Journal of Global Antimicrobial Resistance 23 (2020) 256–262

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection

Ba X. Hoang[a], Graeme Shaw[b], Willian Fang[c], Bo Han[a,*]

[a] Nimni-Cordoba Tissue Engineering and Drug Discovery Laboratory, Department of Surgery, University of Southern California, Los Angeles, California, USA
[b] Integrative Medical Associates, Foster City, California, USA
[c] Western University of Health Sciences, Pomona, California, USA

ARTICLE INFO

Article history:
Received 21 March 2020
Received in revised form 9 September 2020
Accepted 24 September 2020
Available online 13 October 2020

Keywords:
Coronavirus

ABSTRACT

Coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses increase oxidative stress in the body leading to cellular and tissue damage. To combat this, administration of high-dose vitamin C (ascorbic acid or ascorbate), in addition to standard conventional supportive treatments, has been shown to be a safe and effective therapy for severe cases of respiratory viral infection. Morbidity, mortality, infectiveness and spread of infectious diseases are dependent on the host–pathogen relationship. Given the lack of effective and safe antiviral drugs for coronaviruses, there should be more attention in supporting host immune defence, cytoprotection and immunoregulation. Implementation of high-dose vitamin C therapy could dramatically reduce the need for high doses of corticosteroids, antibacterials and antiviral drugs that may be immunosuppressive, adrenal depressive and toxic, complicating the disease course. In order to effectively fight the novel SARS-CoV-2 virus, medical professionals should explore readily available pharmaceutical and nutritional therapeutic agents with proven antioxidant, anti-inflammatory and immunosupportive properties. Supplemental vitamin C may also provide additional benefits for the prevention of viral infections, shorten the disease course and lessen complications of the disease.

Contents

Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection
Oxidative stress
Vitamin C
Ascorbic acid
Viral pneumonia

1. Introduction

Most cases of human coronavirus infection are mild and patients usually recover without complications or treatment. However, the two recent coronavirus epidemics, namely severe

* Corresponding author. Present address: Departments of Surgery and Biomedical Engineering, 1333 San Pablo St., BME-302, Los Angeles, CA 90033, USA. Tel.: +1 323 442 2242.
E-mail address: bohan@usc.edu (B. Han).

http://dx.doi.org/10.1016/j.jgar.2020.09.025
2213-7165/

acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have affected more than 10 000 people with mortality rates of 10% for SARS-CoV [1] and 37% for MERS-CoV [2,3]. A new respiratory illness, coronavirus disease 2019 (COVID-19), is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is genetically similar to SARS-CoV/MERS-CoV but is significantly more infective. In the period between the discovery of the SARS-CoV-2 virus in December 2019 and the time that this article was under revision in June 2020, the World Health Organization (WHO) reported a total of more than 10.5 million confirmed SARS-CoV-2 infections, including more than 512 000 deaths [4]. As the global case number of SARS-CoV-2 infections keeps rising, health experts are focused on finding a solution with fast-track vaccine and antiviral drug development. Using knowledge from the SARS-CoV and MERS CoV vaccine development path, several research groups have been able to start development of a SARS-CoV-2 vaccine within a few weeks of the initial outbreak. However, there is no evidence that this strategy would be timely or successful in combatting the SARS-CoV-2 epidemic. Despite decades of efforts, there are still no vaccines against viruses that kill tens of millions of people every year such as human immunodeficiency virus (HIV) and respiratory syncytial virus [5]. Therefore, we should rigorously explore alternatives for fighting COVID-19.

2. Clinical manifestations

Medical doctors have published several clinical and observational studies documenting the clinical features and outcomes of SARS-CoV-2 infection. In a retrospective observational study of 710 patients with SARS-CoV-2 pneumonia, of 52 critically ill patients enrolled, 98% had a fever, 77% had a cough and 63.5% had dyspnoea. Moreover, 32 patients (61.5%) died after 28 days and the median duration from ICU admission to death was 7 days [6]. Another study of 41 admitted hospital patients with laboratory-confirmed SARS-CoV-2 infection reported that all 41 patients exhibited pneumonia and had complications, including acute respiratory distress syndrome (ARDS) (29%), acute cardiac injury (12%) and secondary infection (10%). Moreover, 13 patients (32%) were admitted to the intensive care unit (ICU) and 6 patients (15%) died after intensive treatment [7]. Wang et al. reported the clinical characteristics of 138 confirmed SARS-CoV-2 cases and showed a 26% ICU admission rate and a 4.3% mortality rate [8]. Among the patients admitted to the ICU, 11.1% received high-flow oxygen, 47.2% received invasive ventilation and 41.7% received non-invasive ventilation, suggesting that patients in the ICU could not breathe spontaneously. Lastly, in a separate report of 99 confirmed cases of SARS-CoV-2 pneumonia, Chen et al. found that 17 patients (17%) developed ARDS that led to 11 patients (11%) quickly worsening in a short period and dying of multiple organ failure [9]. This preliminary clinical evidence demonstrates that considerable uncertainties are present in terms of prognosis and mortality rate. Additional studies are needed to confirm and refine the details of COVID-19. Yet these early observations still show that COVID-19 is a dangerous illness with a poor clinical prognosis.

