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Literature Review

Using Vitamin C as Pre-Exposure Prophylaxis and Treatment to Strengthen the Immune System against COVID-19: A Review of Current Literature

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Abstract

The coronavirus 19 (COVID-19) is a life-threating disease of public health importance. It is caused by the outbreak of a new coronavirus, leading to community-acquired pneumonia, as well as respiratory and multiple organ failure. The disease has spread across the globe, affecting numerous health systems and illustrating the prevailing gap in preventive and curative measures against disease outbreak and severe acute respiratory syndrome (SARS). More than 209,839 confirmed cases have been documented and 8778 deaths have been recorded within the first three months of the emergence of the disease. The high case fatality rate is due to the lack of a curative treatment or availability of a proven vaccine against SARS-CoV-2. Moreover, it is anticipated that the discovery of effective interventions might take longer; meanwhile, the COVID-19 pandemic is skyrocketing.

It is therefore imperative for the use of cost-effective, preventive and readily available interventions to be implemented instantly to curb the disease morbidity and mortality rate - for example, the use of vitamin C against numerous forms of influenza.

Vitamin C has shown a potent antimicrobial property in reducing the pathogenicity of viruses. Previous studies have illustrated the role of vitamin C in the treatment of the severe acute respiratory syndrome (SARS) outbreak during 2002 and the Middle East respiratory syndrome (MERS) outbreak during 2012.

In addition, there is an ongoing randomised control trial study in the Republic of China on the consumption of high-dose vitamin C in the treatment of COVID-19. Based on its pharmacodynamic, vitamin C is an essential adjuvant in the treatment of viral pneumonia and is also a cost-effective measure which can be given while waiting to prevent and treat COVID-19. In contrast, there are a few studies that contradict the effectiveness of vitamin C versus the recovery against influenza viruses. More research is, therefore warranted in order to evaluate the contradicting roles of vitamin C in the management of viral respiratory illnesses.

In this literature review, the authors emphasise the role of vitamin C in preventive and curative measures during the management of COVID-19.

Keywords: *COVID-19; SARS-Cov2; MERS-CoV; Vitamin C; Coronavirus; Immune System*

Introduction

The World Health Organization (WHO) has declared COVID-19 a pandemic disease, pointing to the over 209,839 confirmed cases of the coronavirus illness in over 178 countries and territories around the world, with the sustained risk of further global spread, and having caused 8778 deaths [1]. There is as yet no proven, evidence-based treatment for COVID-19; however, preventive measures based on strict hygiene have demonstrated their efficacy in terms of infection control [2].

Numerous studies have shown that influenza viruses lead to increased production of respiratory free radicals, which are responsible for oxidative stress and play a significant role in the pathogenicity of the viral infection [3,4]. Similarly, coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) predispose to bacterial infection by causing lung injury through substantial lethal molecule production in the respiratory tissue, leading to pulmonary oedema, hypoxia and intense neutrophilic infiltration resulting from the increased permeability of the alveolar-capillary membrane [5,6] [6].

Vitamin C has been the most researched antioxidant - a naturally occurring organic compound - which scavenges the free radicals and reduces the oxidative stress as a lead detoxifying agent and also assists in physiological processes such as hormone and collagen synthesis, as well as immune stimulation [7-9] [9].

In the same way, there is an ongoing study testing *in vitro* molecules for MERS-CoV, human-based SARS-CoV, and COVID-19, which has reported interferon-beta (IFNb) to be the most potent in reducing MERS-Cov replication *in vitro* [10]. Furthermore, improvement in peripheral blood mononuclear cell-derived IL-1, IL-10, and TNF-α after lipopolysaccharide (LPS) stimulation was observed in the healthy human volunteers receiving 1g/day of vitamin C supplement [11].

