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

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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

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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, Sahebnaasagh *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-

inflammatory agent, nuclear factor kappa-B (NF- κ B) (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).

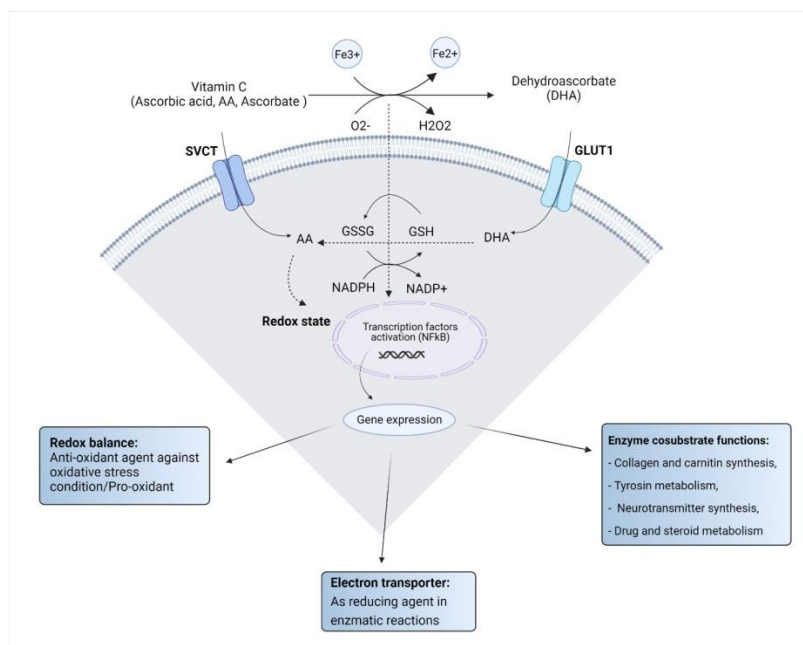


Figure 1. Schematic of the transport of Vit-C into cells and the way it functions as an antioxidant compound. This figure was created with BioRender.com. SVCT: Sodium-dependent vitamin C transporter; AA: Ascorbic acid; DHA: Dehydroascorbic acid.

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**.

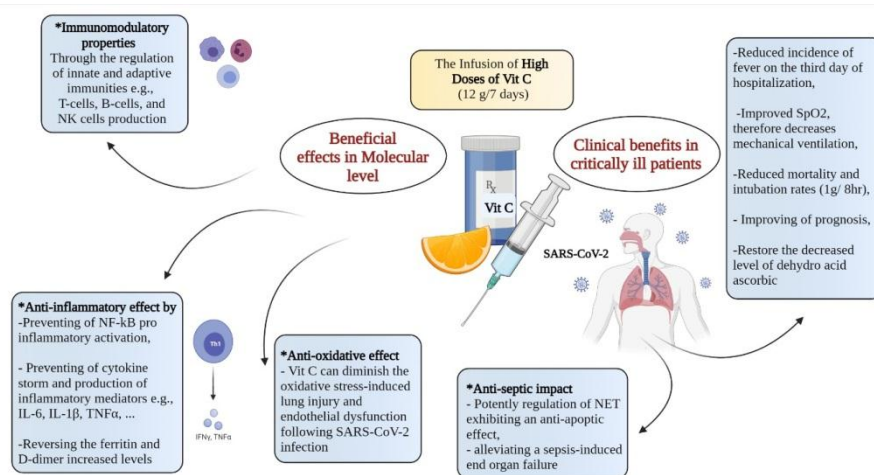


Figure 2. The proposed roles of intravenous high doses of vitamin C in combating SARS CoV2. This figure was created with BioRender.com.

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 $\mu\text{mol/l}$, 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 micronutrient 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- κ B 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

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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2020a)	RCT	COVID-19	44	12 g of Vit-C /50 ml every 12 hours for 7 days	PaO ₂ /FiO ₂ 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 <i>et al.</i> , 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 (Jamali Moghadam Siahkali <i>et al.</i> , 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 SpO ₂ increased in group receiving high doses of Vit-C
Zhang et al. (Zhang <i>et al.</i> , 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 PaO ₂ /FiO ₂ 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 <i>et al.</i> , 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

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 FiO₂ (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 (SpO₂) 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 SpO₂ 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

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/FiO₂. 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-CoV₂ 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. Sahebnaasagh 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.

