Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2024; 9(1): 104-115 Website: jnfs.ssu.ac.ir

High Dose of Vitamin C in Septic and Critically Ill Patients with COVID-19: A Narrative Review

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ARTICLE INFO

NARRATIVE REVIEW

Article history:
Received: 25 Aug 2022
Revised:2 Oct 2022
Accepted: 2 Nov 2022

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ABSTRACT

Background: The coronavirus disease of 2019 (COVID-19) may be considered sepsis on the basis that all the pathological events and the subsequent organ-to-organ interaction in sepsis also occur in COVID-19. In this article, the authors first discussed the rationale for the use of vitamin C (Vit-C) in sepsis and septic patients. They also reviewed the role of a high dose of Vit-C in COVID-19, which included clinical trials designed for the management of this viral disease. **Methods:** The researchers explored databases of PubMed, Scopus, ISI Web of Science, and Google Scholar. Data were extracted to assess the effects of Vit-C in septic patients and also the efficacy of supplementation with a high dose of Vit-C regarding the clinical outcomes of patients with COVID-19. **Results:** Recent research findings indicate that severe inflammatory responses (cytokine storms) and oxidative stress are important causes for the high mortality in COVID-19 patients. It seems, however, that administering high doses of Vit-C can offer a therapeutic benefit. High doses of intravenous Vit-C, with its antioxidant properties and pleiotropic functions, could attenuate the tissue damage caused by excessive levels of free radicals following the cytokine storm and septic shock in severe cases of the disease. **Conclusions**: Recent literature suggests that high doses of Vit-C have a potential role in reducing mortality and intubation rates in critically ill COVID-19 patients. However, determining the optimal duration and dose of Vit-C in these patients requires further studies.

Keywords: *COVID-19; Vitamin C; Cytokine storm; Critically ill; Sepsis.*

Introduction

The coronavirus disease of 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), has been a major global health concern in the past two years. (Grippo *et al.*, 2020). Regarding the immunopathology of COVID-19, the levels of inflammatory cytokines, such as interleukin-6 (IL-6) and interferon-gamma (IFN-γ) have been reported to be elevated in critically ill COVID-19 patients, and they are generally associated with

This paper should be cited as: Amini K, Sahebnasagh A, Amini R, Habtemariam S, Najmeddin F, Mojtahedzadeh M. ***High Dose of Vitamin C in Septic and Critically Ill Patients with COVID-19: a Narrative Review.*** *Journal of Nutrition and Food Security (JNFS)*, 2024; 9 (1): 104-115.

[DOI: 10.18502/jnfs.v9i1.14845]

adverse disease outcomes (Rabby, 2020). This viral disease can be considered sepsis, because all the pathological events of sepsis and the subsequent organ-to-organ interaction also occur in COVID-19 (Vincent, 2021). The overproduction of inflammatory cytokines leads to pathological conditions such as extensive tissue damage and cell death. The high circulating levels of proinflammatory cytokines and the resultant tissue damage in COVID-19 is called cytokine storm. Cytokine storm-induced inflammation is associated with hypotension, changes in vascular structure, and ultimately, organ failure. Yet, the underlying cause of this elevation in cytokine levels remains unknown. Comorbidities such as diabetes, hypertension, and cardiovascular disease which endanger vascular health are associated with poor outcomes in critically ill COVID-19 patients (de Almeida-Pititto *et al.*, 2020). Cytokine storm can eventually lead to pneumonitis, acute respiratory distress syndrome (ARDS), multi-organ failure, and shock (Fara *et al.*, 2020). Studies have shown that cytokine storms are a major cause of mortality as well as the disease severity in COVID-19 patients (Chen *et al.*, 2020). The clinical consequences of changes in tissues and host physiology are often accompanied by persistent fever, weight loss, joint and muscle pain, fatigue and headache (England *et al.*, 2021). The prevalence of hospitalized patients entering the respiratory failure phase is reported to be between 17% and 29% (Guo *et al.*, 2020, Sahebnasagh *et al.*, 2020). The disease can range from a simple infection to acute respiratory failure syndrome.

