Journal of Medicinal and Chemical Sciences 6 (2023) 1055-1064

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Relationship between Adjuvant Thiamine, Ascorbic Acid, and Combinations of These Drugs with Reducing the Incidence, Increasing MMP-9/TIMP-1 Ratio, and Decreasing Score Sofa in Mechanically Ventilated Patients with Severe Sepsis or Septic Shock

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ARTICLE INFO

Article history

Receive: 2022-06-05
Received in revised: 2022-08-07
Accepted: 2022-09-14
Manuscript ID: JMCS-2209-1696
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Sami Sajjadifar

DOI:10.26655/JMCHEMSCI.2023.5.11

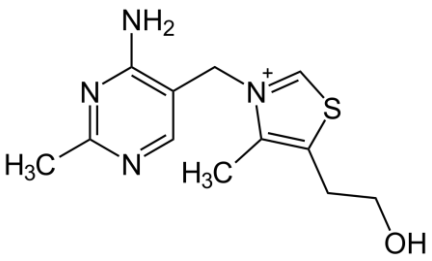
KEYWORDS

Sepsis
MMP-9
TIMP-1
Ratio of MMP-9/TIMP-1 levels
Incidence
Thiamine
Ascorbic acid

ABSTRACT

A high number of sepsis patients demand all health institutions to provide adequate treatment and management. Several therapeutic agents are developed as *adjuvants* for handling sepsis cases. Ascorbic acid and thiamine are the potential to be intensively studied for their benefits in decreasing the sepsis rate. This is a retrospective cohort analytic research carried out at Haji Adam Malik General Hospital. Blood tests are conducted at the Integrated Laboratory of the Faculty of Medicine, *Universitas Sumatera Utara*. This research is conducted for 12 months. There are 147 septic patients divided into four groups (NaCl, thiamine, ascorbic acid, and combined groups). The parameters measured are the enzymes of MMP-9 of TIMP-1. A propensity score analysis is performed to obtain homogeneous patients. There are 25 patients within each group. It can be seen that the combination of ascorbic acid and thiamine on the incidence rate performs an odds ratio of 1.19 (0.37-3.8) at 95% CI. However, a single administration of ascorbic acid can significantly reduce the incidence rate by 0.4 times and 0.67 times in the thiamine single group compared with the control group. In the combination of ascorbic acid and thiamine to the MMP-9/TIMP-1 ratio, the odds ratio is 0.34 (0.09-1.30) at 95% CI. The administration of single ascorbic acid and thiamine alone can also reduce the MMP-9/TIMP-1. Meanwhile, the combination of ascorbic acid and thiamine on SOFA scores results in an odds ratio of 2.66 (0.85-8.36) at 95% CI. For single ascorbate and single thiamine, each performs 1.38 (0.45-2, 24) and 1.17 (0.38-3.83) at 95% CI. Combination therapy of vitamin C and thiamine does not improve treatment outcomes. Thiamine and ascorbate alone showed better benefits compared with the combination therapy viewed from the incidence rate, MMP-9/TIMP-1 ratio, and SOFA score.

GRAPHICAL ABSTRACT



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Introduction

The increasing number of sepsis patients demands all health care providers to prepare better sepsis recognition, faster sepsis management, better application of sepsis bundles, and improved services for critically patients to reduce the incidence rate [1]. Over the last three decades, phases 2 and 3 of clinical trials are tested the different novel pharmacological agents and therapeutic interventions to improve the outcome of patients with severe sepsis and septic shock. These efforts ultimately failed to produce new pharmacological agents. New therapeutic approaches for sepsis are urgently needed to reduce sepsis suffered by people around the world. Such interventions should be effective, inexpensive, safe, and readily available [2-4].

Several therapeutic agents are developed for treating sepsis patients such as vitamin C, vitamin B1, vitamin B12, and vitamin D [2, 3]. Ascorbic acid (vitamin C) and thiamine (vitamin B1) are the potential agents intensively studied for their benefits related to sepsis. Besides, the thiamine effects on enzymes in maintaining hemodynamic responses have also been investigated which is related to a state of physiology [3-7].

