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Research Article

The Effect of Thiamine Administration on Interleukin-6 (Il-6) Enzyem, Lactate and Sequential Organ Failure Assessment (SOFA) Score in Patients with Sepsis

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Abstract

Background: Thiamine, in particular, plays an important role in the treatment of sepsis because it plays a role in Interleukin-6 (Il-6) Enzyem and Lactate.

Method: We conducted a thiamine administration on 24 sepsis patients (SOFA score ≥ 2) divided into 2 groups (thiamine and placebo groups). Thiamine was given in the size of 200 mg per intravenous drop per 12 hours for 72 hours. This study was carried out randomly from January to February 2020, and is an experimental controlled intervention study to examine the effects of thiamine on levels of Interleukin-6 and Lactic Acid, and SOFA scores in sepsis patients. The parameters measured were IL-6, lactic acid and SOFA scores.

Results: In the thiamine group, IL-6 levels were lower compared to the control group, but the difference was not statistically significant. Lactic acid and SOFA scores did not change in both groups and were not statistically significant. The mean value of serial Interleukin-6 in group A at T0 (111.1 ± 40.6 ng/dl), T1 (111.1 ± 40.6 ng/dl), T2 (128.2 ± 80 ng/dl), and T3 (97 ± 45.4 ng/dl). The mean value of serial Lactic Acid in group A at T0 (2.37 ± 0.23 mg/dl), T1 (1.84 ± 0.49 mg/dl), T2 (1.47 ± 0.22 mg/dl), and T3 (1.36 ± 0.26 mg/dl).

Conclusion: We believe that administration of thiamine can reduce levels of Interleukin-6 (IL-6) in patients with sepsis, although this study did not find significant results.

Keywords

Sepsis, Thiamine, IL-6, Lactic acid, SOFA score

Abbreviations

IL-6: Interleukin-6; SOFA: Sequential Organ Failure Assessment

1. Introduction

As morbidity and mortality increase due to sepsis, doctors and researchers continue to produce new targets for therapy. One such target involves the role of vitamin function in the sepsis response because metabolic stress that occurs in the body during sepsis causes a deficiency of this important nutrient. As a result, this vitamin deficiency can function as an alternative mechanism of organ dysfunction which has the potential to prevent the use of oxygen in cells [1].

Sepsis is a complex process of systemic inflammation associated with an intense inflammatory response to injury and trauma. The initial inflammatory response is the activation of the innate immunity pathway. When activated macrophages come into contact with pathogens, macrophages begin to produce TNF-α which is responsible for increasing vascular permeability. In addition, the stimulation of macrophage pathogens leads to the production of IL-1β and IL-6, which have an important role in the occurrence of fever by acting on a central hypothalamic temperature control system [2].

Interleukin (IL)-6 cytokines play an important role in cell development, innate immunity initiation and cell function in adaptive immunity. In 2016 Klag T [2], studied 20 patients with severe bacterial sepsis and their study showed that a rapid decrease in IL-6 concentrations after 24-48 hours to or below baseline was evidence of the success of empirical antibiotic therapy that could be a predictor of survival [2].

One simple value system developed by the working group of the European Society of Intensive Care Medicine is the Sequential Organ Failure Assessment score (SOFA score) which assesses six organ systems from 0-4 degrees of organ failure. In addition, the accuracy of the SOFA score assessment has been well recognized by a number of clinicians. Parameters calculated in the SOFA score include respiratory, renal, hepatic, cardiovascular, hematological, and GCS organs [3].

SOFA scores can help see organ dysfunction or organ failure during treatment and can be used to predict mortality rates of patients treated in the ICU. Although this value system can only provide a picture and quality of organ function and does not provide a picture of patient mortality in the ICU, there is a significant relationship between organ dysfunction and mortality rates. This has been demonstrated by several studies [4].

Thiamine, in particular, plays an important role in the treatment of sepsis because it plays a role in glucose metabolism and lactate production. The use of thiamine in sepsis recently received national media attention when it was included as part of a new treatment protocol that was implemented at one center in the United States [5].