As evidenced by COVID-19, sepsis is not just caused by bacteria, but also by viruses (Vincent, 2021). Following the cytokine storm and septic shock in the severe cases of the disease, the production of free radicals and damage due to the oxidative stress increases (Hiedra *et al.*, 2020a).

Various strategies have been employed for prevention and therapeutic management of this viral disease. However, no globally accepted treatment has been approved for COVID-19 so far, and the control of this pandemic has not yet been adequately achieved. Thereby, efforts are underway to find effective and safe treatments for this disease. In the early stages of the disease, therapeutic modalities which strengthen the immune system and viral excretion from the body have been suggested (Shi *et al.*, 2020). Immunosuppressive and anti-inflammatory drugs can be considered at a stage when a cytokine storm has occurred, and lung is severely involved (Azimi *et al.*, 2020, Zhang *et al.*, 2020b). Vigorous anti-inflammatory medications, such as corticosteroids, are effective in treating the inflammatory phase, cytokine storm, severe pulmonary involvement, and ARDS (Provenzani and Polidori, 2020). Furthermore, antioxidants neutralize free oxygen radicals and the destructive effects of oxidative stress. Therapeutic agents, such as vitamin C (Vit-C), with both antioxidant and anti-inflammatory properties and indirect killing of invasive pathogens, appear to impact COVID-19. In this project, the factors for using Vit-C in sepsis and septic patients was discussed, In addition, the role of high dose of Vit-C in COVID-19 were reviewed, and a general overview of clinical studies of Vit-C recruited for the management of this viral disease was provided.

Materials and Methods

The following databases were searched for related clinical studies: MEDLINE (via PubMed) (www.pubmed.com; National Library of Medicine), Scopus (www.scopus.com), ISI Web of Science (www. thomsonreuters.com), Cochrane, central register for controlled trials (https://www. cochranelibrary.com/ central/about-central), and Google Scholar (www.scholar.google.com). Data were extracted and the effects of Vit-C in septic patients and the efficacy of supplementation with Vit-C were evaluated regarding the clinical outcomes of COVID-19 patients.

Rationale for Vit-C in the management of COVID-19

Vit-C is a water-soluble essential micronutrient which acts as a powerful antioxidant. In addition to antioxidant effects in high concentrations, it has antimicrobial and immunomodulatory properties by preventing the activation of an important pro-

[DOI: 10.18502/jnfs.v9i1.14845]

inflammatory agent, nuclear factor kappa-B (NF-κB) (Mousavi *et al.*, 2019). Vit-C attenuates the production of IL-6 and TNF-α in a dose-dependent manner (Chen *et al.*, 2014, Härtel *et al.*, 2004). High doses of Vit-C regulate the production of T cells, B cells and natural killer (NK) cells (Liu *et al.*, 2020a). Therapeutic effects of Vit-C at high doses have been reported in other inflammatory conditions such as sepsis (Marik, 2018) and cardiac surgery (Hill *et al.*, 2018). Many infections increase the activity of phagocytes, resulting in an increase in free radicals. In this case, Vit-C protects host cells against free radicals released by phagocytes. The antioxidant properties of this micronutrient are mediated by electron donation. As a result of these reactions, Vit-C is converted to its oxidized form–semidehydroascorbic acid or dehydroascorbic acid. Vitamin C oxidized in the extracellular space is then picked up by cells through glucose transporters such as GLUT1. Vitamin C is reduced by glutathione (GSH) within the cell (Bohndiek *et al.*, 2011). **Figure 1** presents the mechanisms via which vitamin C is transported to create a redox balance and also its function as an antioxidant.

In the common cold and some other viral infections, the amount of Vit-C decreases in plasma, leukocytes and urine. A study found that mice suffered more lung damage when they suffered Vit-C deficiency (Li *et al.*, 2006). Many studies have shown that Vit-C is effective in preventing, shortening the duration and improving the symptoms of many infections (Hemilä, 2017). Vit-C can strengthen the immune system and protect against coronavirus infection (Hemilä, 2003). When this vitamin accumulates in phagocytic cells such as neutrophils, it improves chemotaxis, phagocytosis, and pathogen killing properties of these cells. Studies have shown that Vit-C is able to increase the resistance of chickens' tracheal tissue to coronavirus infection (Atherton *et al.*, 1978).