3. Current therapeutics

Unfortunately, there is no vaccine or antiviral treatment approved to treat human SARS-CoV-2. Therapeutic options are being explored in vitro and in animal studies, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, interferon therapies and small-molecule drugs [10]. However, these treatments may take months or even years to reach patients. There is an urgent need for a standard of care regimen for COVID-19 patients in the absence of effective antiviral drugs.

Corticosteroids are frequently used to treat patients with viral illnesses by reducing inflammation-induced organ damage. However, based on historical data, caution should be taken when using corticosteroids in coronavirus infections. Retrospective reviews on SARS and MERS treatment suggest that administration of corticosteroids failed to achieve a reduction in mortality rate and potentially delayed viral clearance [11,12]. According to a large-scale study conducted in 84 cities and 16 provinces in China, high-dose corticosteroids were associated with increased mortality and longer viral shedding in patients with influenza A (H7N9) viral pneumonia [13]. This fact was confirmed by a larger meta-analysis by Zhang et al. of 23 studies with a total patient population of 6105 assessing the efficacy of corticosteroid treatment for influenza A (H1N1). Their analysis confirmed that there was a similar trend of steroid treatment associated with mortality [14]. High doses of corticosteroids were observed to increase the risk of nosocomial infection in patients with acute lung injury/ARDS and severe pneumonia; high-dose steroids were associated with prolonged viral shedding in haematopoietic cell transplant recipients infected with seasonal influenza virus [15,16]. Mechanistically, corticosteroids suppress inflammation induced by severe influenza infection; however, they increase the risk of opportunistic infections that occur secondary to immunosuppression. Administration of corticosteroids is likely to increase overall mortality, with this observation being consistent throughout the literature. Moreover, it has shown been that corticosteroids might be associated with a higher incidence of hospital-acquired pneumonia and a longer duration of mechanical ventilation and ICU stay.

4. Correction of the redox imbalance as an antiviral therapeutic strategy

Understanding how coronaviruses cause damage to human cells and organs could offer clues for developing a more effective therapy. Viruses cause infections that are often associated with redox modification characteristic of oxidative stress. Changes in redox homeostasis in infected cells are one of the key events in the pathogenesis of respiratory viral infections in all phases of the disease, contributing to severe inflammatory reaction and subsequent tissue damage [17]. Redox changes to an oxidised state also play a critical role in the activation of numerous cell pathways that are hijacked by viruses to assure their replication and to suppress the patient's immune response.

Viruses use several strategies to manipulate host cell machinery to their advantage. Among these, the imbalance of intracellular redox state caused by viruses could play an important role in modulating the activity of several signalling pathways. Oxidative imbalance caused by viral infections [18], ligand–receptor binding [19] or cytokine storm [20] could result in localised oxidation of reactive residues of redox-sensitive proteins. Increased oxidative stress leads to a systemic inflammatory response due to increased production of cytokines, contributing to ARDS, the key pathology in the high mortality of acute respiratory viral infections [21]. Despite the antiviral role of cytokines in respiratory infections, their overproduction during the cytokine storm is more damaging to lung tissue than the viruses themselves.

As a common immunological defence mechanism, immune cells respond to foreign infection by producing large quantities of reactive oxygen species (ROS) to destroy invading organisms [22]. Previous pathological and histological examinations showed that coronaviruses and influenza induced significant downregulation of the airway antioxidant system, leading to lethal lung injury and death from ARDS due to oxidative damage [23]. The autopsy pathology of the novel coronavirus is similar to other virus-induced ARDS. In a report of 29 patients with confirmed SARS-CoV-2 pneumonia, 27 (93%) showed increased high-sensitivity C-reactive protein (hs-CRP), a marker of oxidative stress injury [24].

