The Relationship Between Thiamin Administration And Lactic Acid In Sepsis Patients In The Icu Of H. Adam Malik Hospital

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***Abstract*- Background**: Thiamine may be considered as adjunctive therapy in patients with sepsisThiamine administration reduced the Matrix metalloproteinase 9 / Tissue inhibitors of matrix metalloproteinase 1 (TIMP-1/MMP-9) ratio, which could be associated with better survival. Thiamine can reduce Interleukin-6 (IL-6) levels in patients with sepsis. Thiamine is negatively correlated with lactate levels, thiamine deficiency significantly increases lactate levels.

Destination: To determine the effect of giving thiamine to changes in lactic acid levels, in sepsis patients at H. Adam Malik General Hospital Medan.

Method: This study was a double-blind RCT (Randomized Clinical Trial) study on sepsis patients in the Intensive Care Unit (ICU) of H. Adam Malik General Hospital Medan. Patients were divided into two groups, the treatment group was given 200 mg of thiamine with 1 ampoule of 100 mg of 4 ml every 12 hours intravenously. All data obtained were analyzed statistically

Results: The samples obtained were 63 patients, but there were 12 samples who dropped out, so the number of research samples was 50 samples. Total male subjects were 21 people (42%) with 12 people in the group without thiamine (46.2%) and 9 people in the thiamine group (37.5%). While the female sex was 29 people (58%) with a group that was not given thiamine totaling 14 people (53.8%) and a group that was given thiamine totaling 15 people (62.5%). There is a significant difference between all data based on time ($p<0.001$). Using Spearmann Correlation, there was a significant correlation between lactic acid before and after treatment in the thiamine group ($p<0.001$) with $r = 0.946$ or 94.6%. Fisher Exact analysis results show significant a relationship between thiamine administration and patient mortality ($p = 0.001$).

Conclusion: There was a significant difference in lactate levels between the thiamine and without thiamine groups in septic patients.

Index Terms- lactic acid, sepsis, thiamine

I. Introduction

Sepsis is a medical emergency that describes the body's systemic immunological response to an infectious process that can cause end-stage organ dysfunction and death. Despite significant advances in understanding the pathophysiology of this clinical syndrome, advances in hemodynamic monitoring tools, and resuscitation measures, sepsis remains a major cause of morbidity and mortality in critically ill patients. The global epidemiological burden of sepsis is difficult to pinpoint. It is estimated that more than 30 million people get sepsis each year worldwide, which has the potential to cause 6 million deaths each year. (Gyawali et al., 2019)

Current management recommendations for septic shock focus heavily on maintaining hemodynamic stability through infusion of vasopressors and intravenous fluids. Although significantly improved outcomes have improved with the adoption of this strategy, mortality remains high at 20-30%. Cost-effective, low-risk therapeutic approaches to reduce sepsis morbidity and mortality are needed. For example, the combination of thiamine 200 mg every 12 hours, ascorbic acid 1500 mg every 6 hours, and hydrocortisone 50 mg every 6 hours has recently emerged as a potential adjunctive therapy to antibiotics, control of the source of infection, and supportive care for patients with sepsis. and septic shock. There is an increasing focus on non-oxygen delivery-dependent mechanisms of septic organ injury including mitochondrial dysfunction. In this case, the role of thiamine as a key cofactor for mitochondrial aerobic respiration has received considerable attention. (Andersen et al., 2013; Gyawali et al., 2019; Lerner et al., 2016; Moskowitz and Donnino, 2020)

Thiamine is a water-soluble essential B vitamin that is absorbed in the small intestine. It is very important as a coenzyme for the metabolism of carbohydrates and amino acids. In its biologically active form, thiamine pyrophosphate, is a key cofactor for pyruvate dehydrogenase and 2-oxoglutarate (α-ketoglutarate) dehydrogenase. Since both enzymes are required for the formation of adenosine triphosphate via anaerobic glycolysis, thiamine deficiency can cause a metabolic crisis leading to lactic acidosis and death. (Andersen et al., 2013; Lerner et al., 2016; Moskowitz and Donnino, 2020). Increased lactic acid accompanied by acidosis is generally caused by thiamine deficiency and failure to utilize secondary oxygen for mitochondrial metabolism. A number of studies have found that thiamthiamine deficiency0% of cases of septic shock and other critical illnesses. Therefore, relative or absolute thiamine deficiency may exacerbate septic patients. (Andersen et al., 2013; Berg et al., 2017)