Thiamine deficiency is usually found in 20% to 70% of septic shock patients. This figure is based on the cut-off value used to determine the level of thiamine deficiency in the blood. Thiamine deficiency causes reduced pyruvate input to the Krebs cycle, so that lactate production increases with changes in aerobic metabolism [6]. Increased lactic acid accompanied by acidosis is a common manifestation of thiamine deficiency and results in failure of secondary oxygen utilization in mitochondrial metabolism. Several studies have found that thiamine deficiency can be found in 10% - 70% of cases of septic shock and critical illness conditions. Therefore, relative or absolute thiamine deficiency can worsen sepsis shock patients [7]. Thiamine administration can also improves COMT level, which Catechol-O-Methyltransferase (COMT) enzyme levels can also play in mechanism inflammation in sepsis [8].

Based on a previous study, we want to determine the effect of thiamine administration on Interleukin-6, Lactic Acid, and SOFA scores in sepsis patients.

2. Methods

SOFA or Sequential Organ Failure Assessment is a system of assessing the failure of each of the 6 organ functions, namely the central nervous system, cardiovascular, kidney, liver, respiratory, and coagulation. SOFA is measured periodically during the intervention of Thiamine, i.e. before drug administration (T0), at hour 24 (T1), at hour 48 (T2), and at 72 hour (T3). The measurement scale is numeric.

2.1. Participants

The study was conducted for 2 months, and was a randomized, and experimental controlled intervention study aimed at investigating the effects of thiamine administration on Interleukin-6, Lactic Acid, and SOFA scores in sepsis patients. Diagnostic sepsis is based on the qSOFA score that assigning one point for low blood pressure (SBP ≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow coma scale<15) [9]. All sepsis patients who received sepsis therapy in the Emergency Department and Intensive Care Unit were recruited between January to February 2020 at the Haji Adam Malik General Hospital and Hospital Networks. All patients included in the study were randomized using a computer-generated list of random numbers (randomizer.org). Patients were in the age range of 8-70 years. The patients/family of the patients agreed to participate in the study. Patients included in this study were those diagnosed with sepsis with qSOFA ≥2 or SOFA score ≥2 and received Hour One Bundle Sepsis therapy and other therapies that support sepsis therapy according to the procedure, and those with lactate levels ≥2 mmol/L. Patients who had received thiamine supplementation before and were allergic to thiamine were excluded from this study. Patients were classified as drop-out criteria if they died during the intervention and observation or were transferred to another hospital. This study protocol was approved by our Institutional Review Board of the Medical Faculty of the University of North Sumatra (No. 619/TGL/KEPK FK USU HAM General Hospital/2019) and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2 Interleukin-6

ELISA (Enzyme-Linked Immunosorbent Assay) is used for the quantitative measurement of IL-6 levels in serum which a solid phase sandwich ELISA for the in vitro qualitative and quantitative determination of IL-6 in supernatants. In this study Interleukin-6 levels were checked periodically through periodic immunoassay techniques during the intervention of Thiamine before administration of the drug (T0), at hour 24 (T1), at hour 48 (T2) and at hour 72 (Q3).

2.3 Lactic Acid

Lactic acid is measured using spectrophotometrically at 450 nm in a microplate reader. In sepsis patients an increase in lactate production occurs. Lactate >2 mmol/L indicates that there is an impairment of organ dysfunction. In this study, lactic acid levels were checked periodically during the intervention of Thiamine, namely before administration of the drug (T0), at hour 24 (T1), at hour 48 (T2) and at hour 72 (T3).

2.4 Thiamine

Patients were given Thiamin 200 mg/12 hours/ drips intravenously in NaCl 0.9% 50 cc. Drugs were prepared and given by volunteers, namely residents of Anesthesiology and Intensive Therapy Phase II who were undergoing an intensive care unit program and had explained the procedures of this study.

