

Review article

CLINICAL EVIDENCES ON THE SAFETY AND EFFICACY OF VITAMIN C IN COVID-19: AN UPDATED REVIEW

James H. Zothantluanga* and Dipak Chetia

Department of Pharmaceutical Sciences, Faculty of Science and Engineering,
Dibrugarh University, Dibrugarh, Assam, India

Abstract

Background: *Coronavirus disease 2019 (COVID-19) originates from Wuhan, Hubei, China. The causative agent of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 18 November 2020, COVID-19 had infected more than 55.9 million with 1.3 million deaths. As the therapeutic preference against SARS-CoV-2 remains undefined, vitamin C appears to be a promising therapeutic agent. However, its efficacy and safety in COVID-19 remains vague and needs further scrutiny.* **Objective:** *This review aims to identify relevant clinical evidences and provide the current knowledge on the therapeutic efficacy and safety of vitamin C in COVID-19.* **Methods:** *From the database 'PubMed', 92 articles were identified using the keywords 'COVID-19' and 'Vitamin C'. However, only 23 articles containing relevant studies in context with the aim of the paper were selected.* **Results and Discussion:** *Demographic studies revealed that vitamin C was generally given to the majority of COVID-19 patients. Evidence from clinical trials and clinical studies suggested that vitamin C might be an effective therapeutic agent for COVID-19. Worryingly, critically ill elderly COVID-19 patients with co-morbidities like diabetes and hypertension failed to respond to all types of treatments including vitamin C. Moreover, some of the case reports revealed that vitamin C was responsible for the formation of calcium oxalate crystals in the kidney, a condition called oxalate nephropathy.* **Conclusion:** *Although vitamin C offers immunomodulation, protection from oxidative stress, prevention of cytokine storm and antiviral activity, no conclusive statement could be made on the efficacy and safety of vitamin C in the context of COVID-19. Thus, this prompts the need for further studies.*

Keywords: COVID-19; Efficacy; SARS-CoV-2; Safety; Vitamin C

*E-mail: jameshzta@gmail.com

Introduction

Coronavirus disease 2019 (COVID-19) is the term given for the pneumonia-like respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Figure 1). It originates from Wuhan, Hubei, China wherein an unidentified pneumonia-like disease was reported since 8 December 2019. On 30 January 2020, a global health emergency was declared by the World Health Organization (WHO). On 12 March 2020, COVID-19 was declared as a pandemic by the WHO [1]. As of 18 November 2020, COVID-19 had infected more than 55.9 million people and resulted in the death of more than 1.3 million people [2].

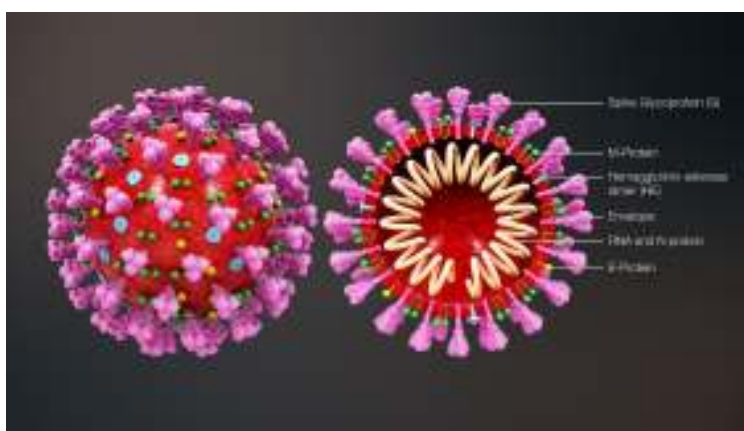


Figure 1: 3D cross-sectional structure of coronavirus

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The level of vitamin C (Figure 2) in critically ill patients, including those with multiple organ failure and sepsis, was reported to be very low. Furthermore, studies had demonstrated that the requirement of vitamin C is higher for critically ill patients [3]. Interestingly, vitamin C was postulated to have a beneficial impact against CoV during the SARS-CoV outbreak in 2003 [4]. Moreover, a study found that vitamin C was labelled as an immune booster to prevent COVID-19 on many internet webpages [5].

