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## Role of high dose vitamin C in management of hospitalised COVID-19 patients: A minireview

Deven Juneja, Anish Gupta, Sahil Kataria, Omender Singh

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### Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as one of the most dreadful viruses the mankind has witnessed. It has caused worldwide havoc and wrecked human life. In our quest to find therapeutic options to counter this threat, several drugs have been tried, with varying success. Certain agents like corticosteroids, some anti-virals and immunosuppressive drugs have been found useful in improving clinical outcomes. Vitamin C, a water-soluble vitamin with good safety profile, has been tried to reduce progression and improve outcomes of patients with coronavirus disease 2019 (COVID-19). Because of its anti-oxidant and immunomodulatory properties, the role of vitamin C has expanded well beyond the management of scurvy and it is increasingly being employed in the treatment of critically ill patients with sepsis, septic shock, acute pancreatitis and even cancer. However, in spite of many case series, observational studies and even randomised control trials, the role of vitamin C remains ambiguous. In this review, we will be discussing the scientific rationale and the current clinical evidence for using high dose vitamin C in the management of COVID-19 patients.

**Key Words:** Ascorbic acid; COVID-19; SARS-CoV-2; Vitamin C

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**Core Tip:** Vitamin C has several biochemical effects including anti-oxidant, anti-inflammatory, immunomodulatory, and anti-viral properties which could make it a possible low-risk, add on to the current therapeutic options for managing coronavirus disease 2019 (COVID-19) patients. As it is a water-soluble vitamin, even high doses have been shown to be safe and only rarely, complications have been reported. In the last couple of years, many case series, observational studies and even randomised control trials have been conducted to evaluate the role of vitamin C in COVID-19, but have shown conflicting results. Hence, as per the current clinical evidence, the role of vitamin C remains ambiguous and it cannot be recommended as a part of routine therapeutic regimen for managing COVID-19 patients.

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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 but 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 which is 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 myriad of severe diseases including sepsis, septic shock, acute pancreatitis and even cancer[8-10]. However, its role in these disease conditions remain 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 multi-organ dysfunction and death attributable to COVID-19. Another important phenomenon is 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, and 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  $\mu\text{mol/L}$ [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  $\mu\text{mol/L}$ , is commonly reported among hospitalized 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 center 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 the increase in metabolic consumption[22].

### **Anti-oxidant properties**

Vitamin C has well described anti-oxidant properties, which may help in scavenging OFRs by increasing nitric oxide levels. It also prevents 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 tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), suppresses activation of nuclear factor kappa-B (NF-kB), 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 immunoglobulin and complement levels[25]. It also exhibits immunomodulatory properties by promoting T-cell maturation and modulation, improving neutrophil chemotaxis and phagocytosis and by enhancing oxidative killing. In addition, it also promotes lymphocytic proliferation, interferon production and increases antibody production[23,24].

### **Prevention of micro and macro vascular dysfunction**

Vitamin C acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine), and vasopressin and increases the sensitivity of vascular musculature to these compounds. Vitamin C also causes inhibition of inducible nitric oxide synthase (iNOS) expression, thereby preventing vasoconstriction. These effects may be particularly helpful in patients with shock and may 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 of 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 common cold to viral ARDS secondary to 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 prevention of mitochondrial dysfunction. In addition, it also prevents septic cardiomyopathy by reducing oxidation injury and apoptosis and by increasing carnitine synthesis[23,24]. Hence, it may prove useful in managing viral myocarditis and improving cardiac dysfunction.

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## **CLINICAL EVIDENCE**

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The first large randomized 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 effect 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 randomised equally into 4 groups to receive a 10-d course of either zinc gluconate, ascorbic acid, both or only standard of care. The study's primary end point was the number of days required for a reduction in symptoms (fever, cough, shortness of breath, and fatigue) by 50%. The results of the study did not show any significant decrease in the duration of symptoms as compared to 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 the management of 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 each in study and control groups. Patients in the study group were given 50 mg/kg/d of IV vitamin C and 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 (IMV) and mortality. Other RCTs also failed to show any difference in the need for IMV 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 in to improved clinical outcomes[33]. One small retrospective cohort study even reported increased mortality in COVID-19 patients treated with IV vitamin C 1.5 gm every 6<sup>th</sup> hourly 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 *et al*[47] 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/d to 24 g per day of vitamin C. The meta-analysis did not show vitamin C to reduce any 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 including heterogeneity in the study population, variable doses of vitamin C and differences in route of administration. In defense, the subgroup analysis also revealed similar results. Moreover, some studies used 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  $\geq 2$  gm/d, 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 terms of 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 IMV in COVID-19 patients. The authors further noted that all the included trials were of high quality but different dosing regimens were used ranging from 2-24 gm of IV vitamin C per day for 3-7 d[45].

