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## INTRAVENOUS VITAMIN C ADMINISTRATION DECREASES NITRIC OXIDE SERUM LEVEL IN SEVERE BURN INJURY

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### ABSTRAK

Oksida nitrat (NO) dapat menyebabkan hipotensi sistemik dan apoptosis, mengakibatkan kerusakan jaringan dan kegagalan organ pada luka bakar, yang meningkatkan aktivitas enzim Nitric Oxide Syntase (NOS) dan pelepasan NO. Sitokin proinflamasi terlibat dalam induksi NOS dan aktivasi dan pelepasan NO. Vitamin C menekan produksi sitokin proinflamasi, sehingga produksi NO dihambat. Penelitian ini bertujuan untuk meninjau intravena vitamin C 3000 mg efek NO kadar serum dalam luka bakar yang parah. Penelitian ini menggunakan randomized pre-test and post-test controlled group design di 12 pasien luka bakar di Unit Luka Bakar, RSUD Dr. Soetomo, Surabaya. NO diperiksa pada 12 pasien yang dibagi menjadi 2 kelompok. Kelompok kontrol (K1) menerima vitamin C 2 x 400 mg/24 jam selama 72 jam dan kelompok perlakuan (K2) menerima infus vitamin C 3000 mg selama 72 jam. NO diambil dari serum darah dan diamati dengan metode Grease. Hasil dianalisis dengan Paired T-Test dan tes statistik dengan  $p < 0,05$ . Kadar NO serum pada K1 tidak menunjukkan peningkatan signifikan pada hari 1 dengan hari 4 ( $p = 0,21$ ). Kadar NO serum tidak menurun signifikan pada hari 1 dibandingkan hari 4 (K2) ( $p = 0,06$ ). Kadar NO menurun signifikan pada K2 dibandingkan dengan K1 ( $p = 0,02$ ). K1 tidak menunjukkan hasil signifikan pada Analisis Gas Darah, Darah Urea Nitrogen, dan serum kreatinin, sedangkan K2 menunjukkan hasil signifikan pada Sel Darah Putih ( $p = 0,01$ ). Kesimpulan, pemberian vitamin C intervena menurunkan kadar oksida nitrat serum pada luka bakar parah. (FMI 2014;50:143-147)

**Kata kunci:** vitamin C, luka bakar parah, oksida nitrat

### ABSTRACT

Nitric oxide (NO) may cause systemic hypotension and apoptosis, contributing to tissue damage and multiple organ failure in severe burn, which increases Nitric Oxide Syntase (NOS) enzyme activity and NO release. Proinflammatory cytokines involves in NOS induction and activation and NO release. Vitamin C suppresses proinflammatory cytokines production, so NO production is inhibited. This study aimed to review intravenous vitamin C 3000 mg effect on NO serum level in severe burn injury. This study used randomized pre-test and post-test controlled group design in 12 severe burns patient at Burn Unit, Dr. Soetomo Hospital, Surabaya. NO was examined in 12 patients who were divided into 2 groups. Control group (K1) received vitamin C 2 x 400 mg/24 hour for 72 hours and treatment group (K2) received intravenous vitamin C 3000 mg for 72 hours. NO was taken from blood serum and observed by Grease method. Results were analyzed by Paired T-Test and statistical assays with  $p < 0.05$ . NO serum level in K1 showed no significant increase compared to day 1 of the day 4 ( $p = 0.21$ ) and NO serum level had no significant decrease on day 1 than that on day 4 (K2) ( $p = 0.06$ ). NO level decreased significantly in K2 compared to that in K1 ( $p = 0.02$ ). K1 showed no significant result in Blood Gas Analisis, Blood Urea Nitrogen, and Serum Creatinine, while K2 showed significant result in White Blood Cell ( $p = 0.01$ ). In conclusion, intravenous vitamin C administration decreases nitric oxide serum level in severe burn injury. (FMI 2014;50:143-147)

**Keywords:** vitamin C, severe burn, nitric oxide

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### INTRODUCTION

Burn management and burn care is still a challenge to the medical world, due to the high rate of its morbidity and mortality rates. In the United States burn case were reported approximately 500,000 patients each year with mortality of about 3-4 thousand deaths/year in 2011. Burn Unit at Dr. Soetomo Hospital the number of burn cases for one year (January 2011 to December 2011) are 167 cases, 94 cases (56.29%) were severe burns.

Numbers of death were 11 people (19.54%) of all major burns. One of the systemic response caused by severe burns is the activation of NF- $\kappa$ B, transcription factor protein on macrophages which will increase the production of inflammatory mediators or proinflammatory cytokines such as tumor necrosis factor (TNF- $\alpha$ ), interleukin (IL) and interferon gamma (IFN- $\gamma$ ). The increase of inflammatory mediators will enhance the expression of nitric oxide (NO) in large numbers via



activation of iNOS. iNOS is expressed by several types of immune cells, especially macrophages.