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References

- Arrigoni O & De Tullio MC 2000. The role of ascorbic acid in cell metabolism: between gene-directed functions and unpredictable chemical reactions. *Journal of plant physiology*. **157** (5): 481-488.
- Atherton J, Kratzing C & Fisher A 1978. The effect of ascorbic acid on infection of chick-embryo ciliated tracheal organ cultures by

- coronavirus. *Archives of virology*. **56** (3): 195-199.
- Azimi S, Sahebnaasagh A, Sharifnia H & Najmeddin F** 2020. Corticosteroids administration following COVID-19-induced acute respiratory distress syndrome. Is it harmful or life-saving? *Frontiers in emergency medicine*. **4** (2s): e43-e43.
- Balakrishnan M, et al.** 2018. Hydrocortisone, vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. *Indian journal of anaesthesia*. **62** (12): 934.
- Barness LA** 1975. Safety considerations with high ascorbic acid dosage. *Annals of the New York Academy of Sciences*. **258** (1): 523-528.
- Berger MM & Oudemans-van Straaten HM** 2015. Vitamin C supplementation in the critically ill patient. *Current opinion in clinical nutrition & metabolic care*. **18** (2): 193-201.
- Bohndiek SE, et al.** 2011. Hyperpolarized [1-13C]-ascorbic and dehydroascorbic acid: vitamin C as a probe for imaging redox status in vivo. *Journal of the American Chemical Society*. **133** (30): 11795-11801.
- Carr AC & Maggini S** 2017. Vitamin C and immune function. *Nutrients*. **9** (11): 1211.
- Carr AC, Shaw GM & Natarajan R** 2015. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Critical care*. **19** (1): 1-8.
- Chen X, et al.** 2020. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clinical infectious diseases*.
- Chen Y, et al.** 2014. Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages. *Mediators of inflammation*. **2014**.
- Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O & Ferrer R** 2020. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Critical care*. **24** (1): 1-3.
- de Almeida-Pititto B, et al.** 2020. Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetology & metabolic syndrome*. **12** (1): 1-12.
- Eipper BA & Mains RE** 1991. The role of ascorbate in the biosynthesis of neuroendocrine peptides. *American journal of clinical nutrition*. **54** (6): 1153S-1156S.
- England JT, et al.** 2021. Weathering the COVID-19 storm: lessons from hematologic cytokine syndromes. *Blood reviews*. **45**: 100707.
- Fara A, Mitrev Z, Rosalia RA & Assas BM** 2020. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. *Open biology*. **10** (9): 200160.
- Ferrón-Celma I, et al.** 2009. Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. *Journal of surgical research*. **153** (2): 224-230.
- Fisher BJ, et al.** 2012. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *American journal of physiology-lung cellular and molecular physiology*. **303** (1): 20-32.
- Fisher BJ, et al.** 2011. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Critical care medicine*. **39** (6): 1454-1460.
- Fowler III AA, et al.** 2017. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World journal of critical care medicine*. **6** (1): 85.
- Fujii T, et al.** 2019. Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan. *Critical care and resuscitation*. **21** (2): 119.
- Grippio F, et al.** 2020. The Role of COVID-19 in the Death of SARS-CoV-2-Positive Patients: A Study Based on Death Certificates. *Journal of clinical medicine*. **9** (11): 3459.
- Guo G, et al.** 2020. New insights of emerging SARS-CoV-2: epidemiology, etiology, clinical

