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EFFECTIVENESS OF HIGH-DOSE VITAMIN C IN PATIENTSWITH COVID-19

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ABSTRACT

Severe respiratory infections are characterized by elevated inflammation and generation of reactive oxygen species (ROS) which may lead to a decrease in antioxidants such as vitamin C and a higher requirement for the vitamin. Administration of intravenous vitamin C to patients with pneumonia and sepsis appears to decrease the severity of the disease and potentially improve survival rate. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes pneumonia, sepsis and acute respiratory distress syndrome (ARDS) in severe cases, and is referred to as coronavirus disease 2019 (COVID-19). Patients with COVID-19 infection also appearto have depleted vitamin C status and require additional supplementation of vitamin C during the acute phase of the disease. To date there have been 12 vitamin C and COVID-19 trials published, including five randomized controlled trials (RCTs) and seven retrospective cohort studies. The current level of evidence from the RCTs suggests that intravenous vitamin C intervention may improve oxygenation parameters, reduce inflammatory markers, decrease days in hospital and reduce mortality, particularly in the more severely ill patients. High doses of oral vitamin C supplementation may also improve the rate of recovery in less severe cases. No adverse events have been reported in published vitamin C clinical trials in COVID-19 patients. Upcoming findings from larger RCTs will provide additional evidence on vitamin supplementation in COVID-19 patients.

KEYWORDS: vitamin C; COVID-19; clinical trials; acute respiratory distress syndrome.

1. INTRODUCTION

Coronaviruses are single-stranded ribonucleic acid viruses comprising a lipid bilayer containing crown-like spikes (Latin, Corona = Crown) on their outer surface (Rabi et al., 2020). Infection with these viruses can affect both the upper and lower respiratory tract and can cause diseases ranging from a mild form, or common cold, to pneumonia (Cui et al., 2019). In early December 2019, there were reports of infections with pneumonia-like symptoms of unidentified causes in China (Zhu et al., 2020).

The infections were subsequently identified as being caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the resultant disease being named coronavirus disease (COVID-19) in February 2020 (Gorbalenya et al., 2020). Globally, as of August 2021, there have been over 200 million confirmed cases of COVID-19, including nearly 4.5 million deaths, reported (WHO, 2021). Initial data indicated that the majority of patients were aged over 40 years, and that the risk of death increased with age (Rabiet al., 2020).

Since then, numerous other risk factors have been identified, including specific underlying health conditions. Currently, there is a global research effort to try and identify therapies that may help in the treatment of COVID-19.

Vitamin C is an essential nutrient that has important roles in immune function, includingantioxidant, anti-inflammatory, antithrombotic, and immuno-modulatory func-tions (Carr et al., 2020; Holford et al., 2020).

Vitamin C deficiency, defined as a plasma concentrations of _11 _mol/L, is more common in the elderly, male gender, people with comorbidities, and low socioeconomic status (Carr and Rowe, 2020). These are also risk factors for COVID-19 infection. Severe respiratory infections, such as pneumonia, are common clinical conditions that lead to a high requirement for vitamin C, thus providing grounds for active vitamin C replacement in patients who suffer from severe respiratory infections (Hemilä et al., 2017).

Although a vitamin C intake of 200 mg daily in healthy

volunteers produces a saturating plasma concentration of 70 to 90 _mol/L (Levine et al., 1996; Levine et al., 2001), at least ten-fold higher doses (i.e., 2–3 g/day) are required to saturate the plasma of critically ill patients (Carr et al., 2017 ;De Grooth et al., 2018). Critically ill patients are defined as patients at high risk for actual or potential life-threatening injuries and illnesses, requiring at least organ support and are continuously monitored in the intensive care unit (ICU). Vitamin C is generally administered parenterally to critically ill patients as it provides significantly higher circulating concentrations than enteral vitamin C (Padayatty et al., 2004). Vitamin C administration in patients with pneumonia, sepsis and acute respiratory distress syndrome (ARDS) has shown potential benefits such as reducing duration of hospital and ICU stay and mortality (Holford et al., 2020). Pneumonia, sepsis and ARDS are common complications of patients with severe COVID-19 and in March 2020, the World Health Organization highlighted vitamin C as a potential adjunctive therapy with biologic plausibility for patients with critical COVID-19 (WHO, 2020).

