

## Effect of Vitamin C and Vitamin B1 Combination on Mortality of Sepsis and Septic Shock Patients in Intensive Care Unit

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### Abstract

*Introduction:* Vitamin C is known as antioxidant and an important co-factor for endogenous adrenaline synthesis while vitamin B1 is known for its effect on lactate clearance which helps sepsis and septic shock condition. This study was conducted to investigate the effect of vitamin C and B1 combination on 28-day mortality in sepsis and septic shock patients.

*Methods:* This is an open-label randomized controlled trial at tertiary hospital between July until September 2019. Inclusion criteria were patients aged 18-60 years diagnosed with sepsis and/or septic shock. Exclusion criteria were “do not resuscitate” status and on immunosuppressive medications. Thirty-one patients were divided into intervention group (n=15) and control group (n=16). Intervention group received 1.5 g vitamin C every 6 hours and 200 mg vitamin B1 every 12 hours through 3 days. Control group received 200 mg vitamin B1 every 12 hours for 3 days. The 28-day mortality was documented after the administration. This study used chi-square continuity correction as statistical analysis.

*Results:* The relative risk for survival rate in 28-day mortality was 1.30 times higher for intervention group compared to control group (CI 95% 0.76 – 2.21 p=0.53). The mortality risk in 28 days was also lower in intervention group compared to control group (RR=0.61 CI95% 0.22 – 1.66 p=0.53).

*Conclusion:* combination of vitamin C and B1 was able to lower the risk of 28-day mortality although the result was not statistically significant.

**Keywords :** mortality, sepsis, septicshock, vitamin C, vitamin B1

### 1. Introduction

Sepsis still becomes a global health issue with a huge global burden, around 32 million cases and 5.3 million deaths each year. Most sepsis cases occur in countries with low income (Marik, 2018). In addition, mortality rates from sepsis and septic shock in low-income countries are around 60% (Marik, Khangoora, Rivera, Hooper, & Catravas, 2017). Because the mortality and morbidity rates in sepsis patients are still very high, antibiotics and source control are being the focus of therapy in this condition (Moskowitz et al., 2018).

A therapeutic approach to sepsis is needed. To affect the global burden of sepsis, this intervention must be effective, inexpensive, safe, and easily available (Marik et al., 2017). In sepsis, microvascular dysfunction occurs due to the activation of transcription of proinflammatory genes that cause proinflammatory tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) cytokines and interleukin (IL-1 $\beta$ ) release. Microvascular endothelial cells in sepsis are the sources of free radicals like radical oxygen species (ROS) and radical nitric species (RNS). When a bacterial infection or inflammation occurs, leukocytes are activated and then release cytokines such as TNF- $\alpha$ , IL-1, and IL-6 into the bloodstream. These cytokines will stimulate liver cells (hepatocytes) to produce C-Reactive Protein (CRP). This condition provides a place for drug therapy or micronutrient supplements such as vitamin C (ascorbate acid), vitamin B1 (thiamine), vitamin D, vitamin E, and selenium which effects are improving microvascular function and anti-free radicals (antioxidants) (Zainal, Puspita, Husin, & Merdasari, 2017).

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Vitamin C was hypothesized to become new and cost-effective adjuvant therapy that can be used to restore the inflammation effects and oxidative stress in sepsis (Teng, Pourmand, & Mazer-Amirshahi, 2018). Vitamin B1 is known for its effect on lactate clearance which helps sepsis and septic shock conditions (Mallat, Lemyze, & Thevenin, 2016). This study was conducted to investigate the effect of vitamin C and B1 combination on 28-day mortality in sepsis and septic shock patients.

## 2. Methods

This prospective study was performed following ethical approval in a double tertiary center. This was an open-label randomized controlled trial at tertiary hospital between July until September 2019. Inclusion criteria were patients aged 18 – 60 years diagnosed with sepsis and/or septic shock by using Sepsis-3 Definition, and patient who was admitted to the ICU within 24 hours. Exclusion criteria were “do not resuscitate” status and immunosuppressive medication. Dropout criteria were mortality within 3 days. Baseline demographic data were measured for all subjects; patients were divided into intervention group and control group. Intervention group received 1.5 g vitamin C every 6 hours and 200 mg vitamin B1 every 12 hours for 3 days. Control group received 200 mg vitamin B1 every 12 hours for 3 days. The 28-day mortality was documented after the administration. This study used chi-square continuity correction for statistical analysis.

## 3. Results

Total of 39 patients met the inclusion criteria; eight of them were dropped out. Therefore, thirty-one subjects were included in the study, 11 subjects died (28-day mortality is 35.5%). The relative risk for survival rate in 28-day mortality was 1.30 times higher for intervention group compared to control group (CI 95% 0.76 – 2.21 p=0.53). The mortality risk in 28 days was also lower in intervention group compared to control group (RR=0.61 CI95% 0.22 – 1.66 p=0.53).

