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Research Article

Effects of Thiamine on Balance between Matrix Metalloproteinases-9 (MMP-9) and Tissue Inhibitors of Metalloproteinases-1 (TIMP-1)

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Abstract

Background: Sepsis is a systemic and syndromic response to infection and is a common final pathway to death from many infectious diseases. Matrix metalloproteinase 9 (MMP-9) and Tissue inhibitors of matrix metalloproteinase 1 (TIMP-1) are potential sepsis biomarkers. Thiamine administration has been suggested to affect MMP-9 and TIMP-1 in several critical conditions, such as brain and lung tumors. This study investigated thiamine effects on MMP-9, TIMP-1, and their balance in sepsis patients.

Method: We conducted a randomized experimental study to investigate the effects of thiamine administration on MMP-9, TIMP-1, and TIMP-1/MMP-9 ratio in sepsis patients. The study was conducted at Haji Adam Malik General Hospital and network hospitals in Medan, Sumatera Utara. The investigation lasted for six months, from April to September 2020.

Results: We found that the MMP-9 values in the thiamine group and the control group were significantly different (p=0.042). The TIMP-1/MMP-9 ratio was also lower in the thiamine group after the administration, and the difference was significant (p = 0.033).

Conclusion: Thiamine administration reduced the TIMP-1/MMP-9 ratio, which could be related to better survival. Thiamine could be considered as adjuvant therapy in patients with sepsis.

Keywords

Thiamine, Sepsis, MMP-9, TIMP-1, TIMP-1/MMP-9 ratio, SOFA score

Abbreviation

MMP-9: Matrix metalloproteinase 9; SOFA: Sequential Organ Failure Assessment; TIMP-1: Tissue inhibitor of matrix metalloproteinase 1

1. Introduction

Sepsis is a systemic and syndromic response to infection and is a common final pathway to death from many infectious diseases [1]. This response is a form of body defense mechanism that aims to eliminate the infecting microorganisms. However, it can also cause mild to severe problems, from hemodynamic disorders to multiple organ failure or severe sepsis. Thiamine is an essential micronutrient. Humans depend on the diet to fulfill the thiamine's daily requirement, for they cannot synthesize it endogenously. A small amount of thiamine was produced by intestinal bacteria, but it is not enough for the body [2].

Thiamine deficiency is common in patients with critical illnesses and correlates with higher mortality [3]. This deficiency was also observed in septic shock in 20% to 70% cases depending on the studies' cut-off [4]. Another study suggested that thiamine deficiency is associated with higher lactic acid levels in sepsis patients [5].

Matrix metalloproteinase 9 (MMP-9) and Tissue inhibitors of matrix metalloproteinase 1 (TIMP-1) are potential sepsis biomarkers. Matrix metalloproteinases (MMPs) are responsible for the extracellular matrix's (ECM) degradation and remodeling process. Additionally, they are involved in proteolysis of intracellular protein, apoptosis, and innate immune mechanism [2]. TIMP-1 regulates MMP-9 activities [6]. A research on MMP-9 and TIMP-1 levels and their ratio suggested an increase in these parameters in sepsis patients [7].

The administration of thiamine analog, oxythiamine, has been shown to have an antiproliferative effect on cancer cells via the pentose phosphate pathway. High doses of oxythiamine supplementation decreased the number and size of lung cancer areas and inhibited MMP-9 expression in the lung tissue [8]. A study by Tarallo *et al.* showed that thiamine and benfotiamine administration did not affect the levels of MMP-9. However, it could increase TIMP-1 [9]. Similar results were found in an animal study, which depicted an increase in MMP-9 expression in thiamine deficiency mice's brain tissue, especially in the thalamus [10].

This study aims to determine thiamine's effects on MMP-9, TIMP-1, and TIMP-1/MMP-9 ratio in sepsis patients.

2. Methods

2.1. Participants

We conducted a randomized experimental study to investigate the effects of thiamine administration on MMP-9, TIMP-1, and TIMP-1/MMP-9 ratio in sepsis patients. The study was conducted at Haji Adam Malik General Hospital and network hospitals in Medan, Sumatera Utara. The investigation lasted for six months, from April to September 2020.

The inclusion criteria were patients ≥18 years old diagnosed with sepsis, qSOFA or SOFA score ≥2 and had received Hour One Bundle Sepsis and other supporting therapies, and those with lactate levels ≥2 mmol/L. Patients or their families gave consent for participation in the study. All eligible subjects were randomized by computerization (randomizer.org).

2.2. Data collection and statistical analysis

Patients underwent blood tests, measuring MMP-9 and TIMP-1 levels at baseline and after thiamine administration. The thiamine dose is 200 mg in 50 ml normal saline, given every 12 hours over 72 hours. ELISA kit from Antibody-Sunlong Biotech Co. Ltd was applied to measure both biomarkers levels. The study protocol was approved by the Institutional Review Board of the Medical Faculty of Universitas Sumatera Utara (No 54/KEP/USU/2020) and was performed according to the Declaration of Helsinki's ethical standards.

