A POSSIBLE ROLE FOR ASCORBIC ACID IN COVID-19

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INTRODUCTION

By the time you read this paper, millions of people globally will have tested positive for the coronavirus, with the United States leading the world in confirmed cases and fatalities.

The pulmonary and other systemic complications of the novel coronavirus (SARS-CoV-2) have created a worldwide emergency. Effective, targeted antiviral drugs are lacking, and symptomatic support is the only therapeutic approach available for the severe acute respiratory infection (SARI) this virus causes. The current guidelines of the National Institutes of Health (NIH) state there is insufficient evidence to either recommend or advise against any particular antiviral, immunomodulatory, or anti-inflammatory therapy in patients with severe coronavirus disease 2019 (COVID-19) infection. A recent NIH report on an ongoing clinical trial of remdesivir says patients receiving the intervention had a 31% faster time to recovery than those who received placebo, and that there is a trend toward decreasing mortality. More comprehensive data regarding this trial will be available in a forthcoming report, but we have at hand something with a remarkable safety record, as well as an array of beneficial clinical effects worth considering for this condition: ascorbic acid.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ASCORBIC ACID

Years of research have shown ascorbic acid (otherwise known as vitamin C or ascorbate – this paper will use these terms interchangeably) to be extremely safe in humans at very high doses. Ascorbic acid is an essential nutrient with important and diverse physiological effects. At high doses (≥7500 mg/day), especially when producing high micromolar or millimolar concentrations, it has been shown to have pharmacological properties. Among its many actions, it plays a role in reducing inflammation (a precipitating factor in SARI), supporting various aspects of the immune system, and having a direct antiviral effect.

ANTIVIRAL EFFECTS OF ASCORBIC ACID

A number of studies describe multiple mechanisms by which ascorbic acid enhances the function of leukocytes including chemokinesis and chemotaxis; phagocytosis; lysosomal enzyme production; generation of reactive oxygen species...
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Ascorbic acid (vitamin C) has been shown to have various beneficial effects in COVID-19 patients. These include the reduction of reactive oxygen species (ROS) and microbial killing, up-regulation of the antibody response, and increasing interferon. These effects, along with enhanced neutrophil chemotactic action, have been documented in humans receiving either intravenous (IV) vitamin C or taking gram doses orally.

In addition, studies have shown that vitamin C lowers the risk of infection. Studies in animal models have demonstrated that parenteral ascorbate improves sepsis and sepsis-induced multiple-organ dysfunction syndrome by preventing cellular immunosuppression. Studies in septic mice suggest that increased survival occurs by activation of Nrf2/HO-1 signals. In vitro observations with pharmacologic concentrations (millimolar range) suggest a direct antiviral effect of ascorbate that is consistent with clinical observations of patients with Epstein–Barr viral (EBV) infection. Pharmacologic IV ascorbate therapy was associated with a significant reduction in EBV antibodies. Moreover, IV ascorbic acid has demonstrated clinical benefits against a variety of viral infections.

**THE HUMAN DISADVANTAGE**

Most vertebrates respond to physiological stress such as sepsis with a dramatic increase in the synthesis of ascorbate. This is done by converting glucose via the enzyme L-gulono-g-lactone oxidase (GLO). When sufficient ascorbate is present, it helps control excess inflammation, support leukocyte function, inhibit microbial pathogen growth, and neutralize harmful ROS. Humans, however, lack both the necessary gene and the GLO enzyme, and are not able to synthesize ascorbate. This means we must supplement with nutritional doses or acquire pharmacologic doses according to the particular physiologic demands at hand.

**ABSORPTION AND PLASMA CONCENTRATIONS IN HEALTH AND DISEASE**

Absorption of ascorbic acid in the intestinal membrane occurs either as ascorbate (ASC) by sodium-coupled active transport via the SVCT1 transporter, or as dehydroascorbic acid (DHA) through facilitated diffusion via GLUT1 or GLUT3 transporters. In addition to being a co-factor required for many physiological functions, ascorbic acid has high electron-donating and hydrogen-donating power. This capacity to move electrons gives ascorbic acid great versatility and makes it a formidable RedOx molecule. Ascorbate concentrations in body fluids and tissues are regulated via intestinal absorption, cellular transport, and excretion. Plasma and tissue concentrations are controlled by various mechanisms including absorption, tissue rate of accumulation, tissue utilization, and renal reabsorption.

The amount of vitamin C needed to prevent scurvy is very small, and generally considered to be obtainable from most western-type diets. However, data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) show that the prevalence of inadequate plasma vitamin C concentrations in the USA are as high as 22%–33%, with 7%–14% of people showing scorbutogenic deficiency. Signs and symptoms of scurvy occur with plasma ascorbate levels below 1.5 mg/L (0.0085 mM), or below 1.9 mg/L [0.011 mM (11 µM)]. People with marginal ascorbate hypovitaminosis, characterized by ascorbate concentrations below 23 µmol/L, can easily develop scurvy when challenged with physiological stressors. Adequate levels to support health are anything above 23 µmol/L, or more specifically, as recommended in several European countries, about 50 µmol/L to compensate for metabolic losses. Consuming five to nine servings of fruits and vegetables daily, or taking a 200-mg ascorbate supplement have been estimated to produce steady-state ascorbate plasma concentrations of 70–80 µmol/L.