The benefits of thiamine in septic patients have been studied where sep. Septic patients who received additional thiamine therapy had a better chance of survival thantients who received additional therapy with ascorbic acid, a combination of both, or 0.9% NaCl. Thiamine administration reduced the Matrix metalloproteinase 9 / Tissue inhibitors of matrix metalloproteinase 1 (TIMP-1/MMP-9) ratio, which could be associated with better survival. The study of thiamine administration also reduced interleukin-6 (IL-6) levels in patients with sepsis. Thiamine may be considered as adjunctive therapy in patients with sepsis. (Lubis et al., 2021; Nasution and Yulianda, 2020)

In the study by Woolum et al., a study with 123 septic patients who received thiamine therapy showed an improvement when lactate clearance decreased (subdistribution hazard ratio, 1.307; 95% CI, 1.002–1.704). Giving thiamine also reduced the mortality rate within 28 days (hazard ratio, 0.666; 95% CI, 0.490–0.905) and there was no difference in the incidence of AKI (Acute Kidney Injury), the need for replacement of kidney therapy, the use of vasopressors, and ventilator-free days in the control group. who were given thiamine therapy or who did not receive thiamine therapy. (Woolum et al., 2018)

In a retrospective before-after clinical study, Litwak et al compared the outcomes and clinical course of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine over a 7-month period (treatment group) with a control group treated in the intensive care unit (ICU). ICU) for a 7-month period (treatment group) with a control group who was admitted to the ICU for a 7-month period. 7 months before. The primary outcome is survival in hospital. The results show that the use of using intravenous thiamine, vitamin C, and corticosteroids effectively prevent progressive organ dysfunction, including acute kidney injury, and reduce in patients with severe sepsis and septic shock. Additional studies are needed to confirm these initial findings. (Litwak et al., 2019)

Research at RSUD Dr. Soetomo Surabaya, an observational study on 65 adult septic patients who came to the hospital with peritonitis and underwent laparotomy. Thiamine concentrations were assessed on days 1, 3, and 5 by liquid chromatography-mass spectrometry. The incidence of thiamine deficiency was 61.5% of patients. Specifically, 29 cases (44.6%) had absolute thiamine deficiency at presentation, 4 patients (6.1%) developed it on day 3, and another 7 patients (10.8%) on day 5. Thiamine negatively correlated with lactate levels (r = -0.600; p = 0.020).: Thiamine deficiency significantly increases lactate levels. (Sinaga et al., 2021)

Based on the research above that giving thiamine has an effect on sufferers of sepsis and septic shock, the researchers wanted to conduct a study to see the effect of giving thiamine to changes in lactic acid levels, in septic patients at H. Adam Malik General Hospital Medan.

II. METHOD

This study is a double blind RCT (Randomized Clinical Trial) study, comparing the relationship between thiamine and lactic acid in septic patients in the Intensive Care Unit (ICU) of H. Adam Malik General Hospital Medan.

The population in this study were all patients with sepsis in the Intensive Care Unit (ICU) of H. Adam Malik General Hospital. The sample in this study is part of the population that meets the inclusion and exclusion criteria. Patients will be divided into two groups based on randomization using a computer randomizer. Patients will be given 200 mg of thiamine in 1 ampoule of 100 mg of 4 ml every 12 hours intravenously in the treatment group and 4 ml of NaCl in the control group. Monitoring and recording of lactic acid levels was carried out every day for 3 days, at the initial admission of the patient (T0), on the first day (T1), the second day (T2), and the third day (T3). All data obtained were analyzed statistically.

III. RESULTS

The purpose of this researchto determine the effect of thiamine administration on lactic acid levels in sepsis patients. The research sample was taken at the Intensive Care Unit (ICU) of the Adam Malik Haj Center General Hospital, Medan. There were 62 samples that fit the inclusion and exclusion criteria. In sampling, there were 12 samples included in the dropout category. So that the number of research samples becomes 50 samples.