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

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## DOSING

Both oral and intravenous formulations of vitamin C have shown similar clinical efficacy, but intravenous route is generally preferred in critically ill patients[49,50]. It is suggested that higher doses of vitamin C, 2-3 gm/day, may be required to maintain the normal serum concentrations in patients with acute viral infections[51]. High doses of up to 100 g/d have been tried in the management of sepsis patients[52]. Although there is no consensus, any dose above 2 g/d is arbitrarily considered as high dose[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 dosing have been shown to rapidly improve serum vitamin C levels, achieve a steady state and maintain therapeutic levels[53,54]. However, no consensus presently exists on the recommended daily dosage regimen for HDIVC.

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## 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

**Table 1** Different studies evaluating the role of high dose intravenous Vitamin C in COVID-19

S. No.	Title	Year of publication	Country of origin	Study design	Sample size in the control arm	Sample size in the intervention arm	Intervention summary	Results in brief
1	Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia[14]	2022	Turkey	Retrospective study	170 patients	153 patients	2 g/d IV	No difference in mortality
2	High-dose intravenous vitamin C decreases rates of mechanical ventilation and cardiac arrest in severe COVID-19[33]	2022	USA	Retrospective cohort study	75 patients	25 patients	3 gm 6 hrly for 7 d IV	HDIVC group had a prolonged hospital stay, prolonged ICU stay, and prolonged time to death CRP levels were lower in the HDIVC group while other inflammatory markers (d-dimer and ferritin) were similar in both groups. HDIVC patients had significantly lower rates of IMV and cardiac arrest
3	Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial[43]	2021	Iran	RCT	11	10	IV vitamin C (2 g, q6hr), oral; melatonin (6 mg, 6 hourly), and oral zinc sulfate (50 mg, 6 hourly) for 10 d	No differences in PaO <sub>2</sub> /FiO <sub>2</sub> , CRP, ESR or LDH levels and ICU LOS
4	Pilot trial of high-dose vitamin C in critically ill COVID-19 patients[12]	2021	China	Multi center RCT	29 in control	27 treatment group	12 g of vitamin C/50 ml every 12 h for 7 d at a rate of 12 mL/h IV	No difference in IMV free days at D28; no difference in 28-d mortality. Steady rise in the PaO <sub>2</sub> /FiO <sub>2</sub> in vitamin C group
5	No significant benefit of moderate-dose vitamin C on severe COVID-19 cases[34]	2021	China	Retrospective cohort study	327	70	2-4 gm/d	No significant difference in clinical improvement or mortality rate
6	Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study[35]	2021	China	Retrospective case series		12 patients	71 to 350 mg/kg/d for 3 d IV	Reduction in CRP Improved PaO <sub>2</sub> /FiO <sub>2</sub> and SOFA score
7	High Dose Intravenous Vitamin C for Preventing The Disease Aggravation of Moderate COVID-19 Pneumonia. A Retrospective Propensity Matched Before-After Study[36]	2021	China	Retrospective before-after study	55 patients	55 patients	100 mg/kg/d IV for 7 d	Significant reduction in progression to severe disease. Reduced levels of CRP, D-dimer and APTT
8	Safety and effectiveness of high-dose vitamin C in patients with COVID-19: A randomized open-label clinical trial[44]	2021	Iran	Randomised open-label study	30 patients	30 patients	6 g/d IV	Reduced temperature and improved SaO <sub>2</sub> in HDIVC group. No difference in ICU or hospital mortality Longer hospital LOS in HDIVC group
9	Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection[37]	2021	USA	Retrospective cohort study	24 patients	8 patients	1.5 grams IV vitamin C every 6 h for up to 4 d	HDIVC group had higher rates of hospital mortality and mean SOFA scores post-treatment. No difference in daily vasopressor requirement or ICU LOS
10	High-dose intravenous vitamin C attenuates hyperinflammation in severe coronavirus disease 2019[38]	2021	China	Retrospective cohort study	151	85	100 mg/kg every 6 h for day 1 followed by 100 mg/kg every 12 h for the next 5 d	Significantly reduced inflammatory markers (hs-CRP, IL-6, TNF-alpha)
11	The efficiency and safety of high-dose	2021	China	Retrospective	30	46	6 g twice a day on day 1	Reduced 28 d mortality. No change in oxygen support