As people can be easily misinformed, addressing the safety and efficacy of vitamin C in the context of COVID-19 seems to be an obligatory duty for researchers. Thus, as the therapeutic preference against SARS-CoV-2 remains undefined, the safety and efficacy of vitamin C in COVID-19

requires an urgent appraisal. Thus, this review aims to identify relevant clinical studies and provide the current knowledge on the therapeutic efficacy and safety of vitamin C in COVID-19.

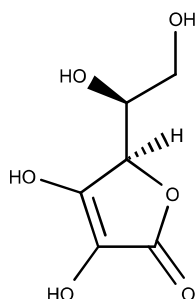


Figure 2: Structure of vitamin C

An online survey of relevant papers was carried out on ‘PubMed’. Keywords such as ‘COVID-19’ and ‘Vitamin C’ were used in combination to aid in the search for relevant papers. As of 9 November 2020, the search resulted in the identification of a total of 92 articles. However, a total of only 23 papers were selected for review. The methodology for the selection of paper is given in Figure 3. The clinical trial website of the National Institute of Health was also accessed. However, a limitation to the present study lies in the utilization of a single database only.

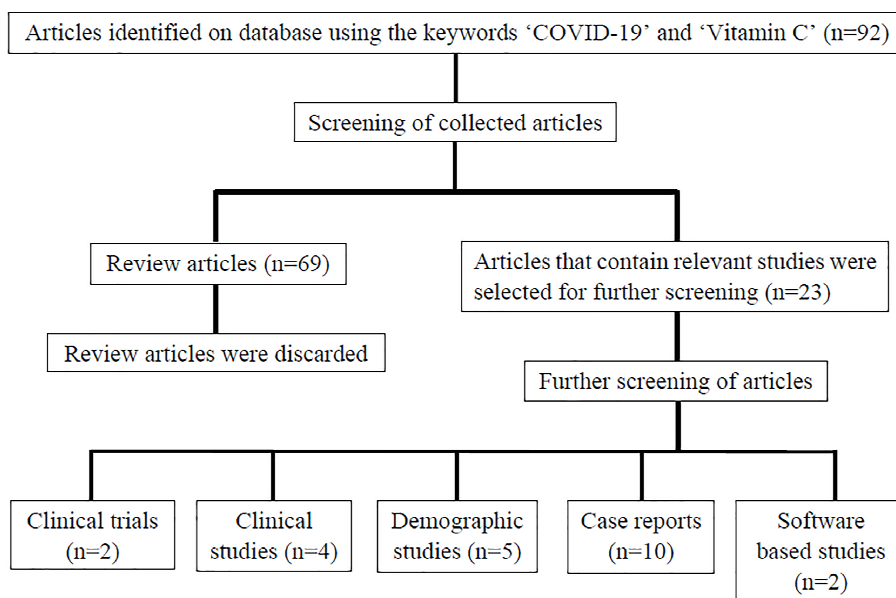


Figure 3: Flow chart depicting the methodology used for the selection of paper

Clinical evidence of vitamin C in treating COVID-19

Clinical trials

Burton *et al.* (2020) had identified a combination of drugs that is to be administered by spraying [6]. The intervention which is branded as ArtemiC consists of vitamin C (60 mg/ml), curcumin (20 mg/ml), artemisinin (6 mg/ml) and frankincense (15 mg/ml) in micellar formulation [6,7]. ArtemiC is currently undergoing phase 2 of the clinical trials (NCT04382040) [7].