Table 3.1 Data Characteristics

Characteristics	**Sample Group**				**Total**	
	No Thiamine		**Thiamine**			
Age	**n**	**%**	**n**	**%**	**n**	**%**
18-25 years	2	7,7	3	12.5	5	10
26-35 years	3	11.5	3	12.5	6	12
36-45 years	2	7,7	2	8,3	4	8
46-55 years	4	15,4	5	20,9	9	18
56-60 years	3	11.5	3	12.5	6	12
>60 years	12	46,2	8	33,3	20	40
Total	26	100	24	100	50	100
Gender						
Man	12	46,2	9	37.5	21	42
Woman	14	53,8	15	62.5	29	58
Total	26	100	24	100	50	100

In Table 3.1, It was found that there were 5 patients aged 18-25 years (10%) with a group without thiamine totaling 2 people (7.7%) and 3 people who were given thiamine (12.5%). Patients aged 26-35 years totaled 6 people (12%) with a group without thiamine 3 people (11.5%) and 3 people who were given thiamine (12.5%). Patients in the age group 36-45 years totaled 4 people (8%) with the group without thiamine totaling 2 people (7.7%) and the thiamine group 2 people (8.3%). The age group of 46 – 55 years totaled 9 people (18%) with patients who were not given thiamine totaling 4 people (15.4%) and those with thiamine amounting to 5% (20.9%). Patients aged 56-60 years totaled 6 people (12%) and the group without thiamine totaled 3 people (11.5%) and the thiamine group 3 people (12.5%). Patients in the age group >60 years had the highest number, namely 20 people (40%) with details in the group without thiamine totaling 12 people (46.2%) and the thiamine group 8 people (33.3%).

In this study, the total number of male subjects was 21 people (42%), with 12 people in the group without thiamine (46.2%) and 9 people in the thiamine group (37.5%). While the female sex was 29 people (58%) with a group that was not given thiamine totaling 14 people (53.8%) and a group that was given thiamine totaling 15 people (62.5%).

The results of descriptive data analysis were carried out using SPSS to determine the distribution of research data. Data normality analysis was also performed using the Kolmogorov-Smirnov test on data >50 and the Shapiro-Wilk test on data <50. In this study, Shapiro-Wilk data analysis was carried out to determine the results of data normality.

Table 3.2 Descriptive Analysis Results and Data Normality

Data type	Means	±SD	Median	Min	Max	P-value
Age	**52,4**	**18,1**	56	6	81	**0.200**
systole	99.32	5.59	**98**	**94**	**128**	0.000
Diastole	53,76	6,32	**56**	**44**	**78**	0.000
HR	89.54	9	**88**	**73**	**123**	0.005
RR	19,18	4.09	**19**	**12**	**28**	0.000
Ur	58,84	64,63	**36**	**11**	**289**	0.000
cr	1.19	1.71	**0.62**	**0.27**	**10.63**	0.000
T0	**5,27**	**2.85**	5,3	0.9	10,7	**0.200**
T1	6,69	3.46	**7,4**	**1**	**12.5**	0.020
T2	7,11	3.56	**7.75**	**1,1**	**12,8**	0.022
T3	7,34	3,6	**7.75**	**1,4**	**13,4**	0.017

Based on the results of the normality test above, it is known that the Age and T0 variables are normally distributed and other variables are not normally distributed. Data is declared normally distributed if the p-value of the normality test is > 0.05 and declared not normally distributed if the p-value of the normality test is <0.05. Data that are normally distributed are interpreted with the mean and standard deviation while data that are not normally distributed are interpreted with the median, minimum, and maximum.

In this study, the average age of the research subjects was 52.4±18.1 years. The median systolic blood pressure in the study subjects was 98 mmHg (94 – 128 mmHg) and the median diastolic blood pressure was 56 mmHg (44 – 78 mmHg). The median heart rate and respiratory rrates are 88 beats per minute (73 – 123 beats per minute) and 19 beats per minute (12 – 28 beats per minute) respectively. In this study, the median blood urea was 36 mg/dL (11 – 289 mg/dL). Serum creatinine levels in this study had a median of 0.62 mg/dL (0.27 – 10.63 mg/dL). Lactic acid levels at T0 or before treatment had an average of 5.27±2.85 mmol/L. Lactic acid levels on the first day after being given treatment had a median of 7.4 mmol/L (1 – 12.5 mmol/L), on the second day the median lactate was 7.75 (1.2 – 12.8 mmol/L), and on the third day 7.75 mmol/L (1.4 - 13.4 mmol/L).

