Role of high dose Vitamin C in management of hospitalised COVID-19 patients

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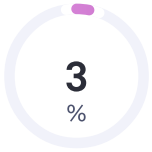

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Introduction

Viruses have always been potential threats and posed challenges to human health. Historically, various respiratory viruses like severe acute respiratory virus (SARS-CoV) in 2002, H1N1 influenza virus in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 have created havoc and wrecked human life. In December 2019, in Wuhan, China, the first pneumonia outbreak secondary to COVID was reported. It was given an interim name of 2019-nCoV by the World Health Organisation and was later renamed SARS CoV-2 by the International Committee on Taxonomy of Viruses.

SARS CoV-2 is one of the most dreadful viruses faced by mankind which not only led to the COVID outbreak in China but also spread throughout the world, infecting more than 528 million people with more than 6.3 million deaths worldwide.[1] This virus led to a disease with a varied clinical spectrum ranging from asymptomatic viral carriers to severe disease characterised by acute respiratory distress syndrome (ARDS).[2,3] The majority of affected individuals had mild symptoms, especially in the initial stages of infection. However, many patients developed life-threatening complications in the later stages with ARDS and consequent multiorgan failure leading to mortality of 7-10%, especially in the elderly and those with pre-existing comorbidities.[2-4]

The primary mechanism by which the virus caused severe disease was the initiation and propagation of a hyperimmune response, which increased pro-inflammatory cytokines and serum biomarkers.[5] The initial viral cytopathic effects were later complicated by a cytokine storm which led to ARDS and other systemic organ involvement.[6] In lieu of this cytokine storm, various anti-inflammatory and immune-modulating medications like corticosteroids, interleukin-6 (IL-6) inhibitors, and Janus kinase (JAK) inhibitors have been tried to prevent, as well as treat this life-threatening complication.

Vitamin C was one of the most commonly prescribed medications for all patients of COVID-19, irrespective of the severity of the disease. Vitamin C is an essential water-soluble vitamin required in humans for collagen synthesis, wound healing, bone development, various biochemical functions, redox reactions, synthesis of carnitine, adrenal steroids and catecholamines and metabolism of amino acids and cholesterol.[7] Over the years, its clinical role has expanded and is now commonly prescribed to treat a myriad of severe diseases, including sepsis, septic shock, acute pancreatitis and even cancer.[8-10] However, its role in these disease conditions remains controversial. Vitamin C has also been suggested as a potential therapeutic option in managing COVID-19 patients, with a few reports showing a beneficial role.[11] However, larger trials have reported variable outcomes, precluding definitive conclusions on vitamin C use in COVID-19 patients.[12-14]

RATIONALE

The pathophysiology of COVID-19 remains incompletely understood. However, some pathophysiological changes, cytokine storm, micro thrombosis and

immune-paralysis, have been described, which may lead to multiorgan dysfunction and death attributable to COVID-19. Another important phenomenon is the release of oxygen free radicals (OFRs), causing oxidative damage and end-organ failure. These pathophysiological changes are similar to those seen with sepsis and septic shock; hence, it was postulated that the use of vitamin C might be clinically beneficial in managing COVID-19.

Vitamin C Deficiency

The normal plasma levels of vitamin C have been described above 50 µmol/L.[15] It is further suggested that although these levels may be sufficient to prevent scurvy, higher levels may be required to strengthen the immune system.[16] However, these levels quickly fall in patients with acute illness, and vitamin C deficiency, defined as levels below 11 µmol/L, is commonly reported among hospitalised patients.[17-19]

Studies in critically ill COVID-19 patients have also shown low mean vitamin C levels. In addition, levels were significantly lower among non-survivors as compared with survivors.[20] In a single-centre study of patients with COVID-19-associated ARDS, more than 90% had almost undetectable serum vitamin C levels.[21] It is postulated that the reason for vitamin C deficiency observed in acute illnesses like infections, trauma, and surgery is increased metabolic consumption.[22]

Antioxidant properties

Vitamin C has well-described antioxidant properties, which may help scavenge OFRs by increasing nitric oxide levels. It also prevents the production of nitrogen species, improving capillary blood flow.[23]

Anti-inflammatory properties

Vitamin C has several anti-inflammatory effects, potentially having clinical benefits in managing COVID-19-induced cytokine storm. It inhibits tumour necrosis factor-α (TNF-α), suppresses nuclear factor kappa-B (NF-ƙB) activation, reduces pro-inflammatory cytokines and lowers histamine levels.[24]

Immune enhancing properties

By affecting lipid synthesis and reinforcing the maintenance of the alveolar epithelial barrier, vitamin C helps in improving innate immunity. Vitamin C potentially helps in immunomodulation by increasing the immunoglobin and complement levels.[25] It also exhibits immunomodulatory properties by promoting T-cell maturation and modulation, improving neutrophil chemotaxis and phagocytosis and enhancing oxidative killing. In addition, it also promotes lymphocytic proliferation and interferon production and increases antibody production.[23,24]