Previous research on sepsis-induced lung injury and patients with severe sepsis showed that intravenous Vit-C inhibits systemic inflammatory responses, vascular damage, and coagulopathy associated with sepsis (Fisher *et al.*, 2012, Fisher *et al.*, 2011, Syed *et al.*, 2014). This antioxidant micronutrient was administered intravenously at high doses in septic patients with ARDS to evaluate its efficacy on organ failure, systemic inflammation, or vascular damage. Compared to the placebo, Vit-C significantly reduced mortality rate and hospital and intensive care unit (ICU) length of stay (Truwit *et al.*, 2019). Following the septic shock and cytokine storms caused by severe forms of COVID-19, the production of free radicals increases, and the subsequent oxidative stress causes tissue damage. Therefore, compounds with robust antioxidant properties influence the management of cytokine storm associated with COVID-19 as they strengthen the immune system (Hiedra *et al.*, 2020a). Moreover, due to its antioxidant properties ,Vit-C can prevent oxidative stress associated with COVID-19 (Liu *et al.*, 2020b).

[DOI: 10.18502/jnfs.v9i1.14845]

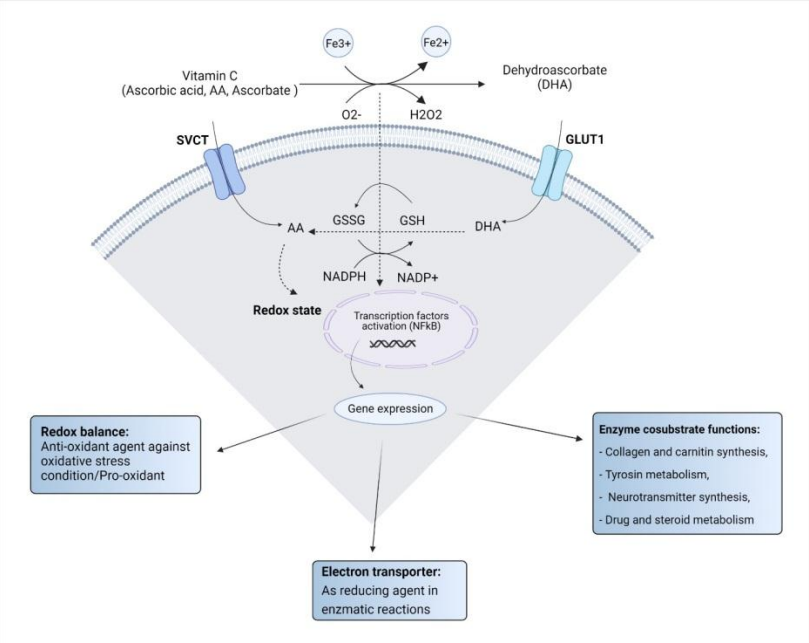

Figure 1. Schematic of the transport of Vit-C into cells and the way it functions as an antioxidant compound This figure was created with BioRender.com. SVCT: Sodium-dependent vitamin C transporter; AA: Ascorbic acid; DHA: Dehydroascorbic acid.

Many studies have shown that Vit-C is effective in preventing, shortening the duration, and improving many infections (Hemilä, 2017). Vit-C can strengthen the immune system and protect against coronavirus infection (Hemilä, 2003). This vitamin accumulates in phagocytic cells such as neutrophils, improves chemotaxis and phagocytosis, and ultimately kills bacteria and viruses. Vit-C is able to increase the resistance of chickens' tracheal tissue to coronavirus infection (Atherton *et al.*, 1978). Because lower respiratory tract infections are common in COVID-19, this vitamin may be effective as an option in the treatment of COVID-19-induced respiratory infections. The proposed roles of intravenous high doses of Vit-C in combating SARS CoV2 is illustrated in **Figure 2**.