2.5 Statistical analyses

All data were analyzed by SPSS 25.0 package program. Mann-Whitney test was used for intergroup comparison of the parametric data that were distributed normally, whereas Mann–Whitney U test was used for intergroup comparison of data that were not distributed normally. The Spearman's rank correlation was performed to see the strength of the correlation between variables. The results were considered statistically significant if p<0.05.

3. Results

3.1 Sample

The sample in this study amounted to 24 samples that fit the inclusion and exclusion criteria. Characteristics are shown in Table 1. Characteristics of the sample in this study were spread homogeneously in both groups.

3.2 Differences in Interleukin-6 levels in the treatment and control groups

The serial measurements of interleukin-6 levels at hour 0 (T0), hour 24 (T1), hour 48 (T2), and hour 72 (T3) in the treatment and control groups are shown in Table 2. Table 2 shows that the levels of Interleukin-6 before treatment (T0) in the thiamine and control groups had differences, but not statistically significant with p = 0.862. While Interleukin-6 levels after treatment at hour 24 (T1), hour 48 (T2), hour 72 (T3) in the thiamine and control groups showed statistical differences with p = 0.862, p = 0.773, and p = 0.729 respectively.

In Table 2 above, it can be seen that the mean value of serial Interleukin-6 in group A at T0 (111.1 ± 40.6 ng/dl), T1 (111.1 ± 40.6 ng/dl), T2 (128.2 80 ng/dl), and T3 (97 ± 45.4 ng/dl). Results of statistical test on group A (treatment) and group B (control) did not show a significant difference (p> 0.05).

3.3 Differences in Lactic Acid levels in the treatment and control groups

The serial measurements of Lactic Acid levels at hour 0 (T0), hour 24 (T1), hour 48 (T2), and hour 72 (T3) in the treatment and control groups are shown in Table 3. Table 3 shows that the mean value of serial Lactic Acid in group A at T0 (2.37 ± 0.23 mg/dl), T1 (1.84 ± 0.49 mg/dl), T2 (1.47 ± 0.22 mg/dl), and T3 (1.36 ± 0.26 mg/dl). Results of statistical test on group A (treatment) and group B (control) did not show a significant difference (p> 0.05), but revealed significant differences in the value of lactic acid based on time observation (p <0.05).

3.4 Differences in SOFA scores in the treatment and control groups

Serial measurements of SOFA scores at hour 0 (T0), hour 24 (T1), hour 48 (T2), and hour 72 (T3) in the treatment and control groups are shown in Table 4. Table 4 shows that the mean value of the serial SOFA score in group A at hour 0 (T0) was 3.17±0.57, at hour 24 (T1) was 3.00 ± 0.73, at hour 48 (T2) was 3.330.88, and hour 72 (T3) was 3.42±0.90. Results of statistical test on group A (treatment) and group B (control) did not show a significant difference (p> 0.05).

Table 1: Sample Characteristics.

Characteristics	Group A	Group B	p Value*
Age (years, mean ± SD)	44± 14.8	48± 15.6	0,2
Interleukin-6 (T0, mean ± SD)	111.1± 40.6	508.7± 658.7	0.862
Lactic Acid (T0, mean ± SD)	2.37± 0.2	2.34± 0.1	0,367
SOFA score (T0, mean ± SD)	3.17± 0.5	3.25± 1.6	0,229

Note: *t-independent test

Table 2: Changes in Interleukin-6 levels in the treatment and control groups.

Observation Time	Group A	Group B	p^a Value
T0	111.1± 40.6	508.7 658.7	0.862
T1	111.1± 40.6	508.7 658.7	0.862
T2	128.2 ± 80	422.2± 601.6	0.773
T3	97± 45.4	459.7 695.4	0.729
p^b Value	0.909	0.572	

Note: p^a = comparison of Interleukin-6 values in group A (treatment) and group B (control); p^b = a comparison of Interleukin-6 values at each observation time, before administration of the drug (T0), at hour 24 (T1), at hour 48 (T2) and at hour 72 (T3).