The effect of the combination of thiamine and ascorbic acid on septic patients has been reported by Iglesias *et al.* (2020). Hydrocortisone, ascorbic acid, and thiamine (HAT) therapy in 140 septic patients is safe to use and can reduce the shock duration and decrease the vasopressor use. However, this research still cannot show that HAT can reduce mortality rate and hospitalization period in the ICU. The patients given with HAT have a 22.6% higher mortality rate compared with the placebo group (20.4%) [8, 9]. Another research has a smaller sample than the previous one. The results reveal that patients given with HAT have a lower mortality rate of 8.5% compared with 40.4% of control groups. Likewise, there is a decrease in SOFA scores in the patients' given HAT. It can be concluded that the initial intravenous use of ascorbic acid together with corticosteroids and thiamine is effective in preventing the progression of organ dysfunctions [10]. However, both kinds of research use a combination of glucocorticoids. Another research in 2020 (the VITAMINS randomized clinical trial) in 216 patients demonstrated that the HAT combination does not increase the survival rate and is free from vasopressor use during seven days of ICU treatment, compared with a group given only hydrocortisone [11]. This finding refutes previous ones that found the preventing effect of the progression of organ dysfunction and decreasing duration of vasopressor use. This research illustrates that treatment by using intravenous ascorbic acid, hydrocortisone, and thiamine does not accelerate the improvement of a septic shock more than intravenous hydrocortisone alone [11].

Lubis *et al.* (2020) conducted one-year research in the ICU room of Haji Adam Malik Hospital in Medan in sepsis patients. They found 186 sepsis patients by using MMP-9 and TIMP-1 biomarkers. They gave thiamine injection of 200 mg, ascorbic acid injection of 50 mg/kg, and a combination of both. The patients are treated every 12 hours for three days. Their findings reveal that thiamine alone provides a better effect than ascorbic acid alone and in combination, as assessed by the biomarkers of MMP-9 and TIMP-1. The thiamine can maintain a balanced MMP-9/TIMP-1 ratio [12]. This research found that there is a high mortality rate (around 36%). However, they do not analyze the mortality of the treatment with thiamine, ascorbic acid, and a combination of both as demonstrated by Marik *et al.*, Iglesias *et al.*, Fujii *et al.*, and Lubis *et al.* [9-12]. Based on this background, the authors are interested in analyzing whether there is a relationship between intravenous administration of thiamine and ascorbic acid and whether a combination of both with mortality rate. The assessed aspects are survival time, MMP-9/TIMP-1 ratio, and SOFA score in septic patients treated in the ICU room.

Materials and Methods

It is a retrospective cohort analytic study that aims to assess the relationship between intravenous adjuvants (thiamine, ascorbic acid, and their combination) with incidence rates, MMP-9/TIMP-1 ratio, and SOFA scores in septic

patients treated in the ICU room. The research is conducted at the Intensive Care Unit (ICU) of Haji Adam Malik General Hospital in Medan. The data and samples are taken from January-December 2020. The samples are patients over the age of 18 years old. They are suffering from sepsis and are treated in ICU and receive therapy of thiamine, ascorbic acid, and a combination of both. They are included as inclusive. The samples will be excluded if the patients do not have data on the MMP-9 or TIMP-1 examination, and they return home at their request during the treatment. The patients receive thiamine at a dose of 200 mg intravenously every 12 hours for three days, and ascorbic acid is given at a dose of 50 mg per kg intravenously every 12 hours for three days. The MMP-9/TIMP-1 ratio compares the MMP-9 and TIMP-1 levels in septic patients before the intervention. SOFA scores are measured by using some parameters obtained from medical records. The research is done after being approved by the health research ethics committee, Faculty of Medicine, *Universitas Sumatera Utara*, and the Health Research Ethics Committee at Haji Adam Malik Hospital (40/KEPK/USU/2022). There should be approved to obtain data such as medical records. The included and excluded data are used as the samples. All samples (including those who have passed away during the intervention of thiamine, ascorbic acid, and their combination) are collected and separated. The samples are traced back to identify their records from experiments and medical records.

