Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof

A Possible Application of High Dose Vitamin C in the Prevention and Therapy for Coronavirus Infections

Ba X. Hoang, D. Graeme Shaw, William Fang, Bo Han

PII: S2213-7165(20)30258-7

DOI: https://doi.org/10.1016/j.jgar.2020.09.025

Reference: JGAR 1378

To appear in: *Journal of Global Antimicrobial Resistance*

Received Date: 21 March 2020

Revised Date: 9 September 2020

Accepted Date: 24 September 2020

Please cite this article as: Hoang BX, Shaw DG, Fang W, Han B, A Possible Application of High Dose Vitamin C in the Prevention and Therapy for Coronavirus Infections, *Journal of Global Antimicrobial Resistance* (2020), doi: https://doi.org/10.1016/j.jgar.2020.09.025

A Possible Application of High Dose Vitamin C in the Prevention and Therapy for Coronavirus Infections

Ba X Hoang, D Graeme Shaw, William Fang, Bo Han bohan@usc.edu

[1]Nimni-Cordoba Tissue Engineering and Drug Discovery Lab, Departments of Surgery University of Southern California, Los Angeles, California, USA

[2]Integrative Medical Associates, Foster City, California, USA

[3]College of Osteopathic, Western University of Health Sciences, Pomona, California, USA

***Corresponding Author:**

Bo Han, PhD. CNS

Associate Professor

Departments of Surgery and BME

1333 San Pablo St., BME-302

Los Angeles, CA 90033

Tel: 323-442-2242

High Lights:

- Viral infections such as SARS-CoV-2 (COVID-19), influenza, RSV, and many others are usually associated with increased oxidative stress leading to oxidative cellular and tissue damage resulting in multi-organ failure.
- Vitamin C has demonstrated favorable therapeutic properties safety profile throughout a wide range of clinical application.
- Administration of high dose of vitamin C as therapeutic agent can favorably impact patient with viral pneumonia and ARDS in severe SAR-CoV-2 infected patients by decreasing inflammation, pathogens infectiveness and virulence,

optimizing immune defense, reducing tissues and organs injuries and improving the overall outcome of the disease.

- Other nutraceutical antioxidants that widely available as OTC drugs or food supplements can be used to improve redox balance and reduce the tissue damages in patients with viral pneumonia and ARDS
- Further clinical trials are needed to validate the effectiveness and develop an optimal therapeutic protocol for high dose of vitamin C treatment for pneumonia and ARDS in patients with viral infection.

Abstract:

Coronaviruses such as 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 the standard conventional supportive treatments, has been shown in literature as a safe and effective therapy for severe cases of respiratory viral infections. Morbidity, mortality, infectiveness, and spread of infectious diseases are dependent on the host-pathogen relationship. Given the lack of effective and safe anti-viral drugs for coronaviruses, there should be more attention in supporting host immune defense, cytoprotection, and immunoregulation. The implementation of a high dose of vitamin C therapy could dramatically reduce the need for high doses of corticosteroids, antibacterial and anti-viral drugs that may be immunosuppressive, adrenal depressive, and toxic, complicating the disease course. In order to effectively fight the novel virus, medical professionals should explore readily available pharmaceutical and nutritional therapeutic agents with proven antioxidant, anti-inflammatory and immune-supportive properties. Supplemental Vitamin C may also provide additional benefits for the prevention of viral infections, shorten the course, and lessen the complication of the disease.

Keywords: coronavirus; Oxidative stress; Vitamin C; Ascorbic Acid; Viral pneumonia

Introduction

Most cases of human coronavirus infection are mild, and patients usually can recover without complication or treatment. However, recent epidemics of the two coronaviruses, severe 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, SAR-CoV-2 (COVID-19), is genetically similar to SARS-CoV/MERS-CoV viruses but is significantly more infective. In the period between the discovery of the virus in December 2019 to the time this article was under revision in June 2020, the WHO has reported a total of 10.5+ million confirmed SARS-CoV-2 infected cases including 512k+ deaths [4]. As the global case numbers of SAR-CoV-2 infection keep rising, health experts are focused on finding a solution with fast track vaccine and anti-viral drug development. By using knowledge from SARS and MERS vaccine development path, several research groups have been able to start the development of the SAR-CoV-2 vaccine within a few weeks of the initial outbreak. However, there is no evidence 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 HIV and respiratory syncytial virus (RSV) [5]. Therefore, we should rigorously explore alternatives for fighting with COVID.