Prevention of micro and macrovascular dysfunction

Vitamin C is a co-factor for synthesising catecholamines (epinephrine, norepinephrine) and vasopressin, increasing vascular musculature's sensitivity to these compounds. Vitamin C also causes inhibition of inducible nitric oxide synthase (iNOS) expression, thereby preventing vasoconstriction. These effects may benefit patients with shock and improve end-organ perfusion.[23,24]

Anti-viral properties

Vitamin C has been shown to have direct and indirect effects on viral replication and can inactivate several viruses in vitro.[26] High-dose vitamin C

may cause viral inactivation by oxidation viral nucleic acids and damage to viral capsids. Vitamin C can also have indirect effects by promoting interferon production, which may, in turn, affect viral replication by binding to the cell surface. Interferons may also aid in immune stimulation leading to virus inactivation.[27] Because of these anti-viral properties, vitamin C has been used clinically to manage viral illnesses ranging from the common cold to viral ARDS secondary to a wide range of viruses like enterovirus/rhinovirus, H1N1, and CHIKV.[28-31]

Other miscellaneous effects

By reducing oxidation injury and apoptosis, vitamin C plays a role in preventing mitochondrial dysfunction. In addition, it also prevents septic cardiomyopathy by reducing oxidation injury and apoptosis and increasing carnitine synthesis.[23,24] Hence, it may prove useful in managing viral myocarditis and improving cardiac dysfunction.

CLINICAL EVIDENCE

The first large randomised clinical trial (RCT) to evaluate the effect of vitamin C in COVID-19 patients was the COVID A to Z trial. It was a multicentre open-label RCT which aimed to assess the impact of high dose zinc (50 mg), high dose ascorbic acid (8000 mg per day in 2-3 divided doses, orally) or a combination of both zinc and ascorbic acid on the duration of symptoms of SARS-COV 2. A total of 214 patients were enrolled in the study and randomly divided into 4 groups to receive a 10-day course of either zinc gluconate, ascorbic acid, or only standard of care. The study's primary endpoint was the number of days required for a reduction in symptoms (fever, cough, shortness of breath, and

fatigue) by 50%. The study's results did not show any significant decrease in the duration of symptoms compared to the standard of care. Additionally, there was no statistically significant difference in the need for hospitalisation and mortality.[32]

Even though vitamin C is widely prescribed in managing COVID-19 patients, the scientific evidence is primarily derived from case series and retrospective studies (table 1).[11,14,33-42] Only a few RCTs have been conducted to evaluate the role of high-dose intravenous vitamin C (HDIVC) in hospitalised COVID-19 patients.[12,13,43,44] The largest RCT was a Pakistani study, which included 150 patients, 75 in study and control groups. Patients in the study group were given 50 mg/kg/day of IV vitamin C compared to those who received only the standard therapy. The authors reported that the patients who received IV vitamin C became symptom-free earlier and had reduced hospital length of stay (LOS).[13] However, there was no significant difference in the need for invasive mechanical ventilation (IVM) and mortality. Other RCTs also failed to show any difference in the need for IVM or reduction in mortality rates (table 1).[12,43,44]

A few studies showed a reduction in inflammatory markers[11,33,35,36,38], but these results were neither consistent nor translated into improved clinical outcomes.[33] One small retrospective cohort study reported increased mortality in COVID-19 patients treated with IV vitamin C 1.5 gm every 6th hour for four days.[37]

A few meta-analyses have also been published evaluating the role of vitamin C in COVID-19 (table 2).[45-47] Rawat D et al. performed a meta-analysis on the

impact of Vitamin C on major clinical outcomes such as mortality, intensive care unit (ICU) admission, duration of hospital stay and need for mechanical ventilation in patients diagnosed with COVID-19. They included 6 RCTs' in their analysis encompassing 572 patients. Amongst the 6 studies, 2 were multicenter RCTs, and 4 were single centre studies. Two studies were conducted on non-severe patients, while 4 studies were conducted on severe cases of COVID-19. Both oral (2 studies) and intravenous vitamin C (4 studies) were used, and the dosage ranged from 50 mg/kg/day to 24 grams per day of vitamin C. The meta-analysis did not show vitamin C to reduce major outcomes in COVID-19 patients. Even in a subgroup analysis based on the dose, route of administration and severity of illness, no significant benefit was observed. However, this meta-analysis had multiple limitations. Firstly, heterogeneity in the study population, variable doses of vitamin C and differences in route of administration. In defence, the subgroup analysis also revealed similar results. Moreover, some studies used a combination of vitamin E and melatonin, which may have confounded the results. Also, the standard treatment used in the control groups differed and the data on the adverse effects of vitamin C was lacking.[47]

A recently published meta-analysis analysed data from five trials in which only HDIVC, defined as IV vitamin C > 2 gm/day, was prescribed to hospitalised COVID-19 patients. Among the included studies, three were RCTs, and two were retrospective studies, including 374 patients. The authors could not find any statistically significant difference in hospital LOS, mortality or adverse effects when patients were treated with HDIVC.[46]