The data were analyzed by SPSS 25.0 package. For bivariate comparison, we analyzed the non-parametric data with the Mann-Whitney U test. The results were considered significant if $p<0.05$.

2.3. Variables recorded

We obtained the data prospectively, including demographic, history of operative procedures, infecting microorganisms, given antibiotics, the pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2), international normalized ratio (INR), furosemide use, Sepsis-related Organ Failure Assessment (SOFA) score, fluid balance, MAP, neutrophil and lymphocyte ratio (NLR), albumin, and central venous pressure (CVP). We assessed MMP-9 and TIMP-1 baseline levels at ICU admission and after thiamine administration during the first 72 hours.

3. Results

Table 1 shows that the average patients' age in this study was 52.1 (+ 16.8) years. Every patient was treated similarly with hour-one bundle resuscitation. The median of lactic acid levels after resuscitation was 2.5 mmol/L. All subjects were euvolemic, with central venous pressure around 6.3 to 9.3 mmHg. However, the NLR observed was relatively high (median: 12.7), indicating sepsis severity.

The MMP-9 values obtained were also higher than the normal reference (11.4–59.4 ng/ml), as shown in Table 2. We found a significant difference in MMP-9 values between the thiamine and control groups, for the MMP-9 values decreased in the thiamine group while they increased in the control group. In the thiamine group, the TIMP-1 declined over the period, whereas it increased in the control patients (Table 3). The TIMP-1/MMP-9 ratio was also lower in the thiamine group, and the difference was significant ($p = 0.033$) (Table 4).

Table 1: Baseline clinical and biochemical characteristics of patients.

Characteristics	Description (n=72)
Age (years, mean ± SD)	52.1± 16.8
Gender Male, n (%) Female, n (%)	 14 (41.2) 20 (58.8)
Fluid balance, L/day, median (percentile 25-75)	-145 (-404.1 – 732.3)
MAP, mmHg (mean ± SD)	96.1 ± 21.1
Lactic Acid, median (percentile 25-75)	2.5 (1.2-4.2)
SOFA score, median (percentile 25-75)	6 (3-8)
NLR, median (percentile 25-75)	12.7 (7.7-25.3)
Albumin, median (percentile 25-75)	2.6 (2.2-3.1)
Central venous pressure (CVP), median (percentile 25-75)	8.1 (6.3-9.3)

Table 2: MMP-9 in septic patients.

Group	Thiamine (Mean±SD); n = 16	Control (Mean±SD); n = 18	p Value
Before	1415.0 (1263.0-1691.0)	794.7 (476.4-1269.4)	0.772
After	1336.6 (1050.2-1569.0)	1041.6 (501.2-1506.9)	0.042*
p Value	0.193	0.044	

Note: Comparison of levels of TIMP-1, MMP-9 enzyme levels, and TIMP-1/MMP-9 ratio between mortality estimation of SOFA score, t-test); *Significant α<0,05

Table 3: TIMP-1 in septic patients.

Group	Thiamine (Mean±SD); n = 16	Control (Mean±SD); n = 18	p Value
Before	546.6 (515.8-633.9)	590.3 (421.6-676.1)	0.003
After	525.1 (464.6-644.1)	603.2 (553.7-724.2)	0.164
p Value	0.286	0.394	

Note: Comparison of levels of TIMP-1, MMP-9 enzyme levels, and TIMP-1/MMP-9 ratio between mortality estimation of SOFA score, t-test); *Significant α<0,05

Table 4: TIMP-1/MMP-9 ratio in septic patients.

Variable	Thiamine Median (percentile 25–75); n = 16	Control Median (percentile 25–75); n = 18	p Value
TIMP-1/MMP-9 ratio	0.40 (0.31-0.59)	0.56 (0.41-1.20)	0.033

Note: Comparison of levels of TIMP-1, MMP-9 enzyme levels, and TIMP-1/MMP-9 ratio between mortality estimation of SOFA score, t-test); *Significant α<0,05

4. Discussion

Thiamine deficiency is associated with a poor prognostic outcome in sepsis patients [4,11,12]. This condition is common in critical patients and correlates with increased mortality in some cases. Besides, thiamine levels are depleted throughout the course of critical illness, and thiamine administration during critical illness can improve organ dysfunction [3]. The predisposing factor for thiamine deficiency from several problems commonly associated with nutritional deficiencies and other accompanying diseases. Several conditions can reduce thiamine levels, such as impaired carbohydrate metabolism, increased metabolic requirements for parenteral or enteral nutrition, diuretics, and hemodiafiltration. The lack of thiamine reduces the pyruvate entering the Krebs cycle, increasing lactate production because it converts metabolism to anaerobes [4].

