The relationship between COVID-19 and blood vitamin C; a systematic review study

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Abstract

Introduction: The rapid worldwide spread of COVID-19 has caused a global health crisis. Unfortunately, no vaccine or special antiviral drug has been developed against COVID-19 to date, symptomatic supportive care has been the most common treatment.
Objectives: the purpose of this systematic review aims to provide a timely, rigorous, and continuously updated summary of the available evidence on the role of vitamin C in treating patients with COVID-19.
Methods: In this review, we identified studies published in 2020 that describe on the relationship between COVID-19 and vitamin C. We searched PubMed, Google Scholar, Scopus, Magiran, SID and Web of Science for research articles published up to 23 December 2020 using the keywords of vitamin C, COVID-19, SARS-COV-2 and coronavirus 2.
Results: At the initial stage of screening, 181articles were excluded after reviewing the title and removing irrelevant and duplicate titles, 52 articles were selected to review the abstract. After reviewing the abstract (or in articles without abstracts after reviewing the original text), nine articles were finally considered suitable for this purpose and were reviewed and finalized. Vitamin C is a pivotal component of the immune system, with proven antioxidant, cytokine storm suppressor and anti-inflammatory properties and has been tested in numerous studies for its role in severe sepsis and ICU care, especially when used as a continuous high-dose intravenous infusion. In addition, some studies indicated high-dose intravenous vitamin C treatment was associated with fewer days on mechanical ventilation, shorter ICU stay, and earlier recovery compared to the average length of mechanical ventilation, disease duration, and ICU stay in critical COVID-19 patients.
Conclusion: Vitamin C can significantly improve clinical symptoms, inflammatory response, immune and organ function in COVID-19 patients. In patients affected with COVID-19, high-dose intravenous vitamin C is expected to improve pulmonary function and reduce mortality for patients with COVID-19 and can be beneficial in aspects of inflammatory response, immune and organ function for aggravation of COVID-19 patients, however further clinical trials are necessary.

Introduction

Coronavirus disease 2019 (COVID-19), the infectious illness caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide health crisis since December 2019.

Studies from various countries have reported that COVID-19 is associated with rapid spread, acute respiratory distress syndrome (ARDS), saturated capacity of intensive care units, and high mortality (1). The severity of COVID-19 is classified into mild, moderate, severe and critical type on the guideline made by National Health and Family Planning Commission of the People's Republic of China (3). The severe patient is mainly characterized with deteriorated respiratory function and rapid progression of radiological lesions, and the critical patient further requires mechanical ventilation, accompanying with shock or multiple organ failure (2). It has affected and continues to affect quite a lot of people from all age groups in the world. General clinical signs of COVID-19 are high fever, cough, nasal congestion, dyspnea, myalgia,

Key point

It has also been shown that high-dose intravenous vitamin C is expected to improve pulmonary function and reduce mortality for patients with COVID-19, rates of intubation and mechanical ventilation. However, in other studies there was no significant difference in the need for mechanical ventilation and mortality. In general, more studies are needed to evaluate the effect of vitamin C on COVID-19.

fatigue, upper and lower respiratory tract infection and diarrhea. The most important and fatal clinical sign of the virus has been described as pneumonia. Unfortunately, no vaccine or special antiviral drug has been developed against COVID-19 yet (3). Several studies have assessed the efficacy and safety of drugs such as lopinavir/ritonavir, remdesivir and chloroquine in patients with COVID-19 (4). To date, symptomatic supportive care has been the most common treatment. It has been reported that the mechanism of COVID-19 is related to cytokine storms and subsequent immunogenic damage, especially damage to the endothelium and alveolar membrane (5).

Immune system has a major role in fighting against different types of infection but needs some supplements such as vitamin C for the immune cells to function properly (6). Vitamin C (ascorbic acid), is a water-soluble compound that can be administered by oral, enteral, and parenteral routes. It is a known antioxidant and maintains endothelial barriers and has been shown in animal studies to prevent cytokine surges which lead to alveolar capillary damage, prevent neutrophil accumulation in alveolar spaces, support phagocytosis of bacteria, and support lymphocyte function. Vitamin C is also involved in non-oxidant processes like biosynthesis of collagen, carnitine, tyrosine and peptide hormones as well as myelin (7). Previous clinical trials found that supplementation with high dose of vitamin C decreased the severity and duration of respiratory viral infections (5). Based on these findings, vitamin C might be used in management of COVID-19 as it might improve the immunological response against the novel coronavirus (SARS-CoV-2) (8). High does intravenous vitamin C (HDIVC), a new developed method of administration, has been proven to exert beneficial effect in various critical illness by animal and clinical study (2,5,8) and proven to block several key components of cytokine storms, and too HDIVC showed safety and varying degrees of efficacy in clinical trials conducted on patients with bacterial-induced sepsis and ARDS (5). Currently, several clinical trials are evaluating the benefits of vitamin C administration for the evolution of COVID-19 infection (9).