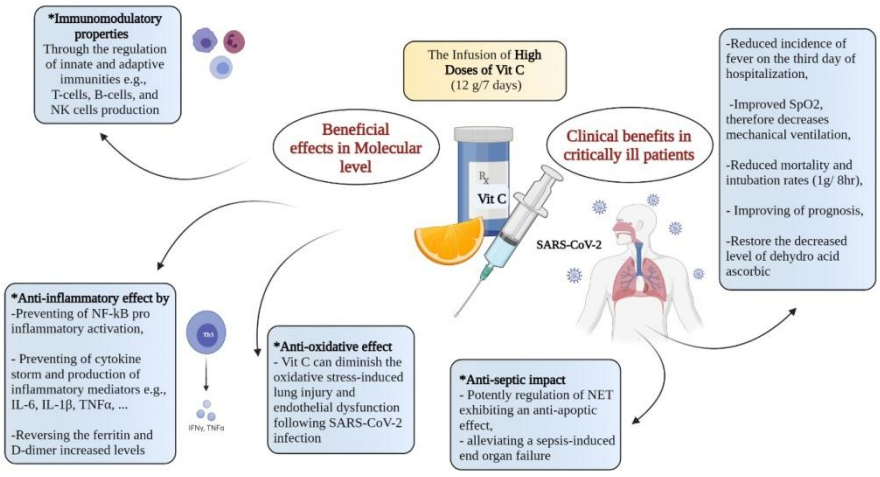

Figure 2. The proposed roles of intravenous high doses of vitamin C in combating SARS CoV2
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[DOI: 10.18502/jnfs.v9i1.14845]

Physiological properties of Vit-C and its rationale in septic patients

It has been shown that overproduction of free radicals and oxidative stress in sepsis contribute to multi-organ failure. Reactive oxygen radicals increase blood vessel permeability and decrease vascular tone, thereby disrupting the endothelial integrity (Hager *et al.*, 2019, Litwak *et al.*, 2019). Moreover, in sepsis, the glycocalyx layer, which is a gel-like layer on the cell membrane, is degraded. Various studies have shown that in sepsis, due to their degradation and shedding, the level of glycocalyx components increases. These components, consisting of heparan, syndecan-1, glycosaminoglycans and hyaluronic acid, cause microcirculatory and multi-organ dysfunction (Uchimido *et al.*, 2019).

Septic patients admitted to ICU usually have very low plasma levels of Vit-C, less than 15 µmol/l, which can only be compensated by prescribing doses of more than 3 g/day of intravenous Vit-C (Balakrishnan *et al.*, 2018, Hager *et al.*, 2019, Marik *et al.*, 2017). Vit-C has different physiological functions in the human body due to its antioxidant properties and pleiotropic functions. This micronutrient is the cofactor of many vital enzymes. By catalyzing and accelerating the production of norepinephrine from dopamine and dopamine from L-dopa and vasopressin, Vit-C increases the biosynthesis of these two endogenous vasopressors. Furthermore, it has been shown to increase the activity of adrenergic receptors (Carr *et al.*, 2015, Eipper and Mains, 1991, Kagan *et al.*, 1992, Noguchi *et al.*, 1997). Considering the destructive effects of exogenous catecholamines and adrenergic responses, including cardiac suppression, increased risk of thrombogenicity, immunosuppression, and increased growth of opportunistic pathogens, any interventions which reduce the need for exogenous vasopressors has a potential therapeutic role in sepsis (Schmittinger *et al.*, 2013, Triposkiadis *et al.*, 2009). Vit-C is involved in wound healing and maintaining connective tissue (Arrigoni and De Tullio, 2000). The micronutrient is involved in the biosynthesis of L-carnitine. Considering that L-carnitine itself transfers the long chain fatty acids into the mitochondria and the down-regulation of the production of inflammatory mediators, this micronurtrient has a potential role in sepsis (Nelson *et al.*, 1981, Rebouche, 1991). Vit-C has been shown to reduce the severity of sepsis shock (Winter *et al.*, 1995). Notably, in critically ill patients, the amount of neutrophil extracellular trap (NET) increases, which leads to the induction of epithelial and endothelial cell death and organ damage. (Ferrón-Celma *et al.*, 2009, Mikacenic *et al.*, 2018, O'Brien *et al.*, 2017, Saffarzadeh *et al.*, 2012). The administration of this vitamin leads to extended neutrophils lifespan and their bactericidal activity. Vit-C is a potent regulator of NET and high doses of intravenous Vit-C has anti- apoptotic properties and reduce sepsis-induced end organ failure in these patients (Mohammed *et al.*, 2013). The protective role of high doses of Vit-C in sepsis-induced ARDS was reported. The underlying mechanism was attributed to increased expression of protein channels such as Na^+/K^+ ATPase (Rodrigues da Silva *et al.*, 2018). The results of a recent meta-analysis on 3133 septic patients showed that the best duration of Vit-C was 3-4 days and administration of this vitamin for less than three days and more than five days was not very effective (Scholz *et al.*, 2021).