5. Possible role of vitamin C in viral infection and related complications

Vitamin C has many properties that make it a valuable therapeutic agent for respiratory infections. It is a potent antioxidant with anti-inflammatory and immunosupportive properties. Vitamin C is a small, water-soluble molecule that readily acts as a one- or two-electron reducing agent for many free radicals and oxidants. Specialised cells can take up reduced vitamin C (ascorbic acid) through Na^+-dependent ascorbate cotransporters (SVCT1 and SVCT2). Most other cells take up vitamin C in its oxidised form, dehydroascorbic acid, via facilitative glucose transporters [25]. Almost all mammals, except for humans, primates and guinea pigs, can synthesise vitamin C in their livers, with increased production during stress. Vitamin C is an essential vitamin that acts as a cofactor for several enzymes and facilitates the production of catecholamines, vasopressin, L-carnitine, collagen neurotransmitters and cortisol [26], which are central to cellular function and homeostasis. Additionally, vitamin C plays a significant role in viral infection, including attenuation of the pro-inflammatory response, enhancement of epithelial barrier function, increased alveolar fluid clearance, and prevention of sepsis-associated coagulation abnormalities [27].

This essential vitamin has a huge role in antiviral activity and immune enhancement. It has been shown that vitamin C is an essential factor in the production of type I interferons during the antiviral immune response [28]. Vitamin C has also been shown to upregulate natural killer cell and cytotoxic T-lymphocyte activity both in vitro and in vivo [26,29] and can be used as an inactivating agent for the fixed rabies virus [30]. Other studies have used this vitamin as an inactivating agent both for RNA and DNA viruses, lessening viral infectivity. In addition, vitamin C can detoxify viral products that produce pain and inflammation [29,31]. Evidence has shown the effectiveness of vitamin C in treating pneumonia and infection owing to its direct inhibitory effects on pathogens [32]. Also, vitamin C is present in the epithelial lining of the respiratory tract where it functions as a local mucosal protecting agent, helping to ameliorate symptoms of upper respiratory tract infection [33].

Sepsis is a life-threatening illness caused by a dysregulated host response to infection. Untreated, it can lead to severe organ damage throughout the body. It is difficult to manage, requiring a combination of different treatments and supportive care for critically ill patients. Fisher et al. demonstrated in a mouse model that vitamin C plays a crucial role in multiple pathways associated with sepsis [34,35]. Mice that were given vitamin C did not experience multiple organ dysfunction syndrome, whilst mice that were deficient in vitamin C were much more susceptible to sepsis-induced organ damage. A proposed mechanism is that ascorbate enhances the synthesis of the vasopressors norepinephrine and vasopressin by acting as a cofactor. Therefore, administration of ascorbic acid (vitamin C) in patients with hypovitaminosis C during severe sepsis or septic shock supports the endogenous synthesis of vasoactive compounds, reducing the need for external vasopressors. These vasopressors help with the widespread vasodilation during sepsis, regulating blood pressure and fluid loss [36].

A high dose of vitamin C may be a proven therapeutic agent that not only ameliorates oxidative stress and inflammation during coronavirus infection, but also suppresses viral replication and improves antiviral immune defence and adrenal function.

6. Vitamin C in human clinical applications in viral infections, pneumonia and sepsis

In a study looking at the impact of vitamin C on oxidative stress and inflammation in community-acquired pneumonia (CAP), a common infectious disease, researchers measured values including reactive oxygen species (ROS), DNA damage, superoxide dismutase (SOD) activity, tumour necrosis factor-alpha (TNFα) and interleukin-6 (IL-6) in patients with CAP. The results show that patients with severe CAP had significantly increased ROS, DNA damage, TNFα and IL-6, but significantly decreased SOD [37]. Administration of vitamin C improved these redox imbalances by mitigating oxidative stress and pro-inflammatory markers, suggesting a possible therapeutic benefit for vitamin C in patients with severe CAP and other types of pneumonia. This antioxidant and anti-inflammatory property has been shown in a multitude of studies, demonstrating efficacy in preventing lung injury and protection against damage to other organs such as the heart, kidneys and liver in animal models of oxidative stress [36,38,39].

Studies have shown that a high percentage of critically ill patients are deficient in vitamin C despite receiving standard nutrition. In an observational study, Carr et al. found that 75% of critically ill patients had plasma levels of vitamin C that were abnormally low, resulting from increased metabolism due to an overactive inflammatory response [40]. A common way to supplement vitamin C in the clinic is through intravenous (IV) vitamin C administration. A phase I trial in patients with severe sepsis demonstrated that IV infusion of ascorbic acid was safe, well tolerated and had positive outcomes, including a significant reduction in multiple organ injury and reduced inflammatory biomarker levels [41]. High-dose IV vitamin C is commonly used by complementary and alternative medicine practitioners to treat a wide variety of conditions, including infections. A survey sent to practitioners showed that over 20 000 patients received IV vitamin C over a period of 2 years, with a mean number of infusions per patient of 19–24. There were no definitive serious adverse events reported and a very small number of minor reported adverse effects [42].