A clinical trial (NCT04370288) was conducted on 5 critically ill COVID-19 patients that were admitted to the intensive care unit (ICU). As a last therapeutic option for critically ill patients that were admitted to the ICU, a combination of vitamin C, methylene blue and N-acetyl cysteine (VCMANC) was given. Though the dosing frequency and route of administration differ among the 5 patients, it was reported that vitamin C was given at a dose of 1500 mg/kg body weight for each patient. Before being treated with VCMANC, the patients received drugs such as azithromycin, hydroxychloroquine, heparin, dexamethasone, ribavirin, lopinavir, ritonavir and hydrocortisone. Among the 5 patients, 4 patients responded well to the VCMANC treatment and were all discharged from the ICU. However, 1 patient succumbed to COVID-19 [8].

Clinical studies

Cheng (2020) stated that oxidative stress was reported to occur in COVID-19 patients. It was also stated that the cytokine storm could induce oxidative stress in COVID-19 patients. Auspiciously, clinical studies had demonstrated that oxidative stress may be ameliorated by treating patients with high doses of antioxidants like vitamin C. Moreover, vitamin C reduced the risk of viral infection and oxidative stress due to acute lung injury. In China, a total of moderate to severe 50 COVID-19 patients were reported to be successfully treated with high doses (10 g to 20 g per day) of vitamin C by intravenous route [9].

Hiedra *et al.* (2020) conducted a single-centred observational study on the use of intravenous vitamin C in 17 COVID-19 patients. In these patients, hypertension and diabetes mellitus were the most prevalent comorbidity. In addition to vitamin C, other drugs like tocilizumab, hydroxychloroquine and prednisolone were also administered to these patients. It was observed that

the inflammatory markers like ferritin and D-dimer were significantly reduced in these patients. Moreover, the requirements for the fraction of inspired oxygen (FiO₂) was also reduced in these patients. However, the authors concluded that further studies are required to justify the safety and efficacy of vitamin C for the treatment of COVID-19 [10].

A study found that the levels of vitamin C in the blood samples of 18 patients were very low. Except for 1 patient that had 2.4 mg/L vitamin C level in blood samples, 17 patients had an undetectable level of vitamin C [11]. Another study found that serum levels of vitamin C in 21 (male=15; female=5) critically ill COVID-19 patients were low. Out of the 21 patients, only 11 survived. The authors of the study suggested that old age and low levels of vitamin C might be a co-dependent risk factor [12].

Demographic studies

Shady *et al.* (2020) studied the demographics of a total of 371 (male=249; female=122) patients in New York, United States of America (USA). Hypertension (n=182) and diabetes (n=156) were the most prevalent comorbidities among patients. The majority of the patients were treated with vitamin C, zinc, azithromycin and hydroxychloroquine [13]. However, the study did not discuss the dosing regimen and the route of administration along with the number of patients that are receiving vitamin C treatment.

Capone *et al.* (2020) studied the demographics of a total of 102 (male=55; female=47) critically ill COVID-19 patients at the Safety-net hospital in Brooklyn, New York, USA. Diabetes (n=50) and hypertension (n=61) were the most prevalent comorbidities among patients. Vitamin C and zinc were received by a total of 73 patients [14]. However, the study concluded that co-administration of vitamin C and zinc had no impact on the survival of the patients.

Liu *et al.* (2020) studied the demographics of foreign-imported COVID-19 cases in on 58 COVID-19 patients in Shanghai, China. Hypertension (n=7) and diabetes (n=4) were the most prevalent comorbidities among patients. Vitamin C was administered to 40 patients [15]. However, the study did not discuss the dosing regimen, the route of administration and the status of the patients taking vitamin C treatment.

Li *et al.* (2020) studied the clinical features of COVID-19 patients with and without cardiovascular disease (CVD). Out of a total of 596 COVID-19 patients, a total of 215 COVID-19 patients had CVD. Among the COVID-19 patients with CVD, 23.3% (n=50) received vitamin C therapy while 11.8% (n=45) of the COVID-19 patients without CVD also received vitamin C therapy. Thus, out of the 596 COVID-19 patients, a total of 15.9% (n=95) of COVID-19 patients received vitamin C therapy. From the study, it was also observed vitamin C treatment was mainly given to those patients with the decreased partial pressure of oxygen and FiO₂ [16].