Table 3.3 Results of Analysis of Differences Between Thiamine and Without Thiamine Groups Based on Time

DataType	route	Min	Max	Median	Means	±SD	P-values
T1	No Thiamine	1	11,2	3.95	4.89	3.39	0.000
	Thiamine	5,6	12.5	8,3	8.85	2.05	

T2	No Thiamine	1,1	11,9	4,9	5,25	3.52	
	Thiamine	5,9	12,8	8,7	9,28	2,13	0.000
T3	No Thiamine	1,4	12,6	5,15	5,43	3.56	
	Thiamine	6,4	13,4	9	9.49	2,11	0.000

Based on Table 3.3,It was known that there was a significant difference between the thiamine and without thiamine groups at T1 (p<0.001). It was found that there was a significant difference between the thiamine and no thiamine groups at T2 (p<0.001). It was found that there was a significant difference between the thiamine and no thiamine groups at T3 (p<0.001).

Table 3.4 Differences in the mean lactic acid in the two groups based on time

	Route	Difference Mean	Percentage Difference
T1-T2	No Thiamine	0.36	7.36%
	Thiamine	0.43	4.85%
T2-T3	No Thiamine	0.18	3.42%
	Thiamine	0.21	2.26%
T1-T3	No Thiamine	0.54	11.04%
	Thiamine	0.64	7.23%

Based on Table 3.4, the percentage difference in mean lactic acid at T1-T2 in the group without thiamine (7.36%) was higher than the thiamine group (4.85%). The mean percentage difference in T2-T3 was also higher in the group without thiamine (3.42%) compared to thiamine (2.26%). Then the percentage difference in mean T1-T3 was higher in the group without thiamine (11.04%) than in the thiamine group (7.23%). Overall there was an increase in lactic acid at T1, T2, and T3, whereas the percentage increase was higher in the group without thiamine.

Table 3.5 Results of the Overall Data Difference Test Based on Time

Data Type	test	P-values
T0-T3	Friedmann	0.000

From Table 3.5, Note that there is a significant difference between the overall data based on time (p<0.001).

Table 3.6 Correlation test results between thiamine and thiamine-free groups before and after treatment

Data Type	r	P-values
T0 Thiamine	-0.259	0.221
T0 Without Thiamine		
T3 Thiamine	-0.121	0.575
T3 Without Thiamine		

T0 Thiamine	0.946	0.000
T3 Thiamine		
T0 Without Thiamine	0.964	0.000
T3 Without Thiamine		

Spearmann Correlation

Based on Table 3.6, It is known that there is no correlation between lactic acid levels in the thiamine group and without thiamine at T0 (before treatment) with a p-value of 0.221. In addition, there was also no correlation between lactic acid levels in the thiamine group and without thiamine at T3, namely after treatment with a p-value of 0.575.

From the table, it can be seen that there is a significant correlation between lactic acid before and after treatment in the thiamine group (p <0.001) with r = 0.946 or 94.6%. This means that there is a very strong positive correlation between giving thiamine and increasing lactate. There was an increase in lactic acid levels despite being given thiamine. Besides that, there is also a correlation between lactic acid before and after treatment in the group that was not given thiamine; r = 0.964 (96.4%). This means that there is a very strong positive correlation between time and increased lactate. There was an increase in lactate in the absence of thiamine.

Table 3.7The Relationship of Giving Thiamine with Mortality Rate

Mortality						
Giving Group	**Life**		**Dead**		**Total**	
	f	**%**	**f**	**%**	**f**	**%**
No Thiamine	9	18	17	34	26	52
Thiamine	20	40	4	8	24	48
Total	29	58	21	42	50	10

Fisher Exact Test

An analysis of the relationship between thiamine administration and mortality was also carried out using an alternative fisher's exact test as a substitute for the Chi-Square test because an expected count <5 was found in the 2x2 table. The results of the Fisher Exact analysis showed a significant relationship between thiamine administration and patient mortality (p = 0.001).