This pragmatic review summarizes the current level of evidence available from published studies (randomized controlled trials [RCTs] and retrospective cohort studies) that have investigated enteral and parenteral vitamin C supplementation in patients with SARS-CoV2 infection and severe COVID-19.

2. Vitamin C Status in Patients with COVID-19

Significant evidence indicates that patients with severe respiratory infections have depleted vitamin C status, with the prevalence of deficiency increasing with the severity of the condition (Carr et al., 2020). The vitamin C status of patients with COVID-19 has been reported in several small observational studies table 1 (Xing et al.,2021; Pincemail et al., 2021) . Plasma concentrations of vitamin C in most of these patients were reported to be very low with 70–80% of the patients having hypovitaminosis C (plasma concentration <23 _mol/L) (Arvinte et al., 2020; Tomasa-Irriguible et al., 2021).

The low concentrations were despite patients receiving on average 124 mg/day vitamin C in their enteral or parenteral nutrition (Pincemail et al., 2021). Interestingly, markers of oxidative stress were elevated in the COVID-19 patients relative to controls and there was an inverse correlation between oxidative stress markers and vitamin C status in the patients (Muhammad et al.,2021).

Thus, vitamin C supplementation appears warranted in these patients to address their hypovitaminosis C and restore adequate plasma vitamin C status (Xing et al., 2021). It should be noted that short-term (i.e., 2–4 day) intervention with intravenous vitamin C may not be of sufficient duration to provide lasting benefit as 15–25% of patients can return to hypovitaminosis C status following cessation of intervention (De Grooth et al., 2018 ;Fowler et al.,2019).

Table 1. Vitamin C status in patients with COVID-19.

Population Location	Method	Findings
18 patients with ARDS 1Barcelona, Spain	Plasma HPLC-PDA 2	17 patients had <8µM vitamin C1 patient had 14 µM vitamin C
21 ICU 3 patients Thornton, Colorado, USA	Serum	Total cohort (n = 21) had 22µM vitamin C (45% were deficient, 70% were hypovitaminosis C)Survivors (n = 11) had 29 µM vitamin C Non-Survivors (n = 10) had 15 µM vitamin C
31 hospitalised patients 51 healthy controlsShanghai, China	Plasma	UHPLC-MS 4 6 patients (no IVC [5]) had 11 µM vitamin C 25 patients given 100 mg/kg/day IVC had 76 µM51 healthy controls had 52 µM vitamin C
50 symptomatic patients 21 healthy controlsJigwa, Nigeria	Serum Colourimetric	Patients had 19µM vitamin C Controls had 25 µM vitamin C
9 ICU patients with severepneumonia Liège, Belgium		Patients had 22 µM vitamin C(reference range: 35–86 _M)
67 patients with ARDSBarcelona, Spain	PlasmaHPLC	Mean vitamin C concentration was 8 _ 3 µM55 patients (82%) had values <23µM 12 patients (18%) had values <6 µM

1 ARDS: acute respiratory distress syndrome, 2 PDA: photo diode array, 3 ICU: intensive care unit, 4 UHPLC-MS: ultra-high-performance liquid chromatography-mass spectrometry, 5 IVC: intravenous vitamin C. Note: vitamin C concentrations <11 _M are considered deficient, and <23 _M are considered hypovitaminosis C.

3. The topicality of vitamin C to the COVID-19 pandemic

Vitamin C is deemed to have conducive effects in critically ill patients. It is a free radical scavenger that influences cellular immunity, anti-inflammatory properties, and vascular integrity, and acts as a cofactor in producing endogenous catecholamines (Wei et al.,

2020). COVID- 19 causes life-denunciatory respiratory diseases in humans like severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome(MERS) (Hou et al.,2020). The virulence mechanisms underlying COVID-19 outcomes are not fully understood yet(Lau et al., 2020).

Different cellular mechanisms such as dipeptidyl peptidase-4 receptor (DPP-4) binding, retinoic acidinducible gene-I-like receptors (RIG-I) and melanoma differentiation-associated 5 (MDA5) host-recognition, papain- like protease (PL-pro)-mediated replication, and breakdown of M- protein-mediated type-1 IFN (Interferon) initiation evasion have beenidentified in the closely linked COVID-MERS virus (Skariyachan et al., 2019).

Of them, DPP-4 has been shown to closely link with COVID- 19 in the case of the S1 domain of the spike glycoprotein, pointing out that it would be a primary intensive factor of COVID-19 infections (Vankadari and Wilce, 2020).