- features, clinical treatment, and prevention. *Frontiers in cell and developmental biology*. **8**: 410.
- Hager DN, et al.** 2019. The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol: a prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial. *Trials*. **20** (1): 197.
- Härtel C, Strunk T, Bucskey P & Schultz C** 2004. Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. *Cytokine*. **27** (4-5): 101-106.
- Hemilä H** 2003. Vitamin C and SARS coronavirus. *Journal of antimicrobial chemotherapy*. **52** (6): 1049-1050.
- Hemilä H** 2017. Vitamin C and infections. *Nutrients*. **9** (4): 339.
- Hiedra R, et al.** 2020a. The use of IV vitamin C for patients with COVID-19: a case series. *Expert review of anti-infective therapy*. **18** (12): 1259-1261.
- Hiedra R, et al.** 2020b. The use of IV vitamin C for patients with COVID-19: A single center observational study. *Expert review of anti-infective therapy*.
- Hill A, et al.** 2018. Vitamin C to improve organ dysfunction in cardiac surgery patients—Review and pragmatic approach. *Nutrients*. **10** (8): 974.
- Jamali Moghadam Siahkali S, et al.** 2021. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. *European journal of medical research*. **26** (1): 1-9.
- Kagan VE, Serbinova E, Forte T, Scita G & Packer L** 1992. Recycling of vitamin E in human low density lipoproteins. *Journal of lipid research*. **33** (3): 385-397.
- Kakodkar P, Kaka N & Baig M** 2020. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). *Cureus*. **12** (4).
- Khan HMW, Parikh N, Megala SM & Predeteanu GS** 2020. Unusual early recovery of a critical COVID-19 patient after administration of intravenous vitamin C. *American journal of case reports*. **21**: e925521-925521.
- Li W, Maeda N & Beck MA** 2006. Vitamin C deficiency increases the lung pathology of influenza Virus-Infected gulo-/- mice. *Journal of nutrition*. **136** (10): 2611-2616.
- Litwak JJ, Cho N, Nguyen HB, Moussavi K & Bushell T** 2019. Vitamin C, hydrocortisone, and thiamine for the treatment of severe sepsis and septic shock: a retrospective analysis of real-world application. *Journal of clinical medicine*. **8** (4): 478.
- Liu E, et al.** 2020a. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *New England journal of medicine*. **382** (6): 545-553.
- Liu F, Zhu Y, Zhang J, Li Y & Peng Z** 2020b. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. *BMJ open*. **10** (7): e039519.
- Marik PE** 2018. Vitamin C for the treatment of sepsis: the scientific rationale. *Pharmacology & therapeutics*. **189**: 63-70.
- Marik PE, Khangoora V, Rivera R, Hooper MH & Catravas J** 2017. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. **151** (6): 1229-1238.
- Masood H, et al.** 2019. Effect of intravenous vitamin C, thiamine, and hydrocortisone (the metabolic resuscitation protocol) on early weaning from vasopressors in patients with septic shock. A descriptive case series study. *Cureus*. **11** (6).
- Messina G, et al.** 2020. Functional role of dietary intervention to improve the outcome of COVID-19: a hypothesis of work. *International journal of molecular sciences*. **21** (9): 3104.
- Mikacenic C, et al.** 2018. Neutrophil extracellular traps (NETs) are increased in the alveolar spaces of patients with ventilator-associated pneumonia. *Critical care*. **22** (1): 1-8.
- Mikrova N, Riordan N & Casciari J** 2016. Modulation of cytokines in cancer patients by intravenous ascorbate therapy. *International*