Objectives

The purpose of this review is to examine whether intake of vitamin C administration is a promising method for the COVID-19 pandemic in accordance with the most recent evidence.

Methods
Protocol and registration
This is a review on the highest interest scientific topic of the day, related to pandemic COVID-19. We have searched major electronic databases (PubMed, Google Scholar and Medline) to identify available evidence providing information on the theoretical correlation of biochemistry of vitamin C as a therapeutic application for the patients with COVID-19 infection in 2020. Keywords used include vitamin C, ascorbic acid, COVID-19, SARS-CoV-2, and coronavirus 2.

Study design
Our study was performed from a review and Analysis of published reports examining the association between COVID-19 and vitamin included clinical trials, prospective and retrospective cohort studies, case-control studies; cross-sectional studies, case series, and case reports.

Intervention
We included clinical studies involving assessment of the relationship between COVID-19 and vitamin C between to 23 December 2020 and 14 Jan 2020 using "vitamin C and COVID-19"assearch term without restrictions on the study type of setting. The extracted information included mortality, clinical benefits, and adverse events. Outcomes were extracted in all data forms (eg, dichotomous and continuous) as reported in the included studies. The results of our databases search were documented and described in Figure1 and Table 1.
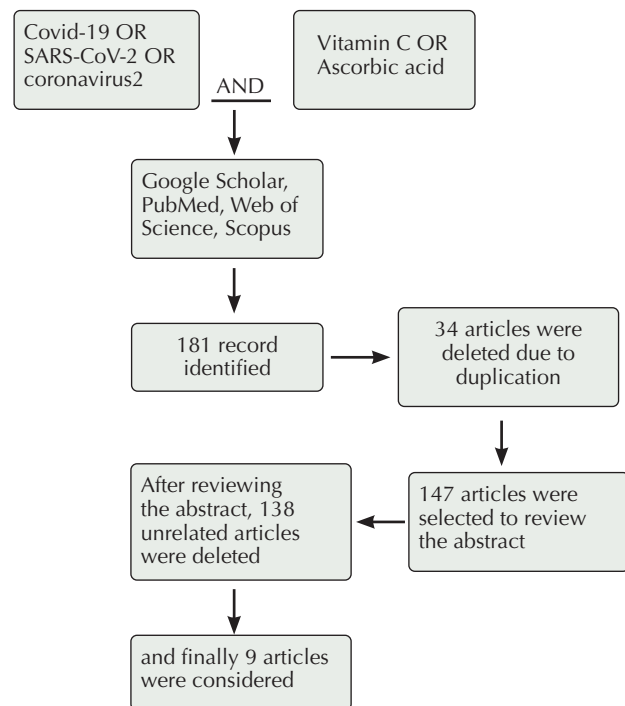

Figure 1. Summary of search strategy and paper exclusion.