Clinical Manifestations

Medical doctors have published several clinical and observational studies that documented the clinical features and outcome of SARS-CoV-2 infection. In a retrospective observational study of 710 patients with SARS-CoV-2 pneumonia, 98% of the patients had a fever, 77% of the patients had a cough, and 63.5% of the patients had dyspnea. Another report with 41 patients reported that all 41 patients exhibited pneumonia and had complications, including acute respiratory distress syndrome (29%), acute cardiac injury (12%), and secondary infection (10%). 13 (32%) patients were admitted to the ICU and 6 (15%) died after intensive treatment [6]. A smaller subset of this population, 52 critically ill patients, had 32 (61.5%) patients died after 28 days with the median duration from ICU admission to deaths being 7 days [7]. Wang et al. reported 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 in the ICU, 11.1% received high flow oxygen, 47.2% received invasive ventilation, and 41.7% received

noninvasive ventilation, suggesting that patients in the ICU could not breathe spontaneously. Lastly, Chen et al. in a separate report of 99 confirmed cases, found that 17 (17%) patients developed acute respiratory distress syndrome (ARDS) that led to 11 (11%) patients quickly worsening in a short period and dying of multiple organ failure [9]. These preliminary clinical pieces of evidence demonstrate considerable uncertainties are present in terms of prognosis and mortality rate. Additional studies are needed to confirm and refine the details of the disease. These early observations still show that COVID-19 is a dangerous illness with a poor clinical prognosis.

Current Therapeutics

Unfortunately, there is no vaccine or anti-viral treatment approved to treat human coronavirus. Therapeutic options are being explored in vitro and 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 coronavirus patients without effective anti-viral drugs.

Corticosteroids are frequently used to treat patients with viral illnesses by reducing inflammatory-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 receiving corticosteroids failed to achieve mortality rate reduction 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 of twenty-three studies with a total patient population of n=6,105 by Zhang et al. assessing the efficacy of corticosteroids 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 infections of acute lung injury/ARDS and severe pneumonia; patients were associated with prolonged viral shedding of hematopoietic cell transplant recipients infected with seasonal influenza virus [15,16]. Mechanistically, corticosteroids suppress inflammation induced by severe influenza infections; 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 was shown that corticosteroids might be associated with a higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay.

Correction the redox imbalance as a therapeutic anti-viral strategy

Understanding how the 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's characteristic of oxidative stress. Changes in redox homeostasis in infected cells are one of the key events in the pathogenesis of respiratory viral infection in all phases of the disease, contributing to severe inflammatory reaction and subsequent tissue damage [17]. Redox changes to an oxidized state also play a critical role in the activation of numerous cell pathways that are hijacked by viruses to assure their replication and suppress the patient's immune defense.

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 signaling pathways. An oxidative imbalance caused by viral infections [18], ligand/receptor binding [19], or cytokine storm [20] could result in localized oxidation of reactive residues of redox-sensitive proteins. Increased oxidative stress leads to a systematic inflammatory response from increased production of cytokines, contributing to ARDS, the key pathology in the high mortality of acute respiratory viral infections [21]. Despite the anti-viral 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 defense 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 examination showed coronaviruses and influenza induced significant downregulation of the airway antioxidant system, lead to lethal lung injuries and death from ARDS due to oxidative damage [23]. The autopsy pathology of the novel coronavirus was similar to other viruses induced ARDS. In a report of 29 patients

confirmed of SAR-CoV-2 pneumonia, 27 (93%) showed increased hs-CRP, a marker of oxidative stress injuries [24].