Vit-C deficiency is associated with neutrophils dysfunction, their decreased phagocytic potency, and increased production of free oxygen radicals (Carr and Maggini, 2017, Chen *et al.*, 2014). This invaluable compound reduced systemic inflammation and reactive oxygen radicals by inhibiting the activation of the NF-κB pathway (Mikirova *et al.*, 2016, Peng *et al.*, 2005). Therefore, in inflammatory conditions such as sepsis, Vit-C can be effective. At high concentrations, it directly inhibits bacterial growth and has bactericidal effects (Shilotri, 1977). Supplementation with intravenous Vit-C increased responsiveness to exogenous vasopressors, improved capillary flow, and decreased procalcitonin concentration, organ failure and mortality rate in septic patients (Fujii *et al.*, 2019, Hager *et al.*, 2019, Masood *et al.*, 2019, Sadaka *et al.*, 2020). As mentioned above, in septic shock, the pathological events eventually lead to

[DOI: 10.18502/jnfs.v9i1.14845]

degradation and shedding of the glycocalyx layer (Uchimido *et al.*, 2019). High doses of intravenous Vit-C have been shown to reduce circulating thrombomodulin (a biomarker of endothelial injury) and plasma levels of syndecan-1 (Puskarich *et al.*, 2016). Syndecan-1 itself is a strong predictor of respiratory failure following pneumonia-induced sepsis (Smart *et al.*, 2018).

Vit-C in critically ill COVID-19 patients

Recent studies have emphasized the crucial effects of Vit-C in the treatment of patients with severe COVID-19. An overview of several clinical trials conducted in the management of COVID-19 is summarized in **Table 1**.

Table 1. Clinical studies on the administration of high doses of vitamin C in critically ill COVID-19 patients.

Authors	Study type	Disease	Number of patients	Intervention group(s)	Outcomes
Hiedra et al. (Hiedra *et al.*, 2020b)	Observational study	COVID-19	17	1 g every 8 h for 3 days	The need for intubation was seen in 17.6% (n=3) of patients Morality was seen in 12% (n=2) patients Vit-C was effective in reducing the need of intubation and morality.
Khan et al. (Khan *et al.*, 2020)	Case report	COVID-19	1	Oral Vit-C 1 g twice a day In critical phase (day 6) the dose was elevated to 11 g per 24 h as a continuous intravenous infusion	Norepinephrine support was stopped on MV day 4 Oxygen saturation was increased by 92% Breathing status was improved with high dose of Vit-C
Zhang et al. (Zhang *et al.*, 2020a)	RCT	COVID-19	44	12 g of Vit-C /50 ml every 12 hours for 7 days	PaO2/FiO2 improved in patients received high doses of Vit-C A significant reduction in 28-day mortality was seen in groups administer by high doses of Vit-C
Fowler et al.(Fowler III *et al.*, 2017)	Case report	Virus-induced ARDS	1	1 g of Vit-C every 8 h	Rapid recovery Extracorporeal membrane oxygenation (ECMO) and mechanical ventilation was stopped on day 7 Rapid resolution of lung injury was occurred.
Jamali Moghadam Siahkali et al (JamaliMoghadamSiahkali *et al.*, 2021)	RCT	COVID-19`	60	1.5 g Vit-C IV every 6 h for 5 days	The mean body temperature in case groups decreased significantly SpO2 increased in group receiving high doses of Vit-C
Zhang et al. (Zhang *et al.*, 2021)	RCT	COVID-19	56	12g of Vit-C /50 ml every 12 h for 7 days	High dose of Vit-C failed to reduce the 28-day mortality Steady rise in PaO2/FiO2 was observed in patients who receiving high doses of Vit-C IL-6 serum level was reduced significantly in patients who receiving Vit-C
Thomas et al. (Thomas *et al.*, 2021)	RCT	COVID-19	214	10 days of zinc (50 mg), Vit-C (8000 mg)	The administration of treatments did not cause significant differences regarding the duration of symptoms