Clinical trials have reported positive results for vitamin C therapy in respiratory infections. Nathens et al. infused ascorbic acid at 1 g every 8 h for 28 days in 594 critically ill surgical patients and found a significantly lower incidence of acute lung injury and multiple organ failure than in patients receiving mechanical ventilation [43]. Vitamin C also significantly improved the 'total respiratory score' in the most severely ill patients with respiratory infection [44]. Fowler et al. reported a case study of a 20-year-old female who contracted respiratory enterovirus/rhinovirus infection that led to acute lung injury and ARDS. At 12 h following the initiation of extracorporeal membrane oxygenation (ECMO), high-dose IV vitamin C was started with a dose of 200 mg/kg every 24 h divided equally into four doses and infused every 6 h. The patient recovered rapidly and ECMO and mechanical ventilation were discontinued by Day 7. The patient recovered with no evidence of post-ARDS fibroproliferative sequelae [21]. Dietary antioxidants rich in vitamin C significantly attenuate hyperoxia-induced acute inflammatory lung injury by enhancing macrophage function via reducing the accumulation of airway high-mobility group box 1 protein (HMGB1) [45]. In the critically ill patient population, there was a significant reduction in 28-day mortality in patients supplemented with antioxidant vitamin C and E [46].

Vitamin C has also been shown to be effective against other medical conditions. Marik et al. reported the use of IV vitamin C in 47 septic ICU patients, finding a significant reduction in mortality rate in the group treated with high-dose IV vitamin C [47]. Several other trials have also shown that administration of vitamin C to patients with sepsis is associated with better patient outcomes

[35,48]. However, in the CITRIS-ALI randomised clinical trial, Fowler et al. did not observe significant differences in either organ failure scores or biomarker levels for 167 patients when comparing vitamin C infusion with placebo [49]. This lack of difference might be explained by the low vitamin C dose of 50 mg/kg body weight daily and short time frame of vitamin C infusion (only 96 h) in these patients with sepsis and ARDS.

Vitamin C has been widely utilised in the prevention and treatment of the common cold with varying degrees of effectiveness. Hemilä and Chalker determined that many of the studies showed that vitamin C reduces the duration and severity of colds [50], but the results were not consistent. Conversely, a recent meta-analysis by Ran et al. of nine randomised placebo-controlled trials did not come to a consistent conclusion. They found that the combination of supplemental and therapeutic doses of vitamin C has effects on reducing symptoms and length of the disease, but only administration of a therapeutic dose of vitamin C (3.0–4.0 g/day) during the disease leads to better recovery [51].

Meta-analyses of randomised controlled studies have shown that vitamin C may protect against contrast-induced acute kidney injury and shorten the duration of hospital and ICU stay of cardiac surgery patients [52]. Hemilä et al. identified 15 trials on the prevention of atrial fibrillation in high-risk patients and found that vitamin C decreased its incidence while shortening the length of hospital stay [53]. Other studies have shown that a high dose of IV vitamin C is effective against viral infections such as the common cold, rhinovirus, avian virus H1N1, Chikungunya virus, Zika virus and influenza [31,54,55].

Optimal dose and administration of vitamin C for treatment of pneumonia and acute respiratory distress syndrome (ARDS)

The dose and pharmacokinetics of vitamin C vary greatly, especially with high-dose vitamin C treatment [56]. Pharmacokinetic trials concluded that 2–3 g/day of IV vitamin C was required only to normalise plasma levels, whilst a higher dose was required to achieve supraphysiological therapeutic levels [57]. For oral supplementation, doses >3 g appear to be safe and demonstrated efficacy in preventing and ameliorating respiratory and systemic infections [40]. The antioxidant capacity of vitamin C is dose-dependent, and direct radical scavenging capacity is maximal at a plasma vitamin C level of >175 mg/L (1000 μmol/L), more than ten times the normal physiological level. Ascorbate prevents the interaction of superoxide and nitric oxide only at very high concentrations [58]. Results from pharmacokinetic studies indicate that oral ascorbic acid doses of 1.25 g/day produce mean peak plasma vitamin C concentrations of 135 μmol/L, which is approximately two times higher than those produced by consuming 200–300 mg/day ascorbic acid from vitamin C-rich foods. Pharmacokinetic modelling predicts that even doses as high as 3 g ascorbic acid taken every 4 h would produce peak plasma concentrations of only 220 μmol/L [59].

Different from oral administration, which is regulated via the sodium-dependent vitamin C transporter-1 (SVCT1), IV administration bypasses this pathway resulting in significantly higher plasma concentrations. Levine et al. documented the dramatic differences between the pharmacokinetics of oral and IV administration of vitamin C [60,61]. They noted that IV vitamin C was much more bioavailable inside the body and there was a significant difference in the amount of ascorbic acid found in the urine between the two groups. In other studies, IV administration was reported to produce plasma concentrations as high as 26 000 μmol/L [62] and vitamin C serum levels reached 70-fold compared with those that may be achieved through oral dosing alone [63]. de Grooth et al. showed in their studies that plasma concentrations ≥1000 μmol/L can be achieved with the administration of 10 g IV vitamin C/day. To restore plasma levels in critically ill patients, a minimum of 2–3 g IV vitamin C is necessary [64]. For therapeutic purposes, the IV dose of vitamin C can be range between 10–16 g/day to achieve plasma levels of >1000 μmol/L and to obtain optimal benefit [41].