During COVID-19, an expansive and unrestrained release of pro- inflammatory cytokines or cytokine storm occurs that is also observed in MERS and SARS-CoV-1 (Zabetakis et al., 2020). Clinically, this cytokine storm induces systemic inflammation and respiratory inflammation and multiple organ failure (Zhang et al.,2020). Vitamin C supplementation has shown conducive effects in infections and sepsis. As severe COVID-19 may induce acute respiratory distress syndrome (ARDS) and sepsis, high doses of vitamin C supplementation may contribute to ameliorating inflammation in patients with COVID-19. In fact, vitamin C-deficient individuals are highly susceptible to systemic inflammation, and severe respiratory infections observed throughout the course of COVID-19 (Calder et al.,2020).

4. Evidence of antiviral action of vitamin C

Vitamin C supplementation has demonstrated a wide range of antiviral effects against several types of viral infections (Colunga Biancatelli et al., 2020). Decreased levels of vitamin C have been observed in different viral infections (Cheng, 2020) such as sepsis, sepsis- related acute respiratory disease syndrome (ARDS) (Fowler et al., 2019), and other critical conditions of illness Carr and Maggini,2017).In viral infections, vitamin C is crucial for destroying neutrophil (Anderson et al., 1990) accumulated within macrophages and is accountable for T cell maturation (Manning et al.,2013). This enhances phagocytosis and apoptosis (Carr and Maggini,2017). In several murine models, vitamin C has promoted survival from lethal infection (Colunga Biancatelli et al., 2020). Treatment with vitamin C (50 mg/kg) in the Venezuelan encephalitis virus-affected mice revealed 50% mortality of the controls with less nitric oxide (NO) content and lipid peroxidation products. The treatment group exhibits an increased survival rate (50%) in comparison with untreated infected mice (0%) (Valero et al.,2015).

A previous study noted that mice infected with the influenza virus could not yield vitamin C, and mice not receiving vitamin C supplementation showed higher lung pathology scores (Li et al.,2006).

Vitamin C decreased mortality rate in dose-dependent fashion (100%, 80%, and 50% at 0, 125, and 250 mg/kg/ day) in H1N1 (hemagglutinin type 1 and neuraminidase type 1) viral-induced pneumonia (Cai et al., 2015). Mice infected with the rabies virus demonstrated nearly 50% mortality while treating intramuscular 100 mg/kg vitamin C daily in comparison with untreated infected mice. Vitamin C supplementation (300 mg/day) in influenza induced pneumonia is protected from severe infection and reduced the duration of hospital stays (Colunga Biancatelli et al., 2020).

Another study in 133 patients demonstrated that the administration of vitamin C promotes the protection (odds ratio 0.25) from herpes simplex keratitis (Kim et al.,2018). Some current studies reported vitamin C as a potential intervention against the coronavirus (Zhang et al.,2020). Hence, it is hypothesized that vitamin C supplementation may reduce the severity of the current COVID-19 pandemic.

5. Mechanism of vitamin C against infections as well as COVID-19

The key reason for severe lung injury in COVID-19 patients is theoxidative stress and excessive free radicals generated from thedysfunctional immune system to kill the virus but end up wounding the patient instead. Vitamin C can reduce oxidative damage and neutralize these free radicals in the lungs. When there is an imbalance between oxidants and antioxidants, body organs' damage occurs and progresses patients to severe disease (Askari et al.,2012).

We can improve the antioxidant status by administering sufficient vitamin C. The white blood cells (immune cells) are highly enriched with vitamin C, implying these immune cells' functional roles. Vitamin C influences phagocytes' functions, replicating viruses, production of interferon, and maturation of T-lymphocytes. Vitamin C also acts as a safeguard of these immune cells against oxidative damage when they clear out viruses from the body (figure 1). Based on these knowledge, many hospitals in China, New York, and Shanghai have already started administrating intravenous vitamin C to manage the COVID-19 infections. However, anecdotal evidence of positive response from these hospitals suggests promising vitamin C results against COVID-19 (The Financial Express,2020).

