

ORIGINAL ARTICLE

THE EFFECT OF HIGH DOSE VITAMIN C (ASCORBIC ACID) ON PROINFLAMMATORY CYTOKINES IN COVID-19

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ABSTRACT

Background: COVID-19 is a new pandemic that has claimed many lives in many countries. This pandemic was caused by the SARSCoV2. Until now, there is no specific antiviral drug or vaccine against Covid-19 for potential therapy in humans. This virus can cause cytokine storms which can worsen symptoms in sufferers due to an imbalance between increased oxidant production and available antioxidants. Vitamin C is an important antioxidant that protects the body from various bad effects of free radicals. At high concentrations vitamin C plays an important role in immunomodulation. This study was conducted to determine the effect of high doses of vitamin C on levels of pro-inflammatory cytokines in Covid-19.

Method: This research type is literature study. The population in this study were journals about Covid-19, vitamin C, antioxidants and free radicals, inflammatory reactions due to viral infections with samples taken from indexed journals published from 2015 to 2020. There are also clinical trials of high doses of vitamin C against inflammation in Covid-19 from these journals.

Results: The results of the study in a clinical trial conducted on 54 patients enrolled in 3 hospitals given a 1: 1 ratio for high-dose intravenous vitamin C (HDIVC) or placebo administration. The HDIVC group received 12 g of vitamin C / 50 ml every 12 hours for 7 days at a rate of 12 ml / hour, and the placebo group received bacteriostatic water for injection in the same way. HDIVC administration showed a reduction in inflammatory markers compared to placebo.

Conclusion: The conclusion of this study shows that high doses of vitamin C play a role in reducing levels of proinflammatory cytokines.

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INTRODUCTION

COVID-19, an infectious disease caused by SARSCoV2, emerged in December 2019 and has spread rapidly, with cases now confirmed in several countries. Infected patients show higher leukocyte counts, abnormal respiratory findings, and elevated plasma levels of pro-inflammatory cytokines. The main pathogenesis of COVID-19 infection as a virus that attacks the respiratory system is severe pneumonia, viral load

(RNAemia) in serum, combined with the incidence of ground-glass opacities, and acute heart injury. Some severe cases treated in intensive care units show high levels of pro-inflammatory cytokines that promote an increase in reactive oxygen species causing extensive damage to the cellular lining of small vessels (capillaries). Oxidative stress in organisms infected with virus provokes free radical oxidation which increases disease severity.¹

An important finding in COVID-19 patients is very high inflammatory parameters, including CRP (C-Reactive Protein) and proinflammatory cytokines IL-6 (Interleukin-6), TNF α (Tumor necrosis factor alfa), IL-8 (Interleukin-8). Cytokine storms are very common in patients with severe COVID-19. Cytokine storm refers to the excessive, uncontrolled release of pro-inflammatory cytokines.²

The antioxidant content of immune cells plays an important role in protecting them against oxidative damage and maintaining their proper function. In addition, in immune cells, antioxidants maintain the integrity and function of membrane lipids, cellular proteins and nucleic acids, and control signal transduction of gene expression. It has been shown that without sufficient antioxidants, ROS (Reactive Oxygen Species) produced by phagocytic immune cells can damage itself.³

Non-enzymatic antioxidants such as vitamin C provide great protection against oxidative stress by neutralizing or binding to reactive species or by breaking chain reactions.⁴ Under normal conditions, the antioxidant system of the lungs protects its cells from oxidative agents through complex and coordinated system interactions. The antioxidant power of vitamin C is related to its electron transport properties such as transferring unpaired ROS electrons to itself. According to research by Bezerra et al. 2006 showed that vitamin C decreased the lung inflammatory response by inhibiting the release of TNF- α and NF- κ B (Nuclear Factor Kappa-B). The histopathological evidence of the vitamin C group suggests that there is a severe reduction in neutrophil infiltration⁵

Currently, there is no specific antiviral drug or vaccine against COVID-19 for potential therapy in humans. For this reason, various kinds of efforts for a person to avoid the SARS-CoV-2 virus one of which is by increasing immunity. Efforts to increase immunity have been tried in various ways, ranging from eating herbs to consuming multivitamins, one of which is vitamin C as an antioxidant vitamin that does not yet know its effective function and properties to fight

a virus. Vitamin C that is produced and marketed has a variety of different dosage sizes, but the effectiveness of vitamin C doses in increasing people's immunity is still unknown. Antioxidant defense mechanisms, such as vitamins C protect tissues against oxidants. For this reason, little is known about the use of vitamin C based on an effective dose to prevent or help relieve inflammation, especially inflammation COVID-19 and a study needs to be done. Therefore, the authors intend to conduct a study in the form of a literature study on the antioxidant effects of high doses of vitamin C on reducing the pro-inflammatory process in COVID-19.

METHODS

The research design used is descriptive research. The facts and circumstances that the researchers wanted to describe in this study were the effect of giving high doses of vitamin C (ascorbic acid) on pro-inflammatory cytokines in COVID-19. The method used was literature study. The topic to be analyzed in this study is the effect of giving high doses of vitamin C (ascorbic acid) on pro-inflammatory cytokines in COVID-19. Population is all or a set of objects under study. The population in this study were articles about COVID-19, vitamin C (ascorbic acid), antioxidants and free radicals, inflammatory reactions due to viral infections. The sample in this study was taken from articles published by international journals indexed by Scimago and Google scholar from 2015 to 2020. This research was conducted in Surabaya from May to September 2020. This research obtained approval from the Health Research Ethics Commission, Faculty of Medicine, Hang Tuah University.