Methods

We undertake an electronic search on Pubmed, CENTRAL and google scholar with the following MESH and key words: "Vitamin C OR ascorbic OR Acid, Ascorbic OR L-Ascorbic Acid OR Acid, L-Ascorbic OR L Ascorbic Acid OR Sodium Ascorbate" AND "SARS OR MERS OR SARS-CoV OR MERS-COV OR COVID-19" AND "Immune system OR immune response OR Antibody-Producing Cells OR Antibody Formation OR Immunity OR Immunity, Cellular OR Lymphocyte Transformation". In addition, we searched ongoing studies on https://clinicaltrials.gov and the WHO COVID-19 database. Out of 207 studies, four studies were eligible. The results are reported as table including the study ID, population, interventions, outcomes, study designs, P-Value or 95%CI and Risk of bias or status.

Study ID	Population	Interventions	Outcomes	Comparisons	Study designs	P-Value or 95%CI	Risk of bias or status
Fowler 2019	After intensive care unit (ICU) admission for sepsis, patients were followed up for development of acute respiratory failure. Among them, 84 were in the intervention group and 83 in the control group	Intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water) every 6 hours for 96 hours.	1. Sequential Organ Failure Assessment score 2. Plasma biomarkers of inflammation (C-reactive protein levels) 3. vascular injury (thrombomodulin levels)	Placebo	Randomized, double-blind, placebo-controlled, multi-center trial	1. MD, -0.10; 95% CI, -1.23 to 1.03; P = .86) 2. MD, 7.94 μg/mL; 95% CI, -8.2 to 24.11; P = .33) 3. MD, 0.69 ng/mL; 95% CI, -2.8 to 4.2; P = .70)	Low risk of bias

Kim 2018	Adult patients with severe pneumonia who were admitted to the medical ICU	Vitamin C protocol (6 g of vitamin C per day)	1. Hospital mortality 2. Mortality in propensity score-adjusted analysis 3. Median improvement in the radiologic score	Baseline characteristics	Propensity score-based analysis of a before-after cohort study	1. 17% vs. 39%; P = 0.04 2. Adjusted odds ratio = 0.15, 95% confidence interval = 0.04-0.56, P = 0.005 3. 4 vs. 2; P = 0.045	Moderate risk of bias
Corrao 2020	500 participants/ all patients consecutively hospitalized with positive swab test of SARS-CoV-2 and interstitial pneumonia or with interstitial pneumonia with indication of intubation	10 gr of vitamin C intravenously in addition to conventional therapy.	1. Change of hospital mortality 2. PCR levels 3. Lactate clearance 4. Symptoms 5. Positive swab 6. Tomography imaging	Baseline characteristics	Interventional (Clinical Trial)	N/A	Ongoing study
Peng 2020	140 participants/ ≥ 18 years old; Diagnosed as serious or critical SARI (according to the 4th version of Diagnosis and Clinical management of 2019-nCoV infected pneumonia); Being treated in the ICU.	12g Vitamin C + sterile water for injection; total volume: 50 ml. 12 ml/h; infusion pump; q12h.	1. Ventilation-free days 2. ICU length of stay 3. Vasopressor days 4. Respiratory indexes 5. Ventilator parameters	Placebo Comparator: Sterile water for injection	Randomized control trial	N/A	Ongoing

Results

Among four studies included in qualitative analysis, only two studies reported that results. There are three ongoing trials. Fowler 2019 [12] has reported that vitamin C was not effective among severe SARS patients; however Kim 2018 [13] has demonstrated that vitamin C improved all the outcomes. Due the variability between the study designs and outcomes, we cannot conclude in this stage on the effectiveness of vitamin C to improve immune responses among SARS-CoV patients. However, the three ongoing trial role may be substantial to clarify the effects of vitamin C among this specific population.

Vitamin C deficiency and the daily cellular need

Various studies across the globe have shown that there is an overall low uptake of fruit consumption among the general population, predisposing them to the potential risk of future illness. Such lower consumption has been attributed to factors such as food access, social influences and attitudes about a healthy diet [14,15]. Correspondingly, vitamin C is an organic compound from plants and can only be obtained from an external source to humans [16].