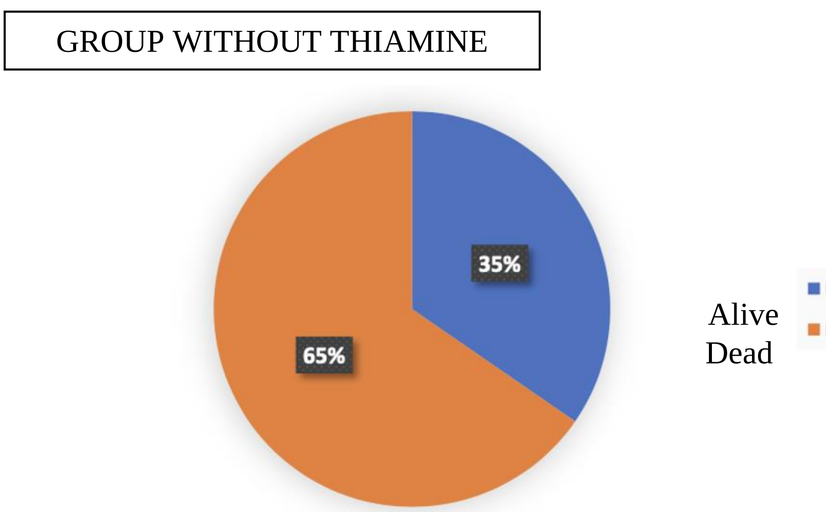

Figure 3.1 Mortality Chart in Patients Without Thiamine

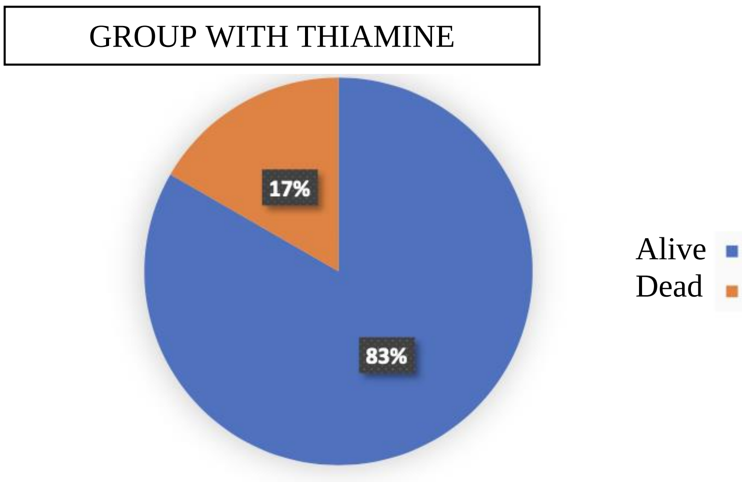

Figure 3.2 Graph of Mortality in Patients with Thiamine

Based on the graph above, it is known that the percentage of patients alive in the group without thiamine was 35% and 65% died, while in the group with thiamine, 83% lived and 17% died. It is known that the mortality ratio in the group without thiamine was 48% higher when compared to the group with thiamine.

Table 3.8 Table of Comparison of Length of Treatment between Groups

Data Type	Means	+SD	Median	Min	Max	P-values
No Thiamine	12.54	2.53	13	7	17	0.247
Thiamine	11.67	2.73	12	4	16	

Independent T-Test

Comparative analysis of length of stay between groups without thiamine and thiamine groups was carried out. It is known that the average of the group without thiamine was 12.54+2.53 days and the average of the thiamine group was 11.67+2.73 days. A comparative analysis of the length of stay between the two groups was also carried out using an independent T-test because the length of stay data was normally distributed based on the Kolmogorov-Smirnov test (p = 0.061). Based on the results of the independent T-test it was found that there was no significant difference in the length of stay between the groups without thiamine and thiamine (p = 0.247).

IV. CONCLUSION

1. In this study, there was no effect of thiamine administration on lactic acid levels in septic patients (p=0.575).
2. In this study, it was known that lactate levels in septic patients were 5.27+2.85 mg.
3. There were differences in lactate levels between the thiamine and non-thiamine groups in septic patients (p<0.001).
4. It is known that there is a change in lactate levels after administration in T0 with T3 in the thiamine group (p<0.001) and in T0 with T3 in the group without thiamine (p<0.001)

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