- medical journal of experimental and clinical research.* **22**: 14.
- Mohammed BM, et al.** 2013. Vitamin C: a novel regulator of neutrophil extracellular trap formation. *Nutrients.* **5** (8): 3131-3150.
- Mousavi S, Bereswill S & Heimesaat MM** 2019. Immunomodulatory and antimicrobial effects of vitamin C. *European journal of microbiology and immunology.* **9** (3): 73-79.
- Nathens A, Neff M & Jurkovich G** 2003. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Nutrition in clinical practice.* **18** (3): 264-264.
- Nelson PJ, Pruitt RE, Henderson LL, Jenness R & Henderson LM** 1981. Effect of ascorbic acid deficiency on the in vivo synthesis of carnitine. *Biochimica et Biophysica Acta (BBA)-General Subjects.* **672** (1): 123-127.
- Noguchi N, et al.** 1997. 2, 3-Dihydro-5-hydroxy-2, 2-dipentyl-4, 6-di-tert-butylbenzofuran: design and evaluation as a novel radical-scavenging antioxidant against lipid peroxidation. *Archives of biochemistry and biophysics.* **342** (2): 236-243.
- O'Brien XM, Biron BM & Reichner JS** 2017. Consequences of extracellular trap formation in sepsis. *Current opinion in hematology.* **24** (1): 66.
- Peng Y, et al.** 2005. Ascorbic acid inhibits ROS production, NF- κ B activation and prevents ethanol-induced growth retardation and microencephaly. *Neuropharmacology.* **48** (3): 426-434.
- Provenzani A & Polidori P** 2020. Covid-19 and drug therapy, what we learned. *International journal of clinical pharmacy.* **42**: 833-836.
- Puskarich MA, Cornelius DC, Tharp J, Nandi U & Jones AE** 2016. Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation. *Journal of critical care.* **36**: 125-129.
- Rabby MII** 2020. Current drugs with potential for treatment of COVID-19: A literature review: Drugs for the treatment process of COVID-19. *Journal of pharmacy & pharmaceutical sciences.* **23**: 58-64.
- Rebouche CJ** 1991. Ascorbic acid and carnitine biosynthesis. *American journal of clinical nutrition.* **54** (6): 1147S-1152S.
- Rodrigues da Silva M, et al.** 2018. Beneficial effects of ascorbic acid to treat lung fibrosis induced by paraquat. *PLoS One.* **13** (11): e0205535.
- Sadaka F, et al.** 2020. Ascorbic acid, thiamine, and steroids in septic shock: propensity matched analysis. *Journal of intensive care medicine.* **35** (11): 1302-1306.
- Saffarzadeh M, et al.** 2012. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PloS one.* **7** (2): e32366.
- Sahebnasagh A, et al.** 2020. A perspective on erythropoietin as a potential adjuvant therapy for acute lung injury/acute respiratory distress syndrome in patients with covid-19. *Archives of medical research.* **51** (7): 631-635.
- Schmittinger CA, et al.** 2013. Histologic pathologies of the myocardium in septic shock: a prospective observational study. *Shock.* **39** (4): 329-335.
- Scholz SS, et al.** 2021. Mortality in septic patients treated with vitamin C: a systematic meta-analysis. *Critical care.* **25** (1): 1-10.
- Shi Y, et al.** 2020. COVID-19 infection: the perspectives on immune responses. *Cell death & differentiation.* **27** (5): 1451-1454.
- Shilotri PG** 1977. Glycolytic, hexose monophosphate shunt and bactericidal activities of leukocytes in ascorbic acid deficient guinea pigs. *Journal of nutrition.* **107** (8): 1507-1512.
- Smart L, et al.** 2018. Glycocalyx biomarker syndecan-1 is a stronger predictor of respiratory failure in patients with sepsis due to pneumonia, compared to endocan. *Journal of critical care.* **47**: 93-98.
- Syed AA, et al.** 2014. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of translational medicine.* **12** (1): 1-10.

- Tan SHS, Hong CC, Saha S, Murphy D & Hui JH** 2020. Medications in COVID-19 patients: summarizing the current literature from an orthopaedic perspective. *International orthopaedics*. **44**: 1599-1603.
- Thomas S, et al.** 2021. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. *JAMA network open*. **4** (2): e210369-e210369.
- Tripodskiadis F, et al.** 2009. The sympathetic nervous system in heart failure: physiology, pathophysiology, and clinical implications. *Journal of the American College of Cardiology*. **54** (19): 1747-1762.
- Truitt JD, et al.** 2019. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *Journal of the American medical association*. **322** (13): 1261-1270.
- Uchimido R, Schmidt EP & Shapiro NI** 2019. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Critical care*. **23** (1): 1-12.
- Vincent J-L** 2021. COVID-19: it's all about sepsis. *Future microbiology*. **16** (3): 131-133.
- Winter B, Fiskum G & Gallo L** 1995. Effects of L-carnitine on serum triglyceride and cytokine levels in rat models of cachexia and septic shock. *British journal of cancer*. **72** (5): 1173-1179.
- Zhang J, et al.** 2020a. High-dose vitamin C infusion for the treatment of critically ill COVID-19.
- Zhang J, et al.** 2021. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Annals of intensive care*. **11** (1): 1-12.
- Zhang W, et al.** 2020b. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clinical immunology*. **214**: 108393.