Nitric oxide (NO) is a cellular mediator, produced by one of three NO synthase: nNOS (neural nitric oxide synthase), eNOS (endothelial nitric oxide synthase) dan iNOS (inducible nitric oxide). iNOS is produced by several types of cell and is the key mediator of several immunological response. iNOS plays a role in the release of NO plays a role in the pathogenesis of septic shock.

In severe burns nitric oxide (NO) has an important contribution, in which nitric oxide (NO) is produced in large amounts by iNOS which is found in macrophages, endothelial cells, and hepatic veins. Production of nitric oxide (NO) is increasing in severe burns cause changes in cardiovascular function as a result of systemic hypotension due to hipocontractility of blood vessels and heart muscle depression, also a circulatory failure may lead to a failure of an organ or a system called the Multi-Organ Dysfunction Syndrome (MODS) (Çakir & Yeğen 2004).

The aim of this research is to determine the effect of vitamin C 3000 mg/24 hours for 72 hours post baxter resuscitation to the level of NO in human blood who suffered severe burns. As an antioxidant, vitamin C can react with Reactive Oxygen Species (ROS) produced by neutrophils and macrophages in the inflammatory phase, converting free radicals to a more inert form. Arachidonic acid cascade, which is activated by ROS will be cut so that the inflammatory reaction will stop. Therefore, the anti-inflammatory effects allegedly associated with vitamin C as an antioxidant nature (Lima et al 2009). Vitamin C as an anti-inflammatory is also capable of suppressing the activation of the transcription factor named nuclear factor  $\kappa$ B (NF- $\kappa$ B). NF- $\kappa$ B is a transcription factor that is responsible for the formation of several proinflammatory cytokines such as TNF- $\alpha$ , interleukin-1 (IL-1), IL-6, and IL-8 (Farris 2005). Based on the above background, a problem is defined as whether giving vitamin C 3000 mg may reduce levels of nitric oxide (NO) in the blood of severe burns.

## MATERIALS AND METHODS

This study is a randomized clinical trial. The reached populations in this study are severe burns patient post resuscitation Baxter admitted to Dr. Soetomo, Surabaya. Patients with severe burns with multiple trauma, patients with HIV, liver disorders, respiratory, heart and kidneys were excluded from this study. History was taken and physical examinations were done. Laboratory

tests include complete blood count, BUN, serum creatinine and Blood Gas Analysis were taken. Then the samples were randomized. The study is divided into two groups. Control group (K1) is the burn patients who were given standard therapy of vitamin C 2 x 400 mg/24 hours for 72 hours, the treated group (K2) is the burn patients were given intravenous vitamin C 3000 mg/24 hour for 72 hours. Peripheral venous blood sample (venous cubiti) must be taken as much as 3 cc in both study groups for examination of serum NO levels before underwent the treatment.

After 72 hours of treatment, venous blood sampling were taken again to determine serum levels of NO in both groups. NO levels examinations conducted by Griess method using a Cayman Chemical Nitrate/nitrite assay. For the safety of this procedure, the drugs for the management of adverse drug reaction (unwanted drug reactions) were prepared and observation was done to the patient every hour in the Burn Unit. Patients were dropped out of this research if they were incapable to follow the research due to their basic disease, heart failure, unwanted drug reactions or the wishes of the patient.

## RESULTS

In this study, 12 severe burns patients who matched the inclusion and exclusion criteria were divided into 2 groups. Group 1 (K1) as the control group and group 2 (K2) as the group receiving vitamin C 3000 mg, 6 patients each group. 7 patients (58.3%) are male and 5 (41.7%) patients are women. The mean age was  $36.17 \pm 12.99$  years. The mean age of group K1 was  $39.2 \pm 15.2$ , the youngest was 17 years old 61 years. The mean age of group K2 is  $33.2 \pm 10.9$  years, the youngest was 20 and the oldest was 51 years. The extent of burn in this study was  $40.2 \pm 18.1$  percent averages. In K1 group the patients suffered  $32.8 \pm 16.6$  percent of burn and  $47.6 \pm 17.7$  percent in K2 group. Data of patient characteristics in both groups are shown in Table 1.