Zhao *et al.* (2020) conducted an online questionnaire-based cross-sectional survey to study the diversity in diet among the Chinese residents during the ongoing COVID-19 pandemic. Interestingly, the study found that out of a total of 1938 participants, 37.7% (n=722) consumed dietary supplements that included vitamin C as a means to cope with the current pandemic. Among the 722 participants, 18.2% (n=122) of the participants intentionally consumed vitamin C to cope with COVID-19 [17].

Case reports

A 29-year-old male was presented to the hospital with dyspnoea, cough, fatigue, myalgia and was subsequently confirmed for COVID-19. The patient had a history of asthma, obesity and the use of tobacco products. At the hospital, the patient was treated with vitamin C and other drugs such as tocilizumab, enoxaparin, diuretics, nitric oxides were also included in his treatment regimen. However, the patient underwent septic shock, developed a cytokine storm and deep vein thrombosis. After being treated for 20 days at the hospital, the patient succumbed to COVID-19 [Deliwala et al 2020].

A 77-year-old female with a history of hypertension and hyperlipidaemia was diagnosed with COVID-19. At the time of admission to the hospital, the patient had a severe fever with worsening cough and respiratory distress. At the hospital, the patient was treated with intravenous vitamin C along with ceftriaxone, azithromycin, hydroxychloroquine, tocilizumab and remdesivir. However, the patient continued to remain critically ill and passed away [19].

Zhang *et al.* (2020) reported three cases of COVID-19 in male children (Case 1 = age 9; Case 2 = age 6; Case 3 = age 8). Case 1 and 3 were reported to have digestive tract symptoms, runny nose, nasal obstruction and fever. Case 2 had wheezing, expectoration and cough. Vitamin C, interferon

atomization and oral Chinese medicine were given for all three cases. Also, case 1 received ceftriaxone while case 2 received ribavirin. All three children made a successful recovery. Although negative results were obtained from throat swab samples, their stool samples tested positive for SARS-CoV-2 even after 10 days. Thus, the study also suggested the possibility of faecal-oral transmission of COVID-19 [20].

A 62-year-old female tested positive for COVID-19 based on an antibody test (IgG antibody specific for SARS-CoV-2). Cephalexin, moxifloxacin, acetaminophen and oseltamivir treatments did not yield fruitful results. As the prescribed drugs started to cause adverse effects, the patient decided to take 200 mg of vitamin C three times a day along with diammonium glycyrrhizinate. A combination of vitamin C and diammonium glycyrrhizinate was able to resolve clinical features like fever, shortness of breath, vomiting, dry cough, nausea, back pain and fatigue [21].

A 34-year-old man tested positive for SARS-CoV-2 and showed clinical features like fever, dry cough, fatigue and poor appetite. The patient had no underlying health-related co-morbidities. In addition to the administration of 3 g of vitamin C four times per day, the patient was also treated with oseltamivir, moxifloxacin, piperacillin sodium tazobactam and interferon α -2a. The patient stayed at the hospital for 15 days out of which vitamin C therapy lasted for 13 days. The symptoms subsided and the patient was discharged from the hospital [22].

A 64-year-old male with a history of diabetes mellitus, hypertension, chronic kidney disease stage III was diagnosed with COVID-19. The patient was also currently on highly active antiretroviral therapy for the human immunodeficiency virus. The patient had shortness of breath and fever at the time of admission to the hospital. The patient was given intravenous vitamin C, zinc and solumedrol. The total dose of vitamin C from day 2 till day 9 at the hospital was 84 g. The patient's condition was complicated with acute oxalate nephropathy which is a condition in which there is a deposition of calcium oxalate in renal tubules. It was suspected that high doses of intravenous vitamin C were the etiological agent for the formation of calcium oxalate crystals. Moreover, the authors stated that other drugs were not responsible for the onset of acute oxalate nephropathy [23].