In healthy volunteers who took 3 g of vitamin C orally every day for 6 days, peak values did not exceed 220 µmol/L. It was only when a supra-physiological (millimolar) concentration of ascorbic acid was achieved by high-gram IV dosing that pharmacologic properties were noted. Table 1 shows the correlation of plasma ascorbate concentrations, doses, and the clinical implications ranging from scorbutogenic deficiency to pharmacologic concentrations.
Clinicians will tell you that sick patients are able to take higher doses of ascorbic acid orally without getting loose stool than they are able to tolerate when well. It has been shown that at least 80% of adult patients will tolerate 10–15 g of ascorbic acid per day without reaching bowel tolerance when it is dissolved in water and taken in divided doses. In the case of serious or very toxic disease states, dosing may need to be every half hour. Short delays in taking these doses may prolong the disease process. Absorption and distribution of ascorbate into diseased tissue presumably occurs because of increased ascorbate metabolism. Frequent dosing is, therefore, thought to meet metabolic demand.

**ASCORBIC ACID IN CLINICAL TRIALS FOR SEPSIS**

Cytokine storm refers to a severe immune reaction in which the body rapidly releases floods of inflammatory cytokines into the blood causing sepsis. The result is an overwhelming production of ROS that damage multiple organelles, cells, and tissues, leading to progressive organ failure. Cytokine storm is one of the most dangerous complications of COVID-19 infection.

Over 500 peer-reviewed papers reporting on both experimental and clinical studies clearly demonstrate the biological and pharmacologic mechanisms by which vitamin C alone, or combined with other agents, can be used in the management of sepsis and other inflammatory disorders.

A coagulopathy is commonly observed in patients with severe COVID-19 infection that correlates with a rise in inflammatory markers [C-reactive protein (CRP)]. Low-molecular-weight heparin (LMWH) is used to treat it. Interestingly, ascorbic acid has been shown to restore impaired fibrinolysis in heavy smokers, whose endothelial capacity to acutely release tissue plasminogen activator (t-PA) is significantly impaired.

A comprehensive randomized study using IV ascorbic acid in 167 patients with severe acute respiratory failure demonstrated a significant reduction in mortality in the ascorbic acid group, from the fourth day onward, compared to the placebo group (P=0.023).

In this study, Fowler et al. gave participants 50 mg/kg of ascorbic acid intravenously every 6 hours, which amounted to a range of 3500–5000 mg every 6 hours for a total of 14,000–20,000 mg every 24 hours, with no unexpected treatment-related side effects.

Recent studies suggest that ascorbic acid, as part of a protective protocol for COVID-19 patients hospitalized with sepsis, may reduce mortality and length of stay in the intensive care unit (ICU), and significantly reduce the time to resolution of shock.

The use of ascorbic acid as a reliable antiviral in many different acute infectious diseases has been documented since 1949. Frederick R. Klenner, MD demonstrated that vitamin C consistently neutralized any toxin when sufficiently dosed and administered for a long enough period of time. This included curing 60 out of 60 patients of polio within 4 days of intramuscular and oral administration of ascorbic acid. In 1951, he reported using ascorbic acid to cure patients with advanced polio and its associated flaccid paralysis.

Marcial-Vega et al. reported on the efficacy and safety of 25–50 g of IV ascorbic acid plus hydrogen...
Ascorbic acid peroxide in the treatment of 56 patients with Chikungunya-related arthralgia. Results showed a greater than 71% post-infusion reduction in pain with no adverse effects reported.61 These results are consistent with earlier in vitro studies which showed that ascorbic acid inactivated the polio,62 herpes,63 vaccinia,64,65 tobacco mosaic,66 bacteriophage,67–70 entero,71 influenza,7 and rabies72 viruses. The antiviral effects of ascorbate have also been shown in animal models including rabies in guinea pigs,73 and VEE virus in mice.74

Previous clinical studies showed that ascorbic acid can resolve polio,9–11,75,76 acute hepatitis,77–79 viral encephalitis,80–83 measles,84 mumps,85 herpes,86 and influenza.87 There are also case reports in humans of IV vitamin C being used to successfully treat influenza,17 mononucleosis,24 Chikungunya,88 and Zika.89

ASCORBIC ACID AND COVID-19 STUDIES AND RECOMMENDATIONS

An NIH-funded study that will take place in Wuhan, China, will investigate using 12 g IV ascorbic acid for patients with severe COVID-19 pneumonia.90 A study using 10 g of IV vitamin C in patients hospitalized with COVID-19 began in Italy in March.91

The Shanghai Expert Consensus on COVID-19 Treatment organized by the Shanghai Medical Association has included ascorbic acid as a treatment for COVID-19-associated pneumonia.92 The Shanghai Guidelines for the Treatment of COVID-19 Infection, an official document endorsed by the Shanghai Medical Association and the Shanghai City government, reveals that thus far in 2020, 50 COVID-19 patients out of 358 cases have been treated with IV ascorbic acid (IVAA), using 10–20 g infused over 24 hours. One patient who continued to deteriorate was put on a 50-g infusion over a 4-hour period. This patient made a complete recovery and was eventually discharged. All patients who received IVAA improved, and had on average a 5-day shorter stay (25 days vs. 30 days) than patients who did not receive IVAA. No mortalities or adverse events were reported in the IVAA treatment group.92

An International Pulmonologist Consensus Group has stated that a moderate dose of IV vitamin C along with other nutrients (1.5 g ascorbic acid IV every 6 hours, plus 200 mg IV thiamine every 12 hours) could be considered as an adjunct protocol for treatment of COVID-19 pneumonia.93

IV ascorbic acid has a long track record of safety.94 It has been used historically in the management of viral infections and more recently for sepsis. Ongoing clinical trials in the United States, Canada, China, Italy, and other countries will hopefully support its widespread use for patients with COVID-19 infection in the larger medical community.

REFERENCES

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A Possible Role for Ascorbic Acid in COVID-19