Table 1. Summary of studied papers

Author name	Location	Population	No. of people surveyed	Type of study	Result
Ohanube et al (4)	Nigerian	Nigerians who used vitamin C based regimen.	4	Case report	The use of ascorbic acid or vitamin C loaded plants as an important supportive medicine for preventing the infection by SARS-CoV-2, or in the management of COVID-19.
Liu et al (5)	Wuhan, China	Adults	308	Prospective RCTs	High-dose intravenous vitamin C is expected to improve pulmonary function and reduce mortality for patients with COVID-19.
Hiedra et al (10)	Philadelphia, USA	Patients who received IV vitamin C for COVID-19.	17	Case series	The inpatient mortality was 12% with 17.6% rates of intubation and mechanical ventilation. Decrease in inflammatory markers, including ferritin and D-dimer, and FiO2 requirements, after vitamin C administration was significant.
Chiscano-Camón et al (11)	Barcelona, Spain	Patients with SARS-CoV-2-associated ARDS	18	Case series	The levels of vitamin C are extremely low.
Arvinte et al (12)	North American	Critically ill COVID-19 patients hospitalized in May 2020 in the ICU of North Suburban Medical Center	21	Cohort	Of 21 critically ill COVID-19 patients, there were 11 survivors. Serum levels of vitamin C was low in most of our critically ill COVID-19 ICU patients. Older age and low vitamin C level appeared co-dependent risk factors for mortality from COVID-19 in our sample. Insulin resistance and obesity were prevalent in this cohort, but smoking was not.
Burugu et al (13)	Karimnagar	COVID-19 patients with mean age 41.70 years	50	Prospective	The recovery rate (94%) was remarkably high and is a good sign of COVID 19 treatment with vitamin C and dexamethasone. The mean serum ferritin levels among recovered and expired patients were 478.81 ng/mL and 1410 ng/ml, respectively.
Kumari et al (14)	Unit of a tertiary care hospital in Karachi, Pakistan	Patients who needed mechanical ventilation within 12 hours of admission	150	Prospective, open-label RCT	COVID-19 patients who received IV VC became symptom-free earlier (7.1 ± 1.8 vs. 9.6 ± 2.1 days, $P < 0.0001$) and spent fewer days in the hospital (8.1 ± 1.8 vs. 10.7 ± 2.2 days, $P < 0.0001$) compared to those who received standard therapy only. There was no significant difference in the need for mechanical ventilation ($P = 0.406$) and mortality ($P = 0.31$) between the two groups.
Chaudhary et al (15)	Department of Pulmonary Critical Care Medicine, Einstein Medical Center Philadelphia, USA	Adult patients with laboratory-confirmed COVID-19 discharged from ICU	128	Retrospective case series	A decrease in vasopressor requirement was noticed in two patients after starting on vitamin C. In our small case series of patients, the mortality was still high despite treatment with vitamin C.
Zhao et al (16)	Shanghai, China	The patients 32-65 years were those with confirmed diagnosis of severe or critical COVID-19 pneumonia, who received HDIVC within 24 hours after disease aggravation.	12	Retrospective case series	C-reactive protein (CRP) was found to decrease significantly from day 0 to 3 and 7 lymphocyte and CD4+ T cell counts in severe patients reached to normal level since day 3. Similar improving trends were observed for PaO2/FiO2 and sequential organ failure assessment score. Better improving effect was observed in severe than critical patients after HDIVC.

Discussion

The results of this study reveal that vitamin C deficiency can present an association with COVID-19 severity, especially in patients with SARS-CoV-2-associated ARDS. Previous reports revealed that cytokine storms, which can be suppressed by vitamin C, are believed to be the main mechanism in the deterioration of patients with COVID-19(5). Vitamin C, traditionally considered a dietary supplement, has antimicrobial and immunomodulatory properties. HDIVC has been proven to be safe and therapeutic in critical care medicine, primarily as an adjunct to the treatment of septic shock and multiple organ failure, where it has been shown to improve outcomes and reduce mortality. Specific treatments for COVID-19 are not available at present. There are several clinical trials exploring immunotherapy. HDIVC has great advantages in terms of stability, availability, safety and cost. HDIVC is expected to improve pulmonary function and reduce mortality for patients with COVID-19. We believe that our methods are well suited to handle the abundance

of evidence that is to come, including evidence on the role of vitamin C for COVID-19. We have identified multiple ongoing studies addressing this question, including nine randomized trials, which will provide valuable evidence to inform researchers and decision-makers shortly. The main limitation of our review results from the absence of any evidence to inform decisions. We hope that the substantial number of studies that are expected to be completed in the next months will shed some light on the role of vitamin C in the treatment of COVID-19. In critical ill patients; serum level of vitamin C is reported to drop to 10–30 mol/L (normal level of 80–100 mol/L). This might be related to rapid exhaustion by reactive oxygen species (ROS), dilution due to rapid fluid resuscitation, insufficiency supplement and elimination by renal replacement therapy. Vitamin C deficiency was reported correlated with the occurrence of multiple organ failure in critically ill patients, and requirement for vitamin C increase with diseases severity. Intravenous administration of vitamin C showed excellent supplementary effect by quickly increasing the serum level from mol/L to mmol/L. Therefore, it is rational to apply HDIVC in the rescue therapy of COVID-19 in severe condition. Recently, treatment with HDIVC for severe ARDS from COVID-19 was recommended (16). Compared to placebo, intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water over 96 hours) was associated with significantly lower 28-day mortality (29.8% vs 46.3%, $P = 0.03$).21 The expert consensus Shanghai Medical Association recommends that 100–200 mg/kg intravenous vitamin C daily can lead to an improvement in the oxygenation index (17).

Conclusion

Novel coronavirus infection is a global pandemic that has affected many people around the world. In the absence of a therapeutic vaccine or drug, the management of COVID-19 is strictly based on preventive measures and supportive treatments. It has also been shown that, high-dose intravenous vitamin C is expected to improve pulmonary function and reduce mortality for patients with COVID-19, rates of intubation and mechanical ventilation. However, in other studies there was no significant difference in the need for mechanical ventilation and mortality. In general, more studies are needed to evaluate the effect of vitamin C on covid-19.

Authors' contribution
NM participated in search and analysis of the paper. MSM is the corresponding author. SH, NM, EM, AS, YK and MSM conducted the final edit and finalized the manuscript. All authors read and signed the final paper.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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