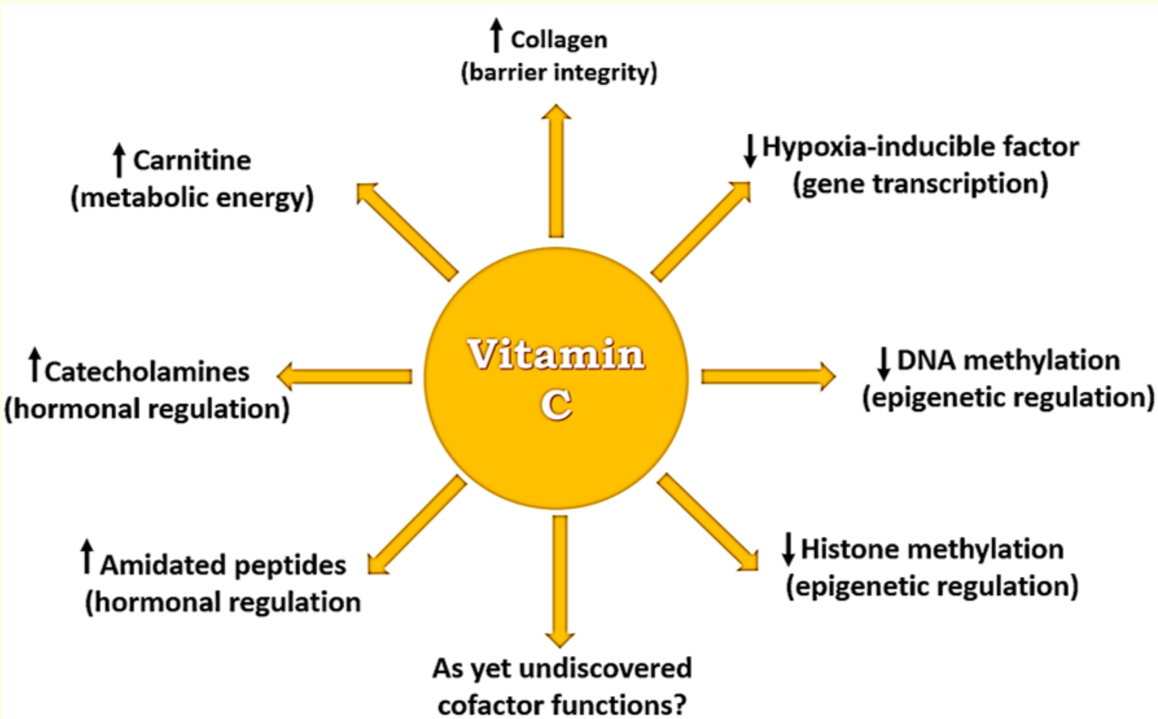

Figure 1: *The enzyme cofactor activities of vitamin C. Vitamin C is a cofactor of a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes. These enzymes contribute to the synthesis of carnitine, collagen, and catecholamine hormones, e.g. norepinephrine and vasopressin. The hydroxylate transcription factors, e.g. methyl DNA, histones and hypoxia-inducible factor-α, are also hydroxylated by these enzymes, which play a significant role in epigenetic regulation and gene transcription. ↑ indicates an increase and ↓ indicates a decrease [17] [17].*

Apart from its immunologic function and antiviral effect, vitamin C has other biochemical functions as it contributes to the production of adrenal steroids and catecholamines, iron absorption, redox-reactions, and the metabolism of amino acids and cholesterol [18,19].

