.050$) between thiamine and lactic acidosis on 0-hour ($n = 65$, $r = -0.632$), 72-hours ($n = 49$, $r = -0.610$) and 120-hours ($n = 45$, $r = -0.658$) (Figure 1).

In this section, we review the results of the analysis in the subgroups. Further analysis from Table 1 showed a significant association ($p<0.05$) between thiamine with other independent variables, such as sex, septic shock, malnourishment, and Mortality. Of the TD population, 29 patients had a septic shock at the time of presentation, while malnourished was detected in 16 patients. Univariate analysis with Chi-square was performed and showed a significant association ($p<0.050$) between thiamine deficiency with septic shock, malnourishment, and Mortality, as represented in Table 2. We further performed multivariate regression analysis and the results revealed that septic shock was the most significant variable in this study (OR= 4.05; 95%CI: 1.25- 13.10; P= 0.020).

DISCUSSION

In our study, 38 patients (58.5%) showed thiamine deficiency at three times of measurement. The interesting finding in this study is that the thiamine concentration on the first measurement at enrollment (0-hour) was still high on >50% of patients with abdominal sepsis. Specifically, 36/65 patients had normal thiamine concentrations at the time of presentation, although they had been in an abdominal sepsis condition.

The patient's body is predicted to have a sufficient amount of reserved thiamine to enable a decent glucose metabolism process during sepsis and acidosis. As noted, thiamine depletion has been reported within 3-25 days in patients with sepsis.[6] Because acute consumption of thiamine in glucose metabolism, long-term use of parenteral nutrition, and inadequate thiamine intake resulted in a gradual decrease of thiamine concentrations in the body.[6] This finding could theoretically indicate a thiamine deficiency from increased metabolic demand.

On the other hand, 10/65 patients showed normal lactate levels (<2 nmol/L) at the time of presentation, although they had been in sepsis condition. These patients were referred from other primary health care units and had given previously fluid resuscitation, oxygenation, and antibiotic therapy. This is considered the reason these patients are still in acidosis condition but have normal lactate levels. Thus, other things that cause acidosis need to be investigated, and source control is needed through laparotomy to overcome the cause of sepsis.

For the overall patient population, there was a strong negative correlation between thiamine and lactate. From a pathophysiologic standpoint, lactate production during sepsis is still a matter of debate. Conservative theory believes that lactic acidosis is caused by tissue hypoxia or hypoperfusion, whereas anaerobic glycolysis due to tissue hypoperfusion is a key factor.[13,14] However, many studies

Table 2. Variables associated with thiamine deficiency

Variable	Participants (N=65)		OR (95% CI)	p
	TD (N=38)	Non-TD (N=27)		
Male, n (%)	21 (50.00)	21 (50.00)	2.83 (0.93-8.59)	0.072
Septic Shock, n (%)	29 (76.40)	10 (37.30)	5.48 (1.86-15.15)	0.002*
Malnourished, n (%)	16 (42.10)	4 (14.80)	4.18 (1.21-14.48)	0.028*
Death from any cause, n (%)	19 (50.00)	4 (14.80)	5.75 (1.67-19.82)	0.004*

TD: Thiamine Deficiency; OR: Odds Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.050

often fail to prove a relationship between hyperlactatemia and any indicators of tissue hypoxia due to sepsis.[15-17] New evidence has been proposed as a more reasonable explanation, such as adrenergic-driven aerobic glycolysis. This theory indicates that non-hypoxic mechanisms such as accelerated aerobic glycolysis induced by sepsis-associated inflammation.[15-17] In other words, hyperlactatemia represents a change in metabolic state, not a response to cell oxygenation issues. The rate of carbohydrate metabolism exceeds the oxidative capacity of the mitochondria. Pyruvate is thus produced faster than it can be transformed into acetyl Co-A by PDH. This increases cellular pyruvate concentration, which in turn increases lactate production by a mass effect. Fluid resuscitation protocols may not directly affect lactate if its production mechanisms are not directly targeted by such activities.[3]

There are so many confounders that will cause lactic acidosis, such as sex, cardiogenic shock, heart failure, severe trauma, carbon monoxide poisoning, severe anemia, cancer, liver disease, malnourishment, drugs (metformin, salicylates, â-agonists), cocaine, toxic alcohol, and cyanide.[3] We already excluded patients with a history of heart failure, liver disease, trauma, poisoning, cancer, and drug consumption that would affect lactate levels from randomization. We need to exclude other independent variables that will produce multicollinearity with thiamine deficiency. From Table 1, we found no significant association between thiamine deficiency with laboratory values (hemoglobin, albumin, creatinine level) and cardiac index. There was a significant association between thiamine deficiency with sex, septic shock, nutritional state, and Mortality. Moreover, from further univariate analysis by Chi-square, we found a potential relationship between thiamine deficiency with septic shock (p=0.002), malnutrition (p=0.028), and mortality (p=0.004). It would be curious to see the variance inflation factor if we performed further multivariable logistic regression with the independent factors.

There was also a correlation between SOFA score and thiamine deficiency. Our rationale is that thiamine deficiency can result in the inadequate function of ATP production from the Krebs cycle resulting in elevated organ dysfunction and death in sepsis patients.[12] Thus, we hypothesized that lower thiamine concentrations would cause a higher SOFA score in sepsis patients, resulting in a higher mortality rate.

In our study, 23/65 patients (35.4%) died during hospital treatment. Overall, for those patients, 11/23 cases (47.8%) had a high SOFA score (≥12) at the time of presentation, and all of them showed thiamine deficiency in an average of three-time measurements. Prior studies showed that adult critically ill patients in ICU who survived had significantly higher thiamine concentrations than those who died.[5,7] However, later reports showed no difference in 24-hour SOFA score between sepsis patients in the placebo group and the thiamine group (8.9±5.0 vs. 8.1±3.5, P= 0.41).[16] Nonetheless, all patients who died received only parenteral nutrition during hospital treatment, while patients who survived received enteral nutrition after no contraindication. Some limitations should be considered in interpreting this result. The effect of an exposure variable on Mortality in sepsis patients can be better studied in specific groups of this study, such as malnutrition and septic shock. Additionally, it would be of interest to further investigate the possible effect of the interaction between thiamine concentrations and mortality risk in this study.

In conclusion, we have found that thiamine deficiency is negatively correlated with lactic acidosis in peritonitis patients with sepsis. Moreover, we investigated a potential relationship between thiamine deficiency and a higher mortality rate in the previous studies. This finding is the basis of our concept that thiamine supplementation needs to be given to surgical patients with sepsis without waiting for the thiamine level. However, the efficacy of thiamine to overcome lactic acidosis needs to be proven in further clinical trials. Future investigation is necessary with multicenter studies to validate our observation that this finding may reflect sepsis patients throughout all centers of the country.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

ETHICS CONSIDERATION

This study has obtained Ethics Approval from the Ethics Committee, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, Indonesia prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

MM collected the data, performed the statistical analysis and drafted the initial version of the manuscript. VSB and JN designed the study and drafted the final version of the manuscript. All authors reviewed the final version of the manuscript and approved its submission to the journal.

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