A 50-year-old man that tested positive for SARS-CoV-2 had no history of kidney problem. Even at the time of admission to the hospital, the kidney function test revealed normal results. To prevent sepsis, the patient received 50 mg of vitamin C through the intravenous route four times a day. The patient was also treated with drugs such as hydroxychloroquine, lopinavir, ritonavir, azithromycin and tocilizumab. However, with the onset of sepsis, it was observed that the patient had developed acute kidney injury. Subsequently, the presence of calcium oxalate crystals in the kidney was confirmed using light microscopy, scanning electron microscopy and energy-dispersive X-ray spectrometry. The authors suggested that although there could be other contributing factors, vitamin C was mainly responsible for inducing oxalate nephropathy in the patient [24].

A 71-year-old man that tested positive for SARS-CoV-2 had no history of kidney problem. However, the patient had a history of type 2 diabetes mellitus, arterial hypertension, hypercholesterolemia and mild liver steatosis. At the time of admission to the hospital, the kidney function of the patient was normal. However, the patient had clinical features like diarrhea, fever and worsening neurologic status. The patient received vitamin C through the intravenous route at a dose of 50 mg/kg body weight four times a day. The patient was also treated with hydroxychloroquine, darunavir, cobicistat, steroids, azithromycin, piperacillin/tazobactam, linezolid, meropenem, ceftriaxone, daptomycin, and oxacillin. From day 8, the patient developed kidney dysfunction that worsened to the point where hemodiafiltration and haemodialysis interventions were required. Even after the patient had negative results for SARS-CoV-2, the kidney dysfunction persists. Subsequently, the presence of calcium oxalate crystals was revealed by light microscopy, scanning electron microscopy and energy-dispersive X-ray spectrometry. The authors suggested that although there could be other contributing factors, vitamin C was responsible for inducing oxalate nephropathy in the patient [24].

A 57-year-old woman with a history of fever, cough, headache and rhinorrhoea was confirmed for COVID-19. A 58-year-old man with a history of anosmia and fever that later developed respiratory distress and productive cough upon admission to the hospital was also confirmed for COVID-19. Both patients were treated with vitamin C at a dose of 3 g per day along with other drugs such as azithromycin, dexamethasone, hydroxychloroquine,

diuretics, zinc and enoxaparin. The 57-year-old woman developed high blood pressure (140/90 mm Hg), tachycardia, other complications and invasive mechanical ventilation were required to stabilize that patient. The 58-year-old man showed signs of alveolar pulmonary edema and was found to have a capillary leak syndrome. However, both patients recovered from COVID-19 [25].

A 74-year-old man with a history of prostate cancer, hyperlipidaemia and hypertension was confirmed for COVID-19. The patient had clinical features such as progressively worsening shortness of breath, non-reproductive cough and fevers. The patient developed acute respiratory distress syndrome even after treatment with azithromycin and hydroxychloroquine. Moreover, after being treated with tocilizumab, ribavirin, lopinavir and ritonavir, the patient's condition was further complicated with cytokine release inflammatory syndrome, acute renal failure, corynebacterium pneumonia and septic shock. Auspiciously, the patient showed signs of improvement after receiving treatment of vitamin C at a dose of 1500 mg every 8 hours along with tocilizumab, thiamine and appropriate antibiotics. On the 15th day of hospitalization, the patient developed methemoglobinemia. However, the patient made a successful recovery [26].

A 74-year-old woman was initially admitted to a hospital for a medical reason other than COVID-19. However, the patient later tested positive for SARS-CoV-2. The patient displayed clinical features like shortness of breath, dry cough, fever and was later additionally burdened with fatigue and diarrhea. It was observed that the patient had worsening respiratory symptoms. The patient was treated with oral vitamin C at a dose of 1 g per day along with cefepime, levofloxacin, hydroxychloroquine, azithromycin and zinc sulfate. Despite the treatments given, the patient's condition worsened. Therefore, norepinephrine was given to ameliorate septic shock and colchicine was given to ameliorate cytokine storm. Subsequently, a high dose (11 g per day) of intravenous vitamin C was administered to the patient for 10 days. The patient made a successful recovery after receiving a high dose of vitamin C [27].