Then, the data are grouped into the thiamine group, ascorbic acid group, and a combined group of both. They are assessed to find out incidence rates, MMP-9/TIMP-1 ratios, and SOFA scores. The researchers write down past data, read, and analyze the data on clinical and laboratory characteristics. Furthermore, the data are analyzed by using the SPSS 25.0 computer application. Normally-distributed numerical data are indicated in the mean + SD (standard deviation), while those not normally distributed are displayed in the median value (the minimum-the maximum). Categorical data are performed in numbers (percentages). The normality test consists of Kolmogorov-Smirnov test. The statistical tests for normally distributed data in four groups are analyzed by using ANOVA, and those not normally distributed are tested by using Kruskal-Wallis. The relationship between two variables with continuous data is analyzed by using the Pearson correlation test. Odds ratios aim to examine whether exposure to interventional thiamine, ascorbate, and their combination are risk factors for incidence rates, MMP-9/TIMP-1 ratios, and SOFA scores.

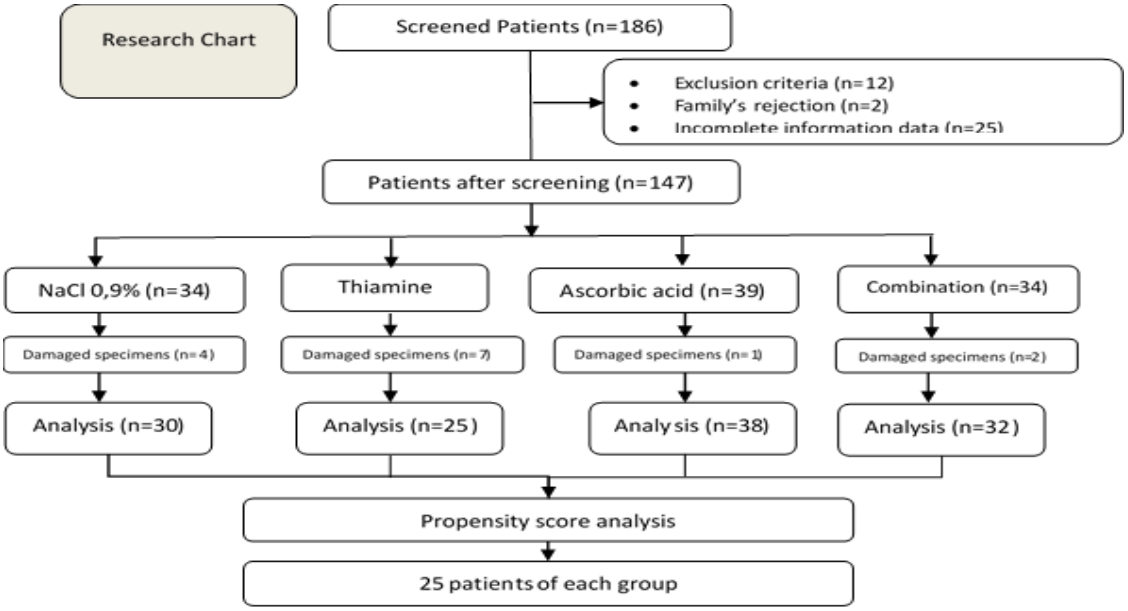

Figure 1: Flow of septic patients in the intensive care unit given with thiamine, ascorbic acid, and a combination of both with propensity score analysis

Results and Discussion

The data are collected based on the principle of a retrospective cohort study. The data are obtained from the septic patients treated in the ICU of the General Hospital from April 2020-April 2021. However, the research should be approved by the Ethics Committee of the USU Medical Faculty/RSHAM. There are 147 patients as the research subjects. The propensity scores are analyzed to evaluate the intervention effect by using the observational data and reducing bias in the research findings. After matching, 25 patients are included in each group (Figure 1).

The characteristics of subjects are recorded on the research observation sheet attached at the beginning of the research. The data include age, gender, MAP, lactic acid, SOFA score, and NLR. The data on the characteristics of subjects can be seen in the following table so that only 86 samples have met the inclusion and exclusion criteria (Table 1).

Figure 2 displays that in the forest plots of the combination of ascorbic acid and thiamine on the incidence rate, the odds ratio is 1.19 (0.37-3.8) at 95% CI. It shows that the combination of ascorbic acid and thiamine significantly increases the incidence rate 1.19 times higher than the control group. However, the single administration of ascorbic acid can reduce the incidence rate by 0.4 times. Meanwhile, the single administration of thiamine reduces the incidence rate by 0.67 times compared with the control group.