A possible role of vitamin C in anti-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 immune-supportive 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. Specialized cells can take up reduced vitamin C (AscA) through Na+-dependent ascorbate cotransporters (SVCT1 and SVCT2). Most other cells take up vitamin C in its oxidized form (DHA) via facilitative glucose transporters [25]. Almost all mammals, except for humans, primates, and guinea pigs, can synthesize 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], these molecules are central to cellular function and homeostasis. Additionally, Vitamin C plays a significant role in viral infection, including attenuation of the proinflammatory response, enhancement of epithelial barrier function, increasing alveolar fluid clearance, and prevention of sepsis-associated coagulation abnormalities [27].

This essential vitamin has a huge role in anti-viral activity and immune enhancement. It has been shown that vitamin C is an essential factor in the production of type I interferons during the anti-viral immune response [28]. Vitamin C has also been shown to up-regulates Natural killer (NK) 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 for both 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 its effectiveness in treating pneumonia and infection due 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 ameliorate symptoms of upper respiratory tract infections [33].

Sepsis is a life-threatening illness from 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 B.J et al demonstrated in a mice 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 syndromes, while 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 vasopressors norepinephrine and vasopressin by acting as a cofactor. Therefore, the 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 ameliorate oxidative stress and inflammation during coronavirus infections, but also suppresses viral replication and improves anti-viral immune defense and adrenal function.

Vitamin C in human clinical applications in anti-viral, pneumonia and sepsis

In a study looking at the impact of vitamin C on oxidative stress and inflammation in common infectious disease, community-acquired pneumonia (CAP), researchers measured values including, reactive oxygen species (ROS), DNA damage, superoxide dismutase (SOD) activity, tumor necrosis factor-alpha (TNF-α), and IL-6 in patients. The results show that severe CAP patients had significantly increased ROS, DNA damage, TNF-α, and IL-6 but significantly decreased SOD.[37] Administration of Vitamin C improved these redox imbalances by mitigating oxidative stress and proinflammatory 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 of has been shown in a multitude of studies, demonstrating efficacy in preventing lung injury and protect against the damage of other organs, such as heart, kidney, 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. [40] found that 75%

of critically ill patients had plasma levels of vitamin C that were abnormally low, resulting from increased metabolism from an overactive inflammatory response. A common way to supplement vitamin C in a clinic is through an 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 out to practitioners showed that over 20,000 patients received IV vitamin C over periods of 2 years, with a mean number of infusions per patient of 19-24. There were no definitive serious adverse events reported and had very low numbers of minor reported adverse effects [42].

Clinical trials have reported positive results in vitamin C therapy for respiratory infections. Nathens et al. infused ascorbic acid at 1 g every 8 hours for 28 days in 594 surgically critically ill 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 a respiratory infection [44]. Fowler III AA et al. reported in a case study of a 20-year-old female who contracted respiratory enterovirus/rhinovirus infection that led to acute lung injury and ARDS. Twelve hours following ECMO (extracorporeal membrane oxygenation) initiation, high dose IV vitamin C began with the dose being 200 mg/kg every 24 hours divided equally into four doses and infused every 6 h. The patient's 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 HMGB1 [45]. In the critically ill patient population, there was a significant reduction in 28-d mortality in patients who supplemented with antioxidant vitamin C and E.[46]

Vitamin C has also been shown to be effective against other medical conditions. Marik et al. [47] reported their use of IV vitamin C in 47 sepsis ICU cases, finding a significant reduction in mortality rate in groups treated with a high dose of IV vitamin C. 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 randomized clinical trial by Fowler et al., the researchers did not observe significant differences in either organ failure scores or biomarker levels with 167 patients comparing vitamin C infusion with placebo [49]. This lack of difference might be explained in the low dose of 50mg/1kg body weight daily and short time frame of only 96 hours vitamin C infusion in these patients with sepsis and ARDS.