In one trial, 80% of the administered dose of vitamin C had been filtered by the kidneys in 6 h following IV administration, suggesting that the optimal frequency of vitamin C treatment should be four times daily [65].

Data from the abovementioned pharmacological studies of vitamin C indicate that IV administration is currently the only way to achieve the optimal therapeutic concentration for the treatment of patients with severe illnesses such as viral pneumonia, ARDS and sepsis. Treatment with a high dose of vitamin C should start with ≥10 g/day. Also, the daily dose of vitamin C as a preventive agent should be started at ≥2000 mg.

7. Safety and possible side effects of vitamin C

Vitamin C has been used for many decades with few significant adverse side effects reported. Only 10 mg/day of vitamin C is necessary to prevent scurvy, but the 'tolerable upper intake level', as recommended by US nutritional recommendations, is stated to be 2 g/day for adults [66]. High-dose IV vitamin C administration has been used clinically for several decades, and a phase I–II study of the effects of IV vitamin C in combination with cytotoxic chemotherapy in patients reported that a high dose of vitamin C (1.5 g/kg body weight per 24 h) is safe and without major side effects [67]. Stephenson et al. demonstrated in another phase I study a dose curve from 30 to 110 g/m^2 of IV vitamin C and showed it to be safe and tolerable to patients even at the maximum dose [68].

Although there have been speculations about the potential harm of larger doses of vitamin C, research has shown that there is no concern for up to 2000 mg daily [61]. Pneumonia patients have been observed receiving as much as 100 g/day of vitamin C without developing diarrhoea or reported adverse side effects. A possible mechanism has been attributed to the changes in vitamin C metabolism caused by a severe infection [69]. Other possible side effects that have been reported with extremely high doses of IV vitamin C include dizziness, nausea, dry mouth, perspiration and weakness [70]. Prevention of these side effects includes proper hydration and fluids before and during treatment. Caution has been advised for the use of IV vitamin C in patients with end-stage renal failure predisposed to oxaluria. It has been reported that vitamin C intake is a possible cause of renal failure and kidney stones through the metabolic conversion of ascorbate to oxalate causing hyperoxaluria and crystalluria [71,72]. However, this has not been supported by prospective trials where risks did not increase and kidney function even improved [73,74]. Case reports have described oxalate nephropathy in burn patients after vitamin C administration (101 g and 224 g in.<24 h), but these levels are much higher than those used in most clinical applications [75].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is typically screened for prior to high-dose IV vitamin C administration owing to two case reports of haemolytic anaemia in G6PD-deficient individuals following IV administration of 80 g of vitamin C [76]. However, the lower IV vitamin C doses typically used for prevention and therapy of <16 g/day would be unlikely to cause haemolytic anaemia in G6PD-deficient individuals owing to a lack of hydrogen peroxide generation at these doses. High concentrations of vitamin C can also affect blood glucose measurements for some point-of-care glucometers, leading to false results [77]. This can lead to hypoglycaemia if aggressive insulin therapy is applied. Therefore, glucose measurements after the administration of pharmacological doses of vitamin C should be performed at the central laboratory [78].

8. Ongoing clinical trials

Several ongoing clinical trials are investigating the effects of vitamin C, or ascorbic acid, in patients with COVID-19. According to the clinical trials database (www.clinicaltrials.gov), there are a total of 13 active studies which are recruiting patients that have listed vitamin C or ascorbic acid as one of the interventions. Three of these studies are specifically studying the interaction of IV infusion vitamin C and its effects on COVID-19. One of these studies (ClinicalTrials.gov ID NCT04323514), conducted in Italy, is an uncontrolled longitudinal study in a cohort of 500 hospitalised patients with COVID-19 pneumonia. The patients will be administered 10 g of vitamin C with 250 mL of saline intravenously on top of conventional therapy. The study will measure endpoints such as mortality, CRP levels, lactate clearance levels, length of hospital stay and resolution of symptoms. A study in Virginia (USA) (ClinicalTrials.gov ID NCT04357782) is also studying the effects of administering IV vitamin C for coronavirus infection and decreased oxygenation. They have a study cohort of 20 patients and are giving the infusion of ascorbic acid at 50 mg/kg L-ascorbic acid every 6 h for 4 days. Lastly, there is a randomised controlled trial being conducted in Quebec, Canada (ClinicalTrials.gov ID NCT04401150) comparing the effects of IV vitamin C (50 mg/kg every 6 h for 96 h) to normal saline for a reduction in morbidity and mortality in patients hospitalised with COVID-19. This study is estimated to enrol 800 participants and is specifically measuring the effect of IV vitamin C on organ dysfunction.