Table 1: Characteristics of Samples

Samples characteristic	NaCl 0,9%	Thiamine	Ascorbic acid	Combination
Age (year, mean ± SD)	48,8± 18,4	52,3± 16,8	53,3± 11,7	50,7±11,1
Gender Male, n (%) Female, n (%)	 10 (38,5) 15 (61,5)	 12 (50,0) 13 (50,0)	 11 (50,0) 14 (50,0)	 20 (68,8) 5 (31,3)
MAP, mmHg (mean ± SD)	94.8 ± 17.0	97,6 ± 25,4	91,4 ± 16.0	92,4 ± 16.0
Lactate, acid	2,0 (1-10,0)	1,3 (1,0-5,5)	1,0 (1-10,0)	2,0 (1,0-4,0)
NLR, median (min-max)	10,6 (2,5-30,3)	14,4 (0,2-86,8)	13,9 (1,6-69,3)	10,7 (1,4-64,6)

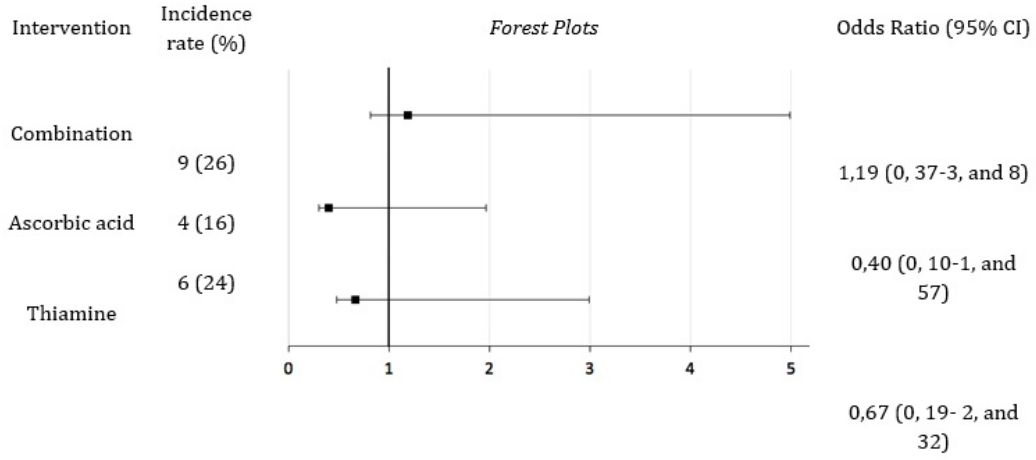

Figure 2: Forest plots of thiamine, ascorbic acid, and a combination of both on incidence rates during the intervention

Figure 3 depicts that in the forest plots of the combination of ascorbic acid and thiamine on the ratio of levels of MMP-9/TIMP-1, the obtained odd ratio is 0.34 (0.09-1.30) at 95% CI. It means the combination of ascorbic acid and thiamine can decrease the MMP-9/TIMP-1 levels (0.34 times higher than the control group). Ascorbic acid and thiamine alone can further reduce the ratio of MMP-9/TIMP-1 by 0.77 and 0.78. The combination of ascorbic acid and thiamine can

decline the MMP-9/TIMP-1 level to about two times higher than that of ascorbic acid and thiamine.

Figure 4 demonstrates a moderate positive correlation between MMP-9 and TIMP-1 in sepsis patients who have passed away during the observation, meaning that the higher level of MMP-9 will further trigger a higher level of enzyme TIMP-1 ($p< 0.001$; $r=0.746$).

Figure 5 shows a linear regression analysis. It indicates a strong positive correlation between MMP-9 enzyme level and the ratio of MMP-9/TIMP-1 in sepsis patients who passed away during the observation ($R2=0.445$; $p<0.001$; $r=0.667$). It also illustrates that increasing the MMP-9 level can increase the ratio of the MMP-9/TIMP-1 level by 44.5%. However, the TIMP-1 level turns out to have a positive correlation (but not significant) on the MMP-9/TIMP-1 ratio ($R2=0.002$; $p=0.809$; $r=0.049$). It can be concluded that in sepsis patients who have passed away, there is an imbalance in the MMP-9/TIMP-1 ratio indicated by the large effect of the MMP-9 enzyme on the MMP-9/TIMP-1 ratio. However, it is not balanced by the influence of the TIMP-1 enzyme.