[DOI: 10.18502/jnfs.v9i1.14845]

There are reports of decreased circulating levels of Vit-C in critically ill COVID-19 patients, so that the serum levels of Vit-C were undetectable in 94.4% of these patients (Chiscano-Camón *et al.*, 2020). This was attributed to mechanisms such as increased metabolism due to increased inflammatory reactions, severe renal excretion following glomerular hyperfiltration, and decreased intestinal absorption (Chiscano-Camón *et al.*, 2020).

Furthermore, the beneficial effects of Vit-C against coronavirus infection have been reported (Atherton *et al.*, 1978). This vitamin reduces lung injury and mortality in surgical and pneumonia patients (Nathens *et al.*, 2003). Vit-C has strong antioxidant and anti-inflammatory properties which affects the immune system and improves cell function by reducing oxidative stress or inflammation (Mousavi *et al.*, 2019). Decreased mortality and intubation rates were reported when 1g of Vit-C was administered every eight hours to critically ill COVID-19 patients. The included patients had moderate to severe forms of the disease. This study reported that inflammatory markers such as ferritin and D-dimer decreased after administration of Vit-C as well as the requirements for FiO_2 (Hiedra *et al.*, 2020b). Although the results of this preliminary study were promising, caution should be taken in the interpretation of the data. This study was performed on only 17 patients with no control group, and patients were concomitantly prescribed other standard medications such as steroids, antivirals and tocilizumab in addition to Vit-C. Therefore, given the small sample size, it is not clear which of these interventions led to better outcomes. Moreover, in this study, Vit-C was administered at a low dose, the treatment duration was short, and only two inflammatory markers of ferritin and D-dimer were tested.

In a case study, administration of high doses of Vit-C in a COVID-19 patient with septic shock resulted in clinical improvement and elimination of mechanical ventilation within 5 days, indicating a therapeutic effect of high dose of Vit-C in critically ill patients of COVID-19 (Khan *et al.*, 2020). Reduction of mortality rate regarding this viral disease were suggested by other studies following the administration of high doses of Vit-C. Continuous intravenous infusion of Vit-C was initiated on patients along with other standards of care. The clinical presentations of the patient were improved as indicated by discontinuing the need for exogenous vasopressor and better pulmonary manifestations on chest X-ray. (Zhang *et al.*, 2020a).

The beneficial role of high doses of Vit-C (12 g infusion twice a day for 7 days) in improving the prognosis of acute respiratory infections in SARS-CoV-2 patients were addressed (Kakodkar *et al.*, 2020).