Vitamin C has been widely utilized in the prevention or treatment of the common cold with varying degrees of effectiveness. Hemila et al. determined that many of the studies shown 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. in 9 randomized placebo-controlled trials did not come to a consistent conclusion. They found that the combination of the supplemental and therapeutic dose of vitamin C has effects on reducing symptoms and length of the disease, but only administration of a therapeutic dose of vitamin C (3.0g/day to 4.0g/day) during the disease to better recover health. [51]

Meta-analyses of randomized 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]. Hemila et al. identified 15 trials about preventing atrial fibrillation in high-risk patients and found that vitamin C affects decreasing incidence while lowering 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, Zika, and influenza [31,54,55].

Optimal dose and administration of Vitamin C for treatment of pneumonia and ARDS

The dose and pharmacokinetics of vitamin C have varied greatly, especially with high dose vitamin C treatment.[56]. Pharmacokinetic trials concluded that IV 2 to 3 g/d of vitamin C was required only to normalized plasma levels, while a higher dose was required to obtain supraphysiological therapeutic levels [21]. For oral supplementation, doses over 3g appear to be safe and demonstrated efficacy in preventing and ameliorate 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 > 175 mg/l (1000 μmol/l), more than ten times normal physiological level. Ascorbate prevents the interaction of superoxide and nitric oxide

only at very high concentrations [57]. Results from pharmacokinetic studies indicate that oral doses of 1.25 g/day ascorbic acid produce mean peak plasma vitamin C concentrations of 135 μmol/L, which are about two times higher than those produced by consuming 200–300 mg/day ascorbic acid from vitamin C-rich foods. Pharmacokinetic modeling predicts that even doses as high as 3 g ascorbic acid taken every 4 hours would produce peak plasma concentrations of only 220 μmol/L [58].

Different from oral administration, which is regulated via the sodium-dependent vitamin C transporter-1(SVCT1), intravenous administration bypasses this pathway and resulting in significantly higher plasma concentrations. Mark Levine's group documented the dramatic differences between the pharmacokinetics of oral and intravenous administration of vitamin C [59,60]. They noted IV vitamin C was much more bioavailable inside the body, and there was a significant difference in the amount of ascorbic acid found in urine between the two groups. In other studies, IV administration can produce plasma concentrations as high as 26,000 μmol/L [61], vitamin C serum levels reached 70-fold compared to those that may be achieved through oral dosing alone [62]. De Grooth et al showed in their studies that plasma concentrations > 1000 μmol/l can be achieved with the administration of 10 g intravenous vitamin C/day. To restore plasma levels in critically ill patients, a minimum of 2–3 g intravenous vitamin C is necessary [63]. For therapeutic purposes, the intravenous dose of vitamin C can be range between 10-16 grams per day to obtain plasma levels of above 1000 μmol/l and to achieve optimal benefit [41].

In one trial, 80% of administered doses of IVC had been filtered by the kidneys in 6 hours following the intravenous administration. That suggests the optimal frequency of vitamin C treatment should be 4 times daily [64].

The data from the above-mentioned pharmacological studies of vitamin C indicate that intravenous 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. The treatment with a high dose of vitamin C should start with 10 grams and above per day. Also, the daily dose of vitamin C as a preventive agent should be started at 2000 mg and above.

Vitamin C safety and possible side effects

Vitamin C has been used for many decades, with few significant adverse side effects reported. Only 10 mg/d 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 [65]. High dose intravenous vitamin C administration has been clinically used for several decades, and a phase I-II study studying the effects of IV vitamin C with cytotoxic chemotherapy in patients states that a high dose of Vitamin C (1.5 g/d body weight per 24 hours) is safe and without major side effects [66]. 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 safe and tolerable to patients even at the max dose. [67]