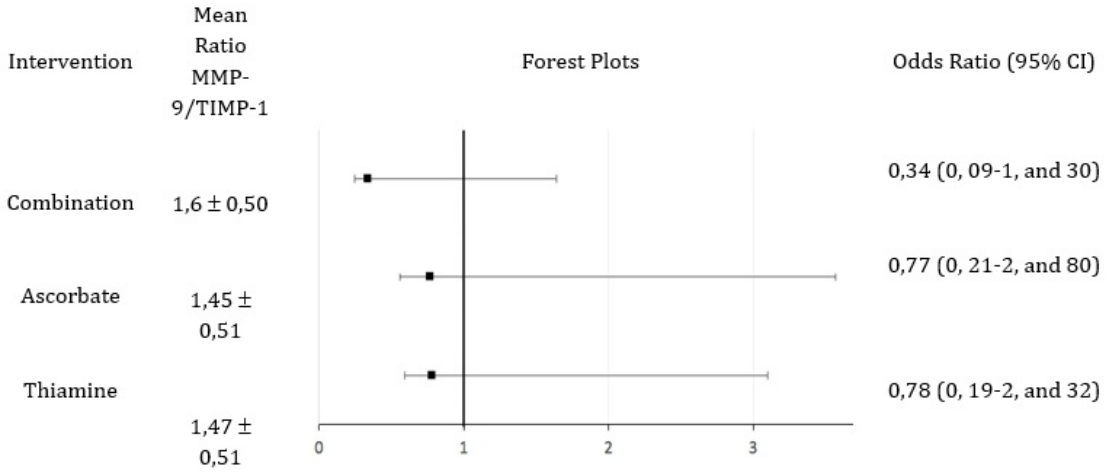

Figure 3: Forest plots of thiamine, ascorbate, and combination on the ratio of MMP-9/TIMP-1 level during the intervention

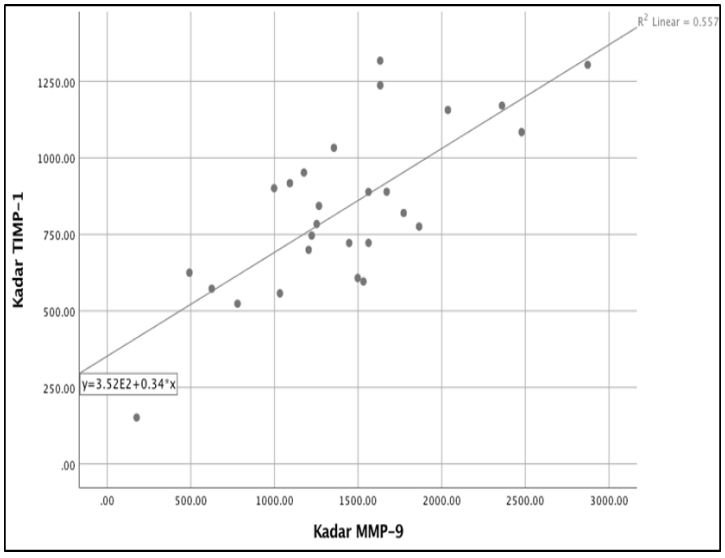

Figure 4: Scatterplot graph of MMP-9 enzyme level with TIMP-1 enzyme level in septic patients who passed away during observation