This study indicates that thiamine administration can reduce the TIMP-1/MMP-9 ratio as a biomarker of sepsis severity. Several studies have identified thiamine deficiency in critically ill patients. Thiamine deficiency can also be observed in septic shock patients, occurring in 20% to 70% depending on the cut-off used to determine the presence of thiamine deficiency.

A prospective observational study suggested an association between thiamine levels and lactic acidosis in 30 patients with septic shock, but we found no correlation between these two variables. However, after excluding patients with abnormal liver function, we found a significant negative correlation between thiamine administration and lactic acidosis. This finding implies a potential association between thiamine levels and lactic acidosis in septic shock patients with normal liver function. Thus, by reducing the activity of the pyruvate dehydrogenase complex, thiamine deficiency contributes to an increase in lactic acid in septic patients [5,13,14].

5. Conclusion

This study showed that thiamine administration reduced the TIMP-1/MMP-9 ratio, which could be related to better survival. We suggest that thiamine should be considered as adjuvant therapy in patients with sepsis.

6. Acknowledgment

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7. Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. A. Rhodes, L. E. Evans, W. Alhazzani, M. M. Levy, M. Antonelli, R. Ferrer, et al. *Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016*, Critical Care Medicine, Springer Berlin Heidelberg, 45 (2017), 486–552.
2. K. C. Whitfield, M. W. Bourassa, B. Adamolekun, G. Bergeron, L. Bettendorff, Brown, et al. *Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs*, Ann N Y Acad Sci, (2018).

3. A. Moskowitz, L. W. Andersen, D. T. Huang, K. M. Berg, A. V. Grossestreuer, P. E. Marik, et al. *Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation,* Crit Care, 22 (2018), 1–7.

4. N. A. Costa, A. L.Gut, M. de Souza Dorna, J. A. Pimentel, S. F. Cozzolino, P. S. Azevedo, et al. *Erratum: Corrigendum to "serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock",* J Crit Care, 36 (2016), 311.

5. M. W. Donnino, E. Carney, M. N. Cocchi, I. Barbash, M. Chase, N. Joyce, et al. *Thiamine deficiency in critically ill patients with sepsis,* J Crit Care, 25 (2010), 576–581.

6. E. Galliera, L. Tacchini, M. M. Corsi Romanelli, *Matrix metalloproteinases as biomarkers of disease: Updates and new insights*, Clin Chem Lab Med, 53 (2015), 349–355.

7. S. Bojic, J. Kotur-stevuljevic, N. Kalezic, P. Stevanovic, Z. Jelic-ivanovic, D. Bilanovic, et al. *Diagnostic value of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 in sepsis-associated acute kidney injury,* (2015) 103–109.

8. C. M. Yang, Y. Z. Liu, J. W. Liao, M. L. Hu, *The in vitro and in vivo anti-metastatic efficacy of oxythiamine and the possible mechanisms of action*, Clin Exp Metastasis, 27 (2010), 341–349.

9. S. Tarallo, E. Beltramo, E. Berrone, P. Dentelli, M. Porta, *Effects of high glucose and thiamine on the balance between matrix metalloproteinases and their tissue inhibitors in vascular cells*, Acta Diabetol, 47 (2010), 105–111.

10. É. Beauchesne, P. Desjardins, A. S. Hazell, R. F. Butterworth, *Altered expression of tight junction proteins and matrix metalloproteinases in thiamine-deficient mouse brain,* Neurochem Int, 55(2009), 275–281.

11. T. Iizasa, T. Fujisawa, M. Suzuki, S. Motohashi, K. Yasufuku, T. Yasukawa, et al. *Elevated levels of circulating plasma matrix metalloproteinase 9 in non-small cell lung cancer patients*, Clin Cancer Res, 5(1999), 149–153.

12. A. Hamonangan Nasution, A. Lelo, E. Effendy, D. W. Wijaya, The effect of thiamine administration on Catechol-O-Methyltransferase (COMT) Enzyme Level and Amsterdam Preoperative Anxiety and Information Scale (APAIS) value in patients with preoperative anxiety, J Drug Alcohol Res, 8 (2019), 6.

13. K. Osiezagha, S. Ali, C. Freeman, N. C. Barker, S. Jabeen, S. Maitra, et al. *Thiamine deficiency and delirium*, Innov Clin Neurosci, 10 (2013), 26–32.

14. A. Hamonangan Nasution, R. Stya Yulianda, *The effect of thiamine administration on Interleukin-6 (Il-6) Enzyem, Lactate and Sequential Organ Failure Assessment (SOFA) Score in Patients with Sepsis,* J Drug Alcohol Res, 9 (2020).