	vitamin C in patients with COVID-19: A retrospective cohort study[39]			cohort study			followed by 6 gm once a day for 4 d IV	
12	High-dose vitamin C ameliorates cardiac injury in COVID-19 pandemic: A retrospective cohort study[40]	2021	China	Retrospective cohort study	62	51	100 mg/kg every 6 h for day 1 followed by 100 mg/kg every 12 h for the next 5 d	HDIVC can ameliorate cardiac injury through alleviating hyperinflammation
13	The Role of Vitamin C as Adjuvant Therapy in COVID-19[13]	2020	Pakistan	RCT	75 patients	75 patients	50 mg/kg/day of intravenous (IV)	Earlier resolution of symptoms and reduced hospital LOS. No significant difference in the need for IMV and mortality
14	Activities of serum ferritin and treatment outcomes among COVID-19 patients treated with vitamin c and dexamethasone:An uncontrolled single-center observational study[41]	2020	India	Prospective, observational study		50 patients	NA	Mortality 6%
15	The use of IV vitamin C for patients with COVID-19: A case series[11]	2020	USA	Case series		17 patients	1 g every 8 h for 3 d IV	Significant decrease in inflammatory markers. Mortality 12%
16	Application of methylene blue -vitamin C - N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial[42]	2020	Iran	Phase I clinical trial	25 ICU COVID-19 patients. 5 received MCN as last resort	25 healthy individuals	Methylene blue (1 mg/kg) along with vitamin C (1500 mg/kg) and N-acetyl Cysteine (1500 mg/kg) orally or intravenously	Reduced methhemoglobin levels, survival of 4/5 patients

IV: Intravenously; HDIVC: High dose intravenous vitamin C; ICU: Intensive care unit; CRP: C-reactive protein; RCT: Randomised control trial; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; LOS: Length of stay; IMV: Invasive mechanical ventilation; SOFA: Sequential organ failure assessment; APTT: Activated prothrombin time; IL: Interleukin; TNF: Tumour necrosis factor; MCN: Methylene blue; USA: United states; COVID-19: Coronavirus disease 2019; RCT: Randomised control trial; NA: Not available.

been reported with both 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 especially 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 IMV and mortality. 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.

**Table 2 Meta-analyses evaluating the role of Vitamin C in COVID-19**

S. No.	Title	Year of publication	Country of origin	Included studies	Included sample size	Results in brief
1	Intravenous vitamin C use and risk of severity and mortality in COVID-19: A systematic review and meta-analysis[45]	2022	China	7 studies (3 RCTs, 4 observational studies)	807 patients	IV vitamin C treatment did not affect disease severity or mortality
2	The effectiveness of high-dose intravenous vitamin C for patients with coronavirus disease 2019: A systematic review and meta-analysis[46]	2022	Korea	5 studies (3 RCTs, 2 retrospective trials)	374 patients (186 HDIVC and 184 control group)	No difference in hospital LOS or mortality
3	Vitamin C and COVID-19 treatment: A systematic review and metaanalysis of randomized controlled trials[47]	2021	India	6 RCTs	572 patients	Vitamin C treatment didn't reduce mortality, ICU LOS, hospital LOS or need for invasive mechanical ventilation

RCT: Randomised control trial; IV: Intravenously; HDIVC: High dose intravenous vitamin C; LOS: Length of stay; ICU: Intensive care unit.

**Table 3 Adverse effects reported with vitamin C**

Item	Description
General	Interference with laboratory tests, phlebitis, nausea, vomiting
Neuro-muscular	Lethargy, fatigue, muscle cramps, headache, altered mental status
Metabolic	Hyperglycemia, hypernatremia
Haematological	Haemolysis, disseminated intravascular coagulation, methemoglobinemia
Renal	Oxalosis, renal stones, acute kidney injury

## CONCLUSION

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 dearth of clinical evidence showing its utility in the management of COVID-19 patients; hence, it cannot be recommended for routine use in these patients. Further larger multi-center RCTs are warranted to prove its safety and potential role.

## FOOTNOTES

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