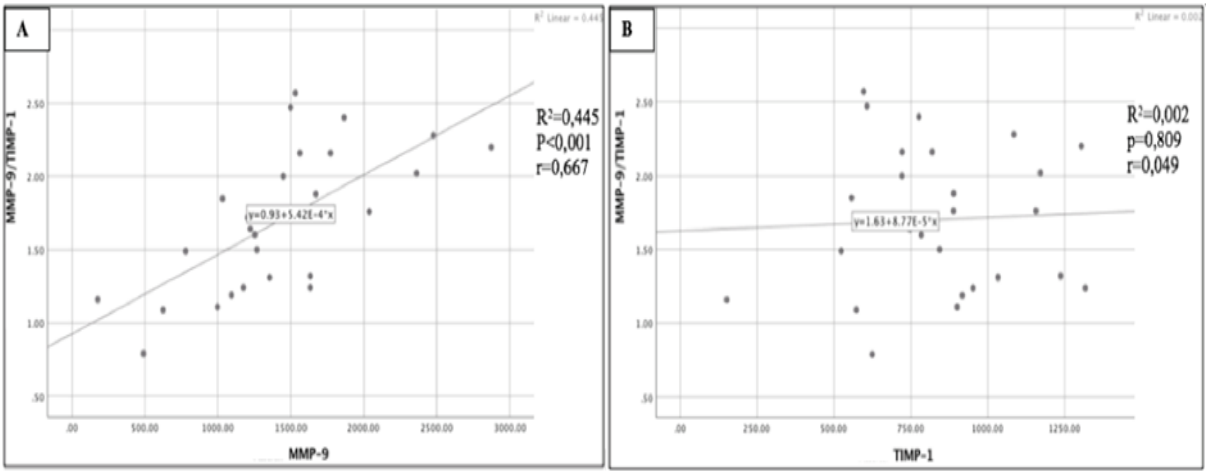

Figure 5: Scatterplot graph of MMP-9 enzyme level and MMP-9/TIMP-1 ratio (A), and TIMP-1 enzyme level and MMP-9/TIMP-1 ratio (B) in sepsis patients who have passed away during observation

Meanwhile, in surviving patients, linear regression analysis between the MMP-9 enzyme and the MMP-9/TIMP-1 ratio has a moderate effect with a positive correlation (R2=0.318; P<0.001; r=0.564) and is offset by the presence of a positive and moderate correlation between the TIMP-1 enzyme and the MMP-9/TIMP-1 ratio with a negative correlation (R2=0.280; p<0.001; r=-0.529) (Figure 6). This means that in living sepsis patients, there is a balance in the MMP-9/TIMP-1 ratio indicated by the large effect of the MMP-9 enzyme on the MMP-9/TIMP-1 ratio and balanced by the influence of the TIMP-1 enzyme.

Figure 7 demonstrates that the forest plots of the combination of ascorbic acid and thiamine on the SOFA score generate an odds ratio of 2.66 (0.85-8.36) at 95% CI. It means that the combination of ascorbic acid and thiamine can significantly increase the SOFA score by 2.66 times higher than the control group. However, ascorbic acid and thiamine alone can further increase the SOFA ratio score by 1.38 and 1.17 times, respectively (compared with the control group). It indicates that ascorbic acid and thiamine can increase the SOFA score about two times more than ascorbate and thiamine alone.

The four studied groups consist of 100 septic patients with almost the same number of women and men. This finding is not following some previous findings. There were more male patients than females.