Furthermore, improvement of lung tissue was reported as a result of this intervention in ARDS induced by infection with other viruses such as enterovirus and rhinovirus (Fowler III *et al.*, 2017). Vit-C deficiency in critically ill patients during infection seems to be one of the leading causes of high mortality rate, and it has been hypothesized that high doses of Vit-C may reduce mortality in such patients (Berger and Oudemans-van Straaten, 2015). There are also reports of decreased susceptibility to lung infection due to Vit-C administration, which indicates the protective effects of Vit-C against lung infection (Messina *et al.*, 2020, Tan *et al.*, 2020). In a recent open-label clinical study on 60 patients, 1.5 g of Vit-C was administered every 6 hours for five days on with COVID-19 patients. The results showed reduction of fever on the third day of hospitalization and improved oxygen saturation (SpO_2) and shorter hospital stay following the administration of Vit-C. This vitamin was also well tolerated. Nevertheless, this intervention did not influence mortality, ICU duration of stay, and SpO_2 on discharge (JamaliMoghadamSiahkali *et al.*, 2021).

Regarding high doses of Vit-C, possible side effect is a concern. However, many studies indicated that these side effects were negligible and well tolerated (Barness, 1975). In a clinical study, the effect of high-dose infusion of Vit-C (12 g) every four hours (repeated every 12 hours for 7 days) was studied on the clinical outcomes of COVID-19 patients. In total, each patient received

[DOI: 10.18502/jnfs.v9i1.14845]

24 g of Vit-C per day. The results of their study showed that 28-day mortality was not reduced as a result of administration of high doses of Vit-C. In comparison to control, a better oxygenation was observed in patients receiving high doses of Vit-C on day seven of treatment as indicated by gradual increase in PaO2/FiO_2. Moreover, the circulating levels of IL-6 decreased after the intervention on patients. One of the major limitations of this study was the late initiation of Vit-C infusion ten days after the onset of symptoms. Therefore, the fact that Vit-C could not reduce mortality in this study could be related to this issue. As mentioned above, Vit-C has known antiviral effects, but given that viral load was not measured in this study, it is unclear whether these antiviral properties are present in combating SARS-CoV_2 or not. Moreover, the majority of included patients in this study were male, which could make it difficult to attribute the results to the general population (Zhang *et al.*, 2021). It appears that Vit-C can reduce the inflammation caused by COVID-19 and reduce the cytokine storm in patients.

However, administration of this micronutrient has not always been effective. In a study by Thomas *et al.*, the effect of high doses of Vit-C along with zinc, compared to the group receiving only the standard treatment, was investigated on the duration and reduction of symptoms of SARS-CoV-2 infection in critically ill patients. In this clinical trial, treatment with high doses of Vit-C, high dose of zinc, or both was not associated with a reduction in the duration of symptoms in patients receiving 8 g of Vit-C and 50 mg of zinc gluconate compared to the standard care. This study was stopped prematurely due to the ineffectiveness of the interventions. However, it should be noted that this study was single-center and open-label (Thomas *et al.*, 2021).

Conclusion

COVID-19 is a viral disease with high levels of inflammatory cytokines associated with severe forms of the disease. This viral disease can be considered sepsis, because all the pathological events of sepsis and the subsequent organ-to-organ interaction occur in COVID-19. Previous studies on sepsis-induced lung injury and patients with severe sepsis showed that intravenous Vit-C inhibits systemic inflammatory responses, vascular damage, and coagulopathy associated with sepsis. Vit-C has strong antioxidant and anti-inflammatory properties which affects the immune system and improves cell function by reducing oxidative stress or inflammation. Therefore, it seems that high doses of Vit-C have a potential role in reducing mortality and intubation rates in critically ill COVID-19 patients. Given the high prevalence of mortality of COVID-19 patients in ICU, as well as the common deficiency of Vit-C in critically ill patients, it is recommended that further studies be conducted in the form of high-quality controlled RCTs to determine the exact beneficial effects of supplementation with high doses of Vit-C in septic critically ill patients. Furthermore, determining the optimal duration and dose of Vit-C administration in these patients requires further well-designed clinical studies.

Authors' contribution

Amini K involved to design and conduction the study and drafting the manuscript. Sahebnasagh A, Ronak A, Najmeddin F and Habtemariam involved to write and edit of manuscript. Mojtahedzadeh M supervised the work. All authors read the manuscript and approved it for publish.

Conflict of interest

The authors of present study declare that they have no conflict of interest.

Funding

None

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[DOI: 10.18502/jnfs.v9i1.14845]