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. [60]. Pneumonia patients have been observed taking as much as 100 g/day of vitamin C without developing diarrhea and reported adverse side effects. A possible mechanism has been attributed to the changes in vitamin C metabolism caused by a severe infection [68]. Other possible side effects that have been reported with extremely high doses IV vitamin C include dizziness, nausea, dry mouth, perspiration, and weakness [69]. Prevention of these side effects includes proper hydration and fluids before and during treatment. The 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 as a possible cause of renal failure and kidney stones through the metabolic conversion of ascorbate to oxalate hyperoxaluria and crystalluria [70,71]. However, this has not been supported by prospective trials where risks did not increase, and kidney function even improved [72,73]. Case reports have described oxalate nephropathy in burn patients after vitamin C administration (101g and 224 g in less than 24 hours), but these levels are much higher than used in most clinical applications [74].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is typically screened for prior to high dose IV C administration due to two case reports of hemolytic anemia in G6PD deficient individuals following 80 g intravenous administration.[75] However, the lower of intravenous vitamin C doses typically used for prevention and therapy with less than 16 g/day would be unlikely to cause hemolytic anemia in G6PD deficient individuals due to 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.[76] This can

lead to hypoglycemia 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.[77]

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.clinical-trials.gov), there are a total of 9 active studies that 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 infusing Vitamin C through IV and its effects on COVID-19. One of these studies (Identifier: NCT04323514), conducted in Italy, is an uncontrolled longitudinal study in a cohort of 200 hospitalized patients with COVID-19 pneumonia. The patients will be administered 10 grams of vitamin C with 250mL of saline intravenously on top of conventional therapy. The study will be measuring endpoints such as mortality, PCR levels, length of hospital stay, and resolution of symptoms. A trial in China (Identifier: NCT04323514) is mirroring the study taking place in Italy, with the same methods and endpoints measured. However, they are using a larger cohort of 500 infected patients. Lastly, a study in Virginia (Identifier: NCT04357782), is also studying the effects of administering intravenous Vitamin C for coronavirus infection and on decreased oxygenation. They have a study cohort of 20 patients and are giving the infusion of ascorbic acid at 50mg/kg L every 6 hours for 4 days.

Other ongoing clinical trials are studying the effects of Ascorbic Acid as a prophylactic taken alongside conventional medication. In a 600-participant double-blinded randomized trial (Identifier: NCT04335084), Ascorbic Acid is given alongside Hydroxychloroquine, Vitamin D, and Zinc to test if the drug Hydroxychloroquine has more effect than normal nutritional supplements. This study is mirrored in sponsored trial ProgenaBiome (Identifier: NCT04334512) who are testing the same treatment. While a study in Turkey (Identifier: NCT04326725) is testing the effects of vitamin C and Zinc alongside hydroxychloroquine to see if the supplements can boost the effects of an experimental drug. Other trials use Ascorbic Acid as a control in double-blinded studies. In a randomized, multi-center blinded trial (Identifier: NCT04328961), Ascorbic Acid (500mg daily) is given as the placebo arm to test against the experimental arm of Hydroxychloroquine.

Conclusion

Viral infections such as SAR-CoV-2 (COVID-19), influenza, RSV, and many others are usually associated with increased oxidative stress leading to oxidative cellular and tissue damage resulting in multi-organ failure. Vitamin C has demonstrated favorable therapeutic properties safety profiles throughout a wide range of clinical applications. Administration of high dose of vitamin C as a therapeutic agent can favorably impact patients with viral pneumonia and ARDS in severe SAR-CoV-2 infected patients by decreasing inflammation, pathogens infectiveness and virulence, optimizing immune defense, reducing tissues and organs injuries 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 for corticosteroids, antibacterial, and anti-viral drugs. Vitamin C also can be effective for primary prevention of viral infections by boosting the innate immune defense. In infected patients, vitamin C therapy may shorten the course and prevent the complication of the disease [47][78]. In addition to vitamin C, other nutraceutical antioxidants that widely available as OTC drugs or food supplements can be used to improve redox balance and reduce tissue damages in patients with viral pneumonia and ARDS. These possible agents included 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 a high. Instead of traditional double-blind control 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 diseases. This may provide timely data on the possible preventive and therapeutic values of vitamin C for the medical and public interest in the current COVID-19 pandemic.

References:

1. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *New England journal of medicine.* 2003;348(20):1953-1966.

2. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *The Lancet.* 2003;362(9380):263-270.
3. de Groot RJ, Baker SC, Baric RS, et al. Commentary: Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. *Journal of virology.* 2013;87(14):7790-7792.
4. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 24 February 2020. 2020.
5. Subbarao K, Murphy BR, Fauci AS. Development of effective vaccines against pandemic influenza. *Immunity.* 2006;24(1):5-9.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet.* 2020.
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine.* 2020.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama.* 2020.
9. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet.* 2020.
10. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). In: Nature Publishing Group; 2020.
11. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS medicine.* 2006;3(9).
12. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *American journal of respiratory and critical care medicine.* 2018;197(6):757-767.
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(6):e318-328.
14. Zhang Y, Sun W, Svendsen ER, et al. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. *Critical Care.* 2015;19(1):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. *Journal of critical care.* 2010;25(3):420-435.
16. Boudreault AA, Xie H, Leisenring W, Englund J, Corey L, Boeckh M. Impact of corticosteroid treatment and anti-viral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. *Biology of Blood and Marrow Transplantation.* 2011;17(7):979-986.
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. *Chemico-biological interactions.* 2019;299:168-178.
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(15):1749-1755.
19. Nakashima I, Kato M, Akhand AA, et al. Redox-linked signal transduction pathways for protein tyrosine kinase activation. *Antioxidants and Redox Signaling.* 2002;4(3):517-531.

20. Nakamura H, Nakamura K, Yodoi J. Redox regulation of cellular activation. *Annual review of immunology.* 1997;15(1):351-369.
21. Fowler III AA, Kim C, Lepler L, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World journal of critical care medicine.* 2017;6(1):85.
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 Radical Biology and Medicine.* 2011;51(7):1271-1288.
23. Huang KJ, Su IJ, Theron M, et al. An interferon- γ- related cytokine storm in SARS patients. *Journal of medical virology.* 2005;75(2):185-194.
24. Chen L, Liu H, Liu W, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases.* 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. *Journal of Biological Chemistry.* 1995;270(40):23706-23712.
26. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients.* 2017;9(11):1211.
27. Bharara A, Grossman C, Grinnan D, et al. Intravenous vitamin C administered as adjunctive therapy for recurrent acute respiratory distress syndrome. *Case reports in critical care.* 2016;2016.
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 network.* 2013;13(2):70-74.
29. Jariwalla RJ, Harakeh S. Antiviral and immunomodulatory activities of ascorbic acid. In: *Subcellular biochemistry.* Springer; 1996:215-231.
30. Madhusudana SN, Shamsundar R, Seetharaman S. In vitro inactivation of the rabies virus by ascorbic acid. *International journal of infectious diseases.* 2004;8(1):21-25.
31. Zarubaev V, Slita A, Lavrentyeva I, Smirnov V. Protective Activity Of Ascorbic Acid At Influenza Infection. *Infektsiya Immunitet.* 2017;7(4):319-326.
32. Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxidants & redox signaling.* 2013;19(17):2129-2140.
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(167):2376-1318.1000167.
34. Fisher BJ, Seropian IM, Kraskauskas D, Thakkar JN, Voelkel NF, Natarajan R. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Critical care medicine.* 2011;39(6):1454-1460.
35. Fisher BJ, Kraskauskas D, Martin EJ, et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 2012;303(1):L20-L32.
36. Carr AC, Shaw GM, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Critical Care.* 2015;19(1):418.
37. Chen Y, Luo G, Yuan J, et al. Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages. *Mediators of inflammation.* 2014;2014.