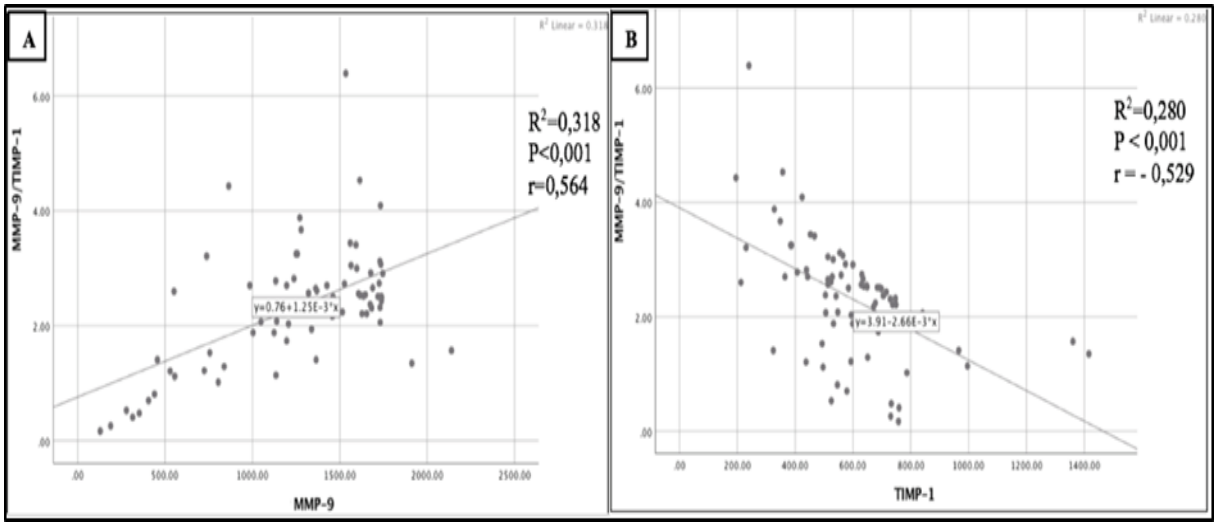

Figure 6: Scatterplot graph of MMP-9 enzyme level and MMP-9/TIMP-1 ratio (A), and TIMP-1 enzyme level and MMP-9/TIMP-1 ratio (B) in survive sepsis patients during observation

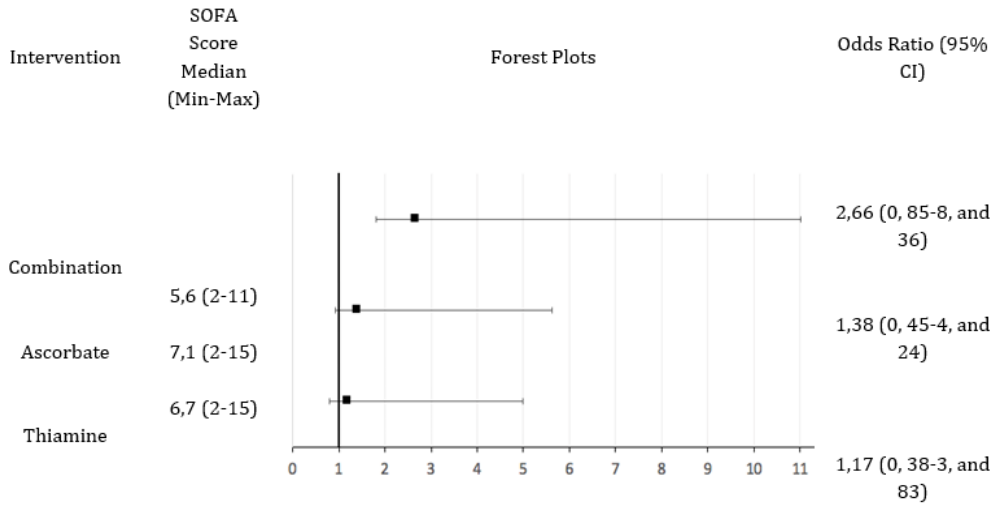

Figure 7: Forest plots of thiamine, ascorbate, and combination of both on SOFA scores during intervention

In this research, the authors have found a mortality rate of 27%. Besides, the SOFA scores from 6-7 can predict the mortality rate of 10-20%. However, a study in Belgium showed that it could lead to a higher risk of death if there is no significant reduction during therapy (84.4%) [13]. In previous studies, the mortality rate in sepsis patients is around 26.4%. It may reach 30% to 80% in sepsis shock patients [14]. In this research, the variables of age, MAP, gender, SOFA score, lactic acid, and NLR are evenly distributed in the four groups. However, the values do not significantly influence the research outcomes.

The research findings show that about 27 patients (27%) passed away before the observation time (less than 72 hours). Of the 27 patients, there is a moderate and significant positive correlation between the levels of MMP-9 and TIMP-1 enzymes. It proves that the increasing MMP-9 enzyme level followed by a higher increase in TIMP-1 enzyme levels reflects its role in the sepsis pathophysiology [15-18].

Although the increasing MMP-9 and TIMP-1 enzymes indicate a severe inflammatory process in septic patients, the MMP-9/TIMP-1 balance can set and influence the cells' survival [18]. The elevated TIMP-1 enzyme levels, low MMP-9 enzyme levels, and low MMP-9/TIMP-1 ratios are found in non-surviving septic patients. Therefore, the MMP-9/TIMP-1 can be a good predictor in assessing the severity and mortality rate [19].