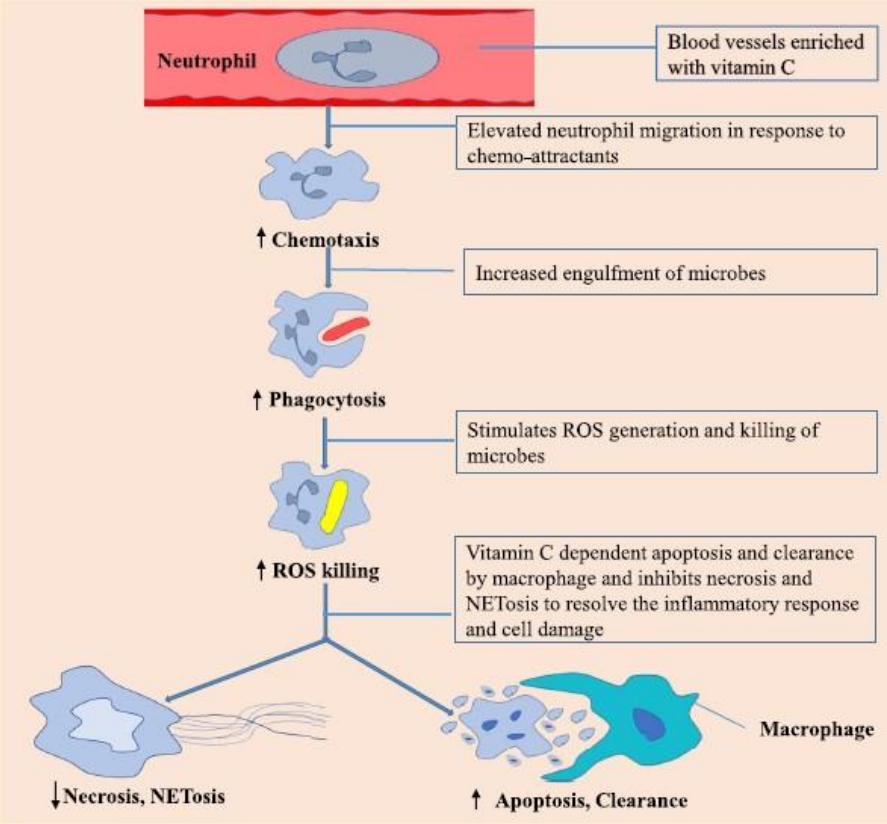

Figure 1: The role of vitamin C in immune cell functions.

6. Clinical efficacy of vitamin C in critically ill patients without COVID-19

More than hundreds of animal studies have demonstrated that a few grams of vitamin C's daily dose may prevent infections (Hemilä, 2017). A pilot study on 24 critically ill patients with sepsis revealed that intravenous (IV) vitamin C administration reduces the Sequential Organ Failure Assessment (SOFA) scores and levels of proinflammatory markers significantly over the 4- day study period in patients who received 50 and 200 mg/kg per day vitamin C in comparison with patients who received placebo (Fowler et al., 2014).

Interestingly, a randomized control trial did not change levels of inflammatory markers or SOFA scores in sepsis-induced ARDS patients (n = 167) after IV vitamin C 200 mg/kg per day administration for 4 days.However, the hospital stays and the mortality rate decreased significantly in the treatment group in 28 days (p = 0.03) (Fowler et al.,2019). Several controlled studies point out that the combination therapy of vitamin C, hydrocortisone, and thiamine had auspicious effects in sepsis or severe pneumonia patients (Marik et al.,2017).

Again, a randomized control trial study in patients with septic shock compared the outcomes of the combination therapy of vitamin C (6 g per day), hydrocortisone (200 mg per day), and thiamine (400 mg per day) to hydrocortisone alone. The study's findings showed that combination therapy did not affect the duration of a shock though significantly improved the SOFA score in treatment groups (p = 0.03) (Fujii et al.,2020).

These clinical findings suggested that vitamin C may play a significant role in the management of COVID-19 infection. 8 Clinical data on vitamin C in critically ill patients with COVID-19 A series of clinical trials related to COVID-19 have been launched or announced from the very beginning of COVID-19 to evaluate the therapeutic benefit of vitamin C alone or in combination therapy with one or more substances (e.g., zinc, vitamin D, hydroxychloroquine, and azithromycin) (Clinical Trials,2020). Randomized controlled trials are currently registered in the National Institutes of Health Clinical Trials (NIHCT)/National Clinical Trial (NCT) to examine monotherapy for severe COVID-19 treatment (to treat, or prevent COVID-19 in combination with hydroxychloroquine and other supplements (Adams et al.,2020).