Table 3: Changes in Lactic Acid levels in the treatment and control groups.

Observation Time	Group A	Group B	p^a Value
To	2.37± 0.23	2.34 0.17	0.676
T1	1.84± 0.49	1.77 0.30	0.815
T2	1.47± 0.22	1.59± 0.24	0.221
T3	1.36± 0.26	1.51 0.21	0.534
p^b Value	0.001**	0.001**	

Note: $p^{a =}$ comparison of lactic acid values in group A (treatment) and group B (control), *Mann-Whitney Test; p^b = comparison of lactic acid value at each time of observation, **Friedman test. before administration of the drug (T0), at hour 24 (T1), at hour 48 (T2) and at hour 72 (T3).

Table 4: Differences in SOFA Scores in the treatment and control groups.

Observation Time	Group A	Group B	p^a Value
To	3.17± 0.57	3.25 1.65	0.704
T1	3.00± 0.73	3.25 1.65	0.541
T2	3.33± 0.88	3.42± 1.44	0.904
T3	3.42± 0.90	3.67 1.49	0.690
p^b Value	0.107	0.008	

Note: p^a = comparison of SOFA scores in group A (treatment) and group B (control); p^b = comparison of SOFA scores at each time of observation. before administration of the drug (T0), at hour 24 (T1), at hour 48 (T2) and at hour 72 (T3).

4. Discussion

The results of the study show that thiamine decreases Interleukin-6 levels even though it is not statistically significant. This is in accordance with the research of Hommes [10], which found that the inflammatory effect on thiamine deficiency, oxidative stress and cellular migration in experimental models of sepsis rats decreased significantly compared to the group of mice that were not induced by sepsis. However, there was no statistical difference between the two groups. Meanwhile, Menezes [11], found that administration of thiamine and riboflavin decreased TNF-α and Interleukin-6 production, thus inhibiting inflammatory activity and acute pain in the subject.

In this study, the results of statistical tests in group A (treatment) and group B (control) did not show a significant difference (p> 0.05) in the mean value of serial Lactic Acid levels. However, based on the time of observation, the two groups showed significant differences in the mean values of Lactic Acid (p <0.05). This result is supported by the study of [12], which states that the administration of thiamine supplementation in patients with critical illnesses such as sepsis improves lactate clearance time and decreases mortality [10].

However, the results of this study are different from the research of Doninno [13], who conducted a double randomized clinical trial in septic shock patients. Eighty eight patients who had a risk of thiamine deficiency symptomatically had lactate levels > 3 mmol/L after fluid resuscitation. The results of Doninno research also found that administration of Thiamine did not have an effect on lactic acid levels in the first 24 hours, but statistically there were significant changes in the level of lactate in the first 72 hours.

Many things might affect lactic acid levels, one of which is liver and kidney disorders, which was not examined in this study due to the varied conditions of the patient's sepsis. In addition, this study has limitations, namely no measurement of thiamine baseline levels in research subjects to determine the occurrence of thiamine deficiency.

Patients with critical conditions such as those with sepsis tend to have thiamine deficiency, and SOFA scores are used to assess organ dysfunction in patients with critical illness such as sepsis. In this study, there were no significant differences in SOFA scores (p> 0.05). This is consistent with which said that giving Thiamine to patients with sepsis did not provide significant changes in SOFA scores, length of stay, and mortality in the ICU. This contrasts with the 2017 Marik study [14], which found a significant difference in the SOFA score at 72 hours in the group receiving vitamin C, hydrocortisone, and thiamine compared with the control group (p <0.001). This difference can be caused by 6 parameter factors used on the SOFA score, namely the central nervous system, cardiovascular, kidney, liver, respiratory and coagulation [15, 16].

5. Conclusion

We believe that thiamine administration can reduce levels of Interleukin-6 (IL-6) in patients with sepsis.

6. Acknowledgement

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Conflict of Interest

The authors declare that there is no conflict of interest.

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