Table 1. Characteristics of Subject's Study

Variables	Control n = 6	Vitamin C n = 6	P value
Sex			1.000
Man	3 (50,0)	4 (66,7)	
Female	3 (50,0)	2 (33,3)	
Age	$39.2 \pm 15.2$	$33.2 \pm 10.9$	0.450
Extensive burns (%)	$32.8 \pm 16.6$	$47.6 \pm 17.7$	0.166

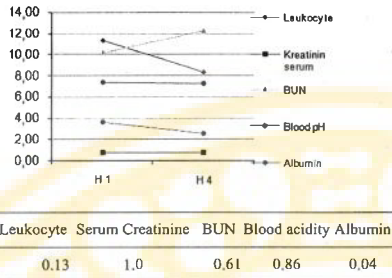


Figure 1. Diagram Characteristics levels of leukocytes, SK, BUN, blood pH, albumin control group (K1)

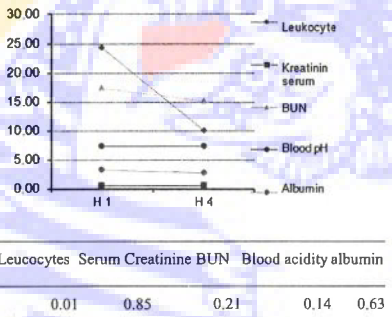


Figure 2. Diagram characteristics leukocyte levels, sk, BUN, blood pH, albumin group vitamin C (K2)

Average levels of leukocytes, serum creatinine, BUN and blood pH encountered no significant difference in the fourth day compared to the first day in the control group (K1) ( $p > 0.05$ ). While the levels of albumin in the control group was (K1) significantly decreasing with  $p = 0.04$  ( $p < 0.05$ ). Vitamin C group (K2), the amount of leukocytes decreased significantly  $p = 0.01$  ( $p < 0.05$ ) in the fourth day compared to the first day. While the levels of serum creatinine, BUN, blood pH and albumin are encountered insignificant difference. Prior to the statistical test, the normality tests on the levels of Nitric Oxide (NO) were made before and after treatment. Normality test is used to determine whether clinical or laboratory parameter data distributed normally. Normality test of levels of NO were done using the Kolmogorov-Sminov techniques. The results According to the table, serum levels of NO in the control group (K1) and vitamin c group (K2), in the first and fourth day normally distributed with  $p > 0.05$ . Using paired t test analysis to analyze changes in the levels of Nitric

Oxide (NO) before and after treatment in each group, a difference was found in the control group (K1). Trend of increasing Nitric Oxide levels from  $4.7 \pm 3.2 \mu\text{M}$  before treatment to  $6, 5 \pm 3.3 \mu\text{M}$  after treatment. However, this increase was statistically not significant ( $p = 0.21$  ( $p > 0.05$ )). Vitamin C 3000 mg group, decreased levels of Nitric Oxide (NO) were found at  $6.6 \pm 3.1 \mu\text{M}$  levels before treatment to  $3.8 \pm 1.4 \mu\text{M}$  after treatment ( $p = 0.06$  ( $p > 0.05$ )). For more details, see Figures 3 and 4.

Table 2. Normality test results of serum levels of NO

	Values		
	Day 1	Day 4	Delta NO
Control group (K1)	0.73	0.55	0.91
Vitamin C group (K2)	0.98	0.98	0.77

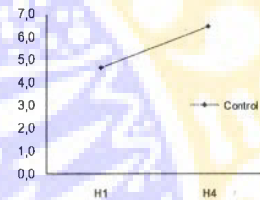


Figure 3. Diagram Analysis of the mean NO control group (K1).

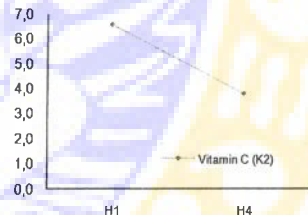


Figure 4. Diagram analysis of the mean NO group vitamin C.

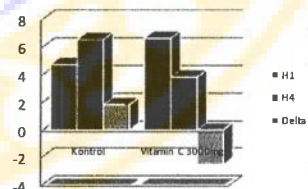


Figure 5. Diagram Analysis of the results of the study control group (K1) and the vitamin C (K2).

Independent t test was done to analyze the mean difference between the control group (K1) with Vitamin C 3000 mg group. The control group gained an increase in the average levels of Nitric Oxide (NO) as much as  $1.8 \pm 3.1 \mu\text{M}$  levels from  $4.7 \pm 3.2 \mu\text{M}$  before treatment to  $6.5 \pm 3.3 \mu\text{M}$  after treatment. The vitamin C 3000mg obtained a decrease of  $-2.6 \pm 2.7 \mu\text{M}$  from  $3.1 \pm 6.6 \mu\text{M}$  levels before treatment to  $3.8 \pm 1.4 \mu\text{M}$  after treatment. Analysis of NO difference (Delta NO) showed a significant reduction in the value of  $p = 0.02$  ( $p < 0.05$ ) in the comparison between the NO on the vitamin C (K2) with NO in the control group (K1).