There are currently two ongoing trials examining the effects of oral supplementation of vitamin C on COVID-19 symptoms. One ongoing trial being held in the Cleveland Clinic in the USA (ClinicalTrials.gov ID NCT04342728) is specifically examining the impact of oral ascorbic acid and zinc gluconate on the management of COVID-19. Patients will be randomised into groups receiving either 8000 mg of ascorbic acid, 50 mg of zinc gluconate, or the combination of both supplements in this controlled trial. The primary outcome measure is to see whether there is any symptom reduction after 28 days. The other trial is being hosted at King Saud University in Saudi Arabia (ClinicalTrials.gov NCT04323228) studying the effects of oral supplement enriched in antioxidants, including 1500 μg of vitamin A (as β-carotene), 250 mg of vitamin C, 90 mg of vitamin E, 15 μg of selenium and 7.5 mg of zinc. Forty COVID-19-positive patients will be randomised into either receiving this supplementation or a placebo and their health status, clinical assessment and biochemical data will be measured from baseline to up to 3 months.

Other ongoing clinical trials are studying the effects of ascorbic acid as a prophylactic taken alongside conventional medication. In a 600-participant double-blinded randomised trial (ClinicalTrials.gov ID NCT04335084), ascorbic acid is being given alongside hydroxychloroquine, vitamin D and zinc to test whether the drug hydroxychloroquine has more effect than normal nutritional supplements. This study is mirrored in a trial sponsored by ProgenaBiome (ClinicalTrials.gov ID NCT04334512) who are testing the same treatment. While a study in Turkey (ClinicalTrials.gov ID NCT04326725) is testing the effects of vitamin C and zinc alongside hydroxychloroquine to see whether the supplement can boost the effects of an experimental drug. Other trials are using ascorbic acid as a control in double-blinded studies. In a randomised, multicentre, blinded trial (ClinicalTrials.gov ID NCT04328961), ascorbic acid (500 mg daily) is being given as the placebo arm to test against the hydroxychloroquine experimental arm.

9. Conclusion

Viral infections such as SARS-CoV-2 (COVID-19), influenza, respiratory syncytial virus and many others are usually associated with increased oxidative stress leading to oxidative cellular and tissue damage resulting in multiorgan failure. Vitamin C has demonstrated favourable therapeutic properties and a good safety profile throughout a wide range of clinical applications. Administration of high-dose vitamin C as a therapeutic agent can favourably impact patients with viral pneumonia and ARDS in severe SARS-CoV-2 infection by decreasing inflammation and pathogen infectiveness and virulence, optimising immune defence, reducing tissue and organ injury, and improving the overall outcome of the disease.

Application of a high dose of vitamin C can dramatically reduce the need for treatment with high doses of corticosteroids, antibacterials and antiviral drugs. Vitamin C also can be effective for primary prevention of viral infections by boosting the innate immune response. In infected patients, vitamin C therapy may shorten the disease course and prevent complications of the disease [47,79]. In addition to vitamin C, other nutraceutical antioxidants widely available as over-the-counter drugs or food supplements can be used to improve the redox balance and reduce tissue damage in patients with viral pneumonia and ARDS. These possible agents include, but are not limited to, tocopherol, lipoic acid, *N*-acetylcysteine, glutathione, L-carnitine, coenzyme-Q10, zinc and selenium compounds.

Given the fact that vitamin C is inexpensive and has a history of efficacy and safety in similar clinical circumstances, further investigation should be done on its prophylactic ability in low doses and therapeutic ability in high doses. Instead of traditional double-blind controlled clinical trials, we recommend conducting comprehensive retrospective studies comparing disease progression and post-infection complications among patients who were or were not self-administering vitamin C during the course of their disease. This may provide timely data on the possible preventive and therapeutic values of vitamin C for medical and public interest in the current COVID-19 pandemic.

Funding: None.
Competing interests: None declared.
Ethical approval: Not required.

References

[1] Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.
[2] Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–70.
[3] de Groot RJ, Baker SC, Baric RS, et al. Commentary: middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013;87:7790–2.
[4] World Health Organization (WHO). Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update. Geneva, Switzerland: WHO; 2020. . [accessed 13 October 2020] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[5] Subbarao K, Murphy BR, Fauci AS. Development of effective vaccines against pandemic influenza. Immunity 2006;24:5–9.
[6] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.
[7] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[8] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
[9] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[10] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19:149–50.
[11] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.
[12] Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med 2018;197:757–67.