RESULTS

The result of this study are based on clinical trials conducted by (J. Zhang et al., 2020) on 54 patients registered in 3 hospitals, namely Leishenshan Hospital (38 patients), Zhongnan Hospital of Wuhan University (10 patients), and Taihe University Hospital Hubei (6 patients). Of the 54 patients included in this

analysis, 48 (88.9%) received the full 7 day treatment course and 6 (11.1%) received only 5 or 6 days of treatment due to death (2) or discharge from the ICU (4). Patients were randomized to receive vitamin C or placebo within 48 hours of admission to the ICU. To accurately control the infusion rate and not affect fluid management in severe patients, researchers administered vitamin C or placebo via a pump-controlled central venous

catheterization. The study group in this trial was 1) HDIVC (High Dose Intra Venous Vitamin C) 24 g of vitamin C per day. The patient was infused with 12 g of vitamin C diluted in 50 ml of bacteriostatic water every 12 hours at a rate of 12 ml / hour with an infusion pump for 7 days. 2) Placebo: 50 ml of bacteriostatic water infused every 12 hours at the same rate.⁶

Table 1 Laboratory findings about proinflammatory marker in a Trial of HDIVC in patients with Covid-19.⁶

Variable	Day	Vitamin C (n =26)	Placebo (n=28)
IL-6 (pg/ml)	1	22.56 [8.87-85.54]	54.73 [12.34-145.47]
	3	113.10 [21.80-288.73]	37.24 [5.59-85.28]
	7	19.42 [10.59-29.16]	158.00 [15.29-259.60]
CRP (mg/L)	1	39.86 [3.91-86.85]	56.84 [40.19-100.20]
	3	43.52 [3.41-65.72]	66.34 [29.76-107.39]
	7	29.47 [10.95-110.93]	30.20 [2.3-131.70]

DISCUSSION

The results of clinical trials show that high doses of vitamin C have a role in the process of reducing pro-inflammatory cytokines and other inflammatory markers such as CRP. Vitamin C is a water-soluble nutrient that the human body cannot synthesize on its own. Vitamin C acts as an anti-oxidant that scavenges reactive oxygen species (ROS), thereby protecting biomolecules such as proteins, lipids, and nucleotides from oxidative damage and dysfunction. Vitamin C accumulates in leukocytes, in concentrations 50-100 times higher than in plasma. During infection, the vitamin C present in leukocytes is used up quickly. Disruption of the balance between antioxidant defenses and oxidant formation can alter several signaling pathways involving the pro-inflammatory transcription factor, NF-κB. Increased oxidant levels lead to activation of NF-

κB, triggering a signaling cascade, with the end result of further production of oxidative species and inflammatory mediators. NF-κB is involved in inflammatory response, pathogenesis of certain diseases and viral infections. Inhibition of NF-κB can be a mode of therapy against viral infections. Vitamin C is also known to increase anti-inflammatory cytokines (IL-10). Clinical studies have shown that 1 g / day of vitamin C increases secretion of IL-10 by peripheral mononuclear cells. IL-10 works as a negative feedback mechanism with IL-6 and controls inflammation, important in COVID-19.⁷

At high concentrations vitamin C plays an important role in immunomodulation. Vitamin C can inhibit the activation of NFκB, which is a major proinflammatory transcription factor, and plays an important role in overall immunity, including genetic regulation of chemokines,

cytokines, adhesion molecules, inflammatory mediators and inhibitors of apoptosis. Vitamin C can inhibit the production of IL-6 and TNF- α . Vitamin C can reduce the GM-CSF signaling response which functions as a regulator of cytokine redox signal transduction in the body's defense cells and has a possible role in controlling the inflammatory response. In addition, high doses of vitamin C can regulate the proliferation and function of T cells, B cells, and natural killer (NK) cells. This can help inhibit the development of cytokine storms and increase host immunity.⁸

Preclinical research on early sepsis reveals that vitamin C prevents sepsis-induced cytokine spikes that activate and sequester neutrophils in the lungs, thereby damaging the alveolar capillaries. Vitamin C enhances clearance of alveolar fluid by preventing the accumulation of activated neutrophils in the alveolar spaces, limiting damage to alveolar epithelial drains. Additionally, vitamin C prevents the formation of neutrophil extracellular traps, a biological event in activated neutrophils that increases vascular injury.⁹

CONCLUSION

From the results of literary studies, it can be concluded that at high concentrations vitamin C plays an important role in immunomodulation. Vitamin C can inhibit the activation of NF κ B, which is a major proinflammatory transcription factor, and plays an important role in overall immunity, including genetic regulation of chemokines, cytokines, adhesion molecules, inflammatory mediators and inhibitors of apoptosis. Vitamin C can inhibit the production of IL-6 and TNF- α . Vitamin C can reduce the GM-CSF signaling response which functions as a regulator of cytokine redox signal transduction in the body's defense cells and has a possible role in controlling the inflammatory response. In addition, high doses of vitamin C can regulate the proliferation and function of T cells, B cells, and natural killer (NK) cells. This can help inhibit the development of cytokine storms and increase host immunity. Vitamin C is also known to increase anti-inflammatory cytokines (IL-10). With this ability, vitamin C plays an important role in

reducing cytokine storms in Covid-19 by reducing levels of pro-inflammatory cytokines.

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