Figure 5 depicts that in sepsis patients who have passed away, there is an imbalance in the MMP-9/TIMP-1 ratio, indicated by the large effect of the MMP-9 on the MMP-9/TIMP-1 ratio but not balanced by the influence of the TIMP-1. MMP-9 increases because it significantly influences cytokine storm followed by the activation of the immune system. MMP-9 has been indicated to aid in the migration of the immune system to sites of inflammation, has a vasoactive effect, and can induce vascular leakage in severe sepsis [20, 21]. Based on the other findings, the MMP-9 enzyme level will increase in the first few hours of systemic inflammation. There is a correlation with the severity of organ injuries [22, 23].

There have been no studies on the effect of ascorbic acid and thiamine on MMP-9, TIMP-1, and the ratio of MMP-9/TIMP-1 levels in septic patients. There are reports on the influence of the combination of thiamine and ascorbic acid on patient outcomes. Hydrocortisone therapy, ascorbic acid, and thiamine (HAT) in 140 septic patients is safe to consume and can reduce the shock duration and decrease vasopressor use. However, this research still cannot prove that the HAT administration can reduce mortality rate and hospitalization period. The patients who consume the HAT have a 22.6% higher mortality rate than the placebo group of 20.4% [10]. Another study with a smaller sample reported that the patients given with HAT have a lower mortality rate of 8.5% compared with 40.4% of control groups. There is also a decrease in SOFA scores in the patients receiving HAT. Thus, the initial intravenous use of ascorbic acid with

corticosteroids and thiamine can prevent the progression of organ dysfunction [10]. However, both studies use a combination of glucocorticoids. Another research conducted in 2020 (the VITAMINS randomized clinical trial) in 216 patients demonstrated that the use of the HAT combination does not increase the survival rate and freedom from vasopressor during seven days of ICU treatment compared with a group given only intravenous hydrocortisone [11]. This research refutes some previous findings which show the effect of preventing the progression of organ dysfunction and decreasing the duration of vasopressor use. This research concludes that the patients' treatment by using intravenous ascorbic acid, hydrocortisone, and thiamine does not lead to a more rapid improvement in septic shock than intravenous hydrocortisone alone [11]. Figure 2 illustrates that the forest plots of the combination of ascorbic acid and thiamine can significantly increase the incidence rate (1.19 times) than the control group. On the other hand, the single administration of ascorbic acid decreases the incidence rate (0.4 times), and the single administration of thiamine decreases the incidence rate (0.67 times) compared with the control group.

Although some studies on the therapeutic effect of thiamine, ascorbic acid, and their combination as adjuvant therapy in sepsis still cannot explain the improvement of septic patients' outcomes, this research tries to examine the therapeutic effect by using the MMP-9 biomarker as an effector in acute inflammatory diseases. MMP-9 stored in the tertiary granule of polymorphonuclear leukocytes can be released by inflammatory factors such as IL-1, IL-8, and TNF [24]. The results prove that the consumption of single thiamine and ascorbic acid alone can maintain the balance of MMP-9/TIMP-1 levels in surviving sepsis patients. It is shown by the decreasing mortality rate, although there is an increase in the group given the combination of thiamine and ascorbate.

Conclusion

The combination therapy of vitamin C and thiamine does not improve treatment outcomes. Thiamine and ascorbate alone showed better benefits compared with combination therapy viewed from the incidence rate, MMP-9/TIMP-1 ratio, and SOFA score.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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HOW TO CITE THIS ARTICLE

Agus Prima, Rr Sinta Irina, Bastian Lubis. Relationship between Adjuvant Thiamine, Ascorbic Acid, and Combinations of These Drugs with Reducing the Incidence, Increasing MMP-9/TIMP-1 Ratio, and Decreasing Score Sofa in Mechanically Ventilated Patients with Severe Sepsis or Septic Shock. *J. Med. Chem. Sci.*, 2023, 6(5) 1055-1064
https://doi.org/10.26655/JMCHEMSCI.2023.5.11
URL: http://www.jmchemsci.com/article_159553.html