Many studies have demonstrated that vitamin C possesses potent antimicrobial properties in reducing the pathogenicity of bacteria, viruses, parasites and fungi. Several studies have reported that vitamin C, especially in the form of dehydroascorbic acid (DHA), inhibits the replication of herpes simplex virus type 1, poliovirus type 1 and influenza virus type A [20]. Moreover, a high dose of vitamin C infusion, ranging from 7.5g to 50g, effectively decreases the Epstein-Barr viral infection (EBV) antibody by lowering the level of antigens in the acute stage of the disease [21,22] [22].

Equally important, another study demonstrated that mice with vitamin C deficiency had substantially more severe pathology of the lungs at day seven in contrast to those with adequate vitamin C in the lungs. However, prior to the lung infection, this group had a higher level of vitamin C concentration in the lungs than in the liver, which signifies that the lungs are more susceptible to vitamin C deficiency during respiratory infection than other organs [24-26] [24] [25] [26].

Vitamin C immune function and antimicrobial effect

Besides its ability to yield electrons, vitamin C has multiple functions that make it a crucial micromineral for humans [27]. Vitamin C supports several cellular functions of the adaptive and innate immune system and contributes to immune defence. Vitamin C is a cofactor for a family of biosynthetic and gene regulatory enzymes. Vitamin C is also a potent antioxidant that promotes the scavenging activity of the skin and supports the epithelial barrier function against pathogens by protecting the human organism against oxidative stress [28]. Vitamin C contributes to microbial destruction by accumulating in phagocytic cells and can improve the generation of reactive oxygen species, as well as chemotaxis and phagocytosis [29].

Likewise, vitamin C deficiency leads to an increased susceptibility to infection due to impaired immunity [30]. On the one hand, the metabolic requirement, as well as the increase in inflammation due to diseases, have a substantial impact on the levels of Vitamin C. On the other hand, the prevention and treatment of systemic and respiratory infections seem to be enhanced by supplementation with Vitamin C.

Therefore, for the prevention of infections and optimisation of vitamin C at cell and tissue levels, it is important to have adequate dietary vitamin C intake, meaning 100 - 200 mg/day. In order to compensate for the increase in the inflammatory responses, higher doses of vitamin C will be required for treatment [27,31].

Treating SARS and MERS with vitamin C

Several authors have argued that treatment with vitamin C could accelerate pneumonia recovery and alter the lower respiratory tract infection, having reported a significantly lower incidence of pneumonia among groups supplemented with vitamin C during three randomised controlled trial studies [32].

Not only the RCT studies but also the experiences from the SARS and MERS outbreaks during 2002 and 2012 respectively have highlighted the use of vitamin C in reducing the morbidity and case fatality rates. Furthermore, the susceptibility of the avian coronavirus responsible for infection of the tracheal organ cultures of chick embryos and broiler chicks has been reduced by vitamin C [33-35] [35].

Moreover, some studies have indicated that the proliferation of T lymphocytes, the functions of phagocytes, the gene expression of monocyte adhesion molecules, and the production of interferon are affected by vitamin C. However, the mechanism whereby vitamin C affects the immune system is unclear and poorly understood [32].

Additional research must be carried out to clarify the data in the literature, knowing that vitamin C is a powerful and efficient antioxidant and is also cost effective, while at the same time it can also behave as a radical trigger producing dangerous biochemicals in the living organism [9].

Conclusion

There is thus far no clinical data supporting the theory on the antioxidant role of vitamin C *in vivo*; however, there is a great deal of data demonstrating that it is a potent antioxidant in other biological systems. An ongoing randomised control trial study is currently being conducted in China on the administration of vitamin C infusion to treat patients with severe infection due to COVID-19 and the preliminary results are expected by September 2020[36] [37]. The results of this study will clarify the path going forward. Current studies did not show the efficacy of vitamin C in enhancing SARS outcomes more specifically in severe and critical SARS stages and there is no evidence about mild and moderate stages. However, the two ongoing clinical trials may clarify the role of vitamin C on immune system among SARS patients. Meanwhile, vitamin C can still be prescribed to the patient since it is a cost-effective intervention and is associated with other preventive benefits.

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