[13] Cao B, Gao H, Zhou B, et al. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. Crit Care Med 2016;44:e318–28.
[14] Zhang Y, Sun W, Svendsen ER, et al. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. Crit Care 2015;19:46.
[15] Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, Meade M. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. J Crit Care 2010;25:420–35.
[16] Boudreault AA, Xie H, Leisenring W, Englund J, Corey L, Boeckh M. Impact of corticosteroid treatment and antiviral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. Biol Blood Marrow Transplant 2011;17:979–86.
[17] Dua K, Malyla V, Singhvi G, et al. Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: an emerging need for novel drug delivery systems. Chem Biol Interact 2019;299:168–78.
[18] Fraternale A, Paoletti MF, Casabianca A, et al. Anti-viral and immunomodulatory properties of new pro-glutathione (GSH) molecules. Curr Med Chem 2006;13:1749–55.
[19] Nakashima I, Kato M, Akhand AA, et al. Redox-linked signal transduction pathways for protein tyrosine kinase activation. Antioxid Redox Signal 2002;4:517–31.
[20] Nakamura H, Nakamura K, Yodoi J. Redox regulation of cellular activation. Ann Rev Immunol 1997;15:351–69.
[21] Fowler 3rd AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med 2017;6:85–90.
[22] Al Ghouleh I, Khoo NK, Knaus UG, et al. Oxidases and peroxidases in cardiovascular and lung disease: new concepts in reactive oxygen species signaling. Free Radic Biol Med 2011;51:1271–88.
[23] Huang KJ, Su IJ, Theron M, et al. An interferon-γ-related cytokine storm in SARS patients. J Med Virol 2005;75:185–94.
[24] Chen L, Liu H, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E005.
[25] Vera JC, Rivas CI, Velásquez FV, Zhang RH, Concha II, Golde DW. Resolution of the facilitated transport of dehydroascorbic acid from its intracellular accumulation as ascorbic acid. J Biol Chem 1995;270:23706–12.
[26] Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9:1211.
[27] Bharara A, Grossman C, Grinnan D, et al. Intravenous vitamin C administered as adjunctive therapy for recurrent acute respiratory distress syndrome. Case Rep Crit Care 2016;2016:8560871.
[28] Kim Y, Kim H, Bae S, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-α/β at the initial stage of influenza A virus (H3N2) infection. Immune Netw 2013;13:70–4.
[29] Jariwalla RJ, Harakeh S. Antiviral and immunomodulatory activities of ascorbic acid. Subcell Biochem 1996;25:213–31.
[30] Madhusudana SN, Shamsundar R, Seetharaman S. In vitro inactivation of the rabies virus by ascorbic acid. Int J Infect Dis 2004;8:21–5.
[31] Zarubaev V, Slita A, Lavrentyeva I, Smirnov V. Protective activity of ascorbic acid at influenza infection. Infektsiia Immunitet 2017;7:319–26.
[32] Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. Antioxid Redox Signal 2013;19:2129–40.
[33] Maggini S, Maldonado P, Cardim P, Fernandez Newball C, Sota Latino E. Vitamins C, D and zinc: synergistic roles in immune function and infections. Vitam Miner 2017;6:3, doi:http://dx.doi.org/10.4172/2376-1318.1000167.
[34] Fisher BJ, Seropian IM, Kraskauskas D, Thakkar JN, Voelkel NF, Natarajan R. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. Crit Care Med 2011;39:1454–60.
[35] Fisher BJ, Kraskauskas D, Martin EJ, et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. Am J Physiol Lung Cell Mol Physiol 2012;303:L20–32.
[36] Carr AC, Shaw GM, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? Crit Care 2015;19:418.
[37] Chen Y, Luo G, Yuan J, Wang Y, Yang X, Wang X, et al. Vitamin C mitigates oxidative stress and tumor necrosis factor-α in severe community-acquired pneumonia and LPS-induced macrophages. Mediators Inflamm 2014;2014:426740.
[38] Hosakote YM, Jantzi PD, Esham DL, et al. Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis. Am J Respir Crit Care Med 2011;183:1550–60.
[39] Andrades M, Ritter C, de Oliveira MR, Streck EL, Moreira JCF, Dal-Pizzol F. Antioxidant treatment reverses organ failure in rat model of sepsis: role of antioxidant enzymes imbalance, neutrophil infiltration, and oxidative stress. J Surg Res 2011;167:e307–13.
[40] Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 2017;21:300.
[41] Syed AA, Knowlson S, Sculthorpe R, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014;12:32.
[42] Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: Intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010;5:e11414.
[43] Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 2002;236:814.
[44] Hemilä H. Vitamin C and community-acquired pneumonia. Am J Respir Crit Care Med 2011;184:621–2.