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. *American journal of respiratory and critical care medicine.* 2011;183(11):1550-1560.
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. *Journal of surgical research.* 2011;167(2):e307-e313.
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. *Critical Care.* 2017;21(1):300.
41. Syed AA, Knowlson S, Sculthorpe R, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of translational medicine.* 2014;12(1):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(7).
43. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Annals of surgery.* 2002;236(6):814.
44. Hemilä H. Vitamin C and community-acquired pneumonia. *American journal of respiratory and critical care medicine.* 2011;184(5):621-622.
45. Patel V, Dial K, Wu J, et al. Dietary Antioxidants Significantly Attenuate Hyperoxia-Induced Acute Inflammatory Lung Injury by Enhancing Macrophage Function via Reducing the Accumulation of Airway HMGB1. *International Journal of Molecular Sciences.* 2020;21(3):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. *Anesthesia & Analgesia.* 2004;99(3):857-863.
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(6):1229-1238.
48. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *Journal of research in pharmacy practice.* 2016;5(2):94.
49. Truwit JD, Hite RD, Morris PE, 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(13):1261-1270.
50. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews.* 2013(1).
51. Ran L, Zhao W, Wang J, 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 research international.* 2018;2018.
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. *Journal of the American College of Cardiology.* 2013;62(23):2167-2175.

53. Hemilä H, Suonsyrjä T. Vitamin C for preventing atrial fibrillation in high risk patients: a systematic review and meta-analysis. *BMC cardiovascular disorders.* 2017;17(1):49.
54. Marcial-Vega V, Idxian GG-T, Levy TE. Intravenous ascorbic acid and hydrogen peroxide in the management of patients with chikungunya. *Boletin de la Asociacion Medica de Puerto Rico.* 2015;107(1):20-24.
55. Duconge J, Rodríguez-López JL, Pedro A, Adrover-López B. High dose intravenous vitamin c treatment for zika fever. *JOM.* 2016;31(1):19.
56. Hemilä H. Vitamin C and infections. *Nutrients.* 2017;9(4):339.
57. Jackson TS, Xu A, Vita JA, Keaney Jr JF. Ascorbate prevents the interaction of superoxide and nitric oxide only at very high physiological concentrations. *Circulation research.* 1998;83(9):916-922.
58. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Annals of internal medicine.* 2004;140(7):533-537.
59. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proceedings of the National Academy of Sciences.* 1996;93(8):3704-3709.
60. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *Jama.* 1999;281(15):1415-1423.
61. Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. *Cmaj.* 2006;174(7):937-942.
62. Chen Q, Espey MG, Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. *Proceedings of the National Academy of Sciences.* 2007;104(21):8749-8754.
63. 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(6):1368-1377.
64. Robitaille L, Mamer OA, Miller Jr WH, et al. Oxalic acid excretion after intravenous ascorbic acid administration. *Metabolism.* 2009;58(2):263-269.
65. Ross A, Taylor C, Yaktine A, Del Valle H. Food and Nutrition Board. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. In: National Academy Press, Washington, DC, USA; 2011.
66. Hoffer LJ, Robitaille L, Zakarian R, 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(4).
67. 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 chemotherapy and pharmacology.* 2013;72(1):139-146.
68. Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. *Medical Hypotheses.* 1981;7(11):1359-1376.
69. 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 chemotherapy and pharmacology.* 2013;71(3):765-775.
70. Auer B, Auer D, Rodgers A. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. *European journal of clinical investigation.* 1998;28(9):695-700.

71. Simon JA, Hudes ES. Relation of serum ascorbic acid to serum vitamin B12, serum ferritin, and kidney stones in US adults. *Archives of internal medicine.* 1999;159(6):619-624.
72. Gerster H. No contribution of ascorbic acid to renal calcium oxalate stones. *Annals of nutrition and metabolism.* 1997;41(5):269-282.
73. 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. *The Journal of urology.* 1996;155(6):1847-1851.
74. Buehner M, Pamplin J, Studer L, et al. Oxalate nephropathy after continuous infusion of high-dose vitamin C as an adjunct to burn resuscitation. *Journal of Burn Care & Research.* 2016;37(4):e374-e379.
75. 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 reports in medicine.* 2017;2017.
76. Cho J, Ahn S, Yim J, et al. Influence of vitamin C and maltose on the accuracy of three models of glucose meters. *Annals of laboratory medicine.* 2016;36(3):271-274.
77. Flannery AH, Bastin MLT, Magee CA, Bensadoun ES. Vitamin C in sepsis: when it seems too sweet, it might (literally) be. *Chest.* 2017;152(2):450-451.
78. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. *Nutrients.* 2019;11(4):708.