## DISCUSSION

Local and systemic changes are caused by inflammatory mediators. Severe burns also cause depression of cellular and humoral immune response and phagocytes aspects of blood-borne macrophages. Burns initiate systemic inflammatory reaction caused by toxins and burns oxygen radicals and eventually lead to peroxidation. Reactive oxygen metabolites cause destruction or damage to the cell membrane by lipid peroxidation. The relationship between the number of products of oxidative metabolism and free radical scavenger naturally determine the result of local and systemic tissue damage, also organ failure subsequent to the burn (Horton 2003). The release of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 and IL-6) is an important mechanism in the regulation of the acute phase response to burns. TNF- $\alpha$  is a triggering cytokine that induce a cascade of secondary cytokines and humoral factors then lead to systemic and local sequele. And then TNF- $\alpha$  is involved in the development of conditions such as shock associated with burns and sepsis (Çakir & Yeğen 2004).

Nitric oxide is a biological molecule produced by different cell types, have a good and bad effect as well to the blood vessels and cellular level. NO is an important key to the pathogenesis of sepsis. INOS activation would lead to the formation of large numbers NO and showed that L-arginine is available in sufficient quantities (Chen et al 1999). Schorah et al (1996) reported a study conducted on patients admitted in the ICU that showed lower levels of total vitamin C, ascorbic acid and dehydroascorbic acid than in patients with gastritis, diabetes, and healthy people. Long et al (2003) found that patient's ascorbic acid plasma levels on parenteral dose of 300 mg/day of ascorbic acid for 2 days is unresponsive. Plasma levels began to rise at 1000 mg/day in 2 days but still below normal levels, it takes 3 days or more after the parenteral dose 3000 mg/day to achieve normal plasma levels.

Transcription factor NF- $\kappa$ B has a crucial role in the inflammatory process. NF- $\kappa$ B is a transcription factor that triggers the production of cytokines. Administering of LPS can activates the NF- $\kappa$ B which increases the production of inflammatory mediators such as IL-8, TNF- $\alpha$ , intercellular adhesion molecule (ICAM) dancycloxygenase-2. Vitamin C as an anti-inflammatory is also able to suppress the activation of the transcription factor nuclear factor  $\kappa$ B (NF- $\kappa$ B) and inhibit tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). NF- $\kappa$ B is a transcription factor that is responsible for the formation of several proinflammatory cytokines such as TNF- $\alpha$ , interleukin-1 (IL-1), IL-6, and IL-8 (Farris 2005).

Observations showed that leukocyte levels of the group given 3000 mg of vitamin C decline significantly in the fourth day compared to the first day. As an antioxidant, vitamin C can react with ROS produced by neutrophils and macrophages in the inflammatory phase, converting free radicals to more inert form. Arachidonic acid cascade, which is activated by ROS will be cut so that the inflammatory reaction will stop. Therefore, the anti-inflammatory effects allegedly associated with vitamin C as an antioxidant nature (Lima et al 2009). Galley et al (1996) discovered in his study of vitamin C concentration of total pre-infusion in septic patients is lower than healthy subjects. This study indicated that patients in sepsis syndrome had a quite much lower total vitamin C than normal controls, and it was consistent with previous studies that found low levels of ascorbic acid in the group of patients at critical illness, as well as the decrease in the ratio of ascorbic acid to dehydroascorbic. Low concentration of Vitamin C levels in patients with sepsis noted that subjects likely susceptible to oxidant stress.

In this study, the result of vitamin C 3000 mg administration showed insignificant decreasing of serum NO levels on day four compared to day one. This insignificant decreasing might be because the drug administration period is too short. But there is a significant decrease in the levels of NO in the fourth day of from the first day (delta NO) in the group given a vitamin C 3000 mg (K2) compared with the group without vitamin C (K1). Antioxidants are the body's protective system against free radical activity generated both endogenous and exogenous which is owned by every normal cells.

Antioxidants are defined as components that can protect itself against oxidation process that can turn it into free radicals despite the very small amount when compared to other components. Giving high doses of vitamin C will cause diarrhea, kidney stones and kidney dysfunction. In this study there was no significant

increase of BUN and serum creatinin levels in the group received 3000 mg of vitamin C in the fourth day compared to the first day. This study has several limitations such as NO examination cannot be performed in Dr. Soetomo hospital, and it is difficult to achieve the number of sample of new severe burns patients which matched the inclusion criteria in determined time.

### CONCLUSION

Intravenous vitamin C administration decreases nitric oxide serum level in severe burn injury.

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