Another larger meta-analysis, including seven trials and 807 patients analysing the role of HDIVC, also failed to show any beneficial results in terms of mortality, hospital or ICU LOS or need for IVM in COVID-19 patients. The authors noted that all the included trials were of high quality, but different dosing regimens ranged from 2–24 gm of IV vitamin C per day for 3–7 days.[45]

Recognising the lack of clinical evidence, the current National Institutes of Health (NIH) guidelines also do not make any recommendation for or against the use of vitamin C in the management of out-patient or hospitalised COVID-19 patients.[48]

DOSING

Both oral and intravenous formulations of vitamin C have shown similar clinical efficacy, but the intravenous route is generally preferred in critically ill patients.[49,50] It is suggested that higher doses of vitamin C, 2-3 gms/day, may be required to maintain the average serum concentrations in patients with acute viral infections.[51] High doses of up to 100 g/day have been tried to manage sepsis patients[52]. Although there is no consensus, any dose above 2 g/day is arbitrarily considered high.[46]

Even though several different dosing regimens have been tried in patients with COVID-19, data regarding dosing regimens are generally extrapolated from the trials on sepsis patients. Six hourly dosings have been shown to rapidly improve serum vitamin C levels, achieve a steady state and maintain therapeutic levels.[53,54] However, no consensus exists on the recommended daily dosage regimen for HDIVC.

ADVERSE EFFECTS

Even when used in high doses, vitamin C is considered harmless as it is a water-soluble vitamin. The major trials have mainly concentrated on the efficacy of vitamin C, and the data regarding adverse effects are primarily derived from case reports and series.[55] Most reported adverse effects are mild and reversible (table 3).[55-57] Rarely, patients may develop serious adverse effects, including haemolysis, disseminated intravascular coagulation and acute kidney injury (AKI). Adverse effects have been reported with oral and intravenous preparations and the use of normal doses and high doses of vitamin C. Patients with underlying renal dysfunction, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are significantly more prone to develop side effects like AKI and haemolysis.[55]

FUTURE DIRECTIONS

Almost 50 trials are presently being conducted to evaluate the role of vitamin C in patients with COVID-19 disease. These trials are being conducted in patients with different severity of disease and are trying to assess different clinical outcomes ranging from the need for hospitalisation, resolution of symptoms, need for organ support, need for IVM and mortality. The role of vitamin C is also being explored in combination with other therapies like zinc, quercetin, and curcumin and comparison to other antioxidants like vitamin E, melatonin, pentoxifylline, and N-acetyl cysteine. These trials may help us better understand vitamin C's clinical efficacy and safety profile and clarify its potential role in the management of COVID-19 patients. Also, these studies may shed light on the dosing of HDIVC, as most of the studies performed till now have used different dosing regimens, which might have affected their results.

CONCLUSIONS

Vitamin C is a relatively safe therapeutic option, and there may be scientific rationale which theoretically may help in the recovery of COVID-19 patients. Many observational studies and some RCTs have been conducted to evaluate its role in COVID-19. However, presently there is a dearth of clinical evidence showing its utility in managing COVID-19 patients; hence, it can not be recommended for routine use in these patients. Further larger multicenter RCTs are warranted to prove their safety and potential role.

1.	*in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012*	Cureus | Physiological Hazard Assessment While Wielding Personal ... https://www.cureus.com/articles/91023-physiological-hazard-assessment-while-wielding-personal-protective-equipment-ppe-among-health-care-workers	Originality
2.	*The study's primary endpoint was the number of*	A randomized studyof yoga therapy for the prevention of recurrent ... https://www.cardioaragon.com/wp-content/uploads/yoga-therapy-for-vasovagal-syncope.Europace.2021.pdf	Originality
3.	*symptoms (fever, cough, shortness of breath, and fatigue*	Are 'COVID Toes' a New Sign of Coronavirus? | Coronavirus ... https://www.anchoragepress.com/news/coronavirus/are-covid-toes-a-new-sign-of-coronavirus/article_ff6b6b96-85c6-11ea-a1ea-df27a6f093c4.html	Originality
4.	*Additionally, there was no statistically significant difference in the*	The Effect of Magnification Loupes on Dental Hygienists' Posture while Exploring	Originality
5.	*compared to those who received only the standard*	Types of Flu Vaccines for Yearly Immunization	Originality
6.	*However, there was no significant difference in the*	Omicron vs. Delta: How the 2 COVID-19 Variants Compare - Health https://www.health.com/condition/infectious-diseases/coronavirus/omicron-vs-delta	Originality
7.	*and need for mechanical ventilation in patients diagnosed with COVID-19.*	Angiotensin-Converting Enzyme Inhibitors Versus Angiotensin II Receptor ... https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.120.007	Originality

		115	
8.	*The authors could not find any statistically significant*	Is Bhutan destined for 100% organic? Assessing the economy-wide effects of a large-scale conversion policy	Originality
9.	*not make any recommendation for or against the use of*	Injections for knee osteoarthritis – subtle but significant impact of ... https://www.wolterskluwer.com/en/news/injections-for-knee-osteoarthritis-subtle-but-significant-impact-of-revisions-in-clinical-practice	Originality