The dosing of vitamin C varies widely in these trials, ranging from 250 to 500 mg orally to 24 g IV daily. Researchers from China have noted that they have successfully treated the moderate to severe COVID-19 patients (n > 50) with large doses of IV vitamin C (10,000–20,000 mg/day). The findings are no incidence of death and a shorter mean hospital stay than untreated COVID-19 patients (Carr et al.,2017).

Besides, the Shanghai Medical Association has recently endorsed the use of high-dose vitamin C for the management and treatment of hospitalized patients with

COVID-19 (Healthline, 2020). A recent review points out that higher doses of IV vitamin C may be required to deplete cytokine storms in ARDS (Boretti and Banik,2020).

High doses of vitamin C are deemed to be administered IV route as they are thinly tolerated orally. However, bowel tolerance for vitamin C is elevated in many patients with the severity of illness. So, some patients may tolerate oral doses up to 200 g/day (Cathcart, 1981).

7. High-dose vitamin C administration in patients with COVID-19

Observational studies have indicated that patients with COVID-19 have high rates of hypovitaminosis C and vitamin C deficiency, which are comparable to patients with sepsis and septic shock (Carr,2020). Previous studies of high-dose vitamin C administration in patients with sepsis and ARDS have shown reduced duration of ICU and hospital stay as well as decreased mortality (Fowle et al., 2019; Hemilä and Chalker,2020).

Based on the evidence from preliminary RCTs and retrospective cohort studies, vitamin C appears to also support positive outcomes in COVID- 19 in both inpatient and outpatient settings, leading to a beneficial effect in patients with moderate symptoms, as well as patients with pneumonia, sepsis and ARDS. Intervention with vitamin C resulted in improved oxygenation and pulmonary function, reduced inflammatory markers and temperature, decreased days in ICU and hospital, and decreased mortality, particularly in the more severely ill patients. Oral supplementation in mild to moderate cases also increased the rate of recovery when taken in high-doses.

Overall, the intervention studies to date have a number of limitations such as small sample sizes and early termination of some studies, differences in vitamin C dose and duration and lack of optimization of these, lack ofplacebo controls, and no pre-and post intervention plasma vitamin Cconcentrations. However, living meta-analysis of the studies as they are published is supporting the premise that high-dose IVC can improve the complications associated with COVID-19 and potentially decrease mortality (Vollbracht and Kraft, 2021). Notably, there have been no adverse events reported in the published trials to date.

DISCUSSION

Until the time of this study, no definite treatment option has been suggested and cleared for COVID-19. While this pandemic is still responsible for death of above two million people and infection of many more, search for better treatment options should never be delayed (World Health Organization;2020). Vitamin C is an essential water-soluble nutrient that has important roles in our body, especially in immune cell functions (Polidori et al., 2004). Studies report that vitamin C can be effective in treatment of bacterial and viral infection (Wu et al., 2020). These studies showed vitamin C weakly inhibits the multiplication of viruses such as influenza type A, Herpes simplex virus type 1 (HSV-1) and poliovirus type 1. A clinical study showed the effect of IV vitamin C therapy on reduction of IgG and IgM antibody levels in EBV infection (Mikirova and Hunninghake, 2014). There is also a report of a case of enterovirus/rhinovirus-induced ARDS where the infusion of HDIVC was associated with rapid resolution of lung injury (Fowler et al.,2020) Marik et al. also suggested MATH + protocol for COVID-19 patients, including methylprednisolone, ascorbic acid, thiamine, heparin, and supplemental oxygen. They suggest using vitamin C 3 g IV q 6 hourly for at least 7 days or until transferred out of ICU (Marik et al.,2020). There are also other large randomized controlled trials (RCTs) using different doses of vitamin C.

Another large study is underway in Italy recruiting 500 patients in whom use of 10 g vitamin C is being tested. [NCT04323514] Although the results of these trials will also help our understanding of the preferred dose of vitamin C in COVID-19 patients, the available results point to the fact that higher doses can also be safe and effective (compared to the six g daily dose used in this study).

Another important topic is the length of vitamin C administration. Some studies suggest better outcome by administering vitamin C for longer duration, i.e., for at least 7 days (Marik et al.,2020).

However, a recent meta-analysis and systematic review of 17 studies reporting the effect of vitamin C supplementation in COVID-19 concluded that the best duration for administering vitamin C is over 3–4 days, with lower efficacy if used less than 3 days or more than 5 days (Scholz et al., 2020).

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