Software-based studies

A systemic biological study suggested that a combination of vitamin C, curcumin and glycyrrhizic acid might be beneficial to regulate the immune

response in COVID-19 patients. It further stated that the combination might be able to prevent the onset of a cytokine storm by inhibiting the excessive inflammatory response. However, the study concluded with the recommendation for further *in vitro* / *in vivo* studies [28]. Based on their bioinformatics study, Li *et al.* (2020) also concluded that a combination of vitamin C and glycyrrhizic acid was able to elevate immunity, suppress inflammatory stress and activate the T cell receptor signalling pathway that seems to be beneficial in the context of COVID-19 [29].

Discussion

From the available evidence, it can be observed that there are on-going clinical trials as well as completed clinical trials for vitamin C [6,8]. Auspiciously, more than 30 clinical trials are underway to evaluate the efficacy as well as safety of vitamin C for the treatment of COVID-19 patients [30].

Many demographic studies revealed that vitamin C was administered to the majority of COVID-19 patients [13–17]. The demographic studies included in this review revealed that vitamin C was included in many of the treatment regimens for COVID-19 patients. However, these demographic studies did not disclose any evidence on the efficacy or safety of vitamin C in treating COVID-19.

According to some of the clinical studies, high doses of vitamin C administered through either intravenous route or oral route also seems beneficial for COVID-19 patients [9,10]. Interestingly, other studies had also found that critically ill COVID-19 patients had low levels of vitamin C [12]. Previously, it was also reported that the levels of vitamin C in critically ill patients with sepsis or multi-organ failure were very low [3]. Thus, correlating the low levels of vitamin C in critically ill COVID-19 patients with the studies that report the beneficial effect of high doses of vitamin C for COVID-19 patients, it seems that high doses of vitamin C might offer an effective treatment regimen for COVID-19.

Some of the case reports included in this study suggested that vitamin C was able to gradually improve the condition of moderate to severe COVID-19 patients [20–22, 25–27]. Previously, vitamin C was reported to stimulate the immune system, prevent cellular damage due to oxidative stress, prevents cytokine storm and increases the production of B- and T- cells [4].

Moreover, the antiviral activity of vitamin C against the influenza virus had also been reported [31]. Considering the previously reported studies on vitamin C along with a few of the clinical studies and case reports included in this study, it can be assumed that vitamin C seems to be effective in COVID-19.

However, some of the case reports that are included in this study concluded that vitamin C was the etiological agent for inducing oxalate nephropathy in some COVID-19 patients, even in those patients with no history of kidney problems [23,24]. Worryingly, it was already reported that vitamin C was able to increase the formation of calcium oxalate crystals in the kidneys [32]. Generally, the use of a drug is considered if the positive effect outweighs the adverse effect [33]. However, based on the evidences available from the case reports, it might not be logical to administer high doses of vitamin C in all the COVID-19 patients.

Conclusion

From one viewpoint, vitamin C looks promising as an effective therapeutic agent for COVID-19. On the other hand, there are safety concerns that cannot be overlooked. Moreover, critically ill elderly COVID-19 patients with co-morbidities like diabetes and hypertension failed to respond to all types of treatments including vitamin C. We know that vitamin C offers immunomodulation, protection from oxidative stress, prevention of cytokine storm and antiviral activity. However, in the context of COVID-19, the evidences for the efficacy and safety of vitamin C seems to remain ambiguous. Thus, this prompts the need for further studies.

Conflict of Interest: The authors declare no conflict of interest.

Funding: Nil

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How to cite this article:

Zothantluanga JH, Chetia D. Clinical evidences on the safety and efficacy of vitamin C in COVID-19: An updated review, *Curr Trends Pharm Res*, 2020; 7 (2): 40-54.