[45] Patel V, Dial K, Wu J, Gauthier AG, Wu W, Lin M, et al. Dietary antioxidants significantly attenuate hyperoxia-induced acute inflammatory lung injury by enhancing macrophage function via reducing the accumulation of airway HMGB1. Int J Mol Sci 2020;21:977.
[46] Crimi E, Liguori A, Condorelli M, et al. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. Anesth Analg 2004;99:857–63.
[47] Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before–after study. Chest 2017;151:1229–38.
[48] Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 2016;5:94.
[49] Fowler 3rd AA, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. 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. JAMA 2019;322:1261–70.
[50] Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013(1)CD000980.
[51] Ran L, Zhao W, Wang J, Wang H, Zhao Y, Tseng Y, et al. Extra dose of vitamin C based on a daily supplementation shortens the common cold: a meta-analysis of 9 randomized controlled trials. Biomed Res Int 2018;2018:1837634.
[52] Sadat U, Usman A, Gillard JH, Boyle JR. Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography: a systematic review with meta-analysis of randomized, controlled trials. J Am Coll Cardiol 2013;62:2167–75.
[53] Hemilä H, Suonsyrjä T. Vitamin C for preventing atrial fibrillation in high risk patients: a systematic review and meta-analysis. BMC Cardiovasc Disord 2017;17:49.
[54] Marcial-Vega V, Idxian GG-T, Levy TE. Intravenous ascorbic acid and hydrogen peroxide in the management of patients with chikungunya. Bol Asoc Med P R 2015;107:20–4.
[55] Duconge J, Rodríguez-López JL, Pedro A, Adrover-López B. High dose intravenous vitamin C treatment for zika fever. JOM 2016;31:19–22.
[56] Hemilä H. Vitamin C and infections. Nutrients 2017;9:339.
[57] Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. Nutrients 2019;11:2412.
[58] Jackson TS, Xu A, Vita JA, Keaney Jr JF. Ascorbate prevents the interaction of superoxide and nitric oxide only at very high physiological concentrations. Circ Res 1998;83:916–22.
[59] Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004;140:533–7.
[60] Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A 1996;93:3704–9.
[61] Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415–23.
[62] Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. CMAJ 2006;174:937–42.
[63] Chen Q, Espey MG, Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. Proc Natl Acad Sci U S A 2007;104:8749–54.
[64] de Grooth H-J, Manubulu-Choo W-P, Zandvliet AS, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. Chest 2018;153:1368–77.
[65] de Grooth H-J, Manubulu-Choo W-P, Zandvliet AS, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. Chest 2018;153:1368–77.
[66] de Grooth H-J, Manubulu-Choo W-P, Zandvliet AS, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. Chest 2018;153:1368–77.
[67] Hoffer LJ, Robitaille L, Zakarian R, Melnychuj D, Kavan P, Agulnik J, et al. High-dose intravenous vitamin C combined with cytotoxic chemotherapy in patients with advanced cancer: a phase I–II clinical trial. PLoS One 2015;10:e0120228.
[68] Stephenson CM, Levin RD, Spector T, Lis CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. Cancer Chemother Pharmacol 2013;72:139–46.
[69] Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. Med Hypotheses 1981;7:1359–76.
[70] Welsh J, Wagner B, Van't Erve T, et al. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial. Cancer Chemother Pharmacol 2013;71:765–75.
[71] Auer B, Auer D, Rodgers A. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Investig 1998;28:695–700.

[72] Simon JA, Hudes ES. Relation of serum ascorbic acid to serum vitamin B12, serum ferritin, and kidney stones in US adults. Arch Intern Med 1999;159:619–24.
[73] Gerster H. No contribution of ascorbic acid to renal calcium oxalate stones. Ann Nutr Metab 1997;41:269–82.
[74] Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol 1996;155:1847–51.
[75] Buehner M, Pamplin J, Studer L, et al. Oxalate nephropathy after continuous infusion of high-dose vitamin C as an adjunct to burn resuscitation. J Burn Care Res 2016;37:e374–9.
[76] Quinn J, Gerber B, Fouche R, Kenyon K, Blom Z, Muthukanagaraj P. Effect of high-dose vitamin C infusion in a glucose-6-phosphate dehydrogenase-deficient patient. Case Rep Med 2017;2017:5202606.
[77] Cho J, Ahn S, Yim J, et al. Influence of vitamin C and maltose on the accuracy of three models of glucose meters. Ann Lab Med 2016;36:271–4.
[78] Flannery AH, Bastin MLT, Magee CA, Bensadoun ES. Vitamin C in sepsis: when it seems too sweet, it might (literally) be. Chest 2017;152:450–1.
[79] Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. Nutrients 2019;11:708.