**Table 1 Subject's Characteristics**

Variable	Total N=31 (100%)	Control N=16 (51.6%)	Intervention N=15 (48.4%)	P
Age (years) <sup>a</sup>	48 (21-60)	47 (22-60)	49 (21-60)	0.593*
<b>Gender<sup>b</sup></b>				
Male	17 (54.8%)	11 (68.7%)	6 (40.0%)	0.108**
Female	14 (45.2%)	5 (31.3%)	9 (60.0%)	
<b>Source of Infection<sup>b</sup></b>				
Medical	17 (54.8%)	11 (68.7%)	6 (40.0%)	0.108**
Surgical	14 (45.2%)	5 (31.3%)	9 (60.0%)	

\*Mann-Whitney test \*\*Chi-Square

<sup>a</sup>Data presented in median (min-max)

<sup>b</sup>Data presented in mean (percentage)

**Table 2 Comparison Between Intervention Group and Control Group in 28-day Mortality**

Group	Mortality 28 days		Total	RR	CI 95%	P Value
	Yes	No				
<b>Intervention</b> <b>(1.5 g vitamin C every 6 hours</b> <b>and 200 mg vitamin B1 every 12</b> <b>hours)</b> For 3 days	4 (26.7%)	11 (73.3%)	15	RR for no Mortality 1.304	0.768 – 22.13	0.537
<b>Control</b> <b>(200 mg vitamin B1 every 12</b> <b>hours)</b> For 3 days	7 (43.7%)	9 (56.3%)	16	RR for mortality 0.610	0.223 – 1.668	

#### 4. Discussion

Several studies have shown that critically ill patients with vitamin C deficiency and inflammatory processes can inhibit the absorption of vitamin C into endothelial cells. Furthermore, decreased of vitamin C concentrations in patients are associated with increased inflammation, organ failure, and mortality (Teng et al., 2018). The need for vitamin C may be increased in septic shock due to increase of oxidative stress, redistribution of blood volume from intravascular to extravascular space, and loss of urine or dialysis (Oudemans-van Straaten, Spoelstra-de Man, & de Waard, 2014). High doses of intravenous vitamin C up to 3 – 6 g each day are needed to restore normal plasma concentrations in critically ill patients (Oudemans-van Straaten, Elbers, & Spoelstra-de Man, 2017). Thiamine deficiency occurs in 20-70% patients with septic shock. Lactic acid increase in sepsis patients occurs because of reduced of pyruvate dehydrogenase complex activity due to thiamine deficiency. Thiamine deficiency reduces infiltration of pyruvate into the Krebs cycle and increases lactate production through the transfer of aerobic metabolism (Donnino et al., 2016).

A study that randomize 24 postoperative patients with septic shock who were given vitamin C infusion (1.5 – 2.5 gram IV every 6 hours) vs placebo reported that mortality rate and vasopressors needed for patients who were given vitamin C therapy were significantly lower (Zabet, Mohammadi, Ramezani, & Khalili, 2016). Research conducted on sepsis and septic shock patients who were given combination therapy of hydrocortisone, vitamin C, and thiamine showed satisfactory results that were significant by comparing cases and control of hospital mortality (Marik et al., 2017).

In this prospective randomized controlled trial, there were no significant differences in age, sex, and source of infection between intervention and control group. In this study, combination of vitamin using vitamin C and B1 was able to lower the risk of 28-day mortality although its result was not statistically significant. In this study, a combination of vitamin C and B1 can reduce the risk of mortality within 28 days even the results are not statistically significant. These results were different from studies conducted by Zabet et al. (14.28% vs 64.28%,  $p = 0.009$ ) and Marik et al. (8.5% vs 40.4%,  $p < 0.001$ ) where the combination of vitamin C, B1 and hydrocortisone gave results which is statistically significant. This was likely due to the absence of corticosteroids administration in patients at this study. In this study, corticosteroids were not used because at the condition of sepsis, immunodysregulation was occurred which is a condition where patient experienced hyperinflammation but in the same period there was an immunodepression described as a counter anti-inflammatory response syndrome (CARS) so that in a parallel theory of sepsis, administration of one therapy can be effective but also can be dangerous on the other side (Ronco et al., 2004). Because of this idea, the authors did not use corticosteroids in this study, although the latest study did not show a significant decrease in ICU mortality (40.4% vs. 40.4%;  $p = 1.000$ ) (Litwak, Cho, Nguyen, Moussavi, & Bushell, 2019).

The results of this study are consistent with a research (18.5% vs 17.5%;  $p = 0.84$ ) where combination of vitamin C and B1 can reduce the risk of mortality within 28 days even the results are not statistically significant (Shin et al., 2019). This is likely due to the administration of the same combination therapy, but there are only one differences in this study that is the sampling locations (in the emergency department) and early administration (<6 hours) and given only to patients in septic shock.

Our study has several limitations. First, the hospital that we used was a tertiary hospital so that the patients who are admitted are patients who have received therapy from the previous hospital (late case). Second, we did not distinguish which patients are sepsis or who are septic shock. Third, the authors did not assess the severity of the patient's comorbidity. Fourth, the length of stay in the ICU was different so that the longer the day of treatment was associated with the possibility of increased nosocomial risk thereby aggravated the patient's clinical condition.

#### 5. Conclusion

Combination of vitamin C and B1 was able to lower the risk of 28-day mortality although the result was not statistically significant.

#### Conflict of interests

The authors declare no conflict of interest

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